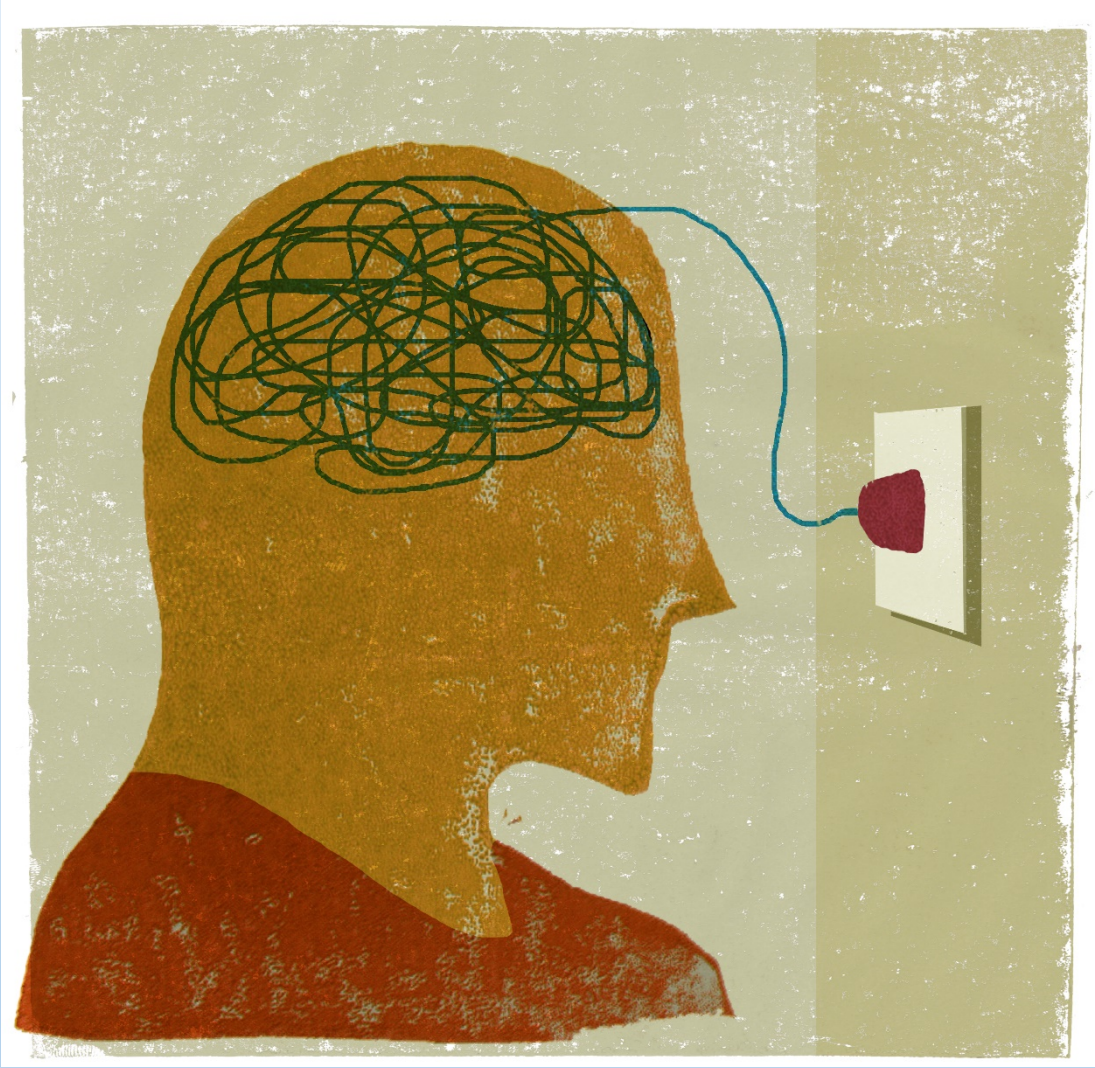
DEEP BRAIN STIMULATION FOR DRUG-RESISTANT EPILEPSY

Efficacy and Mechanism of Action



Mathieu Sprengers

Promotor: Prof. Dr. Kristl Vonck
Copromotor: Prof. Dr. Paul Boon

Faculty of Medicine and Health Sciences
Department of Neurology
4BRAIN

Deep brain stimulation for drug-resistant epilepsy: efficacy and mechanism of action

Mathieu Sprengers

Promotor: Prof. Dr. Kristl Vonck
Copromotor: Prof. Dr. Paul Boon

Thesis submitted to fulfill the requirements
for the degree of Doctor in Medical Sciences
– 2020 –

Promotor	Prof. Dr. Kristl Vonck Ghent University, Belgium
Copromotor	Prof. Dr. Paul Boon Ghent University, Belgium
Examination / reading board	Prof. Dr. Marie-Anne Vanderhasselt (chair) Ghent University, Belgium
	Prof. Dr. Christian Vanhove (secretary) Ghent University, Belgium
	Prof. Dr. Veerle De Herdt Ghent University, Belgium
	Prof. Dr. Günther Deuschl Christian-Albrecht University of Kiel, Germany
	Prof. Dr. Dirk De Ridder University of Otago, New Zealand
	Prof. Dr. Bart Smolders Eindhoven University of Technology, the Netherlands

Colophon

ISBN: 978-94-6407-516-8

Cover: Scott Lauman, *Head*, with permission

The work reported in this thesis has been funded by an Aspirant Fellowship grant of the Research Foundation - Flanders (FWO, Fonds voor Wetenschappelijk Onderzoek - Vlaanderen).

If the brain were simple enough for us to understand it,
we would be too simple to understand it

Emerson Pugh

Table of contents

List of abbreviations and symbols

A	ampere (SI [Système International] unit of electric current)
AddSE	additional stimulation electrode
AED	antiepileptic drug
AF	activation function (with AF_n activation function at node of Ranvier *n*)
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AP	anteroposterior
ATN	anterior thalamic nucleus
ATP	adenosine triphosphate
BAEP	brainstem auditory evoked potential
CA	cornu Ammonis
CC	corpus callosum
CI	confidence interval
CMT	centromedian thalamic nucleus
CPS	complex partial seizure
DBS	deep brain stimulation
EEG	electroencephalography
E_{Ca}	Nernst equilibrium potential of calcium (Ca2+)
E_{Cl}	Nernst equilibrium potential of chloride (Cl-)
E_K	Nernst equilibrium potential of potassium (K+)
E_{Na}	Nernst equilibrium potential of sodium (Na+)
EP	evoked potential
EpSE	evoked potential stimulation electrode
EPSP	excitatory postsynaptic potential
eq.	equation
F	Faraday constant
fEPSP	field excitatory postsynaptic potential
FTT	fast Fourier Transform
GABA	gamma-aminobutyric acid
Gpe	external globus pallidus
Gpi	internal globus pallidus
GTCS	generalized tonic-clonic seizure
I	electric current

I_{th}	treshold current
I_{rh}	rheobase current
HS	hippocampal sclerosis
ILAE	International League Against Epilepsy
IPSP	inhibitory postsynaptic potential
LC	locus coeroleus
LFP	local field potential
LGS	Lennox-Gastaut syndrome
LTD	long-term depression
LTP	long-term potentiation
MEG	magnetoencephalography
MEP	motor evoked potential
ML	mediolateral
MRI	magnetic resonance imaging
MTL	medial temporal lobe
NMDA	N-methyl-D-aspartic acid
OR	odds ratio
PET	positron emission tomography
PS	population spike
PW	pulse width
Q	charge
Q_{th}	treshold charge
R	gas constant
r	distance
RCT	randomized controlled trial
rTMS	repetitive transcranial magnetic stimulation
s	second (SI [Système International] unit of time)
SD	standard deviation
SISCOM	Substraction ictal SPECT co-registered to MRI
SNr	substantia nigra pars reticulata
SPECT	single-photon emission computed tomography
SSEP	somatosensory evoked potential
STN	subthalamic nucleus
tDCS	transcranial direct current stimulation

T	aboslute temperature
t_c	chronaxie
t_m	membrane time constant
TNS	trigeminal nerve stimulation
tVNS	transcutaneous vagus nerve stimulation
UPDRS	unified Parkinson's disease rating scale
U	electric potential difference or voltage
$U_{e,\,n}$	extracellular potential at node *n*
V	volt (SI [Système International] unit of voltage)
VEP	visual evoked potential
VNS	vagus nerve stimulation
WADA	intracarotid amobarbital procedure
WHO	World Health Organization
Z	Impedance
z	valence or valency
Ω	Ohm (SI [Système International] unit of impedance / resistance)

CHAPTER 1

Rationale and research aims

Epilepsy has a lifetime prevalence of 7.6 per 1000 persons, corresponding to around 50 million people affected by epilepsy worldwide [1]. In terms of disability-adjusted life years epilepsy is the second most important neurological cause of disease burden [2]. Uncontrolled epilepsy is associated with increased adverse psychosocial, behavorial and cognitive consequences and excess injury and mortality, leading to a low quality of life and high both direct and indirect economic costs [3-6]. Despite the exponential growth of currently available antiepileptic drugs, around 30% of epilepsy patients do not achieve seizure freedom with pharmacological treatment [7-9]. This figure is even higher in patients with temporal lobe epilepsy [10, 11]. Epilepsy surgery should be considered in all patients with drug-resistant epilepsy. The majority of drug-resistant epilepsy patients, however, are not suitable candidates for resective surgery due to the generalized or multifocal nature of the disease, the impossibility to delineate the epileptogenic zone or its localization in eloquent cortex. Some patients refuse resective surgery and in up to 50% of patients long-term seizure freedom is not achieved by resective surgery [12, 13]. Hence, an enormous group of epilepsy patients suffers from uncontrolled seizures and requires alternative treatment options (see Chapter 3) such as deep brain and cortical stimulation.

Deep brain and cortical stimulation are intrancranial neurostimulation techniques that use small electrical pulses to modulate ongoing neuronal activity. In the past 40 years and especially since the beginning of the new millennium various trials have evaluated its potential in drug-resistant epilepsy patients and shown promising results. Various constraints, however, limit the full appreciation of the role of deep brain and cortical stimulation in the treatment of drug-resistant epilepsy patients. The vast majority of trials had an uncontrolled open-label design which makes them susceptible to several types of bias. Most trials were performed in small series of patients. The optimal stimulation protocol remains unknown, including the optimal stimulation target and the optimal stimulation parameters. As a quintessential example, continuous and intermittent stimulation have been used interchangeably in epilepsy patients without substantiate grounds to prefer one strategy above the other. Furthermore, the duration of follow-up varied greatly amongst the different trials, ranging from months to several years of follow-up. This seems an important difference as an increasing efficacy over time has been reported in various trials although this requires further study [14-19]. Besides the increasing efficacy over time, the outlasting effect observed after cessation of deep brain stimulation (DBS) in some trials is another remarkable finding remaining a matter of debate and urging further investigation [17, 18, 20-22].

Despite its widespread use or active investigation for various neuropsychiatric disorders including epilepsy, the mechanism of action of DBS remains incompletely understood. Increasing our knowledge on this issue could rationalize the selection of the patients most likely to benefit from DBS, of the stimulation parameters and of the stimulation target, eventually leading to increased efficacy, reduced side effects and the prevention of the initiation of DBS therapy in patients unlikely to benefit from this treatment. Different mechanisms have been proposed including a depolarization block, synaptic depression, synaptic (GABAergic) inhibition, axonal conduction block, overriding of pathological activity by imposing new (stimulus-locked) activity to neuronal networks, desynchronization and suppression of pathological oscillations, local increase in adenosine or extracellular potassium, neuroplasticity, neurogenesis and neuroprotective effects (see Chapter 4). However, the specific contribution of each of these mechanisms remains unknown. Although they should not be mutually exclusive, some studies have reported seemingly conflicting results. This highlights the importance of the experimental protocol and the methods used to unravel the mechanism of action of DBS.

Different techniques have been used to unravel the mechanism of action of DBS, each with its specific advantages and drawbacks. An interesting technique to study several of the proposed mechanisms of action is the measurement of monosynaptically evoked potentials (EPs). Previous studies using EP have been performed in *in vitro* preparations or in urethane-anesthetized rats [23-29]. The results obtained in these studies could differ from those in freely moving rats as the complex three-dimensional architecture and physiological network activity are lost in *in vitro* conditions and urethane anesthesia has been shown to affect hippocampal neurotransmission, neuronal electrical properties as well as both short-term (e.g. paired-pulse inhibition) and long-term plasticity (e.g. long-term potentiation) [30, 31]. Therefore, the subject of investigation (DBS), its characteristics (especially the stimulation intensity), the method used (EPs), the changes induced by DBS and their temporal dynamics may all be affected by the *in vitro* setup and urethane anesthesia. Conclusions based on these studies should be interpreted with caution.

Except for a few studies such as those evaluating the neuroprotective effects of DBS, nearly all studies on the mechanism of action of DBS have investigated the effects of a couple of hundreds of milliseconds to minutes of DBS only. This is remarkable given the reported increasing efficacy of DBS with longer stimulation durations in epilepsy as well as various other neuropsychiatric disorders including dystonia, obsessive-compulsive disorder, depression, Tourette's syndrome and cluster headache [32-39]. Besides neurogenesis and neuroprotective effects, neuroplasticity has been proposed to be involved in this delayed or increasing efficacy of DBS ([32, 38], see also Chapter 4). One type of plasticity which could be particularly relevant is homeostatic plasticity, referring to changes in synaptic strength and intrinsic excitability occurring after prolonged changes in neuronal or network activity aiming to stabilize the activity within a certain physiological range [40]. It is possible that homeostatic plasticity mechanisms are recruited by the continuous neuronal activation brought about by DBS. Although this hypothesis has previously occasionally been suggested e.g. by Wyckhuys and colleagues [41], it was never the objective of a dedicated experimental set-up.

The aim of this doctoral dissertation is to increase our knowledge on:

- the outcome of drug-resistant epilepsy patients treated with DBS (*);
- the optimal DBS protocol (**);
- the mechanism of action of DBS (***).

More specifically, we will:

A. evaluate the **efficacy, safety and tolerability of DBS** as a treatment for **drug-resistant epilepsy patients** by

   1. evaluating the long-term outcome of hippocampal DBS in temporal lobe epilepsy in an uncontrolled open-label trial, with a focus on the efficacy (*), safety and tolerability (*), optimal stimulation protocol (**), potential increasing efficacy over time (*) (***) and potential effects outlasting the stimulation duration (*) (***);
   2. critically reviewing the current evidence on deep brain and cortical stimulation in epilepsy by performing a systematic review and meta-analysis including only randomized controlled clinical trials (RCTs) (*);

B. **investigate the mechanism of action of DBS** by evaluating the effects of hippocampal DBS on hippocampal EPs and spontaneous EEG (local field potentials, LFPs) in freely moving rats, both in acute and chronic DBS experiments, assessing

   3. if and how short-term (order of minutes) DBS modulates EPs and EEG in freely moving rats (***);
   4. whether additional or more profound changes occur with longer DBS durations (***);
   5. how the effects of intermittent DBS relate to those of continuous DBS (**) (***).

REFERENCES

[1] Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology 2017;88(3):296-303.

[2] Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet (London, England) 2012;380(9859):2197-223.

[3] Bazil CW. Comprehensive care of the epilepsy patient--control, comorbidity, and cost. Epilepsia 2004;45 Suppl 6:3-12.

[4] Cardarelli WJ, Smith BJ. The burden of epilepsy to patients and payers. Am J Manag Care 2010;16(12 Suppl):S331-6.

[5] Tomson T, Beghi E, Sundqvist A, Johannessen SI. Medical risks in epilepsy: a review with focus on physical injuries, mortality, traffic accidents and their prevention. Epilepsy Res 2004;60(1):1-16.

[6] Wirrell EC. Epilepsy-related injuries. Epilepsia 2006;47:79-86.

[7] Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012;78(20):1548-54.

[8] Brodie MJ, Schachter SC, Kwan P. Fast facts: epilepsy (revised 5th edition). Abingdon, United Kingdom: Health Press Limited; 2012.

[9] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342(5):314-9.

[10] Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology 1998;51(5):1256-62.

[11] Tatum WOt. Mesial temporal lobe epilepsy. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society 2012;29(5):356-65.

[12] de Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WF, Sander JW, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet 2011;378(9800):1388-95.

[13] Wyllie E. Wyllie's treatment of epilepsy: principles and practice (6th edition). 6 ed. Philadelphia, United States: Wolters Kluwer; 2015.

[14] Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51(5):899-908.

[15] Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, et al. Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 1992;33(5):841-51.

[16] Morrell MJ, Group RNSSiES. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 2011;77(13):1295-304.

[17] Velasco AL, Velasco F, Velasco M, Trejo D, Castro G, Carrillo-Ruiz JD. Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. Epilepsia 2007;48(10):1895-903.

[18] Velasco AL, Velasco M, Velasco F, Menes D, Gordon F, Rocha L, et al. Subacute and chronic electrical stimulation of the hippocampus on intractable temporal lobe seizures: preliminary report. Arch Med Res 2000;31(3):316-28.

[19] Velasco F, Carrillo-Ruiz JD, Brito F, Velasco M, Velasco AL, Marquez I, et al. Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. Epilepsia 2005;46(7):1071-81.

[20] Andrade DM, Zumsteg D, Hamani C, Hodaie M, Sarkissian S, Lozano AM, et al. Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy. Neurology 2006;66(10):1571-3.

[21] Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, Chen JL, et al. Long-term anterior thalamus stimulation for intractable epilepsy. Chang Gung Med J 2008;31(3):287-96.

[22] McLachlan RS, Pigott S, Tellez-Zenteno JF, Wiebe S, Parrent A. Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: impact on seizures and memory. Epilepsia 2010;51(2):304-7.
[23] Anderson TR, Hu B, Iremonger K, Kiss ZH. Selective attenuation of afferent synaptic transmission as a mechanism of thalamic deep brain stimulation-induced tremor arrest. J Neurosc 2006;26(3):841-50.
[24] Feng Z, Yu Y, Guo Z, Cao J, Durand DM. High frequency stimulation extends the refractory period and generates axonal block in the rat hippocampus. Brain Stimul 2014;7(5):680-9.
[25] Feng Z, Zheng X, Yu Y, Durand DM. Functional disconnection of axonal fibers generated by high frequency stimulation in the hippocampal CA1 region in-vivo. Brain Res 2013;1509:32-42.
[26] Iremonger KJ, Anderson TR, Hu B, Kiss ZH. Cellular mechanisms preventing sustained activation of cortex during subcortical high-frequency stimulation. J Neurophysiol 2006;96(2):613-21.
[27] Kim E, Owen B, Holmes WR, Grover LM. Decreased afferent excitability contributes to synaptic depression during high-frequency stimulation in hippocampal area CA1. J Neurophysiol 2012;108(7):1965-76.
[28] Li B, Piriz J, Mirrione M, Chung C, Proulx CD, Schulz D, et al. Synaptic potentiation onto habenula neurons in the learned helplessness model of depression. Nature 2011;470(7335):535-9.
[29] Schiller Y, Bankirer Y. Cellular mechanisms underlying antiepileptic effects of low- and high-frequency electrical stimulation in acute epilepsy in neocortical brain slices in vitro. J Neurophysiol 2007;97(3):1887-902.
[30] Riedel G, Seidenbecher T, Reymann KG. LTP in hippocampal CA1 of urethane-narcotized rats requires stronger tetanization parameters. Physiol Behav 1994;55(6):1141-6.
[31] Shirasaka Y, Wasterlain CG. The effect of urethane anesthesia on evoked potentials in dentate gyrus. Eur J Pharmacol 1995;282(1-3):11-7.
[32] Herrington TM, Cheng JJ, Eskandar EN. Mechanisms of deep brain stimulation. J Neurophysiol 2016;115(1):19-38.
[33] Johnson MD, Miocinovic S, McIntyre CC, Vitek JL. Mechanisms and targets of deep brain stimulation in movement disorders. Neurotherapeutics 2008;5(2):294-308.
[34] Krack P, Hariz MI, Baunez C, Guridi J, Obeso JA. Deep brain stimulation: from neurology to psychiatry? Trends Neurosci 2010;33(10):474-84.
[35] Pedersen JL, Barloese M, Jensen RH. Neurostimulation in cluster headache: a review of current progress. Cephalalgia : an international journal of headache 2013;33(14):1179-93.
[36] Sachdev PS, Mohan A, Cannon E, Crawford JD, Silberstein P, Cook R, et al. Deep brain stimulation of the antero-medial globus pallidus interna for Tourette syndrome. PLoS One 2014;9(8):e104926.
[37] Servello D, Porta M, Sassi M, Brambilla A, Robertson MM. Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation. Journal of neurology, neurosurgery, and psychiatry 2008;79(2):136-42.
[38] Udupa K, Chen R. The mechanisms of action of deep brain stimulation and ideas for the future development. Prog Neurobiol 2015;133:27-49.
[39] Yianni J, Bain PG, Gregory RP, Nandi D, Joint C, Scott RB, et al. Post-operative progress of dystonia patients following globus pallidus internus deep brain stimulation. Eur J Neurol 2003;10(3):239-47.
[40] Turrigiano G. Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. Cold Spring Harb Perspect Biol 2012;4(1):a005736.
[41] Wyckhuys T, Boon P, Raedt R, Van Nieuwenhuyse B, Vonck K, Wadman W. Suppression of hippocampal epileptic seizures in the kainate rat by Poisson distributed stimulation. Epilepsia 2010;51(11):2297-304.

PART I:
INTRODUCTION

CHAPTER 2

General introduction

General introduction to neurophysiology

Cells of the central nervous system

The human central nervous system contains about 100 billion neurons, the basic building blocks of the nervous system. The main function of these cells is to receive, integrate and transmit information in the brain by using electrical and chemical signals. Although the morphology of different types of neuron may vary, they all contain three distinct regions with different functions (see figure 1):

- The **cell body**, soma or perikaryon contains the nucleus and is the site of synthesis of most proteins and membranes.
- Most neurons have multiple **dentrites**, which are processes extending outward from the cell body with typically extensive arborizations. They receive information from other neurons by chemical signals and convert these into small electrical impulses that are conducted towards the cell body.
- **Axons** are long extensions from the cell body transmitting signals to other neurons or other cells (muscle, gland or other internal organ cells). They are specialized for the conduction of action potentials (see below) which originate at the somewhat thickened junction between the axon and the cell body, the axon hillock, and are propagated down the axon to the axon terminals, small branches of the axon that from the synapses or connections with other cells.

At the (chemical) **synapses** endogenous chemical substances, called neurotransmitters, are released from the axon terminals to transmit the signal from the pre- to the postsynaptic neuron. Most synapses are axodendritic connecting axons to dendrites, but many other synapses are axosomatic and axoaxonic. The total number of synapses formed by the 100 billion neurons is estimated to be around 200 trillion or on average 2000 synapses per neuron.

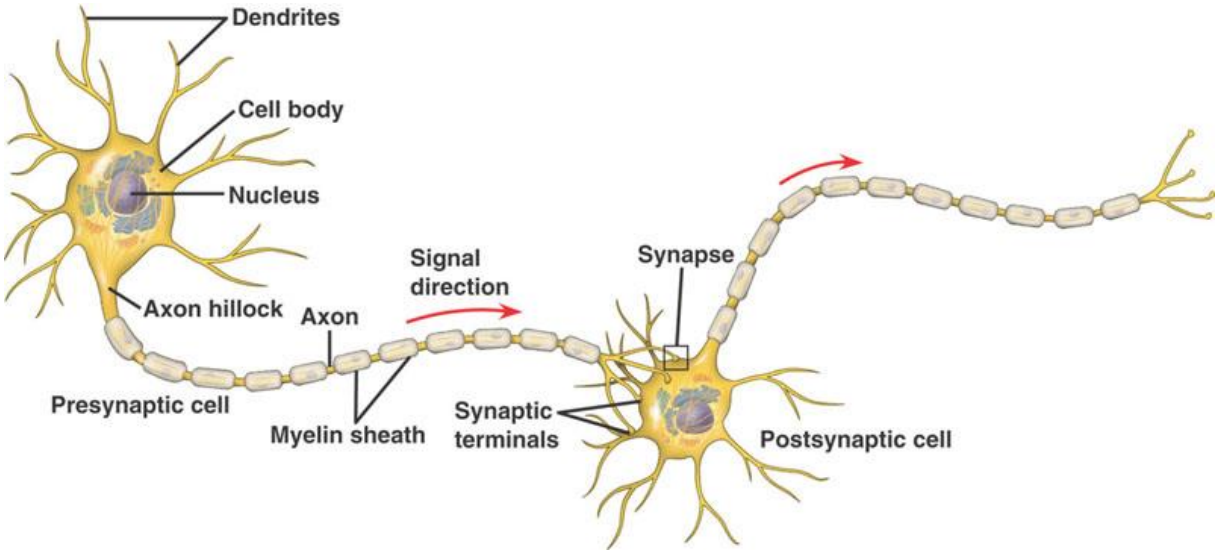


Figure 1. The typical structure of a neuron, consisting of the dendrites, the cell body and the axon. In an axodendritic synapse, information is transferred from the presynaptic axon to the dendrites of the postsynaptic neuron [1].

Besides neurons, the central nervous also contains **glial cells** such as astrocytes, microglia, oligodendrocytes and ependymal cells. Their function is to support neurons. **Astrocytes** have a major role in establishing the blood-brain barrier, remove neurotransmitters and potassium from the extracellular space, produce substances tropic to neurons and participate in phagocytosis of old synapses. They are important in maintaining the internal environment of the central nervous system constant. **Microglia** consists of scavenger cells capable of phagocytosis and resemble tissue macrophages. They originate from the bone marrow and enter the central nervous system from the circulating blood vessels. **Oligodendrocytes** form myelin sheaths in the central nervous system by wrapping their membrane around axons (see below). **Ependymal cells** line the ventricular system in the brain and the spinal cord [2-4].

Resting membrane potential

The neuronal cell membrane is composed of a phospholipid bilayer. This membrane only allows passive diffusion of gases and small, uncharged molecules. It is essentially impermeable to large uncharged molecules, charged molecules and ions which need membrane transport proteins to cross the neuronal cell membrane. These include adenosine triphosphate (ATP)-powered pumps, ion channels and other transporter proteins. ATP-powered pumps use the energy of ATP hydrolysis to move ions or small molecules across the membrane. Ion channels exhibit specificity for one or more type of ions, e.g. K+ channels allow K+ but not Na+ and vice versa for the Na+ channels. Ion channels can be open most of the time (non-gated ion channels) or open only in response to specific chemicals or electrical signals (gated ion channels).

A crucial ATP-powered pump in neurons is the Na+/K+ ATPase which moves three Na+ ions out and two K+ ions into the cell per ATP molecule hydrolyzed. In this way a concentration gradient for Na+ and K+ across the membrane is established, with high intracellular K+ (circa 150 millimolar) and extracellular Na+ (circa 145 millimolar) concentrations and low extracellular K+ (circa 4 millimolar) and intracellular Na+ (circa 15 millimolar) concentrations. Plasma membranes of neurons contain many open non-gated K+ channels but few open Na+, Ca2+ or Cl- channels, being the four most important ions. Therefore the outward movement of K+ driven by its concentration gradient is the main ionic movement across the cell membrane. As this leaves an excess of positive charge on the outside, an inside-negative transmembrane potential difference is created: the resting membrane potential. The magnitude of a transmembrane electrical potential difference resulting from the selective movement of a particular ion (in this case K+) across a semipermeable membrane can be calculated by the Nernst equilibrium equation. For K+, this equation (eq.) is given by:

$$E_K = \frac{\mathrm{RT}}{\mathrm{zF}} \ln \frac{[\mathrm{K_{out}}]}{[\mathrm{K_{in}}]} \qquad (\mathrm{eq.}\ 1),$$

where R is the gas constant, T the absolute temperature, z is the valency or charge of K+ (+1), F the Faraday constant and $[K_{out}]$ and $[K_{in}]$ the extra- and intraacellular K+ concentration respectively. When the actual potential difference between a microelectrode inserted into the interior of and a reference electrode outside the cell is measured, a resting membrane potential of around -70 mV is observed in neurons. This is close to but lower in magnitude than the potential calculated from the Nernst equation of K+ (around -97 mV), reflecting a few open Na+ channels.

As a result of the resting membrane potential, the transmembraneous movement of a substance carrying a net charge is not only influenced by its concentration gradient but also by its charge and the membrane potential. The combination of these two factors is called the electrochemical gradient [3, 4].

Action potential

Action potentials are specific 1-2 ms lasting rapid alterations of the transmembrane potential resulting from opening and closing of voltage-gated ion channels and are essential for signal transduction within neurons (see figure 2a). The first step required for an action potential to occur is a stimulus leading to an initial membrane depolarization (i.e. making the inside more positive). In neurons this is typically caused by opening of Na+ channels gated by excitatory neurotransmitters such as glutamate, resulting in the influx of Na+ ions following their electrochemical gradient. When this initial depolarization reaches a certain threshold, voltage-gated Na+ channels closed in resting neurons, will open (activated state). This results into an increase in Na+ influx, further membrane depolarization and thus activation of additional voltage-gated Na+ channels. This sets into motion an explosive entry of Na+ ions with the transmembrane potential evolving towards the Na+ Nernst equilibrium potential ($E_{Na} \approx +60$ mV). After about 1 ms, however, a cytosol facing channel-inactivating segment moves into the open channel preventing passage of further Na+ ions (inactivated state) (see figure 2b). In addition, membrane depolarization also slowly opens voltage-gated K+ channels. As the dynamics of these voltage-gated K+ channels are slower than these of the voltage-gated Na+ channels (which is necessary for the action potential to occur), they sometimes are called ‘delayed K+ channels’. The subsequent increased efflux of K+ from the cell together with the halt in Na+ influx drives the neuron again towards the K+ Nernst equilibrium potential restoring the inside-negative membrane potential. Due to their slower dynamics, the K+ channels only close slightly after the negative resting membrane potential has been reestablished leading to a negative overshoot of the membrane potential called the after-hyperpolarization.

Following an action potential, a neuron remains absolutely or relatively refractory to reactivation for a few milliseconds. The absolute refractory period results from the fact that the channel-inactivation segment is only displaced from the pore of the Na+ channels shortly *after* membrane repolarization has occurred, thus creating a time window during which the neuron cannot be reactivated no matter how strong the stimulus is. This period is followed by the relative refractory period. During this period, a neuron can be reactivated as the Na+ channels are closed but not inactivated (deactivated state). Due to the open K+ channels associated after-hyperpolarization, however, this requires a larger depolarization stimulus than during resting conditions [3, 4].

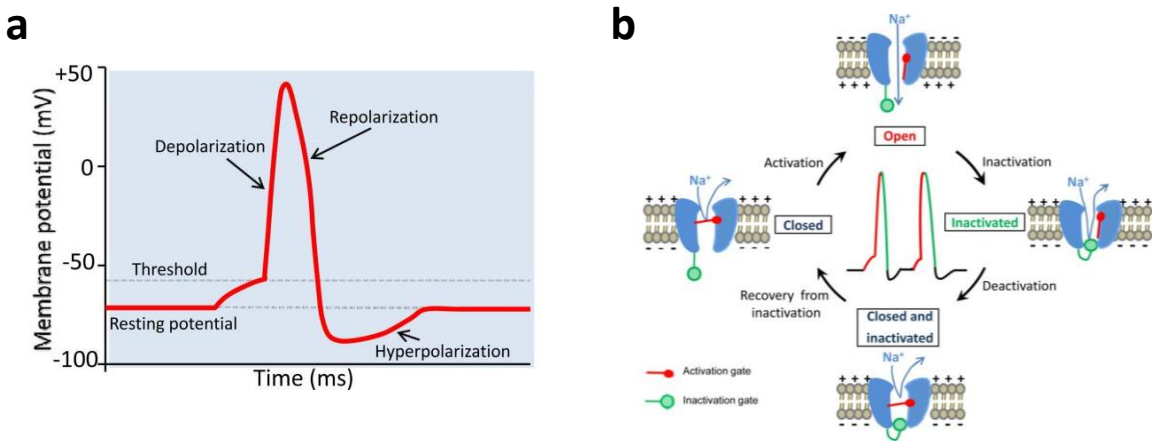


Figure 2. Membrane potential changes during the course of an action potential (panel a) and associated sequential activation, inactivation and deactivation of the voltage-gated sodium channels (panel b) (see text for more details) [5]

Axonal action potential propagation

When an axon potential is generated at the axon hillock, passive spread of intracellular Na+ ions depolarizes adjacent segments of the axon. This depolarization causes voltage-gated Na+ channels to open ultimately resulting in the generation of another action potential more distant from the axon hillock. By iteration of this process, the action potential is propagated down the axon. This propagation is unidirectional towards the axon terminals as the axonal membrane closer to the cell body is still in its refractory period because it has just been depolarized. Velocities of up to 2 meters per second can be reached in this way, with higher conduction velocities in larger axons.

Conduction velocities can be strongly increased by axonal myelination. The myelin sheat is produced by oligodendrocytes in the central and Schwann cells in the peripheral nervous system. Individual oligodendrocytes or Schwann cells wrap extensions of their plasma membrane around the axons over a certain distance, interrupted by small unmyelinated regions of about 1 µm: the nodes of Ranvier. The extracellular fluid is in direct contact with the axonal membrane only at the nodes of Ranvier. Moreover, the axonal Na+/K+ pumps and voltage-gated Na+ channels are also restricted to these nodes. These small unmyelinated regions are therefore the only regions in the axon where influx of Na+ ions and hence action potential generation can take place. As myelin is an effective insulator, cations entering the axonal cytosol during an action potential efficaciously spread passively to the next node of Ranvier with little loss of current. In this way, action potentials in fact 'jump' from node to node, resulting into conduction velocities of up to 120 meters per second [3, 4].

Synaptic communication

When an action potential reaches the axon terminals, the associated membrane depolarization opens voltage-gated Ca2+ channels resulting into an influx of Ca2+ ions from the extracellular fluid into the axon terminals. The increased cytosolic Ca2+ concentration and binding to its target proteins induces fusion of neurotransmitter-filled synaptic vesicles with plasma membrane and hence exocytosis of the neurotransmitters.

Neurotransmitters diffuse over the synaptic cleft (the space between the pre- and postsynaptic neuron) and bind to its receptors on the surface of the postsynaptic cell. There are two types of receptors: ionotropic and metabotropic receptors. Ionotropic receptors are ligand-gated ion channels wich open immediately upon neurotransmitter binding. In contrast, binding of neurotransmitters to metabotropic receptors (often G protein-coupled receptors) activates a intracellular signaling cascade which may have different downstream effects, including – with a certain delay – the opening or closing of a separate ion channel.

There exist many different neurotransmitters. The amino acid glutamate is the main excitatory neurotransmitter in the brain and the spinal cord, being responsible for around 75% of excitatory transmission. Binding of glutamate to its postsynaptic ionotropic receptor (kainate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) or N-methyl-D-aspartic acid (NMDA) receptors) opens ion channels that admit Na+ ions and depending on the particular ion channel also Ca2+ or K+ ions. This cation influx depolarizes the postsynaptic plasma membrane and the associated potential is called the excitatory postsynaptic potential (EPSP).

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain. $GABA_A$ and $GABA_B$ receptors are its main targets in the human central nervous system. The $GABA_A$ receptor is an ionotropic receptor allowing influx of Cl- ions upon activation, whereas the metabotropic $GABA_B$ receptor is coupled to G proteins and amongst others increases K+ conductance and inhibits Ca2+ influx. Increases in Cl- influx (E_{Cl} = -64 mV with $[Cl_{IN}]$ = 10 mmol/L and $[Cl_{OUT}]$ = 110 mmol/L) and K+ efflux and decreases in Ca2+ efflux (E_{Ca} = +137 mV with $[Ca_{IN}]$ = 70 nmol/L and $[Ca_{OUT}]$ = 2 mmol/L) hyperpolarize neurons. The associated potential is called the inhibitory postsynaptic potential (IPSP).

A single EPSP is unlikely to result into the generation of an action potential. However, postsynaptic neurons receive numerous excitatory and inhibitory projections from many different presynaptic neurons. When multiple EPSPs arrive at different synapses of the postsynaptic neuron at the same time or shortly after each other, they passively spread from the dentrites to the soma and the axon hillock where they are summed up. This phenomenon is referred to as spatial and temporal summation, respectively. If the resultant membrane depolarization is large enough to activate a sufficient number of voltage-gated ion channels at the axon hillock (typically requiring a +10-15 mV membrane depolarization), an action potential is generated. Likewise, simultaneous EPSPs and IPSPs may cancel each other out, making neurons complex integrators of incoming signals with a binary output modus: generating an action potential or not [3, 4].

General principles of neurostimulation

In the previous sections we described the central role of the electrical phenomena occurring in the brain. Further research on these phenomena will further increase our knowledge on how the brain works, both in normal and pathological conditions. Besides the academic aspect of merely describing these phenomena, knowledge about it can also be used for diagnostic and therapeutic purposes by means of electrical stimulation. Electromyography and evoked potentials (see below) are widely used in clinical practice and probably the best example of how neurostimulation can assist in or even be indispensable for proper disease diagnosis. Functional mapping in the presurgical evaluation in drug-resistant epilepsy patients is another example. The possible therapeutic applications of electrical stimulation in the central and peripheral nervous system are even more diverse. Well-known examples

are the use of deep brain stimulation in Parkinson's disease and other movement disorders, spinal cord and transcutaneous electrical stimulation in chronic pain patients, vagus nerve stimulation in epilepsy and the use of electrical pulses to stimulate the auditory and optical nerve in cochlear implants and visual prostheses, respectively.

Given their central role in this dissertation, both from a therapeutic and diagnostic point of view, the main principles underlying electrical stimulation of neural tissue will be described in the following sections.

Action potential generation by electrical stimulation

As intracellular current injection by a microelectrode is not feasible in the in vivo situation, neuronal depolarization must be achieved by current injected in the extracellular space. In clinical applications this is accomplished by creating a potential difference between two electrodes, placed in close vicinity to the neuron. According to Ohm's law, the injected current I depends both on the voltage or electric potential difference U and the impedance Z between both electrodes ($U = I \cdot Z$ (eq. 2)). The electrode connected to the negative output is referred to as the cathode, whereas the electrode connected to the positive output is the anode. The negative charge injected at the cathode will counter the positive charge outside the neuronal membrane and repell the negative charge inside the membrane. If the resulting reduction of the inside-negative transmembrane resting potential is large enough to activate a sufficient number of Na+ channels, an action potential is generated [6-8].

The activation function

It can be shown that the change in transmembrane potential is determined by the second spiatial difference of the electric field along the axon, referred to as the activation function. The activation function at node of Ranvier *n* (AF_n) of a myelinated nerve is given by

$$AF_n = U_{e,\,n-1} - 2\,U_{e,\,n} + U_{e,\,n+1} \qquad \text{(eq. 3)},$$

with $U_{e,\,n-1}$, $U_{e,\,n}$ and $U_{e,\,n+1}$ being the extracellular potentials at node n-1, n and n+1. In other words, neuronal depolarization occurs when $U_{e,\,n}$ is more negative than the average value of $U_{e,\,n-1}$ and $U_{e,\,n+1}$. The field potential of a cathodic current source and the associated activation function is illustrated in figure 3. As the field potential is inversely related to the distance to the cathode, the node closest to the cathode will have the most negative $U_{e,\,n}$ and largest AF_n and hence be depolarized most [6, 7].

Further away from the cathode, depolarization will decrease and eventually hyperpolarization (virtual anode effect) will occur as can be appreciated in figure 3. This hyperpolarization, however, has a much smaller amplitude than the depolarization close to the cathode. In concept, it can be seen that hyperpolarization occurs at those nodes where the positive charges entering the axon near the cathode again leave the axon but then dispersed over more nodes. The opposite response is observed at a nerve fibre in the vicinity of an anode with anodic hyperpolarization in the vicinity of the anode and depolarization further away from it (virtual cathode effect). Given the smaller amplitudes of the latter, anodic excitation consequently requires much higher current amplitudes than cathodic excitation [6, 7].

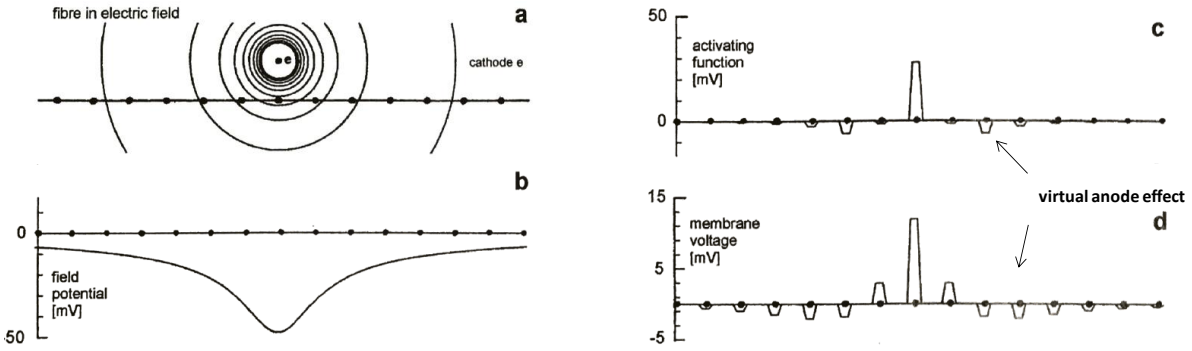


Figure 3. Calculated distribution of nodal membrane potentials elicited by stimulation. (a) Myelinated nerve fibre (dots indicate nodes of Ranvier) near a cathodic current source 'e' in a homogeneous conducting medium; (b) field potential distribution along the fibre; (c) distribution of nodal activating functions; (d) distribution of changes in membrane voltage and the virtual anode effect (adapted from [6]).

On theoretical grounds, hyperpolarization occurring close to the anode and further away from the cathode could block the propagated action potential. This is referred to as anodic and cathodic block, respectively. However, both require much higher stimulation intensities than cathodic excitation and in addition only occur during a very short time window. Therefore, anodic and cathodic block are unlikely to occur in clinical neurostimulation applications [6].

The internodal spacing in a myelinated nerve fiber is proportional to its diameter (around 100 times as a rule of thumb). This means that $U_{e,\,n-1}$ and $U_{e,\,n+1}$ will be higher in smaller axons as the field potential is inversely related to the distance from its source. This means that smaller axons consequently have lower activation functions and thus higher thresholds for action potential generation [6, 7].

Stimulus parameters and the strength-duration relationship

The threshold current (I_{th}) required to initiate an action potential is dependent on the duration or pulse width (PW) of the applied current. The relationship between the PW and I_{th} is known as the strength-duration relationship and was first described by Weiss in 1901 [9] and later reworked by Lapicque in 1907 [10] who proposed the equation

$$I_{th} = I_{rh} (1 + (t_c / PW)) \qquad \text{(eq. 4)}.$$

This equation describes how current pulses with longer PW require lower amplitudes to induce an action potential (see figure 4). For theoretically infinitely long pulse widths the current asymptomically approaches a minimum, called the rheobase current (I_{rh}). The chronaxie, t_c, is the PW corresponding to twice the rheobase current [6, 7, 11].

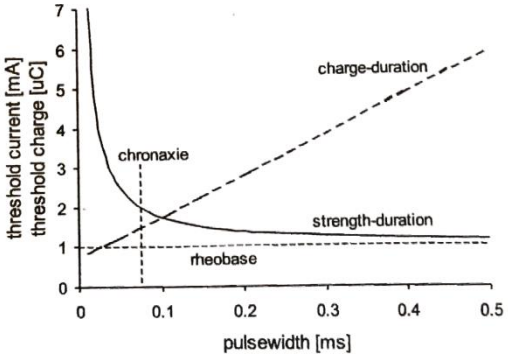


Figure 4. Relationship between the the pulse width and the treshold current to elicit a response (strength-duration curve), and between the pulse width and the threshold charge (charge-duration curve) (see text for more details) [6].

One of the major determinants of the value of the chronaxie t_c is the value of the membrane time constant t_m which is defined as the product of the membrane resistance and capacitiy. Due to the large difference in membrane resistance, the membrane time constants and hence chronaxie values are substantially higher for dendrites and cell bodies than for axons. Typical chronaxie values are around 30-200 µs for large myelinated axons, 200-700 µs for small axons and 1-20 ms for cell bodies and dendrites. In clinical neurostimulation pulse widths are in general well below 1 ms, which means that direct excitation of dendrites and cell bodies is unlikely to occur in these applications [6, 12].

The I_{th} and its associated PW can also be used to calculate the threshold charge (Q_{th}), with $Q_{th} = I_{th} \cdot PW$ (eq. 5). The charge-duration curve plots the threshold charge versus the pulse width (see figure 4). The curve shows that the threshold charge rises when the PW is increased. This can be explained by the fact that longer durations to change the membrane potential are associated with charge redistribution along the nerve fiber, more K+ efflux and increased sodium channel inactivation, all resulting into higher charges necessary for action potential generation with increasing pulse widths [6, 7, 11].

Mono- and bipolar stimulation

Stimulation requires a cathode and anode to create a potential difference between the locations where the current enters and leaves the patient. Monopolar stimulation refers to the situation where the cathode is in or near the targeted structure and the anode is from an electrical standpoint at an infinite distance, at least several times larger than the distance from the cathode to the target (e.g. the pulse generator under the skin over the chest). In bipolar stimulation, both the cathode and the anode are in or near the nervous system target. Monopolar and bipolar configurations differ in terms of the intensity, shape and distribution of the electrical fields they generate [6, 8].

In monopolar stimulation, the current injected by the cathode is distributed more or less equally in all directions. In contrast, in bipolar configurations the current distribution is less uniform and preferentially follows the cathode-anode axis (see figure 5) [6, 8]. The strength of the electrical field diminishes as neural elements are further away from the cathode, but the decay is faster in bipolar (~ $1/r^2$, with r = the distance to the cathode) than in monopolar (~ 1/r) than electrical fields. Bipolar stimulation configurations are thus associated with more 'concentrated' electrical fields [8].

The distance between the cathode and the anode in bipolar stimulation has an important influence on the resulting electrical field [6, 8]. At a large distance, the cathodic excitation is mostly unaffected by the anodic electrical field. When the anode gets closer to the cathode, however, the anodic excitation

(virtual cathode effect) summates with the cathodic excitation resulting into higher cathodic peak values and hence slightly lower excitation thresholds. When the two poles get too close, however, the anodic hyperpolarization will counteract the cathodic excitation. With smaller distances between the cathode and the anode, the excitation threshold is thus first gradually reduced and then sleeply raised [6]. In the clinically available stimulation electrodes, the latter is typically the case resulting into a more intense electrical field with wide compared to narrow bipolar configurations [8].

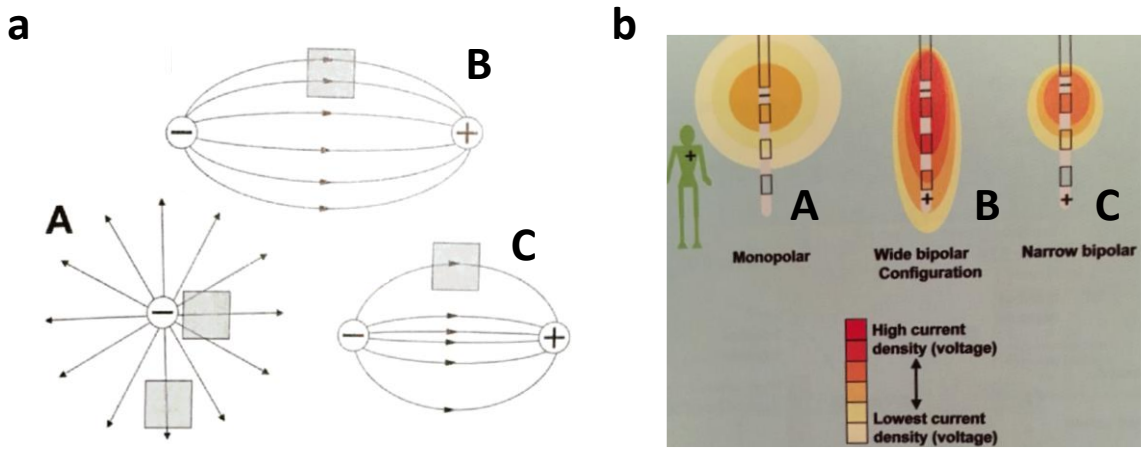


Figure 5. Schematic representation of the different sizes, shapes and intensities of electrical fields generated by a monopolar (A), a wide (B) and a narrow (C) bipolar stimulation configuration. In panel (a), the strength of the electrical fields in any spatial location can be inferred from the lines of electrical forces traversing that volume (boxes). In panel (b), current voltage / density is represented by a color as illustrated in the color bar (adapted from [8]).

Constant-voltage and constant-current stimulation

In theory, stimulation intensity can be programmed by adjusting either stimulation current or voltage. Voltage-controlled stimulators deliver an adjustable voltage across the stimulation electrodes. Following Ohm's law ($U = I \cdot Z$ (eq. 2), see above), the amount of current delivered to the tissue and hence the volume of activated tissue consequently depends on the impedance of the electrode, the electrode / brain tissue interface and the brain tissue. An increase in impedance will reduce the amount of current injected into the brain, and vice-versa. In contrast, constant-current stimulators dispose of a feedback circuitry to adjust the potential difference across the stimulation electrodes to the actual system's impedance. In this way a constant amount of current can be delivered to the brain. An important limitation is when the system's impedance is so high that the required voltage exceeds the maximum voltage range of the stimulator.

From a practical point of view, at least in the beginning, voltage-controlled stimulators were simpler and thus cheaper to construct as these required fewer electrical components. Nowadays most clinically available DBS systems are still voltage-controlled. As the volume of activated tissue is dependent on the amount of injected current and impedances can change over time, constant-current stimulators can theoretically provide more predictable and constant neurophysiological effects than voltage-

controlled systems. However, more research is necessary to investigate whether and to what extent this is associated with an additional clinical benefit [7, 13, 14].

The electrode / electrolyte interface

In a metal electrode, charge is carried by electrons whereas in the physiological medium, or in more general terms the electrolyte, charge is carried by ions such as Na+, K+ and Cl-. Injection of current to the brain is thus not as simple as it might appear as it requires the transduction of charge carriers from electrons in the metal electrode to ions in the extracellular fluid. Charge transfer at the electrode / electrolyte interface can occur by two primary mechanisms: non-faradaic and faradaic reactions, characterized respectively by the absence or presence of electron transfer between the electrode and the electrolyte.

When a potential difference is applied between two electrodes, an excess of negative charge will build up at the cathode. This will attract positive ions (cations) and repell negative charge (anions). The opposite processes occur at the anode. If the total amount of charge is sufficiently small, there will be only a charge redistribution without electron transfer across the electrode / electrolyte interface. This interface can be modeled as a simple capacitor, with reversal of the charge redistribution when the polarity of the applied voltage source is reversed. In some circumstances the resulting ion movement (current) induced in the electrolyte can be sufficient to generate an action potential.

However, the amount of current induced by non-faradaic reactions is limited and sometimes may be insufficient. Further charge injection requires electron transfer between the metal electrode and the electrolyte inducing processes of reduction and oxidation in the electrolyte near the cathode and anode, respectively. The degree of reversibility of these faradaic reactions depends on the relative rates of kinetics (electron transfer at the interface) and mass transport of reactants to the electrode surface, reversible reactions being characterized by fast kinetics and slow mass transport. Products from irreversible reactions may be soluble in the electrolyte, precipitate in the electrolyte or evolve as a gas (such as H_2) but always result in a net change in the chemical environment and thus be potentially damaging to the tissue (e.g. reactive oxygen species, gasses,…) or the electrode (e.g. electrode corrosion). Avoiding irreversible faradaic reactions is therefore a general objective of electrical stimulation. An important concept in this respect is the use of biphasic pulses, with current flow in one direction during the first phase and subsequently in the reversed direction during the second phase. The first phase is used to elicit the desired physiological effect (typically action potential generation) whereas the second phase is used to reverse the reversible faradaic reactions occurring during the first phase, ultimately resulting into a net zero accumulation of electrochemical species. To be reversible, the reaction products still need to be near the electrode when the reversed current is passed. In the ideal situation the reactions products from reversible faradaic reactions even remain bound to the electrode surface so that it is certain that the reactant may be recovered upon phase reversal (so-called pseudocapacity, e.g. $Pt + e^- + H^+ \rightarrow Pt–H$). For irreversible faradaic reactions, on the contrary, reversal of the electrochemical product cannot occur upon passing current in the reverse direction as the product is no longer available for reversal (it has diffused away). In summary, reversible processes necessary for safe electrical stimulation include non-faradaic reactions, pseudocapacity reactions and reversible faradaic reactions where the solution phase product remains near the electrode due to mass diffusion limitations [7, 11]. Given their favorable profile with regards to preventing irreversible

reactions, commercially available DBS hardware systems typically use platinum-iridium electrodes to minimize the risk of DBS-induced tissue damage. In addition, pulse widths are typically kept below 1 ms in clinical trials as longer pulse widths have a higher risk of inducing irreversible reactions given the longer time window before the polarity of the applied voltage source is reversed

Extracellular field recordings and electroencephalography (EEG)

Recording of the brain's electrical activity is widely used both for diagnostic and research purposes. While it is possible to measure the electrical signals from the inside of the neuron with respect to the outside, typically these **signals are measured between two points in the extracellular space rather than across the membrane**. As outlined above, these electrical fields are established by inward and outward current flows associated with neuronal activity. When a neuron is depolarized, the inward current flow is called a **current 'sink'** as it leaves the extracellular space. As electrical charges cannot build up in a neuron, each inward current flow is accompanied by an opposite outward current flow at another location of the neuron, **current 'sources'**. Current sources and sinks are referred to as active if they result from changes in membrane conduction as is the case in action potential generation. Passive sources and sinks, on the contrary, result from current flows out or in the cell by passive leakage or capacitive effects [15, 16].

When an extracellular recording electrode is located at a current sink, a negative potential will be recorded with respect to a distant ground electrode. Likewise, a positive potential will be recorded at a current source. To illustrate these general principles, we briefly describe the extracellular field recordings in two particular situations: the recording of an action potential along a nerve fiber and recordings made near an active neuron (or more in general: a layer of uniformly oriented neurons).

The **recording of an action potential along a nerve fiber** is illustrated in figure 6a. If an action potential is elicited at point A, a positive potential will be recorded at B (passive source). As the action potential propagates, point B eventually becomes an active sink and exhibits an extracellular negativity. Further propagation of the action potential towards point C makes point B a passive source again (positive potential). Overall, during the propagation of an action potential a triphasic waveform will be recorded at point B [16].

Each **active neuron can be considered an electric dipole**, with the pattern of current flow depending on the specific situation (see figure 6b). Consider the following examples. 1) When an action potential is initiated in the soma (figure 6.b.A), the soma becomes an active sink whereas the dendrites are a passive source. 2) Excitatory synaptic input to the dendrites will produce an active sink in the dendrites and a passive source in the soma (figure 6.b.B). 3) Inhibitory synaptic input to the soma produces an active source in the soma and a passive sink in the dendrites. Note that, despite completely different underlying physiological processes, the two latter situations result into similar extracellular recordings [15, 16].

EEG typically refers to the recording of potential differences from electrodes applied to the scalp. These potentials are generated by large population of neurons and thus are the sum of the current sinks and sources generated by individual neurons spreading in the conducting medium surrounding them (the volume conductor). EEG is believed to primarily reflect summated postsynaptic potentials (EPSP and IPSP), with only a minor contribution of action potentials given their much shorter duration

and smaller potential field distribution [17, 18]. As only a small fraction of the EPSP and IPSP-assciated currents spreads to the scalp, potential differences recorded by scalp EEG are relatively small, typically in the range of 10 to 100 µV.

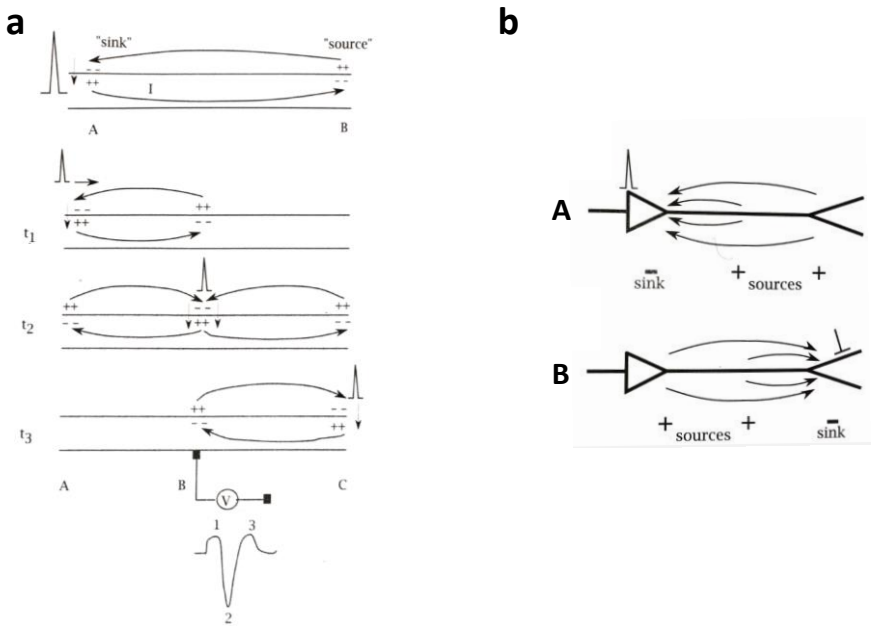


Figure 6. Extracellular field recordings. Panel (a) demonstrates the recording of an action potential along an axon. Panel (b) illustrates that each active neuron is an electric dipole. See text for more detail (adapted from [16]).

The first EEG recordings were described in 1929 by Hans Berger, a psychiatrist at the Jena Unversity in Thüringen [19]. He described rhythmic activity with a frequency around 10 Hz and named this the alpha rhythm (8-13 Hz). Other **frequency bands** later described in humans include delta (< 4 Hz), theta (4-7 Hz), beta (14-30 Hz) and gamma (> 30 Hz) activity, although the specific classification may differ among species [18, 20].

Besides from scalp electrodes, field potential recordings may also be obtained from **invasive subdural or depth electrodes** stereotactically implanted into specific brain regions. These local field potentials (LFPs) typically have larger amplitudes (hundreds of µV) resulting into a better signal to noise ratio [21, 22]. The most important application of such depth and subdural electrodes in clinical neurology is in the presurgical evaluation of drug-resistant epilepsy patients to identify the epileptogenic zone (see Chapter 3). In number, however, the most frequent application of such electrodes is in preclinical animal studies where they are used to increase our knowledge on the physiology of the healthy brain and specific diseases, including their diagnosis and treatment. However, despite its frequent use and clinical relevance, the exact physiological interpretation of the recorded EEG signals remains extremely complex [7, 23].

There are **various ways to analyze EEG signals**. Visual inspection of simple measures such as amplitude and frequency and the identification of specific EEG patterns (e.g. epileptic discharges) is typically used in clinical neurology. More complex analyses include source localization, connectivity and frequency

analyses [24-27]. As the latter is used in the experimental work presented in Chapter 7 and 8, we will briefly discuss this analysis here.

The most commonly used algorithm for frequency analysis is the Fourier transform. The fundamental of this analysis first described by Jean-Baptiste Joseph Fourier (1768-1830), is that any periodic time series can be decomposed into a number of oscillatory frequency components, formed by harmonically related sine and cosine waves. The Fourier transform thus transfers a signal from the time to the frequency domain. The most widely used Fourier analysis method in EEG is the **fast Fourier Transform (FTT)** which accepts time series sampled at discrete times and is a very efficient and fast algorithm to calculate the frequency components. A FTT of a time series with a duration *t* consisting of a number of *n* samples (which should be a power of 2 for FTT) will yield *n* frequency components, referred to as frequency bins, separated by $1/t$. The frequencies range from 0 (the direct current component) to $n/2$ *t* Hz, the frequency resolution being $1/t$. In practice, the direct current component is usually removed from the signal before calculating the FTT by subtracting the mean and any linear trend. The result of the FTT is a complex number ($a + b\,i$) for each frequency bin. The modulus or magnitude ($\sqrt{a^2 + b^2}$) of this complex number represents the amplitude of the frequency bin, whereas its argument or angle ($\tan^{-1}(\frac{b}{a})$) is the phase of the frequency bin. Calculating the magnitude of each frequency bin allows to assess how the power of a specific signal is distributed in the frequency domain. The FFT is calculated on a discrete signal with a limited duration (not a continuous infinite signal) and assumes that the signal repeats itself periodically. However, this assumption is only met by frequencies which complete an integer number of periods within the interval *t*. Other frequencies failing to meet the periodicity condition will lead to 'power leakage' into nearby frequency components. To avoid this, the borders of the signal are tapered by multiplying the original signal by a particular window function ('windowing') such as the Blackman or Hanning window. As this reduces the 'effective length' of the signal, a tradeoff needs to be made between the power leakage and the frequency resolution [21, 27, 28].

Evoked potentials (EPs)

In general, EPs refer to electrical field potentials extracellularly recorded in specific regions of interest in response to a specific stimulus. Typically, EPs are recorded by averaging time-locked electrical responses to the stimulus of interest, allowing to cancel out random background activity or noise that compromises the interpretation of the often low amplitude EPs.

In clinical practice, EPs are used to test the functional integrity of specific pathways, to 1) establish objective evidence of abnormality when signs or symptoms are equivocal, 2) detect subclinical lesions, 3) define the anatomical level of impairment along a pathway and 4) monitor changes over time. Common EPs used in clinical neurology include visually evoked potentials (VEP, visual stimulus to test visual pathways), brainstem auditory evoked potentials (BAEP, auditory clicks to test the auditory pathways), somatosensory evoked potentials (SSEP, electrical stimlulation of peripheral nerve to evaluate the peripheral and central sensory pathways) and motor evoked potentials (MEP, transcranial magnectic stimulation of the motor cortex to test the corticospinal tract) [29, 30].

Another type of EPs used in preclinical studies (including those presented in Chapter 7 and 8) involves the administration of an electrical stimulus to a bundle of nerve fibers projecting to a specific region in

order to assess its response. Such electrically EP have typically been investigated in the hippocampus due to its orderly anatomical neuronal arrangement and highly laminated pattern of inputs and outputs. This organization allows to detect the currents evoked by synchronous activity in many neurons via extracellular electrodes and thus providing surprisingly detailed information on cellular activity (see figure 7). Electrically evoked hippocampal potentials include the dentate gyrus response after electrical stimulation of the perforant path originating from the entorhinal cortex, and the cornu Ammonis area 1 (CA1) response after stimulation of the Schaffer collaterals originating from the CA3 region. Stimulation of the perforant path / Schaffer collaterals will induce an axonal fiber volley propagating towards their synapses with the dendrites in the dentage gyrus / CA1 region. Due to its small amplitude, however, this presynaptic fiber volley is often not detected. The field potential associated with the subsequent EPSPs in the postsynaptic dendrites are referred to as the population or field EPSP (fEPSP). If sufficient postsynaptic depolarization occurs to reach the threshold for synchronous action potential generation, the associated potential is called the population spike (PS). The time course of the synaptic current is roughly the same as that of the extracellularly measured fEPSP. If the time-to-peak of the synaptic current is constant, the peak of the fEPSP will be proportional to the slope of the rising phase. This is a very useful relationship, as peak measures of the fEPSP such as the fEPSP amplitude are often contaminated by PS, fIPSPs and polysynaptic events. In contrast to the fEPSP peak amplitude which shows a nonlinear relationship with the synaptic conductance, there is an almost linear relationship for the fEPSP slope. Therefore, the fEPSP slope is typically the measure of choice to describe the fEPSP [16, 31].

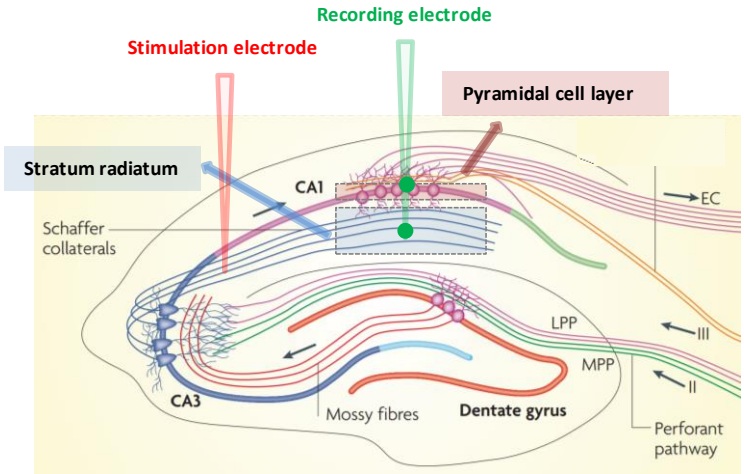


Figure 7. Illustration of the neural circuitry in the rodent hippocampus. Axons from the enthorinal cortex (EC) project to the dentate gyrus through the perforant pathway. The dentate gyrus connects to the CA3 region of the hippocampus via the mossy fibers. The CA3 region sends projections to the pyramidal cells in the CA1 region, called the Schaffer collaterals. The Schaffer collaterals terminate on the apical dentrites of the CA1 region in the stratum radiatum. The CA1 pyramidal cells, located in the pyramidal cell layer, eventually send back-projections to the enthorinal cortex. The typical location of the stimulation and the recording electrode (with contacts in the stratum radiatum and the pyramidal cell layer) to measure Schaffer collateral stimulation evoked potentials (as shown in figure 8) are indicated in red and green, respectively (adapted from [32]).

A typical Schaffer collateral stimulation EP recorded in the CA1 region is illustrated in figure 8. The lower recording electrode is located in the stratum radiatum where Schaffer collaterals terminate on the apical dendrites of the CA1 neurons. The upper recording electrode is located in the pyramidal cell layer (stratum pyramidale or pyramidal cell layer) containing the cell bodies of the CA1 neurons. The fEPSP will thus be recorded as a negative potential in the stratum radiatum (active current sink) and a positive potential in the pyramidal cell layer (passive current source). In contrast, a population spike is negative in the pyramidal cell body layer (active current sink) and positive in the stratum radiatum (passive current source) [31, 33].

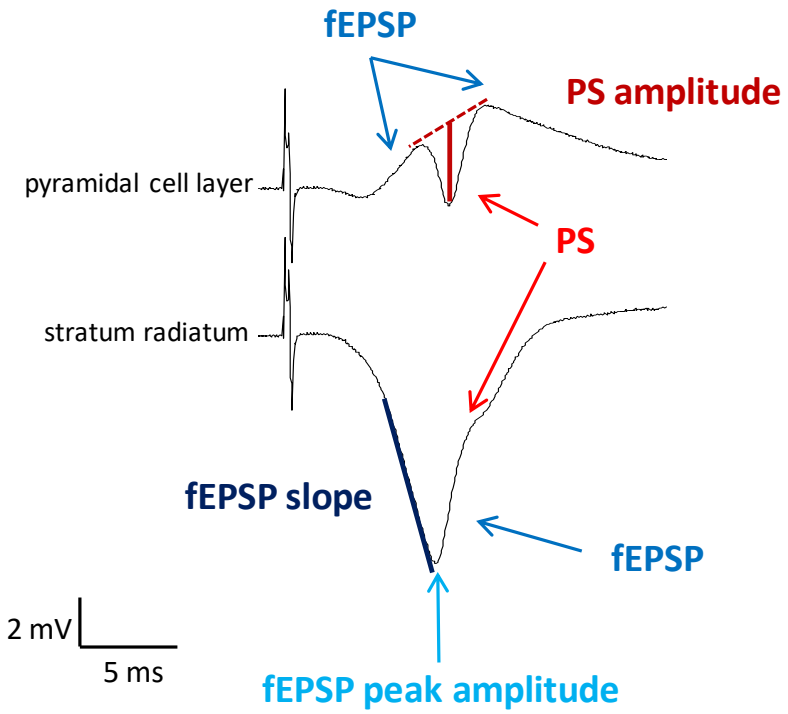


Figure 8. A typical Schaffer collateral stimulation evoked potential recorded in the CA1 region. The field excitatory postsynaptic potential (fEPSP) is measured as a negative potential in the stratum radiatum and a positive potential in the pyramidal cell layer. In contrast, the population spike (PS) is negative in the the pyramidal cell layer and positive in the stratum radiatum. Features of the fEPSP include the fEPSP slope and the fEPSP peak amplitude, the PS is (amongst others) characterized by its amplitude. The location of the stimulation and recording electrode are shown in figure 7.

In summary, the fEPSP reflects the monosynaptic excitatory synaptic transmission ('input') whereas the population spike is the response ('output') of the postsynaptic neurons to this input. Their relationship (PS / fEPSP) can be used to describe postsynaptic neuronal 'intrinsic excitability'. Electrically EPs have been used commonly to investigate changes in neuronal activity occurring in diverse neuronal disorders (e.g. epilepsy) or by specific drugs or other interventions [34-40].

Neuroplasticity

Neuroplasticity is the capacity of the neural activity generated by an experience to modify neural circuit function, a property closely associated with learning and memory formation. Synaptic plasticity specifically refers to the activity-dependent modification of the strength or efficacy of synaptic transmission [41]. We first describe the most common types of short-term plasticity lasting tens to hundreds of milliseconds to several minutes, followed by a discussion of long-term potentiation and depression. We conclude with a specific type of plasticity aiming to stabilize overall neural circuit function, homeostatic plasticity.

❖ Short-term forms of synaptic plasticity

➢ Paired-pulse depression

At many synapses, two stimuli delivered at a short time interval lead to a transient decrease in synaptic strength. The first stimulus is referred to as the conditioning pulse, whereas the second is called the test pulse. Typically, mainly presynaptic mechanisms are thought to contribute to the decreased synaptic efficacy. The most widespread mechanism appears to be a depletion of the release-ready pool of neurotransmitter-filled vesicles docked at the presynaptic terminal. Depletion is more likely to occur at synapses characterized by a high probability of stimulus-induced vesicle release and with higher frequency of activation. Other mechanisms include the inactivation of release sites due to the time it takes to clear vesicular membrane proteins incorporated in the plasma membrane upon vesicle fusion, an activity-dependent reduction in presynaptic calcium influx (e.g. by calcium-dependent inactivation of calcium channels), postsynaptic desensitization of ligand-gated receptors and the release of modulatory substances from the activated presynaptic terminals, postsynaptic cells or neighboring cells [41-43].

➢ Paired-pulse facilitation

Paired-pulse facilitation refers to an enhancement of synaptic transmission when two stimulation pulses are administered within a short time interval and lasts up to hundreds of milliseconds. In contrast to synaptic depression, synaptic facilitation typically occurs at synapses with a low initial probability of release. Presynaptic calcium is thought to play a key role in synaptic facilitation. It is clear that residual calcium left over from the invasion of a prior action potential will increase neurotransmitter release upon subsequent activation, but this mechanism seems insufficient to fully explain synaptic facilitation. Other mechanisms that have been proposed include saturation of presynaptic calcium buffers, use-dependent facilitation of presynaptic calcium channels, the activation of calcium-dependent pathways leading to a higher neurotransmitter release and the modulation of presynaptic ionotropic and metabotropic receptors by their agonists released by presynaptic, postsynaptic or neighbouring (including glia) cells.

Whether a synapse exhibits paired-pulse facilitation or paired-pulse depression depends on the relative importance of the mechanisms described above, including the initial release probability which amongst others is also under the control of neuromodulators activating presynaptic receptors [41-43].

➢ Augmentation and post-tetanic potentiation

Longer-lasting forms of enhanced neurotransmitter release are observed after repetitive or tetanic stimulation of synapses with prolonged (approximately 200 ms to 5 s) high-frequency (10-200 Hz) trains. These increases are caused by similar presynaptic mechanisms as paired-pulse facilitation, but the integrated effect of such a train of hundreds of pulses can lead to a many-fold enhancement and some processes become more important as the number of stimuli in a train is increased. At some synapses a distinction can be made between augmentation and post-tetanic potentiation. Post-tetanic potentiation lasts tens of seconds to minutes and becomes longer lasting with increased stimulus frequency and duration. Augmentation is induced with less prolonged stimulation and grows and decays with a time constant of 5 to 10 seconds. Different synapses show differences in the frequency and the number of stimuli necessary to induce augmentation and post-tetanic potentiation, and for some synapses it is very difficult to make a distinction between these two phenomena.

Similar to the distinction between paired-pulse facilitation and depression, at some synapses longer-lasting repetitive activation leads to depression lasting seconds or even minutes instead of augmentation and post-tetanic potentiation. Different types of short-term plasticity may also occur simultaneously though with different life times, such as facilitation, post-tetanic potentiation and depression, which complicates the prediction of the eventual overall response [41-43].

➢ Paired-pulse inhibition

Similar to paired-pulse depression, paired-pulse inhibition is characterized by a decreased response to a test stimulus administered shortly after a conditioning pulse. However, the underlying mechanism is different. In contrast to paired-pulse depression, paired-pulse inhibition is established by GABAergic inhibition from activated interneurons. This activation is typically explained as being established by the activated principal / pyramidal cells (recurrent or feedback inhibition) [31, 36, 44-46] although direct activation by the afferent stimulation (feedforward inhibition) could also play a role [46]. Early (< 100 ms, strongest at ± 20 ms) paired-pulse inhibition is thought to correspond primarily to the activation of the ionotropic $GABA_A$-receptor [31, 40, 44-46], whereas late paired-pulse inhibition (200 to 1000 ms) is associated with the activation of the $GABA_B$ metabotropic receptor [44, 46]. The extent of paired-pulse inhibition is higher with increasing stimulation intensities as these result into higher population spikes and hence more recurrent inhibition.

❖ Long-term forms of synapic plasticity

➢ Long-term potentiation

Long-term potentiation (LTP) is probably the most extensively studied form of neuroplasticity and refers to a long-lasting increase in synaptic strength occurring between 2 neurons, typically lasting multiple days and sometimes even more than one year. LTP has prototypically been investigated in the hippocampus but also occurs in other brain regions. It is considered as one of the major mechanisms underlying learning and memory formation. LTP is characterized by three important properties. The first is input-specificity, LTP is only elicited at activated synapses and not at adjacent inactive synapses. The second is cooperativity, LTP is only induced when the inducing stimulus is sufficiently strong, i.e. above the ‘cooperativity treshold’. The third characteristic is associativity, the capacity to potentiate a

weak input – below to he cooperativity threshold – when it is associated with another strong input, although the distinction of the latter two is essentially semantic.

Experimentally, LTP can be induced by different protocols: 1) one or more trains of tetanic stimulation (100 Hz for 1 second or multiple shorter trains), 2) pairing protocols where single stimuli repeated at low frequency are paired with depolarizing pulses inducing brisk firing of the postsynaptic cell, and 3) spike timing-dependent potentiation where an afferent stimulus is followed by a brief depolarizing pulse that makes the target cell fire only once. All these protocols have in common that a synapse will only be potentiated if, and only if, it is active at a time when its dendritic spine is sufficiently depolarized.

Although NMDA receptor independent forms of LTP have been described, the classical form of LTP is NDMA receptor dependent. At resting membrane potential, glutamate or other NMDA receptor ligands induce negligible currents through the NMDA receptor channel as it is blocked by magnesium. When the membrane is sufficiently depolarized, however, magnesium dissociates from its binding site allowing calcium and other ions to enter the cell. This dual-gate characteristic of the NMDA receptor provides a molecular explanation for the three properties of LTP and the efficiency of the different induction protocols. The resulting increase in intracellular calcium activates diverse signaling pathways which will eventually cause a long-lasting increase in synaptic strength. Note that LTP can also be induced by calcium entering the cytoplasm from intracellular calcium stores or via voltage-gated calcium channels, as is the case in NMDA receptor independent forms of LTP.

LTP is characterized by three distinct temporal components: short-term potentiation, early LTP and late LTP. Short-term potentiation usually lasts less than one hour, is mainly presynaptic in nature and decays in an activity-dependent manner. Early LTP involves multiple protein kinase-depedent mechanisms (including protein kinase C, calcium/calmodulin-dependent protein kinase II, protein kinase A,…) and usually lasts several hours. Expression of early LTP is associated with both the incorporation of additional AMPA receptors in the postsynaptic membrane and the increase in AMPA receptor conduction. Late LTP is responsible for the longer-lasting changes in synaptic strength and is protein synthesis dependent presumably amongst others resulting into structural remodeling. In the initial phase protein synthesis occurs by translation of the mRNA that is present locally in the dendrite but eventually after several hours requires gene transcription in the nucleus followed by protein transport to the involved dendritic compartiments.

Although LTP is typically considered to be mainly a postsynaptic process, the involvement of presynaptic mechanisms such as increased neurotransmitter release has been demonstrated in multiple studies. At the mossy fiber synapses with CA3 neurons, it is even the dominant mechanism responsible for LTP (‘NMDA receptor-independent presynaptic LTP’). Furthermore, in addition to the proportionate increase of the population spike resulting from the LTP-associated EPSP increase, EPSP-spike potentiation has also been shown to occur [31, 41, 47].

- **Long-term depression**

The discovery of **NMDA receptor-dependent long-term depression** (LTD) confirmed that synaptic strength could be bidirectionally modulated. A typical way to induce it is by prolonged repetitive low-frequency stimulation (typically 900 stimuli at 1 Hz). The predominant current hypothesis is that large

rapid increases in postsynaptic calcium induce LTP via the activation of protein kinases, whereas lower and slower increases yield LTD via activated protein phosphatases. Another possibility is spike timing-dependent induction of LTD where (in contrast to LTP induction) the postsynaptic spike precedes or is administered in a symmetric 10-30 ms time window before / after the presynaptic one, depending on the experimental setup. Although a presynaptic contribution has been demonstrated in some studies, expression of NMDA receptor-dependent LTD is mainly a postsynaptic phenomenon and involves AMPA (and NMDA) receptor internalization and decreased AMPA channel conductance. Furthermore, a late protein-synthesis dependent phase of NMDA receptor-dependent LTD has also been shown.

Another type of LTD which is not blocked by NMDA repector antagonists is dependent on metabotropic glutamate receptors. **Metabotropic glutamate receptor-dependent LTD** can be induced either by administration of metabotropic glutamate receptor agonists or by prolonged repetitive paired-pulse stimulation (900 pairs at 100 Hz with an interpulse interval of 50 ms). The intracellular signaling pathways are incompletely understood but appear (at least in the hippocampus) to be dependent on postsynaptic local protein synthesis. Similar to NMDA receptor-dependent LTD, AMPA receptor endocytosis has also been shown in metabotropic glutamate receptor-dependent LTD be it through different signaling cascades. In addition, however, presynaptic mechanisms seem (especially in young animals) much more important in metabotropic glutamate receptor-dependent LTD, which thus would require a retrograde signaling molecule with 12-lipoxygenase metabolites of arachidonic acid being an important candidate.

Endocannabinoid-mediated LTD is another type of LTD and is mediated by endocannibinoids. These retrograde messengers are released by postsynaptic cells upon strong depolarization and/or activation of G-protein coupled receptors, and transiently inhibit presynaptic neurotransmitter release via activation of presynaptic CB1 receptors.

We conclude with the remark that LTD is conceptually different from **depotentiation**. LTD refers to 'de novo' LTD, whereas depotentiation is the reversal or erasure of LTP. It is important to make this distinction as LTD and depotentiation rely on different mechanisms. In an analogous way, LTP is different from **de-depression** [31, 41].

❖ Homeostatic plasticity

Both LTP and LTD exhibit many of the features described in a model by Donald Hebb in 1949 and are often referred to as 'Hebbian plasticity' [48]. Hebbian forms of plasticity are input-specific, rapidly induced, long-lasting and inducible by correlated firing of the pre- and postsynaptic neurons. However, Hebbian plasticity poses a stability problem to neural networks as it could lead to positive feedback loops of more excitable synapses resulting into hyperexcitability. Conversely, synapses depressed by LTD could more easily undergo further depression and ultimately lead to synapse silencing. These considerations made many to hypothesize that homeostatic mechanisms must exist to counter runaway excitation or depression. Mainly in the last three decades, several distinct types of such plasticity have been described and these are commonly referred to as homeostatic plasticity. Homeostatic plasticity mechanisms aim to maintain overall levels of neuronal activity within biologically-determined setpoints by bidirectional regulation of synaptic strength and intrinsic excitability in response to prolonged changes in neuronal or network activity (i.e. hours to days). In

essence, an upward regulation is found when neuronal activity is reduced over a longer time period and, vice versa, a downward regulation is seen after prolonged enhanced activity [49-52].

Conceptually, homeostatic plasticity requires both mechanisms to 'sense' neuronal or network activity and effectors to regulate neuronal excitability in the homeostatic direction, acting over a relatively long time course. Homeostatic plasticity was initially shown on a network-wide level, but further in vitro and in vivo studies also showed the existence of cell-autonomous and later on even synapse-autonomous homeostatic plasticity, sensing thus not only changes in action potential firing but also in excitatory postsynaptic currents [51, 52].

Homeostatic plasticity can involve both changes in synaptic strength, called 'synaptic scaling', and changes in intrinsic excitability. Both post- and presynaptic scaling mechanisms have been shown. Similar to Hebbian types of plasticity, changes in AMPA receptor abundance have been demonstrated to occur in synaptic scaling. Moreover, some studies have also shown changes in subunit composition, favoring more or less calcium permeable subunits. Many different molecules interfering with the expression of postsynaptic scaling have been identified, including calcium sensing proteins (as intracellular calcium correlates well with neuronal activity), scaffolding proteins, transcriptional and translational regulators, cell-adhesion and transsynaptic signaling molecules and soluble released factors such as tumor necrosis factor alfa and brain-derived neurotrophic factor [49, 50].

Homeostatic regulation of presynaptic neurotransmitter release was first described at the neuromuscular junctions, but subsequently also demonstrated in the human central nervous system. Changes in neurotransmitter release are dependent on modulation of presynaptic calcium influx through voltage-gated calcium channels, of the readily releasable pool of vesicles and of vesicle fusion. Similar to presynaptic changes in LTP and LTD, this requires a retrograde messenger (e.g. brain-derived neurotrophic factor in the hippocampus) [49].

Besides changes in synaptic strength, homeostatic plasticity can also be established by intrinsic excitability regulation. Although the underlying mechanisms are still being further explored, this regulation can occur through the modulation of the abundance and spatial distribution (e.g. the location and length of the axon initial segment) of voltage-gated channels, and on their biophysical characteristics. In contrast, neuronal passive electrical properties do not seem to be changed [49, 50, 53].

To conclude, we have described different types of neuroplasticity which can serve different purposes. Short-term neuroplasticity can act as high- or low-pass filter, LTD and LTP are involved in learning and memory and homeostatic plasticity aims to stabilize neuronal activity and networks. Neuronal plasticity has been shown both at excitatory and inhibitory synapses and its expression is often age-dependent and may be affected in disease. With around 100 billion neurons and on average 2000 synapses per neuron, the ultimate result is a very complex interplay of many factors which makes the nervous system by far the most sophisticated human organ.

REFERENCES

[1] https://biology.stackexchange.com/questions/22011/neurons-with-thousands-of-connections-where-are-the-extra-connections-coming-fr, 3 January 2019.
[2] Schünke M, Schulte E, Schumacher U. Anatomische atlas Prometheus: hoofd, hals en neuroanatomie (2de druk). Houten, The Netherlands: Bohn Stafleu van Loghum; 2010.
[3] Lodish H, Berk A, Matsudaira P, Kaiser CA, Krieger M, Scott MP, et al. Molecular cell biology (5th edition). New York, United States: W.H. Freeman and Company; 2004.
[4] Ganong WF. Review of medical physiology (22nd edition). New York, United States: The McGraw-Hill Companies; 2005.
[5] Dong K, Du Y, Rinkevich F, Nomura Y, Xu P, Wang L, et al. Molecular biology of insect sodium channels and pyrethroid resistance. Insect Biochem Mol Biol 2014;50:1-17.
[6] Holsheimer J. Principles of neurostimulation. In: Simpson BA, editor Pain research and clinical management., Amsterdam, The Netherlands: Elsevier; 2003.
[7] Krames ES, Peckham PH, Rezai AR. Neuromodulation. London, United Kingdom: Academic Press, Elsevier; 2009.
[8] Montgomery EB, Jr. Deep brain stimulation programming: principles and practice. New York, United States: Oxford University Press; 2010.
[9] Weiss G. Sur la possibilité de rendre comparables entre eux les appareils servant à l'excitation électrique. Arch Ital Biol 1901;35(1):413-46.
[10] Lapicque L. Recherches quantitatives sur l'excitation électrique des nerfs traitée comme une polarisation. Journal de Physiology et de Pathologie Générale 1907;9:620-35.
[11] Arle J, Shils J. Essential neuromodulation. London, United Kingdom: Academic Press, Elsevier; 2011.
[12] Holsheimer J, Demeulemeester H, Nuttin B, de Sutter P. Identification of the target neuronal elements in electrical deep brain stimulation. Eur J Neurosci 2000;12(12):4573-7.
[13] Bronstein JM, Tagliati M, McIntyre C, Chen R, Cheung T, Hargreaves EL, et al. The rationale driving the evolution of deep brain stimulation to constant-current devices. Neuromodulation 2015;18(2):85-8; discussion 8-9.
[14] Lettieri C, Rinaldo S, Devigili G, Pisa F, Mucchiut M, Belgrado E, et al. Clinical outcome of deep brain stimulation for dystonia: constant-current or constant-voltage stimulation? A non-randomized study. Eur J Neurol 2015;22(6):919-26.
[15] Daube JR. Clinical neurophysiology (2nd edition). New York, United States: Oxford University Press; 2002.
[16] Johnston D, Miao-Sin Wu S. Foundations of cellular neurophysiology. Massachusetts, United States: MIT Press; 1995.
[17] Fisch BJ. Fisch and Spehlmann's EEG Primer: basic principles of digital and analog EEG (3rd edition). Ney York, United States: Elsevier Health; 1999.
[18] Rowan AJ, Tolunsky E. Primer of EEG with a mini-atlas. Philadelphia, United States: Elsevier Science; 2003.
[19] Berger H. Uber das Elektrenkephalogramm des Menschen. Eur Arch Psychiatry Clin Neurosci 1929;87(1):527-70.
[20] Buzsaki G. Rhythms of the Brain. New York, United States: Oxford University Press; 2006.
[21] Cooper R, Binnie CD, Billings R. Techniques in clinical neurophysiology: a practical manual. Amsterdam, The Netherlands: Elsevier; 2005.
[22] Van Loo P, Carrette E, Meurs A, Goossens L, Van Roost D, Vonck K, et al. Surgical successes and failures of invasive video-EEG monitoring in the presurgical evaluation of epilepsy. Panminerva Med 2011;53(4):227-40.
[23] Herreras O. Local Field Potentials: Myths and Misunderstandings. Front Neural Circuits 2016;10:101.

[24] Michel CM, Murray MM, Lantz G, Gonzalez S, Spinelli L, Grave de Peralta R. EEG source imaging. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2004;115(10):2195-222.
[25] van Mierlo P, Papadopoulou M, Carrette E, Boon P, Vandenberghe S, Vonck K, et al. Functional brain connectivity from EEG in epilepsy: seizure prediction and epileptogenic focus localization. Prog Neurobiol 2014;121:19-35.
[26] van Mierlo P, Carrette E, Hallez H, Raedt R, Meurs A, Vandenberghe S, et al. Ictal-onset localization through connectivity analysis of intracranial EEG signals in patients with refractory epilepsy. Epilepsia 2013;54(8):1409-18.
[27] Freeman WJ, Quiroga RQ. Imaging brain function with EEG: advanced temporal and spatial analysis of electroencephalographic signals. New York, United States: Springer; 2013.
[28] Nunez PL, Srinivasan R. Electric fields of the brain: the neurophysics of EEG (2nd edition). New York, United States: Oxford University Press; 2005.
[29] Nuwer MR. Fundamentals of evoked potentials and common clinical applications today. Electroencephalogr Clin Neurophysiol 1998;106(2):142-8.
[30] Sand T, Kvaloy MB, Wader T, Hovdal H. Evoked potential tests in clinical diagnosis. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke 2013;133(9):960-5.
[31] Andersen P, Morris R, Amaral D, Bliss T, O'Keefe J. The hippocampus book. New York, United States: Oxford University Press; 2007.
[32] Deng W, Aimone JB, Gage FH. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? Nature reviews Neuroscience 2010;11(5):339-50.
[33] Leung LW. Orthodromic activation of hippocampal CA1 region of the rat. Brain Res 1979;176(1):49-63.
[34] Abraham WC, Mason SE. Effects of the NMDA receptor/channel antagonists CPP and MK801 on hippocampal field potentials and long-term potentiation in anesthetized rats. Brain Res 1988;462(1):40-6.
[35] Albertson TE, Joy RM. Modification of evoked hippocampal dentate inhibition by diazepam and three antagonists in urethane-anesthetized rats. Exp Neurol 1989;106(2):142-9.
[36] Kamphuis W, Gorter JA, Wadman WJ, Lopes da Silva FH. Hippocampal kindling leads to different changes in paired-pulse depression of local evoked field potentials in CA1 area and in fascia dentata. Neurosci Lett 1992;141(1):101-5.
[37] King GL, Dingledine R, Giacchino JL, McNamara JO. Abnormal neuronal excitability in hippocampal slices from kindled rats. J Neurophysiol 1985;54(5):1295-304.
[38] Maru E, Goddard GV. Alteration in dentate neuronal activities associated with perforant path kindling. II. Decrease in granule cell excitability. Exp Neurol 1987;96(1):33-45.
[39] Maru E, Goddard GV. Alteration in dentate neuronal activities associated with perforant path kindling. I. Long-term potentiation of excitatory synaptic transmission. Exp Neurol 1987;96(1):19-32.
[40] Queiroz CM, Gorter JA, Lopes da Silva FH, Wadman WJ. Dynamics of evoked local field potentials in the hippocampus of epileptic rats with spontaneous seizures. J Neurophysiol 2009;101(3):1588-97.
[41] Citri A, Malenka RC. Synaptic plasticity: multiple forms, functions, and mechanisms. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 2008;33(1):18-41.
[42] Fioravante D, Regehr WG. Short-term forms of presynaptic plasticity. Curr Opin Neurobiol 2011;21(2):269-74.
[43] Zucker RS, Regehr WG. Short-term synaptic plasticity. Annu Rev Physiol 2002;64:355-405.
[44] Shirasaka Y, Wasterlain CG. Chronic epileptogenicity following focal status epilepticus. Brain Res 1994;655(1-2):33-44.
[45] Tuff LP, Racine RJ, Adamec R. The effects of kindling on GABA-mediated inhibition in the dentate gyrus of the rat. I. Paired-pulse depression. Brain Res 1983;277(1):79-90.
[46] Waldbaum S, Dudek FE. Single and repetitive paired-pulse suppression: a parametric analysis and assessment of usefulness in epilepsy research. Epilepsia 2009;50(4):904-16.

[47] Nicoll RA. A Brief History of Long-Term Potentiation. Neuron 2017;93(2):281-90.
[48] Hebb DO. The organization of behavior. New York, United States: Wiley; 1949.
[49] Fernandes D, Carvalho AL. Mechanisms of homeostatic plasticity in the excitatory synapse. J Neurochem 2016;139(6):973-96.
[50] Turrigiano G. Too many cooks? Intrinsic and synaptic homeostatic mechanisms in cortical circuit refinement. Annu Rev Neurosci 2011;34:89-103.
[51] Turrigiano G. Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. Cold Spring Harb Perspect Biol 2012;4(1):a005736.
[52] Lee KF, Soares C, Beique JC. Tuning into diversity of homeostatic synaptic plasticity. Neuropharmacology 2014;78:31-7.
[53] Desai NS. Homeostatic plasticity in the CNS: synaptic and intrinsic forms. J Physiol Paris 2003;97(4-6):391-402.

CHAPTER 3

Epilepsy

Historical perspectives, definition and epidemiology

The first description of an epileptic seizure dates back from 3000 years ago in Mesopotamia (now Iraq) and was written in Akkadian, the oldest written language. The seizure was attributed to the god of the moon. Further reports were described in Egypt, China, India and Babylonia. In his book 'The sacred disease', Hippocrates (460-377 BC) was the first to attribute the origin of seizures to the brain, rejecting prior beliefs that gods, demons, spirits or other supernatural forces caused epilepsy:

'The brain is the seat of this disease, as it is of other very violent diseases'

Hippocrates believed that epilepsy resulted from the superfluity of phlegm leading to an abnormal brain consistency. However, the supernatural origin remained the prevailing view and it was only in the 17th and 18th centuries that the concept of epilepsy as a brain disorder reemerged in Europe. In those days it was widely believed that epilepsy had a vascular basis attributable to either acute anemia or acute congestion of the brain. Robert Bentley Todd (1809-1860) was the first to develop an electrical theory on epilepsy. Further supported by work of amongst others Caton, Jackson, Penfield, Berger and Lennox, electrical theories were finally accepted to replace the vascular theories at the second International Neurological Congress in 1935 [1, 2].

Nowadays epilepsy (derived from the Greek word επιλαμβανειν, meaning 'to seize' or 'to attack') is one of the most common neurological disorders. A distinction should be made between epilepsy and epileptic seizures. An epileptic seizure is defined as 'a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain' [3]. Epilepsy is conceptually defined as 'a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures in a patient who has had one seizure, and by the neurobiologic, cognitive, psychological and social consequences of this condition'. The initial practical definition of epilepsy required two unprovoked seizures occurring at least 24 hours apart. Provoked or acute symptomatic seizures (e.g. due to hypoglycemia or alcohol withdrawal) are thus excluded. As this initial practical definition was too restrictive, a new Internation League Against Epilepsy (ILAE) practical clinical definition was published in the 2014 defining epilepsy as a disease of the brain characterized by any of the following:

1. At least two unprovoked (or reflex) seizures occurring >24 hours apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epilepsy syndrome (e.g. benign epilepsy with centro-temporal spikes,…) (even if the risk of subsequent seizures is very low)

After a single unprovoked seizure, about one third of patients was found to have further seizures within five years. This number increased to about three quarters of patients after two (or more) unprovoked seizures [4].

A recent systematic review and meta-analysis identified 222 studies pooling over 124 million persons and estimated the active and lifetime prevalence of epilepsy to be 6.4 and 7.6 per 1000 persons respectively. This corresponds to around 50 million people affected by epilepsy worldwide. The incidence rate of epilepsy was 61.4 per 100 000 person-years [5]. The World Health Organization (WHO)'s 2010 Global Burden of Disease study ranks epilepsy as the second most important

neurological cause (after migraine) of disease burden in terms of disability-adjusted life years (note that cerebrovascular disease was classified amongst the cardiovascular and circulatory disorders) [6].

The incidence varies greatly with age, with high rates in early childhood (mainly <12 months) and in the elderly [4, 7]. The incidence and prevalence of epilepsy are also higher in developing compared to developed countries, amongst others reflecting a higher prevalence of selected risk factors such as traumas and infections [5, 8, 9].

Diagnosis

The **diagnosis** of epilepsy is primarily based on clinical evaluation, EEG and brain imaging. The **patient's history** includes a detailed description of the events experienced by the patient and if possible observed by a witness before, during and after a seizure remains the cornerstone in the diagnosis of epilepsy. Other important elements in the patient's history are the birth history, childhood febrile convulsions, severe head trauma or other neurological insult, central nervous system infections, drug history including alcohol use and family history. The **neurological examination** aims to detect focal signs that might implicate or localize cerebral pathology. The general physical examination can provide further clues such as skin abnormalities suggesting a neurocutaneous disorder such as neurofibromatosis or tuberous sclerosis. **EEG** can support the diagnosis and help with the classification of epilepsy by identifying interictal epileptiform discharges, although a negative routine EEG does not exclude epilepsy given its relative low sensitivity (about 50%). The diagnostic yield can be increased by activation procedures (hyperventilation, photic stimuluation), repeat recordings or – in difficult cases – prolonged (video-) EEG monitoring to record seizures or to look for infrequent interictal epileptiform discharges. Structural **brain imaging** aims to detect underlying structural abnormalities. Magnetic resonance imaging (MRI) has a higher sensitivity than computed tomography (CT) is the imaging modality of choice. Other tests include routine blood tests, electrocardiography and cerebrospinal fluid examination and are primarily used to identify underlying syndromes, acute symptomatic seizures or exclude other possible diagnoses (see Table 1). Metabolic evaluation and genetic testing can be useful to search for specific and rare underlying syndromes [10, 11].

Common differential diagnoses of seizures	
Neurological	transient ischemic attack, migraine with aura, transient global amnesia, narcolepsy
Cardiac	vasovagal syncope, reflex anoxic seizure, sick sinus syndrome, arrhythmias, hypotension
Endocrine and metabolic	hypoglycemia, hyponatremia, hypocalcemia, hypomagnesemia
Sleep disorders	obstructive sleep apnea, hypnic jerks, benign neonatal sleep myoclonus, REM sleep disorder
Psychological	non-epileptic psychogenic seizures

Table 1. Common differential diagnoses of seizures [10].

Classification

Epilepsy classification serves many purposes. It provides a framework for basic and clinical research to increase our understanding of epilepsy and seizures, provides information about the prognosis, potential triggers and co-occurrence of other types of seizures the patient may have, informs about possible comorbidities, and last but not least guides treatment decisions (selection of antiepileptic drugs, non-pharmacological treatment). Epilepsy classification encompasses **three levels** (see figure 9 and 10). First the seizure type is classified. The next step is the diagnosis of epilepsy type. The third level is that of epilepsy syndrome, where a specific syndrome diagnosis is made [12].

Seizures are classified into focal onset, generalized onset and unknown onset (see figure 9). **Focal seizures** are conceptually defined as originating within networks limited to one hemisphere, and may be discretely localized or more widely distributed [13]. Focal seizures may be associated with retained or impaired awareness, corresponding to 'simple partial' and 'complex partial' seizures in the ILAE 1981 classification [14]. Focal seizures can have a motor or nonmotor onset reflecting its first symptom, which can be different from the most dominant symptom (except for a focal behavior arrest seizure for which cessation of activity should be the dominant feature throughout the entire seizure). These motor-onset of nonmotor-onset symptoms can be further specified by an additional descriptor as shown in figure 9, e.g. automatisms, sensory, emotional,… [15]. **Generalized epileptic seizures** are conceptualized as originating at some point within, and rapidly engaging, bilaterally distrubted networks [13]. Generalized seizures are further divided into motor and nonmotor (absence) seizures, which can be further specified by additional terms (see figure 9). **Focal to bilateral tonic-clonic seizures** are seizures that start focally and subsequently spread to bilateral networks, corresponding to 'secondarily generalized seizures' in the ILAE 1981 classification. Seizures with an **unknown onset** may be referred to by the single word **'unclassified'** (due to incomplete information or inability to place in other categories) or with additional features, including motor, nonmotor, tonic-clonic, epileptic spasms and behavior arrest [15].

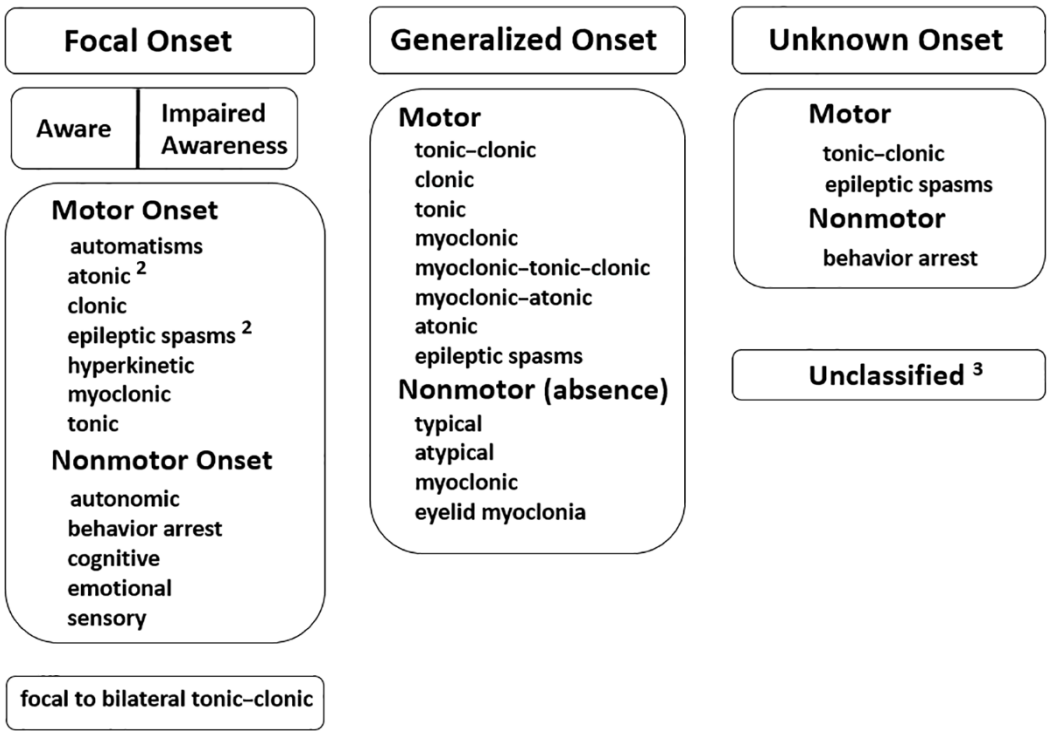


Figure 9. The International League Against Epilepsy (ILAE) classification of seizures [15].

The second step is to classify the **epilepsy type** (see figure 10). The diagnosis of epilepsy type is made on clinical grounds and supported by EEG findings. Patients with **generalized epilepsy** typically show generalized spike-wave activity on EEG and may have a range of seizure types, including absence, myoclonic, atonic, tonic and tonic-clonic seizures. In case of patients with generalized tonic-clonic seizures and a normal EEG, additional information is needed to make a diagnosis of generalized epilepsy such as myoclonic jerks or a relevant family history. **Focal epilepsies** include unifocal and multifocal disorders, as well as seizures involving one hemisphere. Multiple focal seizure types can be seen including focal to bilateral tonic-clonic seizures. The interictal EEG typically shows focal epileptiform discharges, although the diagnosis can often also be made solely based on seizure description. Patients with **combined generalized and focal epilepsy** have both generalized and focal seizures and epileptiform discharges on the EEG. A common example are patients with Lennox-Gastaut syndrome. When there is insufficient information to determine if the epilepsy type is focal or generalized, the term '**unknown**' is used (e.g. patients with symmetrical tonic-clonic seizures without focal features and normal EEG findings) [12].

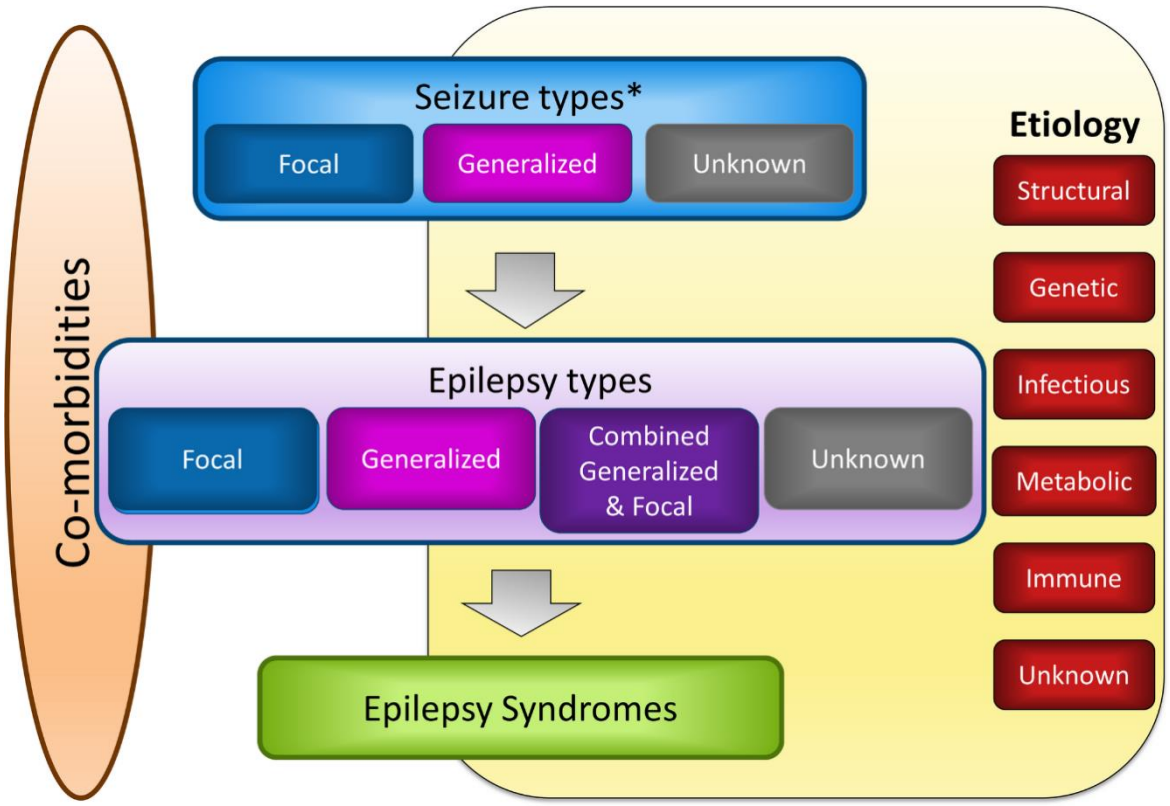


Figure 10. The Internation League Against Epilepsy (ILAE) classification of the epilepsies [12].

The final level is the diagnosis of an **epilepsy syndrome**. An epilepsy syndrome refers to a cluster of features incorporating seizure types, EEG and imaging finding that tend to occur together. It can also have additional features such as age-dependency (typical age of onset and remission), seizure triggers, diurnal variation, distinctive comorbidities, prognosis and treatment implications. Typical syndromes include childhood absence epilepsy, juvenile myoclonic epilepsy, Lennox-Gastaut syndrome and Dravet syndrome [12]. It should be noted, however, that the ILAE has never developed a formal classification of epilepsy syndromes, although a list with electroclinical syndromes and particular 'constellations' (which have distinctive features but show less developmental and genetic components) was published by the ILAE commission in 2010 (see Table 2) [13]. Within the generalized epilepsies is the well-recognized subgroup of idiopathic generalized epilepsies, encompassing four well established epilepsy syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy and generalized tonic-clonic seizures alone. These epilepsies have a presumed genetic origin, although the specific underlying genetic mutations remain to be found for most epilepsies. The term 'idiopathic generalized epilepsies' was retained, however, as there was a considerable desire to do so, although in individual cases the term 'genetic generalized epilepsies' may also be used when a genetic etiology is presumed by the clinician [12].

Electroclinical syndromes and particular constellations

Electroclinical syndromes arranged by age at onset

- Neonatal period
  - Benign familial neonatal epilepsy (BFNE)
  - Early myoclonic encephalopathy (EME)
  - Ohtahara syndrome
- Infancy
  - Epilepsy of infancy with migrating focal seizures
  - West syndrome
  - Myoclonic epilepsy in infancy (MEI)
  - Benign infantile epilepsy
  - Benign familial infantile epilepsy
  - Dravet syndrome
  - Myoclonic encephalopathy in nonprogressive disorders
- Childhood
  - Febrile seizures plus (FS+) (can start in infancy)
  - Panayiotopoulos syndrome
  - Epilepsy with myoclonic atonic (previously astatic) seizures
  - Benign epilepsy with centrotemporal spikes (BECTS)
  - Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
  - Late onset childhood occipital epilepsy (Gastaut type)
  - Epilepsy with myoclonic absences
  - Lennox-Gastaut syndrome
  - Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
  - Landau-Kleffner syndrome (LKS)
  - Childhood absence epilepsy (CAE)
- Adolescence – Adult
  - Juvenile absence epilepsy (JAE)
  - Juvenile myoclonic epilepsy (JME)
  - Epilepsy with generalized tonic–clonic seizures alone
  - Progressive myoclonus epilepsies (PME)
  - Autosomal dominant epilepsy with auditory features (ADEAF)
  - Other familial temporal lobe epilepsies
- Less specific age relationship
  - Familial focal epilepsy with variable foci (childhood to adult)
  - Reflex epilepsies

Distinctive constellations

- Mesial temporal lobe epilepsy with hippocampal sclerosis
- Rasmussen syndrome
- Gelastic seizures with hypothalamic hamartoma
- Hemiconvulsion–hemiplegia–epilepsy

Table 2. List of electroclinical syndromes and particular constellations [13].

Causes

Epilepsy should not be regarded as a uniform disorder as it may have many possible underlying causes. Along with the attempts to classify the seizure and epilepsy type, the clinician should try to identify the underlying cause which were grouped into six categories in the ILAE 2017 classification: structural, genetic, infectious, metabolic, immune and unknown causes (see figure 10). A patient's epilepsy may also be classified into more than one etiologic category, e.g. a patient with tuberous sclerosis has both a structural and genetic etiology.

A **structural etiology** is identified by neuroimaging and sometimes requires specific MRI protocols to identify subtle lesions [16]. Common acquired structural etiologies include stroke, trauma, tumors and hippocampal sclerosis. Malformations of cortical development (e.g. focal cortical dysplasia, polymicrogyria, periventricular nodular heterotopias,…) and vascular malformations (e.g. cavernomas) are congenital structural causes which may be either acquired (e.g. due to intrauterine cytomegalovirus infection) or genetic [12, 17, 18].

Genetic epilepsies result from a known or presumed genetic mutation in which seizures are the core symptom of the disorder. Examples include Dravet syndrome (SCN1A mutation) and autosomal-dominant nocturnal frontal lobe epilepsy (CHRNA4, CHRNB2 or CHRNA2 mutation). Sometimes the genetic mutation is unknown but assumed based on familial aggregation or twin studies, as is the case for childhood absence and juvenile myoclonic epilepsy [10, 12].

An **infectious etiology** is worldwide the most common etiology. It refers to patients with an infection in which seizures are a core symptom of the disorder, rather than with seizures occurring in the setting of an acute infection such as meningitis or encephalitis (acute symptomatic infections). Examples include neurocysticercosis, tuberculosis, HIV and cerebral toxoplasmosis. It may also refer to the postinfectious development of epilepsy and often has a structural correlate [12].

Metabolic epilepsy is the result of a known or presumed metabolic disorder in which seizures are a core symptom of the disorder. In many cases, metabolic disorders will be associated with a genetic mutation. Examples include porphyria, aminoacidopathies and pyridoxine-dependent seizures.

Immune epilepsy results from immune disorders associated with auto-immune mediated central nervous system inflammation. Typical examples are anti-NMDA and anti-LGI1 receptor encephalitis.

Sometimes the cause of epilepsy remains **unknown**, especially in settings where the extent of evaluation is limited [12].

(Mesial) temporal lobe epilepsy and hippocampal sclerosis

Temporal lobe epilepsy is the most common type of focal epilepsy. In two observational studies the epileptogenic was located in the temporal lobe in 66 and 73% of all focal epilepsy patients where this zone could sufficiently reliably be determined [18, 19]. Hippocampal onset accounts for at least 80% of all temporal lobe seizures and at least half of these patients have evidence of hippocampal sclerosis on MRI which might even be an underestimation of its true histopathological prevalence [18, 20-22]. Mesial temporal lobe epilepsy is typically considered as a distinct entity, syndrome or ‘constellation’. A history of a childhood cerebral insult is found in the majority of patients, including (complicated) febrile seizures, status epilepticus, birth trauma, cerebral infections, head injury and infarction in posterior cerebral artery territory, suggesting that a brain insult during a critical period of development play a role in initiating hippocampal damage [20, 23]. The FEBSTAT study followed 226 children (1 to 6 years old) with febrile status epilepticus and showed that hippocampal T2 hyperintensity after the acute insult (present in 10% of children) evolved to hippocampal sclerosis in the great majority of these patients, and even in the absence of T2 hyperintensity there was evidence of more subtle hippocampal injury after one year [24].

Hippocampal sclerosis is a pathological finding that was first described by Sommer in autopsy studies of epilepsy patients in 1880 and is characterized by hippocampal cell loss and gliosis [21, 22, 25]. A clinicopathological classification of hippocampal sclerosis has been proposed by Blumcke and collagues based on the affected hippocampal subfields: no mesial temporal sclerosis, mesial temporal sclerosis type 1a (19%, severe cell loss in CA1 regions and moderate cell loss in all other subfields except for CA2), type 1b (53%, extensive cell loss in all regions), type 2 (6%, cell loss restricted to CA1) and type 3 (4%, cell loss restricted to hilar region) [26]. The initial precipitating injury typically occurs before the

age of 3 in type 1a and 1b, at the age of 6 in type 2 and beyond the age of 13 to 16 years in type 3 and in no mesial temporal sclerosis.

Temporal lobe epilepsy is associated with a worse response to antiepileptic drugs than extratemporal lobe epilepsy (see also below) [18]. Especially the presence of hippocampal sclerosis is a bad prognostic factor with only 11 to 42% of patients becoming seizure-free [18, 22]. Conversely, surgical outcomes are just most favorable is these patients approaching 70-80% seizure freedom rates [27-30]. Drug resistant temporal lobe epilepsy should therefore always be referred for epilepsy surgery [31]. Surgical options include standard anterior temporal lobectomy or selective amygdalahippocampetcomy to minimize the disturbance of temporal language areas [32].

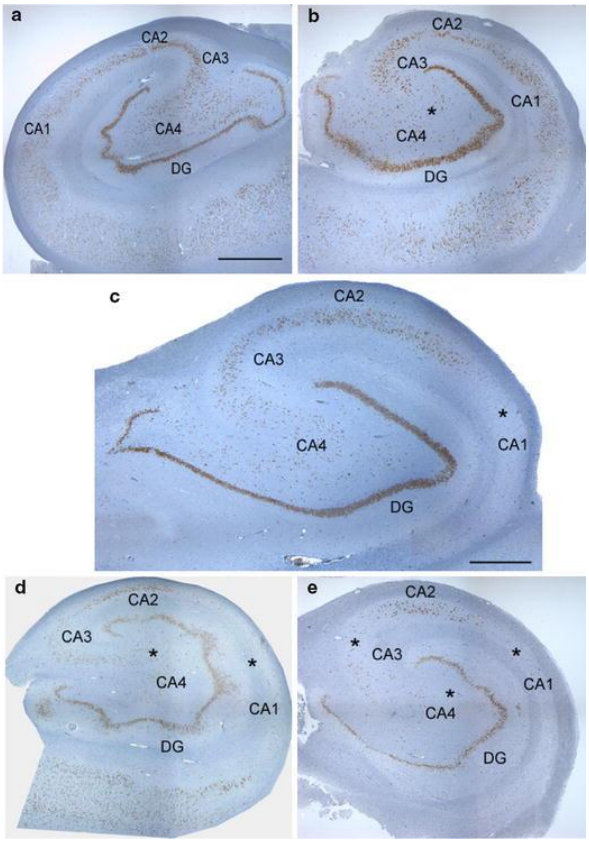


Figure 13. Histopathological findings in mesial temporal lobe sclerosis. Asterisks indicates regions with predictive cell loss patterns. The different categories proposed by Blumcke and colleagues include: **(a)** no mesial temporal sclerosis, **(b)** mesial temporal sclerosis type 3 (cell loss restricted to hilar region), **(c)** mesial temporal sclerosis type 2 (cell loss restricted to CA1 region), **(d)** mesial temporal sclerosis type 1a (severe cell loss in CA1 regions and moderate cell loss in all other regions except for CA2, 'classical hippocampal sclerosis) and **(e)** mesial temporal sclerosis type 1b (extensive cell loss in all regions). Scale bars represent 1 mm [26].

Pathophysiology

Epilepsy is generally considered as the result of a disruption of the equilibrium between excitation and inhibition in (a part of) the brain. This imbalance can occur at many levels of brain function, from genes and subcellular signaling cascades to widespread neuronal circuits. It can be genetic in origin or acquired. For example, genetic mutations can lead to abnormal synaptic connectivity (e.g. in cortical dysplasia), aberrant receptor function (e.g. abnormal GABA receptor subunits in Angelman syndrome) or abnormal ionic channel function (e.g. potassium channel mutations in benign familial neonatal epilepsy) [11].

An important concept with regard to acquired epilepsies is **epileptogenesis**. Epileptogenesis is the process by which a brain network that was previously normal is functionally altered to generate spontaneous seizures. For a long time it was conceptualized as beginning after the occurrence of an insult (traumatic brain injury, stroke, status epilepticus,…) and ending at the time of the first seizure occurrence. However, many molecular and cellular changes triggered by an epileptogenic insult have been shown to continue after the first seizure appearance and contribute to the progression of the epileptic condition. Therefore, according to the new terminology, epileptogenesis refers not only to the development of the epileptic condition but also to the progression of the epilepsy after it is established [33, 34]. Many different mechanisms have been considered to contribute to the process of epileptogenesis including neurodegeneration, neurogenesis, gliosis, axonal damage and sprouting, dendritic plasticity, blood-brain barrier damage, neuroinflammation and recruitment of inflammatory cells into brain tissue, reorganization of the extracellular matrix, reorganization of the molecular architecture of individual cells, angiogenesis, changes in neurotransmitter receptors and ion channels, altered gene expression, post-translational and epigenetic modulation. Epileptogenesis remains incompletely understood and no consensus has emerged about which of the observed changes are causal and consequential [33, 35-37].

Epileptogenesis shoud not be confused with **ictogenesis**, which encompasses the transition from the interictal condition into seizure generation and is perhaps even less understood than the former. In classical textbooks ictogenesis is explained by excessive synchronization of excitatory neural networks associated with a paroxysmal depolarization shift recorded in individual cells [38-40]. Suprisingly, multiple intracranial and intracellular recording studies could not demonstrate increased synchrony at seizure onset [41-43]. Multiple explanations that could account for these findings have been suggested, including differences between recordings 1) at seizure onset (not synchronous) and during seizures (synchronous), 2) with surface EEG (synchronous) and of large-scale single-unit activity (not synchronous), and 3) between the ictal ‘core’ (synchronous) and ‘penumbra’ (not synchronous) [40-42, 44, 45]. An increasing number of studies have suggested a major role of increased interneuron activity and GABAergic signaling in ictogenesis. Subsequent intracellular chloride accumulation could make GABA synapses depolarizing and/or increase extracellular potassium concentration, causing hyperexcitability. Others, however, just consider this increased inhibitory activity as a restraint to further seizure propagation [39, 41, 45].

Initial (pharmacological) treatment

Uncontrolled epilepsy is associated with increased adverse psychosocial, behavorial and cognitive consequences (including anxiety and depression) and excess injury and mortality, resulting in a low quality of life and an enormous burden of both direct and indirect economic costs [46-49]. Once the diagnosis is established, treatment should therefore in principal be initiated in all epilepsy patients.

Antiepileptic drugs are the first-line treatment for epilepsy. The number of antiepileptic drugs has rapidly increased since 1990 and now more than 20 different drugs are available (see figure 11) [11, 50]. A non-limitative list of currently available antiepileptic drugs grouped according to the mechanism of action is shown in Table 3. Antiepileptic drug selection depends on the seizure type(s), the potential side-effect profile, age, sex and childbearing potential, comorbidities, pharmacokinetics, pharmacodynamics and drug-drug interactions. Because of their mechanism of action, all antiepileptic

drugs are at risk for central nervous system side effects such as somnolence, dizziness, cognitive and behavorial problems. Other safety concerns include idiosyncratic reactions which can sometimes be life-threatening such as Stevens-Johnson syndrome with lamotrigine or carbamazepine. The general principle is 'start low, go slow' to avoid side effects. The dose is increased until seizure freedom is achieved, important side effects arise or the maximum recommend dose is reached. Serial monotherapy of two antiepileptic drugs is generally recommended before polytherapy is initiated as the latter is associated with more side effects (including teratogenicity), more interactions and lower compliance [10, 11].

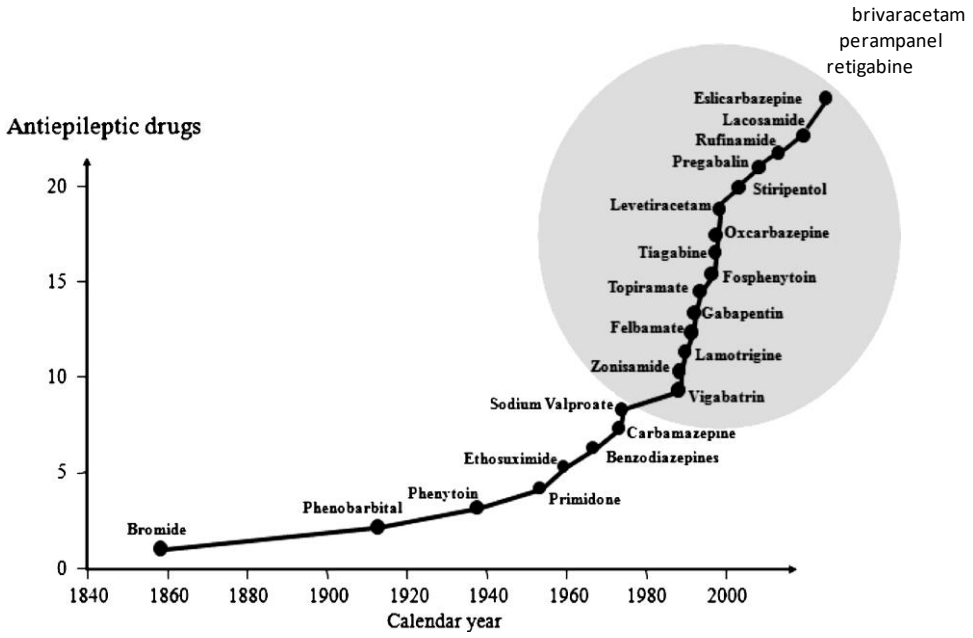


Figure 11. Chronology of antiepileptic drug introduction over the past 150 years. Note the exponential growth since 1990 (adapted from [50]).

Around 70% of epilepsy patients treated with antiepileptic drugs will achieve seizure freedom. The chance of remission gradually decreases with number of antiepileptic drugs unsuccessfully tried. Approximately 50% of newly diagnosed patients will be able to tolerate and become seizure-free with the first antiepileptic drug. This number increases to 60-65% of patients with the second drug. Thereafter the chances get relatively low [10, 51, 52]. These findings have led to define drug-resistant epilepsy as the failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [52]. The aforementioned figures imply that drug-resistant epilepsy is not synonymous to the impossibility of becoming seizure-free with further trials with antiepileptic drugs, but rather indicates that other treatment options – in particular epilepsy surgery – should be considered.

Antiepileptic drugs grouped according to the mechanism of action
Sodium channel blockers - Block repetitive activation (fast-inactivated state): phenytoin, carbamazepine, lamotrigine, oxcarbazepine, eslicarbazepine, topiramate - Enhance slow inactivation: lacosamide, rufinamide
Calcium channel blockers: ethosuximide, sodium valproate, gabapentin, pregabalin, lamotrigine, topiramate, zonisamide
GABA-ergic drugs - Prolonged chloride channel opening: barbiturates - Increased frequency of chloride channel opening: benzodiazepines - Inhibiting GABA-transaminase: vigabatrine - Blocking synaptic GABA reuptake: tiagabine
Synaptic vesicle protein 2A modulation: levetiracetam, brivaracetam
Glutamate receptor antagonists - AMPA receptor: perampanel, topiramate - NMDA receptor: felbamate
Carbonic anhydrase inhibition: acetazolamide, topiramate, zonisamide
Potassium channel opening: retigabine
Modulation of H currents: gabapentine, lamotrigine

Table 3. Antiepileptic drugs grouped according to the mechanism of action (adapted from [11, 50]).

Treatment of drug resistant epilepsy

Excluding 'pseudoresistant' epilepsy

Prior to considering more invasive treatment options, it is evident that causes of pseudoresistance should be excluded. These include incorrect diagnosis (e.g. psychogenic non-epileptic seizures), incorrect antiepilepticum selection, incorrect dosage, drug-drug interactions, nonadherence and lifestyle and psychosocial factors [23].

Epilepsy surgery

The goal of epilepsy surgery is to render drug-resistant epilepsy patients seizure-free by removing the epileptogenic zone. The epileptogenic zone has been theoretically defined as 'the area of cortex that is necessary and sufficient for initiating seizures and whose removal (or disconnection) is necessary for complete abolition of seizures' [53]. Epilepsy surgery requires a thorough presurgical evaluation, which aims to establish the presence of drug resistance, delineate the epileptogenic zone in focal epilepsy and demonstrate that its removal will not cause additional unacceptable neurological or cognitive deficits [10]. The presurgical evaluation should always comprise a complete history taking, MRI of the

brain and video-EEG monitoring; dependent on the results tailored additional investigations can be performed:

- *New history taking*: a thorough review of the patient's medical and seizure history and antiepileptic drugs trials;
- *Video-EEG monitoring*: continuous and synchronized recording of brain activity and behavior to identify interictal epileptiform discharges ('irritative zone'), ictal discharges ('seizure onset zone') and seizure semiology ('symptomatogenic zone', i.e. the region cortex that generates the initial seizure symptoms);
- *MR imaging of the brain*: to identify a structural lesion that provokes the seizures ('epileptogenic lesion'). A dedicated 'epilepsy surgery protocol' and a 3 Tesla MRI increase the diagnostic yield (e.g. subtle focal cortical dysplasia);
- *Neuropsychological testing*: extensive evaluation of the patient's cognitive functions (e.g. memory, attention, language, laterality of language and memory,…) to estimate the cognitive and psychological impact and feasibility of resective surgery and to identify functional abnormal brain regions showing discrepant findings with respect to other tested functions ('functionial deficit zone');
- *Positron Emission Tomography (PET) imaging*: to identify regions with functional abnormalities based on abnormalities in brain metabolism suggesting underlying pathology (especially in the case of normal MRI findings) ('functional deficit zone')
- *Magnetoencephalography (MEG)*: to identify and localize the magnetic fields generated by interictal epileptiform discharges ('irritative zone'). Magnetic source imaging combining MEG and MRI data can provide a more accurate localization of the anatomic region generating the interictal discharges;
- *Single-photon emission computed tomography (SPECT) imaging:* to identify brain regions with increased blood flow at the onset of a seizure to obtain more information about where the seizure starts. Images from an ictal and interictal scan are typically substracted and superimposed on the MRI images (substraction ictal SPECT co-registered to MRI, SISCOM);
- *Functional MRI*: non-invasive mapping of language and memory function and lateralization;
- *Intracarotid amobarbital procedure (WADA test)*: invasive test to lateralize language and memory function and to predict / simulate consequences of resective surgery;
- *Invasive video-EEG monitoring with intracranial subdural strips/grids and/or depth electrodes*: invasive and final step in the presurgical evaluation if the previous investigations have yielded one or limited number of hypotheses on the localization of the epileptogenic region, but 1) uncertainty remains due to normal MRI findings or discordant noninvasive results or 2) there is (potential) overlap with eloquent cortex necessitating brain function mapping by using small electrical currents [10, 23, 54, 55].

The results of the presurgical investigations are discussed in a multidisciplinary team meeting where the decision is made whether or not epilepsy surgery is indicated based on the chances of seizure freedom and the estimated adverse events. The most typical case of respective surgery is an anterior temporal lobectomy or selective amygdalohippocampectomy in patients with temporal lobe epilepsy and hippocampal sclerosis, but lesionectomies can theoretically involve any other brain region including normal appearing brain tissue in patients with MRI-negative epilepsy.

The efficacy of resective surgery in drug-resistant epilepsy is currently widely accepted and therapeutic superiority over best medical therapy has been demonstrated in a RCT [23, 56]. About 50% of patients remain seizure-free as long as a decade after surgery [23, 28]. The chances of seizure freedom are two to three times higher in the presence of a lesion and patients with temporal epilepsy do better than those with extratemporal epilepsy [27-30]. Best results are thus obtained after anterior temporal lobectomy or temporal lesionectomy where up to 70-80% of patients achieve long-term seizure freedom [27-30]. In contrast, of the patients with extratemporal nonlesional epilepsy usually no more than 30 to 40% of patients remain seizure-free at long-term follow-up [23, 28, 30].

The risk to achieve seizure freedom should always be balanced against the potential risks and complications of resective surgery. The most frequent medical complications include cerebrospinal fluid leak (8.5%), aseptic meningitis (3.6%), bacterial infection (3.0%), intracranial hematoma (2.5%), deep vein thrombosis / pulmonary embolus (1.0%), hydrocephalus (1.0%) and pneumonia (0.7%). These medical complications are typically minor, with major complications only occurring in 1.5% of patients [57]. The range of possible neurological complications is strongly dependent on the location and extent of the resection, the 'functionality' of the resected region and the proximity to eloquent cortical regions (e.g. hemiparesis in central resections, hemianopsia in occipital resections,…). Typical risks associated with temporal lobe surgery include visual fields deficits (up to 50% but mostly only minimal; severe deficits in 2-4%), language and memory problems. The latter are more frequent when surgery is performed in the dominant (mostly left-sided) hemisphere with reported risks of 44% of verbal memory and 34% of naming decline. It should be noted, however, that these language and memory problems are often only mild and even unnoticed by many patients, differ with different surgical techniques, depend on the sensitivity of the evaluation method (e.g. other series report only 1-3% persistent language problems) and should be balanced against the natural evolution of language and memory problems associated with epilepsy as well as the number of patients with gains in these or other cognitive domains, especially on the long term and in case of good seizure control [23, 58-60]. Perioperative mortality is reported in 0.6% of patients (0.4% temporal versus 1.2% extratemporal) [57].

Disconnective surgery is an alternative surgical strategy in patients rejected for traditional resective surgery because the epileptogenic zone cannot be identified, is too extensive or located in eloquent cortex. Corpus callosotomy (typical in generalized epilepsy patients with (atonic) seizures with falling), hemispherotomy (extensively diseased and epileptogenic hemisphere) and multiple subpial transections (lesion located in eloquent cortex) are examples of disconnective surgery [10, 23]. Hemispherotomy is associated with a 50 to 80% chance of long-term seizure freedom but can only be performed in a selected group of typically young patients with preexisting deficits ascribed to the diseased hemisphere [23, 28]. On the other hand, corpus callosotomy and multiple subpial transections – although occasionally curative – should be more regarded as palliative procedures aiming to reduce seizure frequency and/or severity [23].

MRI-guided laser interstitial thermotherapy and stereotactic radiosurgery have recently gained more interest showing promising results as minimally invasive alternatives to resective surgery, especially for MTL epilepsy and hypothalamic hamarthomas. Preliminary evidence suggests that seizure outcomes are similar to or slightly worse than conventional resective surgery [61-65]. The delayed therapeutic effect with on average 14 months to become seizure-free in MTL epilepsy, may be a particular disadvantage of stereotactic radiosurgery [62]. Lower complication rates, decreased

postoperative discomfort and morbidity, and better cognitive outcomes have been suggested as potential advantages but more, larger and randomized-controlled trials with more prolonged follow-up periods are required [61-65].

Trials with other antiepileptic drugs

As mentioned earlier, drug-resistant epilepsy is not synonymous to the impossibility of becoming seizure-free with further trials with antiepileptic drugs. Such trials are in fact common practice in everyday clinical neurology. In a large study following 1098 patients trying a third antiepileptic drug regimen resulted in seizure freedom in 24.4% of patients, corresponding to 3.7% of all patients. The success rate decreased to 12.5% with the fifth or sixth regimen (0.4 and 0.2% of patients respectively) [51]. A meta-analysis evaluating the placebo-corrected net efficacy of adjunctive treatment with modern antiepileptic drugs showed that, compared to placebo, an additional 6% of patients became seizure-free and 21% of patients experienced a 50% seizure frequency reduction [66].

Dietary treatments

The ketogenic diet is a high-fat, adequate protein (1 g/kg) and low-carbohydrate diet that has been used as an alternative treatment in mainly pediatric epilepsy patients. It produces metabolic changes also seen in starvation, although the exact mechanism of seizure suppression remains unclear [10, 23]. A meta-analysis of 14 studies reported a 15.6% estimated rate for obtaining complete seizure control and 33% of patients experiencing a >50% reduction in seizure frequency [67]. An RCT confirmed the efficacy with 38% and 7% of patients showing a >50 and >90% seizure reduction after 3 months, compared to 6 and 0% in the placebo group [68]. Adverse events include vomiting, constipation, diarrhea, weight loss, hypoglycemia, acidosis, lack of energy and hunger [23, 67, 69]. The main cause of the limited use of the ketogenic diet in everyday practice (especially in adults) is that many patients find it difficult to adhere to this restrictive dietary regimen. The modified Atkins diet or the medium-chain triglyceride diet are less restrictive alternatives with proven efficacy in RCTs [70, 71].

Neurostimulation

The central nervous system uses both electrical and chemical signals for communication. Analogous to antiepileptic drugs modulating the brain's chemistry neurostimulation techniques deliver electrical or magnetic currents to modulate neuronal activity to achieve seizure suppression. We will shortly discuss different neurostimulation techniques that have been explored in (typically drug-resistant) epilepsy patients. Broadly speaking, a distinction can be made between invasive and noninvasive neurostimulation techniques.

A. Invasive neurostimulation techniques

1. Vagus nerve stimulation (VNS)

VNS is an FDA-approved adjunctive treatment for patients with drug-resistant epilepsy since 1997. Nowadays it is routinely available in many epilepsy centers and more than 100 000 patients have

received VNS therapy worldwide, which makes it by far the most frequently used neurostimulation treatment for epilepsy [72]. The VNS therapy system is comprised of a programmable pulse generator implanted in the subclavicular region and a bipolar lead that connects the generator to the left vagus nerve in the neck region where a helical electrode is wrapped around the vagus nerve (see figure 12). Typical stimulation parameters are: >1.5-2.0 mA output current (range: 0-3.5 mA), 250-500 µs pulse width (130-1000 µs) and 20-30 Hz signal frequency (1-30 Hz) delivered with a 30 s ON (7-60 s) / 5 min OFF (0.2-180 min) duty cycle (which should never exceed more than 50% stimulation time) [23, 72]. The mechanism of action is incompletely understood but involves – amongst others – afferent vagus nerve fibers modulating the activity of brainstem nuclei such as the nucleus of the solitary tract (the predominant afferent target) and its multitude of downstream projections including the locus coeroleus and the raphe nucleus with widespread noradrenergic and serotonergic projections in the brain [73, 74].

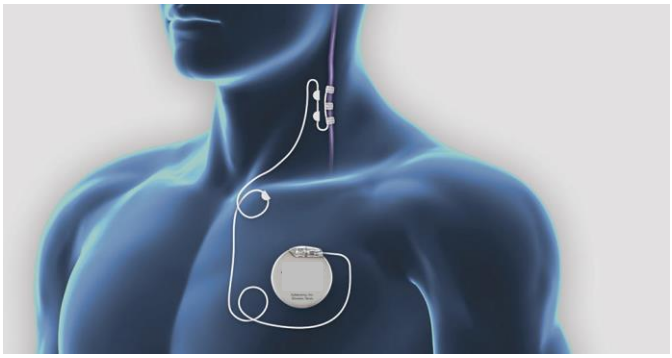


Figure 12. Schematic illustration of the vagus nerve stimulation (VNS) system. The pulse generator is implanted in the subclavicular region and connected to a helical electrode wrapped around the vaugs nerve in the neck through a bipolar lead (adapted from [75]).

The efficacy of VNS was demonstrated in two large RCTs showing 24.5% and 27.9% reductions in seizure frequency after 3 months of VNS with a high-stimulation assumed therapeutic paradigm compared to 6.1% (p=0.01) and 15.2% (p=0.04) with a low-stimulation assumed subtherapeutic paradigm, respectively. A 50% or more reduction in seizure frequency was found in 31% (low-stimulation 13%, p=0.02) and 23.4% (low-stimulation 15.7%, p>0.05) of patients [76, 77]. This figure increased to 44% of patients showing ≥50% seizure reduction after 2 and 3 years of open-label extended follow-up [78]. Other uncontrolled open-label trials have confirmed ≥50% seizure reductions in 50 to 64% of patients after a mean follow-up of 3 to 59 months [79-83]. Seizure freedom at long-term follow-up is observed in less than 10% of patients [79-81, 83]. Side effects are typically mild and tend to improve over time. These include hoarseness, throat paresthesia or pain, coughing and dyspnea occurring during the stimulation ON periods and almost always resolve with adjustment of parameter settings [10, 23, 74, 76-78]. A novel feature of the newest VNS models is the ability to detect ictal tachycardia and then automatically deliver additional stimulation to abort the seizure or reduce its duration and/or severity [72, 84, 85]. Three retrospective open-label trials have reported additional seizure control after replacement of an open-loop VNS device with a cardiac-based closed loop system [86-88].

2. Cortical and deep brain stimulation

Cortical and deep brain stimulation are invasive intracranial neurostimulation techniques that have been investigated as a treatment option for drug-resistant epilepsy patients since more than 40 years [89]. Following positive results in two large RCTs, FDA approval has been granted to both responsive stimulation of the ictal onset zone (2013) and anterior thalamic deep brain stimulation (2018) as a treatment for medically drug-resistant focal epilepsy patients [90, 91]. As cortical and deep brain stimulation are the main topic of this dissertation, a more detailed introduction is presented in Chapter 4.

B. Noninvasive neurostimulation techniques

1. Trigeminal nerve stimulation (TNS)

After promising results in a pilot trial, a larger RCT (n=50) was initiated to evaluate the efficacy, tolerability and safety of noninvasive transcutaneous bilateral stimulation of the supraorbitary branches of the trigeminal nerve [92, 93]. The 50% responder rate (30.2 versus 21.1%, p=0.31) and percentage seizure frequency reduction (-16.1 versus -10.5%, p=0.51) were not statistically significantly different between the high (assumed therapeutic) and the low (assumed subtherapeutic) stimulation group over the entire 18-week stimulation period (primary outcome measure). Subgroup analysis did show increasing efficacy over time with a significant number of 50% responders after 18 weeks in the high-stimulation group only (40.5 versus 15.6%). Adverse events were mild: anxiety (4%), headache (4%) and skin irritation (14%) [93]. Open-label extended follow-up showed a -34.8% reduction in seizure frequency after 12 months, with 30.6% of patients experiencing a ≥50% reduction in seizure frequency [94]. Another uncontrolled unblinded trial reported a nonsignificant -11% mean reduction in seizure frequency after 18 weeks [95].

2. Transcranial direct current stimulation (tDCS)

Transcranial direct current stimulation is different from other neurostimulation techniques in the sense that it does not induce action potentials but is assumed to modulate neuronal excitability by changing the resting membrane potential by constant transcranial delivery of weak currents (1-2 mA) via two electrodes that are placed on the skull. However, tDCS has received considerable criticism because it has been questioned whether and remains largely to be shown how the small intracranial electrical fields induced by tDCS may significantly affect neuronal activity [96-99]. Alternative theories on the mechanism of action of tDCS include placebo effects, modulation of peripheral nerves, arousal effects, effects on blood vessels and other non-neuronal mechanisms [98, 100].

Cathodal tDCS has been investigated as a treatment for drug-resistant epilepsy in eight RCTs as various research groups have hypothetized that it may suppress seizures by inducting membrane hyperpolarization. Four studies evaluated the effect of a single 20-min session of cathodal tDCS in [101-104]. Only Assenza and colleagues found a statistically significant and clinically relevant -71% reduction in seizure frequency compared to sham stimulation (+25%) in the week following tDCS in 10 patients with drug-resistant temporal lobe epilepsy [101]. Zoghi and colleagues also evaluated the effect of cathodal tDCS in temporal lobe epilepsy and observed a -41% seizure reduction in the active tDCS

group compared to -17% in the sham group, but the level of significance was not reported [104]. The seizure reduction observed by Fregni and colleagues in 10 patients with malformations of cortical development (-44.0 versus -11.1%) was only borderline significant (p=0.06) [103]. No clinically significant effect on seizure frequency was shown by Auvichayapat and colleagues in 27 patients with drug-resistant focal epilepsy [102].

Three studies evaluated the effect of 3 to 5 sessions of cathodal tDCS. Auvichayapat and colleagues reported a significant 99.8% reduction in seizure frequency in 22 patients with Lennox-Gastaut syndrome on the fifth day of tDCS applied over the primary motor cortex. After 4 weeks, seizure frequency was still significantly lower in the tDCS (56.0% reduction) compared to the sham group. Additionally, a significant reduction in interictal epileptiform discharges was demonstrated [105]. The other 2 studies evaluated the effects of tDCS in drug-resistant temporal lobe epilepsy. San-Juan and colleagues reported significant reductions in seizure frequency following 3 (-43.4%) and 5 (-54.6%) sessions of tDCS compared to placebo after two months (not after one month) [106]. Differences in 50% responder rate did not achieve statistical significance. Tekturk and colleagues performed a crossover study with 12 patients and showed a significant -84.2% reduction in seizure frequency compared to baseline in the sinusoidal tDCS group but not in the sham group (-12.6%) [107]. However, they did not directly compare both groups. This was also the case for the the 50% responder rate, with 83.3% and 16.7% 50% responders in the tDCS and sham group, respectively. Half of the patients were even seizure-free in the month following active tDCS. Reported adverse events are rather mild and include tingling sensations, mild itch, moderate headache and the occurrence of skin burn under the reference electrode [108, 109].

Yang and colleagues were the only to evaluate the effect of 14 consecutive days of cathodal tDCS in randomized controlled conditions in 70 patients with drug-resistant focal epilepsy [110]. Compared to sham stimulation, one 20-min tDCS session per day resulted into a -38% to -50% reduction in seizure frequency during and for one to two weeks after tDCS. Two 20-min tDCS sessions per day were found to be even more efficacious, with a -40% to -63% seizure reduction during and for up to 8 weeks after tDCS. A significant impact on the quality of life could not be demonstrated.

Although various RCTs have demonstrated significant reductions in seizure frequency in patients with focal epilepsy and temporal lobe epilepsy, the quality of the evidence is only of low quality. Besides the fact that only a small number of patients have been included in RCTs so far, there is also a great heterogeneity in the study design of these RCTs with regards to the number of tDCS sessions, the stimulation protocol, the type of electrodes and the patient population.

3. Repetitive transcranial magnetic stimulation (rTMS)

Transcranial magnetic stimulation uses magnetic fields to affect nerve cells in the brain as deep as 2 centimeters. Low-frequency repetitive TMS has been shown to induce long-lasting reductions in cortical excitability and consequently has been proposed as a treatment for epilepsy [109, 111]. Eight RCTs (n=11 to 64) have evaluated the efficacy of 5 to 10 days low-frequency (0.33-1 Hz) rTMS in drug-resistant focal epilepsy patients [112-119]. In most of these studies the epileptogenic focus was targeted (vertex in case of multifocal or nonlocalizable), but in 2 trials the vertex was the target independent of the localization of the epileptogenic region [112, 117]. Five studies compared active (assumed therapeutic) to sham stimulation [112, 113, 115, 117, 118], one compared two stimulation

intensities (20 and 90% of resting motor treshold) [116], one evaluated 2 different stimulation parameters differing in the number of pulses per session (1500 versus 3000 pulses) [114] and Wang compared TMS with conventional antiepileptic drug treatment [119].

In only three trials a significant reduction in seizure frequency compared to baseline was found. Sun showed a significantly lower seizure frequency after two weeks of high-stimulation rTMS (8.9 to 1.8 seizures per week) but not low-stimulation rTMS (8.6 to 8.4 seizures per week), corresponding to a significant 80.6% greater reduction in seizure frequency with the first group [116]. Fregni found a significant 72% reduction in seizure frequency in the active rTMS group compared to baseline. This was not found in the control group, but an active comparison between both groups was not reported [113]. In the study of Tergau and colleagues, actively treated patients experienced a significant approximately 40% reduction in seizure frequency compared to baseline, but this difference was not significant when compared to the placebo group [117]. The 50% responder rate was only reported in three trials [112-114]. Of these, only Fregni and colleagues found a significant higher number in the active treatment group (10/12 patients versus none of the patients) [113]. In contrast to the limited effects on seizure frequency, all five studies that evaluated the effect of rTMS on the number of interictal epileptiform discharges observed significant reductions [112-114, 116, 119]. Reported adverse events include headache, dizziness and tinnitus, but in none of the RCTs these occurred at statistically significantly higher rates in the active treatment group [111]. In conclusion, although there is some evidence that rTMS is safe and well-tolerated, there is insufficient evidence that proves its efficacy in reducing seizure frequency in drug-resistant epilepsy patients [108, 109, 111]. Unresolved questions remain with regard to patient selection, the optimal stimulation protocol (parameters and target), the duration of the putative treatment effect and how to adequately blind participants.

4. Transcutaneous vagus nerve stimulation (tVNS)

Transcutaneous VNS was developed as a noninvasive alternative to vagus nerve stimulation and stimulates the auricular branch of the vagus nerve. Three uncontrolled open-label trials demonstrated 50-65% reductions in seizure frequency, with similar numbers of patients experiencing a ≥50% reduction in seizure frequency [120-122]. In contrast, only 1 out of 20 patients showed a ≥50% reduction in seizure frequency in another uncontrolled open-label trial and there was no significant improvement in seizure frequency in patients with post-stroke epilepsy [123, 124]. Results from 3 RCTs were mixed. Bauer and colleagues (n=76) found no significant difference between 1 Hz (assumed subtherapeutic) and 25Hz (assumed therapeutic) stimulation groups in terms of seizure frequency or 50% responder rates, although seizure frequency was -34.2% lower compared to baseline only in the 25 Hz group [125]. Aihua and colleagues (n=47) found a statistically significant lower monthly seizure frequency after 12 months of stimulation in the treatment group (assumed therapeutic stimulation of Ramsay-Hunt zone) compared to the control group (stimulation of earlobe) and to baseline (around 40% decrease), but did not directly compare differences in changes in seizure frequency between the stimulation and the control group [126]. Finally, Rong and colleagues (n=144) found a statistically significant treatment effect between transcutaneous auricular vagus and non-vagus nerve stimulation in terms of seizure frequency (-42.6 versus -11.5%) and 50% responder rates (41.0 versus 27.5%) [127]. Side effects of transcutaneous VNS include local skin irritation (18.2%) and headache (3.6%) [128]. More, large and well-designed RCT are needed to confirm these promising results [108].

REFERENCES

[1] Goldensohn ES, Porter RJ, Schwartzkroin PA. The American Epilepsy Society: an historic perspective on 50 years of advances in research. Epilepsia 1997;38(1):124-50.

[2] Reynolds EH. Milestones in epilepsy*. Epilepsia 2009;50(3):338-42.

[3] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55(4):475-82.

[4] Hauser WA, Rich SS, Lee JR, Annegers JF, Anderson VE. Risk of recurrent seizures after two unprovoked seizures. N Engl J Med 1998;338(7):429-34.

[5] Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology 2017;88(3):296-303.

[6] Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet (London, England) 2012;380(9859):2197-223.

[7] Olafsson E, Ludvigsson P, Gudmundsson G, Hesdorffer D, Kjartansson O, Hauser WA. Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. Lancet Neurol 2005;4(10):627-34.

[8] Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia 2010;51(5):883-90.

[9] Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: a systematic review and meta-analysis. Neurology 2011;77(10):1005-12.

[10] Brodie MJ, Schachter SC, Kwan P. Fast facts: epilepsy (revised 5th edition). Abingdon, United Kingdom: Health Press Limited; 2012.

[11] Stafstrom CE, Carmant L. Seizures and epilepsy: an overview for neuroscientists. Cold Spring Harb Perspect Med 2015;5(6).

[12] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(4):512-21.

[13] Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010;51(4):676-85.

[14] Epilepsy CoCaTotILA. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;22(4):489-501.

[15] Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia 2017;58(4):531-42.

[16] Gaillard WD, Chiron C, Cross JH, Harvey AS, Kuzniecky R, Hertz-Pannier L, et al. Guidelines for imaging infants and children with recent-onset epilepsy. Epilepsia 2009;50(9):2147-53.

[17] Desikan RS, Barkovich AJ. Malformations of cortical development. Ann Neurol 2016;80(6):797-810.

[18] Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology 1998;51(5):1256-62.

[19] King MA, Newton MR, Jackson GD, Fitt GJ, Mitchell LA, Silvapulle MJ, et al. Epileptology of the first-seizure presentation: a clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients. Lancet (London, England) 1998;352(9133):1007-11.

[20] Engel J, Jr. Mesial temporal lobe epilepsy: what have we learned? Neuroscientist 2001;7(4):340-52.

[21] Landazuri P. Mesial temporal lobe epilepsy: a distinct electroclinical subtype of temporal lobe epilepsy. Neurodiagn J 2014;54(3):274-88.

[22] Tatum WOt. Mesial temporal lobe epilepsy. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society 2012;29(5):356-65.

[23] Wyllie E. Wyllie's treatment of epilepsy: principles and practice (6th edition). 6 ed. Philadelphia, United States: Wolters Kluwer; 2015.
[24] Lewis DV, Shinnar S, Hesdorffer DC, Bagiella E, Bello JA, Chan S, et al. Hippocampal sclerosis after febrile status epilepticus: the FEBSTAT study. Ann Neurol 2014;75(2):178-85.
[25] Sommer W. Erkrankung des Ammonshorns als aetiologisches Moment der Epilepsie. Arch Psychiatr Nervenkr 1880;10(3):631-75.
[26] Blumcke I, Pauli E, Clusmann H, Schramm J, Becker A, Elger C, et al. A new clinico-pathological classification system for mesial temporal sclerosis. Acta Neuropathol 2007;113(3):235-44.
[27] Cohen-Gadol AA, Wilhelmi BG, Collignon F, White JB, Britton JW, Cambier DM, et al. Long-term outcome of epilepsy surgery among 399 patients with nonlesional seizure foci including mesial temporal lobe sclerosis. J Neurosurg 2006;104(4):513-24.
[28] de Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WF, Sander JW, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet 2011;378(9800):1388-95.
[29] Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain 2005;128(Pt 5):1188-98.
[30] Tellez-Zenteno JF, Hernandez Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. Epilepsy Res 2010;89(2-3):310-8.
[31] Engel J, Jr., McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA 2012;307(9):922-30.
[32] Muzumdar D, Patil M, Goel A, Ravat S, Sawant N, Shah U. Mesial temporal lobe epilepsy - An overview of surgical techniques. Int J Surg 2016;36(Pt B):411-9.
[33] Pitkanen A, Lukasiuk K. Mechanisms of epileptogenesis and potential treatment targets. Lancet Neurol 2011;10(2):173-86.
[34] Pitkanen A, Lukasiuk K, Dudek FE, Staley KJ. Epileptogenesis. Cold Spring Harb Perspect Med 2015;5(10).
[35] Chang BS, Lowenstein DH. Epilepsy. N Engl J Med 2003;349(13):1257-66.
[36] Loscher W, Brandt C. Prevention or modification of epileptogenesis after brain insults: experimental approaches and translational research. Pharmacol Rev 2010;62(4):668-700.
[37] Pitkanen A, Bolkvadze T. Head trauma and epilepsy. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AVD, editors. Jasper's basis mechanisms of the epilepsies (4th edition), United States: Oxford University Press; 2012.
[38] Bower MR, Stead M, Meyer FB, Marsh WR, Worrell GA. Spatiotemporal neuronal correlates of seizure generation in focal epilepsy. Epilepsia 2012;53(5):807-16.
[39] de Curtis M, Avoli M. GABAergic networks jump-start focal seizures. Epilepsia 2016;57(5):679-87.
[40] Schevon CA, Weiss SA, McKhann G, Jr., Goodman RR, Yuste R, Emerson RG, et al. Evidence of an inhibitory restraint of seizure activity in humans. Nature communications 2012;3:1060.
[41] Lillis KP, Staley KJ. Optogenetic dissection of ictogenesis: in search of a targeted anti-epileptic therapy. J Neural Eng 2018;15(4):041001.
[42] Truccolo W, Donoghue JA, Hochberg LR, Eskandar EN, Madsen JR, Anderson WS, et al. Single-neuron dynamics in human focal epilepsy. Nat Neurosci 2011;14(5):635-41.
[43] Wendling F, Bartolomei F, Bellanger JJ, Bourien J, Chauvel P. Epileptic fast intracerebral EEG activity: evidence for spatial decorrelation at seizure onset. Brain 2003;126(Pt 6):1449-59.
[44] Schindler K, Leung H, Elger CE, Lehnertz K. Assessing seizure dynamics by analysing the correlation structure of multichannel intracranial EEG. Brain 2007;130(Pt 1):65-77.
[45] Trevelyan AJ, Schevon CA. How inhibition influences seizure propagation. Neuropharmacology 2013;69:45-54.
[46] Bazil CW. Comprehensive care of the epilepsy patient--control, comorbidity, and cost. Epilepsia 2004;45 Suppl 6:3-12.

[47] Cardarelli WJ, Smith BJ. The burden of epilepsy to patients and payers. Am J Manag Care 2010;16(12 Suppl):S331-6.
[48] Tomson T, Beghi E, Sundqvist A, Johannessen SI. Medical risks in epilepsy: a review with focus on physical injuries, mortality, traffic accidents and their prevention. Epilepsy Res 2004;60(1):1-16.
[49] Wirrell EC. Epilepsy-related injuries. Epilepsia 2006;47:79-86.
[50] Brodie MJ, Sills GJ. Combining antiepileptic drugs--rational polytherapy? Seizure 2011;20(5):369-75.
[51] Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012;78(20):1548-54.
[52] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342(5):314-9.
[53] Carreño M, Lüders HO. General principles of presurgical evaluation. In: Lüders HO, Comair YG, editors. Epilepsy surgery (2nd edition), Philadelphia, United States: Lippincott, Williams & Wilkins; 2011, p. 185-200.
[54] Rosenow F, Luders H. Presurgical evaluation of epilepsy. Brain 2001;124(Pt 9):1683-700.
[55] Kim S, Mountz JM. SPECT Imaging of Epilepsy: An Overview and Comparison with F-18 FDG PET. Int J Mol Imaging 2011;2011:813028.
[56] Wiebe S, Blume WT, Girvin JP, Eliasziw M, Effectiveness, Efficiency of Surgery for Temporal Lobe Epilepsy Study G. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 2001;345(5):311-8.
[57] Hader WJ, Tellez-Zenteno J, Metcalfe A, Hernandez-Ronquillo L, Wiebe S, Kwon CS, et al. Complications of epilepsy surgery: a systematic review of focal surgical resections and invasive EEG monitoring. Epilepsia 2013;54(5):840-7.
[58] Helmstaedter C. Neuropsychological aspects of epilepsy surgery. Epilepsy & behavior : E&B 2004;5 Suppl 1:S45-55.
[59] Helmstaedter C. Cognitive outcomes of different surgical approaches in temporal lobe epilepsy. Epileptic disorders : international epilepsy journal with videotape 2013;15(3):221-39.
[60] Sherman EM, Wiebe S, Fay-McClymont TB, Tellez-Zenteno J, Metcalfe A, Hernandez-Ronquillo L, et al. Neuropsychological outcomes after epilepsy surgery: systematic review and pooled estimates. Epilepsia 2011;52(5):857-69.
[61] Baumgartner C, Koren JP, Britto-Arias M, Zoche L, Pirker S. Presurgical epilepsy evaluation and epilepsy surgery. F1000Research 2019;8.
[62] Feng ES, Sui CB, Wang TX, Sun GL. Stereotactic radiosurgery for the treatment of mesial temporal lobe epilepsy. Acta Neurol Scand 2016;134(6):442-51.
[63] LaRiviere MJ, Gross RE. Stereotactic Laser Ablation for Medically Intractable Epilepsy: The Next Generation of Minimally Invasive Epilepsy Surgery. Frontiers in surgery 2016;3:64.
[64] McGonigal A, Sahgal A, De Salles A, Hayashi M, Levivier M, Ma L, et al. Radiosurgery for epilepsy: Systematic review and International Stereotactic Radiosurgery Society (ISRS) practice guideline. Epilepsy Res 2017;137:123-31.
[65] Shimamoto S, Wu C, Sperling MR. Laser interstitial thermal therapy in drug-resistant epilepsy. Curr Opin Neurol 2019;32(2):237-45.
[66] Beyenburg S, Stavem K, Schmidt D. Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: systematic review and meta-analysis. Epilepsia 2010;51(1):7-26.
[67] Keene DL. A systematic review of the use of the ketogenic diet in childhood epilepsy. Pediatr Neurol 2006;35(1):1-5.
[68] Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol 2008;7(6):500-6.
[69] Neal EG, Cross JH. Efficacy of dietary treatments for epilepsy. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association 2010;23(2):113-9.

[70] Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. Epilepsia 2009;50(5):1109-17.
[71] Sharma S, Sankhyan N, Gulati S, Agarwala A. Use of the modified Atkins diet for treatment of refractory childhood epilepsy: a randomized controlled trial. Epilepsia 2013;54(3):481-6.
[72] Wheless JW, Gienapp AJ, Ryvlin P. Vagus nerve stimulation (VNS) therapy update. Epilepsy & behavior : E&B 2018;88S:2-10.
[73] Krahl SE, Clark KB. Vagus nerve stimulation for epilepsy: A review of central mechanisms. Surg Neurol Int 2012;3(Suppl 4):S255-9.
[74] Vonck K, de Herdt V, Sprengers M, Ben-Menachem E. Neurostimulation for epilepsy. Handb Clin Neurol 2012;108:955-70.
[75] https://www.epilepsysociety.org.uk/vagus-nerve-stimulation. 16 January 2019.
[76] Group VS. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. Neurology 1995;45(2):224-30.
[77] Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998;51(1):48-55.
[78] Morris GL, 3rd, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. Neurology 1999;53(8):1731-5.
[79] De Herdt V, Boon P, Ceulemans B, Hauman H, Lagae L, Legros B, et al. Vagus nerve stimulation for refractory epilepsy: a Belgian multicenter study. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society 2007;11(5):261-9.
[80] Elliott RE, Morsi A, Kalhorn SP, Marcus J, Sellin J, Kang M, et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. Epilepsy & behavior : E&B 2011;20(1):57-63.
[81] Labar D. Vagus nerve stimulation for 1 year in 269 patients on unchanged antiepileptic drugs. Seizure 2004;13(6):392-8.
[82] Renfroe JB, Wheless JW. Earlier use of adjunctive vagus nerve stimulation therapy for refractory epilepsy. Neurology 2002;59(6 Suppl 4):S26-30.
[83] Vonck K, Thadani V, Gilbert K, Dedeurwaerdere S, De Groote L, De Herdt V, et al. Vagus nerve stimulation for refractory epilepsy: a transatlantic experience. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society 2004;21(4):283-9.
[84] Boon P, Vonck K, van Rijckevorsel K, El Tahry R, Elger CE, Mullatti N, et al. A prospective, multicenter study of cardiac-based seizure detection to activate vagus nerve stimulation. Seizure 2015;32:52-61.
[85] Fisher RS, Afra P, Macken M, Minecan DN, Bagic A, Benbadis SR, et al. Automatic Vagus Nerve Stimulation Triggered by Ictal Tachycardia: Clinical Outcomes and Device Performance--The U.S. E-37 Trial. Neuromodulation 2016;19(2):188-95.
[86] Tzadok M, Harush A, Nissenkorn A, Zauberman Y, Feldman Z, Ben-Zeev B. Clinical outcomes of closed-loop vagal nerve stimulation in patients with refractory epilepsy. Seizure 2019;71:140-4.
[87] Kawaji H, Yamamoto T, Fujimoto A, Uchida D, Ichikawa N, Yamazoe T, et al. Additional seizure reduction by replacement with Vagus Nerve Stimulation Model 106 (AspireSR). Neurosci Lett 2020;716:134636.
[88] Hamilton P, Soryal I, Dhahri P, Wimalachandra W, Leat A, Hughes D, et al. Clinical outcomes of VNS therapy with AspireSR (R) (including cardiac-based seizure detection) at a large complex epilepsy and surgery centre. Seizure-Eur J Epilep 2018;58:120-6.
[89] Van Buren JM, Wood JH, Oakley J, Hambrecht F. Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. J Neurosurg 1978;48(3):407-16.

[90] Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51(5):899-908.
[91] Morrell MJ, Group RNSSiES. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 2011;77(13):1295-304.
[92] DeGiorgio CM, Murray D, Markovic D, Whitehurst T. Trigeminal nerve stimulation for epilepsy: long-term feasibility and efficacy. Neurology 2009;72(10):936-8.
[93] DeGiorgio CM, Soss J, Cook IA, Markovic D, Gornbein J, Murray D, et al. Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy. Neurology 2013;80(9):786-91.
[94] Soss J, Heck C, Murray D, Markovic D, Oviedo S, Corrale-Leyva G, et al. A prospective long-term study of external trigeminal nerve stimulation for drug-resistant epilepsy. Epilepsy & behavior : E&B 2015;42:44-7.
[95] Slaght SJ, Nashef L. An audit of external trigeminal nerve stimulation (eTNS) in epilepsy. Seizure 2017;52:60-2.
[96] Huang Y, Liu AA, Lafon B, Friedman D, Dayan M, Wang X, et al. Measurements and models of electric fields in the in vivo human brain during transcranial electric stimulation. eLife 2017;6.
[97] Jackson MP, Rahman A, Lafon B, Kronberg G, Ling D, Parra LC, et al. Animal models of transcranial direct current stimulation: Methods and mechanisms. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2016;127(11):3425-54.
[98] Liu A, Voroslakos M, Kronberg G, Henin S, Krause MR, Huang Y, et al. Immediate neurophysiological effects of transcranial electrical stimulation. Nature communications 2018;9(1):5092.
[99] Voroslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernandez-Ruiz A, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nature communications 2018;9(1):483.
[100] Asamoah B, Khatoun A, Mc Laughlin M. tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. Nature communications 2019;10(1):266.
[101] Assenza G, Campana C, Assenza F, Pellegrino G, Di Pino G, Fabrizio E, et al. Cathodal transcranial direct current stimulation reduces seizure frequency in adults with drug-resistant temporal lobe epilepsy: A sham controlled study. Brain Stimul 2017;10(2):333-5.
[102] Auvichayapat N, Rotenberg A, Gersner R, Ngodklang S, Tiamkao S, Tassaneeyakul W, et al. Transcranial direct current stimulation for treatment of refractory childhood focal epilepsy. Brain Stimul 2013;6(4):696-700.
[103] Fregni F, Thome-Souza S, Nitsche MA, Freedman SD, Valente KD, Pascual-Leone A. A controlled clinical trial of cathodal DC polarization in patients with refractory epilepsy. Epilepsia 2006;47(2):335-42.
[104] Zoghi M, O'Brien TJ, Kwan P, Cook MJ, Galea M, Jaberzadeh S. Cathodal transcranial direct-current stimulation for treatment of drug-resistant temporal lobe epilepsy: A pilot randomized controlled trial. Epilepsia open 2016;1(3-4):130-5.
[105] Auvichayapat N, Sinsupan K, Tunkamnerdthai O, Auvichayapat P. Transcranial Direct Current Stimulation for Treatment of Childhood Pharmacoresistant Lennox-Gastaut Syndrome: A Pilot Study. Front Neurol 2016;7:66.
[106] San-Juan D, Espinoza Lopez DA, Vazquez Gregorio R, Trenado C, Fernandez-Gonzalez Aragon M, Morales-Quezada L, et al. Transcranial Direct Current Stimulation in Mesial Temporal Lobe Epilepsy and Hippocampal Sclerosis. Brain Stimul 2017;10(1):28-35.
[107] Tekturk P, Erdogan ET, Kurt A, Vanli-Yavuz EN, Ekizoglu E, Kocagoncu E, et al. The effect of transcranial direct current stimulation on seizure frequency of patients with mesial temporal lobe epilepsy with hippocampal sclerosis. Clin Neurol Neurosurg 2016;149:27-32.
[108] Boon P, De Cock E, Mertens A, Trinka E. Neurostimulation for drug-resistant epilepsy: a systematic review of clinical evidence for efficacy, safety, contraindications and predictors for response. Curr Opin Neurol 2018;31(2):198-210.

[109] Lin Y, Wang Y. Neurostimulation as a promising epilepsy therapy. Epilepsia open 2017;2(4):371-87.
[110] Yang D, Wang Q, Xu C, Fang F, Fan J, Li L, et al. Transcranial direct current stimulation reduces seizure frequency in patients with refractory focal epilepsy: A randomized, double-blind, sham-controlled, and three-arm parallel multicenter study. Brain Stimul 2020;13(1):109-16.
[111] Chen R, Spencer DC, Weston J, Nolan SJ. Transcranial magnetic stimulation for the treatment of epilepsy. Cochrane Database Syst Rev 2016(8):CD011025.
[112] Cantello R, Rossi S, Varrasi C, Ulivelli M, Civardi C, Bartalini S, et al. Slow repetitive TMS for drug-resistant epilepsy: clinical and EEG findings of a placebo-controlled trial. Epilepsia 2007;48(2):366-74.
[113] Fregni F, Otachi PT, Do Valle A, Boggio PS, Thut G, Rigonatti SP, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in patients with refractory epilepsy. Ann Neurol 2006;60(4):447-55.
[114] Joo EY, Han SJ, Chung SH, Cho JW, Seo DW, Hong SB. Antiepileptic effects of low-frequency repetitive transcranial magnetic stimulation by different stimulation durations and locations. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2007;118(3):702-8.
[115] Seynaeve L, Devroye A, Dupont P, Van Paesschen W. Randomized crossover sham-controlled clinical trial of targeted low-frequency transcranial magnetic stimulation comparing a figure-8 and a round coil to treat refractory neocortical epilepsy. Epilepsia 2016;57(1):141-50.
[116] Sun W, Mao W, Meng X, Wang D, Qiao L, Tao W, et al. Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy: a controlled clinical study. Epilepsia 2012;53(10):1782-9.
[117] Tergau F, Neumann D, Rosenow F, Nitsche MA, Paulus W, Steinhoff B. Can epilepsies be improved by repetitive transcranial magnetic stimulation?--interim analysis of a controlled study. Suppl Clin Neurophysiol 2003;56:400-5.
[118] Theodore WH, Hunter K, Chen R, Vega-Bermudez F, Boroojerdi B, Reeves-Tyer P, et al. Transcranial magnetic stimulation for the treatment of seizures: a controlled study. Neurology 2002;59(4):560-2.
[119] Wang X, Yang D, Wang S, Zhao X, Zhang L, Chen Z, et al. Effects of low-frequency repetitive transcranial magnetic stimulation on electroencepahologram and seizure frequency in 15 patients with temporal lobe epilepsy following dipole source localization. Neural Regeneration Research 2008;3(11):1257-60.
[120] He W, Jing X, Wang X, Rong P, Li L, Shi H, et al. Transcutaneous auricular vagus nerve stimulation as a complementary therapy for pediatric epilepsy: a pilot trial. Epilepsy & behavior : E&B 2013;28(3):343-6.
[121] Rong P, Liu A, Zhang J, Wang Y, Yang A, Li L, et al. An alternative therapy for drug-resistant epilepsy: transcutaneous auricular vagus nerve stimulation. Chin Med J 2014;127(2):300-4.
[122] Liu A, Rong P, Gong L, Song L, Wang X, Li L, et al. Efficacy and Safety of Treatment with Transcutaneous Vagus Nerve Stimulation in 17 Patients with Refractory Epilepsy Evaluated by Electroencephalogram, Seizure Frequency, and Quality of Life. Medical science monitor : international medical journal of experimental and clinical research 2018;24:8439-48.
[123] Song GF, Wang HY, Wu CJ, Li X, Yang FY. A retrospective study of transcutaneous vagus nerve stimulation for poststroke epilepsy. Medicine 2018;97(31):e11625.
[124] Barbella G, Cocco I, Freri E, Marotta G, Visani E, Franceschetti S, et al. Transcutaneous vagal nerve stimulatio (t-VNS): An adjunctive treatment option for refractory epilepsy. Seizure 2018;60:115-9.
[125] Bauer S, Baier H, Baumgartner C, Bohlmann K, Fauser S, Graf W, et al. Transcutaneous Vagus Nerve Stimulation (tVNS) for Treatment of Drug-Resistant Epilepsy: A Randomized, Double-Blind Clinical Trial (cMPsE02). Brain Stimul 2016;9(3):356-63.

[126] Aihua L, Lu S, Liping L, Xiuru W, Hua L, Yuping W. A controlled trial of transcutaneous vagus nerve stimulation for the treatment of pharmacoresistant epilepsy. Epilepsy & behavior : E&B 2014;39:105-10.
[127] Rong P, Liu A, Zhang J, Wang Y, He W, Yang A, et al. Transcutaneous vagus nerve stimulation for refractory epilepsy: a randomized controlled trial. Clinical science (London, England : 1979) 2014.
[128] Redgrave J, Day D, Leung H, Laud PJ, Ali A, Lindert R, et al. Safety and tolerability of Transcutaneous Vagus Nerve stimulation in humans; a systematic review. Brain Stimul 2018;11(6):1225-38.

CHAPTER 4

Deep brain stimulation

Concept and hardware

Deep brain stimulation is an intrancranial neurostimulation technique that uses small electrical pulses to modulate ongoing neuronal activity. These electrical pulses are delivered to deep brain nuclei by stereotactically implanted depth electrodes. An analogous but different term – although often used interchangeably – is cortical (brain) stimulation where cortical regions are targeted by cortical electrodes.

A deep (or cortical) brain stimulation system consists of three components:

- An implantable pulse generator that contains a power source, electronic hardware and software to generate electrical pulses. The stimulus shape and timing can be noninvasively programmed by an external wand. Some implantable pulse generators can also analyze recorded brain signals, e.g. in responsive neurostimulation devices. Implantable pulse generators typically have a flat rounded shape and are implanted in the subclavicular or abdominal region;
- One or more multicontact depth electrodes stereotactically implanted in deep brain nuclei and / or subdural electrodes placed over the cortical convexity, serving as an interface medium to transfer current from the generator to the the neural tissue;
- A subcutaneously implanted extension lead connecting the pulse generator to the depth electrode [1-3].

Figure 14. Schematic illustration of a deep brain stimulation system. A stereotactically implanted quadripolar depth electrode is connected to an implanted pulse generator located in the subclavicular or abdominal region via a subcutaneous extension lead [4].

Indications

Chronic stimulation of subcortical structures was first used in the early 1950s, very soon after the introduction of human stereotaxy. The possibility of transcutaneous activation of a subcutaneously implanted receiver by an external transmitter in the 1970s and the development of a fully implantable pulse generator in the 1980s were important milestones in the history of DBS. Initial domains of investigation included psychiatric disorders, pain and movement disorders [3, 5]. The modern era of DBS arrived in 1987 when Prof. Ali-Louis Benabid and his colleagues reported the successful use of continuous high-frequency thalamic DBS in extrapyramidal tremor patients [6]. Other milestones were

the first report of subthalamic (STN) DBS in a patient with Parkinson's disease in 1993 and of internal global pallidus (GPi) DBS for dystonia in 1999 [7, 8].

Indication	CE marking	FDA approval
Tremor (VIM)	1993	1997
Parkinson's disease		
VIM	1997	1999
STN / GPi	1998	2002
Dystonia (GPi)	2003	2003 (HDA)
Obsessive-compulsive disorder (VC/VS)	2009	2009 (HDA)
Epilepsy		
ATN	2010	2013
Responsive ictal onset zone		2018

Table 4: overview of approved DBS indications.

Abbreviations: CE Conformité Européenne; FDA Food and Drug Administration; VIM ventral intermediate nucleus; STN subthalamic nucleus; GPi internal globus pallidus; VC/VS ventral capsule/striatum; HDA Humanitarian Device Exemption; ATN anterior thalamic nucleus

By 2018, DBS had received CE mark registration and FDA approval for essential tremor, Parkinson's disease, dystonia, obsessive-compulse disorder and epilepsy (see Table 4). It is estimated that nowadays more than 150 000 DBS implants have been performed worldwide [9]. The vast majority of implanted patients have Parkinson's disease. Six RCTs have shown – compared to medical therapy only – significant improvements in motor symptoms on (Unified Parkinson's Disease Rating Scale-III (UPDRS-III) [range 0-108] +15.20) and off (+4.36) medication, a reduction of the on time with troublesome dyskinesias (+3.25 hours per day), a levodopa dose reduction (-452 mg per day), decreased medication-induced complications (UPDRS-IV [range 0-23] +3.37), better performance in activities of daily living off (UPDRS-II [range 0-52] +7.39) and off (+1.77) medications and increased quality of life (Parkinson's Disease Questionnaire [range 0-100] +7.43) [10, 11]. In essential tremor patients, 40-80% reductions in tremor severity and corresponding improvements in quality of life were reported with ventral intermediate nucleus thalamic DBS. Up to 10% do not have adequate tremor control and 15-20% lose the efficacy within the first year of treatment [12]. Internal global pallidus DBS was associated with 40-50% improvements in RCTs with patients with primary dystonia. The response to secondary dystonias is more variable and appears to be depedent on the cause, where the best results are seen in tardive dystonia patients [8, 12]. A meta-analysis of RCTs evaluating the effects of DBS in patients with obsessive-compulsive disorder calculated a significant -8.93 reduction of the Yale-Brown Obsessive Compulsive Scale (range 0-40, baseline 31.98), representing partial remission [13].

Besides the approved indications, DBS has been investigated as an alternative treatment option in many other (drug resistant) patient groups with various neurological, psychiatric or other disorders. An overview is provided in Table 5.

Category of disorders	Indication	Target(s)
Movement disorders	Parkinson's disease	STN, GPi, PPN
	Essential tremor	Vim, STN
	Dystonia	GPi, Vim, STN
	Chorea	GPi
	Holmes tremor	Vim, STN
	Orthostatic tremor	Vim
	Postural instabilities	PPN
	Restless leg syndrome	STN
Other neurological Disorders	Epilepsy	See next section
	Alzheimer's disease	NMB, fornix / hypothalamus
	Cluster headache, chronic paroxysmal hemicrania	PH
	Disorder of consciousness	CM/PF
	Stroke	Affected cortical area
	Trigeminal neuralgia / neuropathy	Hypothalamus
Psychiatric disorders	Obsessive-compulsive disorder	VC/VS, ALIC, Nac, ITP, STN
	Addiction	STN, Nac, hypothalamus, insula
	Aggressive behavior	BLA, PH
	Anorexia	Nac, Cg25
	Bipolar disorder	SGCC
	Depression	Cingulum, VC/VS, STN, GPi, ITP, Nac, ALIC, LHb, Cg25
	Post-traumatic stress disorder	Amygdala
	Schizophrenia	Nac/VS, VTA
	Tic disorder (Tourette's syndrome)	GPi, GPi, ALIC, CM/PF
Miscellaneous disorders	Chronic pain	VPL, VPM, TVc, PAG/PVG
	Obesity	VMH, LH
	Tinnitus	LC

Table 5: Deep brain stimulations indications and targets (adapted from [14, 15]).

Abbreviations: ALIC anterior limb of the internal capsule; BLA basolateral amygdale; Cg25 cingulate area 25 or subgenual cingulated; CM/PF centromedian/parafascicular complex of thalamus; CT central thalamus; GPi globus pallidus internus; ITP inferior thalamic peduncle; LC locus of caudate; LH lateral hypothalamus; LHb lateral habenula; Nac nucleus accumbens; NBM nucleus basalis of Meynert; PAG/PVG periaquaductal / periventricular gray matter; PF parafascicular thalamic nucleus; PH posterior hypothalamus; PPN peduncolpontine nucleus; SGCC subgenual cingulated cortex; STN subthalamic nucleus; TVc thalamic nucleus ventralis caudalis; VC/VS ventral capsule / striatum; Vim ventral intermediate nucleus of thalamus; VMH ventromedial hypothalamus; VPL ventral posterolateral thalamus; VPM ventral posteromedial thalamus; VTA ventral tegmental area.

DBS and cortical stimulation in epilepsy

Review published in 2013

A review on invasive brain stimulation, i.e. cortical and deep brain stimulation, in drug-resistant epilepsy was published in 2013.

INVASIVE BRAIN STIMULATION IN THE TREATMENT OF EPILEPSY

MATHIEU SPRENGERS*, DIRK VAN ROOST§, ALFRED MEURS*, ROBRECHT RAEDT*, EVELIEN CARRETTE*, PAUL BOON*, KRISTL VONCK*

** Department of Neurology, Ghent University Hospital, De Pintelaan 185 9000 Ghent, Belgium*

§ Department of Neurosurgery, Ghent University Hospital, De Pintelaan 185 9000 Ghent, Belgium

Published in: Recent advances in predicting and preventing epileptic seizures (2013): 42-60.

Invasive brain stimulation has emerged as an alternative treatment for refractory epilepsy patients and an increasing number of trials evaluating its efficacy and safety have been published. Various brain structures have been targeted, including the cerebellum, the anterior and centromedian thalamic nucleus, the hippocampus, the ictal onset zone and the subthalamic and caudate nucleus. The rationale for each of these targets and the results obtained in open-label and randomized controlled trials (RCTs) are discussed, with particular emphasis on two large RCTs that investigated open-loop anterior thalamic deep brain stimulation and responsive stimulation of the ictal onset zone. We conclude that promising results have been published for most targets, mainly in open-label trials, and that more RCTs are needed.

1. Introduction

1.1. *General Introduction*

Epilepsy and epileptic seizures are characterized by both electrical and chemical abnormalities. Research on the treatment of epilepsy patients has mainly focused on the neurochemical part, leading to the development of many antiepileptic drugs (AEDs). Over the past decades, interest in neurostimulation as an alternative treatment for refractory epilepsy patients has grown. Neurostimulation can be defined as the administration of electrical or magnetic pulses to neural tissue in order to modulate neuronal activity. A distinction should be made between invasive and noninvasive neurostimulation strategies. Invasive neurostimulation modalities can be subdivided in extracranial, today still being synonymous to vagus nerve stimulation (VNS), and intracranial stimulation. Whereas VNS is

nowadays the only neurostimulation treatment which has become routinely available in clinical practice and has received FDA approval, this review focuses on the experience gained with invasive intracranial stimulation.

1.2. *Historical Background*

The concept of stimulating the brain to treat epilepsy patients is not new. Already in the 19th century Brown-Séquard[1], Jackson[2] and Gowers[3] suggested 'counter-irritation' as a potential strategy to abate epileptic activity[4]. In the mid-20th century animal studies and preliminary acute human experiments provided further evidence to support this hypothesis[5,6]. The first chronic trials in humans were initiated in the seventies[7,8]. Promising results in these and various other open-label trials[7,9-12] led to the initiation of three randomized-controlled trials[13-15] (RCTs) but these failed to confirm the optimistic outcomes reported in the initial pilot trials. However, given the vast progress in biotechnology along with the experience with brain stimulation in movement disorders and other neuropsychiatric diseases[16,17], interest in intracranial stimulation for the management of medically intractable epilepsy has been renewed over the past 10-15 years and has resulted into an exponential growth of publications on this topic.

1.3. *Classification of Intracranial Neurostimulation*

There are several ways to categorize intracranial neurostimulation. One way is to focus on the anatomical location of the targeted structure: intracranial electrodes may be inserted into deep subcortical targets for deep brain stimulation (DBS) or be placed over the cortical convexity for cortical stimulation (CS). Another possibility is to classify intracranial stimulation treatments according to the presumed pathophysiological function of the targeted structure, being either the ictal onset zone (e.g. the neocortex, the hippocampus in medial temporal lobe epilepsy,…) or a more remote structure thought to be involved in the epileptic network (e.g. anterior thalamic nucleus, centromedian thalamic nucleus, cerebellar stimulation, caudate nucleus, subthalamic nucleus,…). Finally, with regards to the timing of stimulation, a distinction should be made between open- and closed-loop stimulation paradigms. In open-loop or scheduled stimulation, stimulation is administered at certain prespecified given time points, either continuously or intermittently (following a specific duty cycle). On the contrary, in closed-loop or responsive stimulation, electrical stimuli are only delivered upon seizure detection.

2. Overview of the Different Targets

2.1. *Cerebellar Stimulation*

The rationale behind cerebellar stimulation is that inhibitory Purkinje cells are activated and thus intensify the inhibitory cerebellar output to the ventrolateral thalamus which results into a decreased excitation of thalamocortical projections and ultimately into diffuse cortical inhibition[18,19]. Although a decreased number of Purkinje cells in epilepsy patients[7,11,13] and a further reduction with cerebellar stimulation[20] as well as a decreased activity[21,22] of Purkinje cells in response to cerebellar stimulation have been used as arguments against this theory[18,23], it should be noticed that none of these truly discard the hypothesis of increased efferent[24] output.

After animal studies[6,18,22,25,26] had shown variable but at the same time hopeful results, Cooper and colleagues conducted a first chronic cerebellar cortical stimulation trial in humans and reported at least 50% seizure reduction in 18 of their 32 patients (56%) suffering from various forms of medically intractable epilepsy[7]. Various open-label trials followed and demonstrated a significant improvement in the majority (up to > 90%) of patients, who often even achieved seizure freedom[11,12,18,20,27]. Inspired by these promising results, Van Buren *et al.*[13] and Wright *et al.*[14] recruited five and twelve patients respectively with focal and/or generalized seizures for two randomized controlled cross-over trials. Although family members of all the subjects in Van Buren's trial and 11 out of 12 patients of Wright's trial felt better for cerebellar stimulation, this probably reflected a placebo effect as statistically significant seizure frequency reductions could not be demonstrated. Looking at the individual patient data, there was no more than one patient who clearly did benefit from the stimulation (97% seizure reduction) in the Wright's trial[14]. On the contrary, although Van Buren *et al.*[13] reported increased seizure frequency with regard to the baseline period in 4/5 patients (with as well as without stimulation), directly comparing seizure frequency of (only) 2 weeks with and without stimulation leads to somehow more favourable – albeit still heterogeneous – results: blinded evaluations during hospital admissions in the first 10 months after electrode implantation revealed unknown, -69%, -73%, unknown and +102% changes in seizure frequency (not enough data in 2/5 patients), whereas late blinded evaluations during hospital admissions 10-21 months after electrode implantation showed -53%, -12%, -7%, -19% and +131% differences in seizure frequency. The most recent RCT was performed in 2005 by Velasco and coworkers and included five patients with intractable motor seizures (generalized epilepsy (n=3) or (multi)focal epilepsy from frontal origin (n=2))[28]. During the 3-month randomized blinded phase of the trial, generalized tonic-clonic seizures (GTCS) (n=5) decreased with 67% in the

stimulated group (n=3) compared to 7% in the control group (n=2) (p=0.023). Seizure rate reductions for tonic seizures (TS) (n=4) and drop attacks (DA) (n=2) were comparable for both groups and not statistically significantly different. After the randomized period, stimulators were turned on in all patients. This resulted in a 59% GTCS reduction (n=5), a 48% TS reduction (n=4), a 74% DA reduction (n=2) and a 84% reduction in myoclonic seizures with atypical absences (n=1). Cerebellar stimulation was well-tolerated across the different studies[13,14,18,29], but electrode migration necessitating repeated surgery constitutes a non-negligible complication that needs to be resolved[14,29].

As conflicting results have been published, considerable interest in cerebellar stimulation remains and further investigation is warranted. Identifying optimal stimulation protocols will be an important step in this process, e.g. both animal and human studies have suggested that stimulation of the superomedial surface of the cerebellum (as in all RCTs) may be most efficacious[18,25,30].

2.2. *Anterior Thalamic Nucleus Stimulation*

Being part of the circuit described by Papez, the anterior thalamic nucleus (ATN) has widespread projections to the limbic structures and ultimately also to the – mainly frontal and temporal – neocortex[31]. Besides these anatomical connections, its relatively small size[19,32], its involvement in seizure propagation[33], the improved seizure control in lesional studies in animals[34-37] and humans[38], and the promising results in some acute[36,37,39,40] (but not chronic[41]) animal models, have made the ATN an appealing target for DBS in epilepsy.

Cooper and Upton[9] were the first to explore chronic ATN stimulation in humans and reported an over 60% seizure reduction in 5/6 patients suffering from refractory (multi)focal epilepsy (2-6 years of follow-up). Many other open-label trials have followed and have reported variable results with mean seizure reductions of 14-76% and 50% responder rates of 25-100%[9,42-48] (see Table 1). Except for 2 (or 3) patients with symptomatic generalized epilepsy in Hodaie's[42] and Andrade's[44] patient series (same patients but different follow-up), all patients included so far suffered from (multi)focal epilepsy. Although seizure reductions reported by Hodaie *et al.*[42] were more pronounced in (multi)focal (75 and 89% reduction) compared to symptomatic generalized (23 and 34% reduction) epilepsy patients, conclusions on this topic are too premature to draw. Most favourable results were reported by Osorio *et al.*[46] in 4 patients with inoperable medial temporal lobe epilepsy. Stimulation of the ATN in idiopathic generalized epilepsy has not been evaluated yet. Despite the encouraging results published in literature, doubt about the efficacy of ATN stimulation as such remained, as 1) Lim *et al.*[42] and Hodaie *et al.*[47] reported a significant postoperative seizure reduction, but no further improvement after initiation of stimulation (suggestion of lesional or

implantation effect), and 2) turning stimulation off for 2 months in a single-blind manoeuvre and unblindedly for months or years thereafter did not increase seizure frequency in Hodaie's and Andrade's patient series[42,44]. In contrast, Osorio *et al.*[46] did not observe an important and immediate postoperative prestimulation seizure reduction and Kerrigan *et al.*[43] did report an increased seizure frequency after switching stimulation off (as also in one of Osorio's patients[46]).

Table 1. Overview of open-label trials evaluating anterior thalamic nucleus stimulation

Study	Number of Patients	Follow-up (months)	Mean Seizure Reduction	Responder Rate
Cooper *et al.* 1985[9]	6	24-72	> 60% reduction in 83%	
Hodaie *et al.* 2002[42,43]	5	12-21	54%	60%
Kerrigan *et al.* 2004[43]	5	6-36	14%	20%
Andrade *et al.* 2006[44]	6	48-84	64%	83%
Lee *et al.* 2006[45]	3	?	75%	100%
Osorio *et al.* 2007[46]	4	36	76%	100%
Lim *et al.* 2007[47]	4	24	49%	25%
Lee *et al.* 2012[48]	15	27	70%	?

Ultimate evidence with regards to the efficacy and safety of ATN stimulation has been provided by the SANTE trial[49]. This multicenter double-blind, parallel-design RCT recruited 110 adults (18-65 years, IQ ≥ 70) suffering from refractory partial-onset epilepsy (failure of ≥ 3 AEDs and ≥ 6 seizures per month). About half of the patients had prior VNS and/or resective surgery. In the first postoperative month seizure frequency decreased by 22% and this was before any stimulation took place (just as had been reported in some of the open-label trials). However, in the ensuing 3-month randomized period, median percentage seizure frequency change increased from 33.9 to 40.4% in the stimulation group and decreased from 25.3 to 14.5% in the control group, resulting in a net treatment effect of -17% over the entire blinded period (p=0.04). This net stimulation effect became statistically significant only in the third month of the randomized phase (-29%, p=0.002; month 1: -10%, month 2: -11%). Differences in seizure freedom and the 50% responder rate were not statistically significant. With further follow-up (AEDs kept constant for another 9 months) median percentage seizure reduction increased to 41% at 13 months (n=99) and 56% (n=81) at 25 months. The same trend for increasing efficacy over time was observed for the 50% responder rate, being 43% and 54% respectively, and 6/81 patients were seizure-free in the 3-month period preceding the 25-month follow-up visit. However, this moderately improved seizure control was not without any cost. Over the entire study period, five – albeit asymptomatic – haemorrhages were detected

incidentally by neuroimaging and 14 participants (13%) developed implant site infections (but no parenchymal brain infections). Moreover, there were more subjects with self-reported depression (14.8 versus (vs) 1.8%, p=0.02) and subjective memory impairment (13.0 vs 1.8%, p=0.03) in the stimulated group compared to the control group, and one subject experienced a dramatic (but reversible) seizure frequency increase linked to the stimulation. On the contrary, there were less epilepsy-related injuries (7.4 vs 25.5%, p=0.01).

In conclusion, good evidence exists that ATN stimulation can reduce seizure frequency in highly refractory focal epilepsy patients. However, benefits in double-blind and controlled conditions were less substantial than what could have been expected based on open-label trials.

2.3. *Hippocampal Stimulation*

As outlined in the introductory part, targeting the area of presumed ictal onset instead of more remote network structures is another strategic DBS approach in epilepsy. In medial temporal lobe epilepsy (MTLE), the hippocampus plays a crucial role in the ictal onset, as has been demonstrated by various (invasive) electrophysiological and other studies in humans[50-53]. Significant seizure reductions observed after selective amygdalohippocampectomy are in line with this presumed key function of the hippocampus in MTLE[54-56].

Velasco *et al.*[57] were the first to use diagnostic depth electrodes in humans to deliver electrical pulses to medial temporal lobe structures for 2-3 weeks prior to resective surgery. In 7/10 patients whose stimulation contacts were placed within the hippocampal formation and gyrus, one week of stimulation completely abolished seizures and significantly decreased the number of interictal spikes. At Ghent University Hospital, we were able to confirm these preliminary results in a chronic pilot trial in 2002[58]. After 3-6 months of hippocampal and amygdalar stimulation, a 50-95% seizure reduction in three patients was found. Since then more patients were included in this open-label trial[59,60]. After 6-10 years of stimulation, 3/11 patients are now seizure-free for > 3 years, 3/11 achieved > 90% seizure reduction, 3/11 responded moderately with a 40-70% seizure reduction and two patients are considered non-responders[60]. Interestingly, in some of the unilateral MTLE patients maximum seizure frequency reduction was only achieved after initiation of bilateral hippocampal stimulation (further reduction compared to unilateral stimulation in 3/5 patients). These results are comparable to those in two other open-label trials with long-term follow-up and a similar number of patients[60-62] (see Table 2). However, although in one RCT reported seizure frequency reductions reached statistical significance[63], patients in two (albeit small) RCTs did not improve to the same extent[63,64].

Velasco and colleagues[62] reported a slower (after 6-8 months vs 1-2 months) and less pronounced seizure reduction (50-70% vs 95-100%) in 4 patients with hippocampal sclerosis (HS) on magnetic resonance imaging (MRI). This discrepancy was not distinctly observed in other open-label trials with however slightly smaller numbers of HS patients[60,61]. Boëx *et al.*[61] hypothesized that the reduced efficacy reported by Velasco and coworkers in their HS patients[62] could result from suboptimal stimulation parameters settings, as Boëx and colleagues did report the need for stronger stimulation (higher stimulus amplitudes or/and multipolar configuration) in HS patients[61]. Because 5/6 patients in the RCTs[63,64] showed typical findings of HS on their MRI, it is difficult to draw any conclusions with regards to this issue from these studies.

Table 2. Overview of trials evaluating hippocampal stimulation in MTLE

Study	Number of Patients	Follow-up (months)	% Seizure Reduction	Responder Rate	Seizure Freedom
Velasco *et al.* 2007[62]	9	18-84	84%	100%	44%
Boëx *et al.* 2011[61]	8	12-74	67%	75%	25%
Vonck *et al.* 2013[60]	11	66-120	67%	73%	27%
Tellez-Zenteno *et al.* 2006[64]*	4	3x 1	26%[#]	25%	0%
McLachlan *et al.* 2007[63]*	2	3	33%[¶]	0%	0%

* Randomized controlled trial; [#] and [¶]: 15 and 29% respectively when comparing ON and OFF periods (no responders)

With long-term seizure freedom of 50-75%, resective surgery remains the treatment of choice for pharmacologically refractory MTLE patients[65-67]. However, hippocampal DBS seems a valuable alternative for those patients who are unsuitable surgical candidates (independent bitemporal foci, high risk of memory decline,…) or who are reluctant to undergo resective brain surgery. In this context, it is worthwhile mentioning that with appropriate stimulation parameter settings neither uni- nor bilateral hippocampal stimulation resulted in neuropsychological deterioration and has actually been associated with enhanced emotional well-being[60-62,64,68]. Future research and optimization of the stimulation protocol could further improve outcome of hippocampal DBS.

2.4. *Centromedian Thalamic Stimulation*

The centromedian thalamic nucleus (CMTN) is part of the reticulo-ascending system with diffuse projections from the brain stem to the cerebral cortex and is

thought to mediate cortical excitability and desynchronisation and thus having seizure modulating potential[69-72].

Velasco and colleagues were the first to explore CMTN stimulation during 2 hours/day (h/d) for 3 months in five patients, with significant reductions in GTCS (80-100% reductions, 3/5 seizure-free) and complex partial seizures (CPS) (4/5 seizure-free)[10]. Further experience with this technique in larger patient series (n=23[73], n=5[74]) confirmed the efficacy for GTCS but could not reproduce the beneficial effects on CPS. In addition, > 90% seizure reductions in 3 patients with partial motor seizures was found[73]. Results in Lennox-Gastaut type patients were more inconclusive[73,74], but more recent trials (n=8[75], n=13[76]; stimulation 24 h/d) showed very favourable seizure outcomes especially in this difficult-to-treat patient group (mean seizure frequency reduction of 81% compared to 57% in five patients with (multi)focal epilepsy). Subgroup analysis of patients with optimal (*i.e.* in the ventrolateral or parvocellular region of the CMTN) stereotactic electrode placement yielded even higher seizure reductions. Surprisingly, turning stimulators off for 3 months in a double-blind protocol did not increase seizure frequency[75]. Authors attributed this phenomenon to residual stimulation effects. This effect, however, may not be present in every single patient and could only be temporary, as could be derived from – in some cases delayed – seizure frequency increases after mainly unblinded discontinuations in five other patients due to battery depletion, pulse generator removal or lead rupture[75,76].

After the hopeful initial results of Velasco *et al.*[10], Fisher and coworkers conducted a RCT in seven patients[15]. One patient had CPS only, another had CPS and secondarily GTCS and five suffered from primarily generalized seizures (2/5 with Lennox-Gastaut syndrome (LGS)). There were no significant differences between stimulation ON (2 h/d) and OFF periods in this cross-over trial with a 3-month washout period, even after exclusion of one patient with only CPS who reported a seizure increase during the trial (ON -30% versus OFF -8%, p=ns). In fact, only one LGS patient seemed to benefit from CTMN stimulation (-89% reduction with stimulation ON but then dropped from the blinded protocol due to a seizure increase in the washout period). However, during the unblinded open-label phase of the study (stimulation 24 h/d) 3/6 patients showed a > 50% response.

In line with the negative findings in the randomized period of the RCT, two other research groups[44,77] failed to demonstrate important seizure reductions with CMTN stimulation in very small open-label trials (n=1 with generalized epilepsy, n=2 with multifocal epilepsy). In contrast, Cukiert *et al.*[78] revealed a 65-98% improvement and increased attention level after 1-2 years of CMTN stimulation in 4 patients with generalized epilepsy who had previously been submitted to callosotomy.

In conclusion, Velasco and colleagues have demonstrated marked seizure frequency reductions after initiation of CMTN stimulation, especially in patients suffering from GTCS, atypical absences and LGS. Nevertheless, apart from Cukiert *et al.*[78], other smaller trials including one RCT failed to confirm these results. In future, large RCTs in homogeneous patient populations and with 24 hours of stimulation per day are needed before making unambiguous statements with regards to the efficacy of CMTN stimulation.

2.5. *Subthalamic Nucleus Stimulation*

Inhibition of the excitatory output of the subthalamic nucleus (STN) to the reticular part of the substantia nigra reduces inhibitory output of the substantia nigra to the dorsal midbrain anticonvulsant zone and in this way ultimately leads to decreased inhibition of the GABAergic tectocortical projections[79]. Besides this mechanistic rationale, supporting animal studies[80-82] coupled with ample experience with STN DBS in Parkinson's disease[16] have resulted into various pilot trials in epilepsy patients.

Not surprisingly, STN DBS was first explored by Benabid's group, who reported a significant seizure frequency reduction (67-80%) in three patients with focal epilepsy originating from the central region[83]. Improvement was less pronounced in a patient with Dravet syndrome (-42%) and no effect could be observed in a patient with autosomal dominant nocturnal frontal lobe epilepsy with hypermotor seizures (left insulofrontal focus). Other open-label trials reported similar results with significant improvements in about half of the patients: Loddenkemper *et al.*[79] showed a 60-80% reduction in 2/5 patients suffering from focal intractable epilepsy and 33 to 50% reductions were observed by Handforth *et al.*[84] in 2 patients with unifrontal and bitemporal epilepsy respectively.

In addition to these focal epilepsy patients, STN DBS has also been investigated in generalized epilepsy. In a case report published in 2001, STN DBS completely abolished GTCS and diminished myoclonic and absence seizures with >75% in one LGS patient LGS[85]. More recently Wille *et al.*[86] reported on five patients with progressive myoclonic epilepsy who had been treated with STN DBS. In all patients a reduction of myoclonic seizures was observed and ranged between 30 and 100%. Temporary discontinuation of stimulation was associated with an almost immediate deterioration in 3/3 patients. Stimulation of the ventral intermediate thalamic nucleus in the same study failed to achieve acute therapeutic effects and therefore was interrupted, so no long-term data are available.

2.6. *Caudate Nucleus Stimulation*

Sramka, Chkhenkeli and their coworkers have published several reports on stimulation of the caudate nucleus[77,87-89], activation of which has been correlated with hyperpolarization of cortical neurons via the 'caudate loop'[77,87,90]. After having demonstrated a decrease in interparoxysmal activity and focal discharges in neocortical and mesial temporal lobe foci as well as abrupt cessation of spreading and generalized discharges[89], they published their results of chronic low-frequency stimulation of the ventral part of the head of the caudate nucleus[77]. Patients suffered from epilepsy with various and not well-described seizure origins, but the majority had temporal lobe epilepsy. An impressive 53% of participants achieved seizure-freedom and an additional 29% experienced a 'worthwhile' improvement. Comparable figures were obtained in 21 patients after combined DBS and ablation (total cryoamygdalohippocampectomy or anterior temporal lobectomy) of the dominant epileptic focus. However, as these results were those of 25 years of follow-up, they should be interpreted with caution because significant medication-related improvements cannot be excluded. In addition, in 1980 Sramka *et al.*[88] reported good early therapeutic effects in only 2 out of 10 patients.

2.7. *Various Targets*

Electrical stimulation of the epileptogenic region may be an alternative in focal epilepsy patients with seizures originating from a well-circumscribed focus in the motor cortex which cannot be resected for obvious reasons. Elisevich *et al.*[91] (n=1) and Velasco *et al.*[92] (n=2) observed >90% seizure reductions with elimination of spreading and Todd's phenomenon. One patient even became seizure-free[92]. There were no adverse events, including preserved motor function.

Franzini *et al.*[93] employed DBS for stimulating two unconventional targets. Posterio-medial hypothalamus DBS led to 75-80% reductions in 2 patients with multifocal epilepsy and stimulation of the caudal zona inserta in focal motor epilepsy was associated with a 85% seizure reduction in one patient and focal motor status disappearance in another.

Various research groups have evaluated the potential of DBS to treat intractable seizures related to hypothalamic hamartomas[94-97]. Khan *et al.*[94] found significant improvements of gelastic and CPS in 2 patients after initiation of mamillothalamic tract stimulation, with no seizures for the last 10 months in one patient. In another trial (n=1) direct stimulation of the hamartoma resulted into complete abatement of gelastic seizures, a significant reduction of CPS and had no effect on drop attacks[95]. In contrast, two other case reports could not observe any beneficial effect[96,97].

Two older publications report on stimulation of the locus coeroleus (LC)[98] and the corpus callosum (CC)[99]. Unilateral LC stimulation in 2 epilepsy patients appeared to reduce both incidence and severity of seizures, but Feinstein and coworkers[98] warned at the same time this was not 'rigorously established' yet. Finally, Marino Junior *et al.*[99] planned to evaluate chronic CC stimulation in several patients, but disappointing results in their first patient along with negative experimental findings in cats[100] made them focus on stereotactic anterior callosotomy.

2.8. *Closed-loop Stimulation*

In studies investigating closed-loop stimulation, implanted intracranial electrodes serve a dual function: continuous monitoring of electro-encephalographic activity and delivery of electrical pulses. In concept, electrical stimuli are only administered after epileptiform electro-encephalographic activity has been detected, aiming to disrupt ongoing seizure activity. Potential advantages of this responsive strategy include minimization of adverse effects, temporary use of higher stimulation settings, lower daily doses, prolonged battery life and higher efficacy[101]. An additional challenge compared to open-loop stimulation is that, apart from an effective stimulation paradigm, the applicability and success of closed-loop stimulation is highly dependent on the implementation of a sensitive, specific and fast seizure detection or prediction algorithm. Finally, one could hypothesize that possible but still controversial long-term neuromodulatory effects of intracranial stimulation are less likely to occur with – inherently less frequent – closed-loop stimulation.

Early proof-of-concept trials provided initial evidence that responsive stimulation is feasible, safe and has seizure reducing potential in focal epilepsy[4,102-104]. Six to 24 months of stimulation resulted in a >45% reduction in seizure frequency in 7/8 patients[104] and 50-75% reductions after 2 years of follow-up were reported by Anderson and coworkers (n=4)[103]. These trials selected the seizure focus as stimulation target but in a short-term trial (4-12 days) Osorio *et al.*[4] demonstrated that responsive stimulation of the ATN may be efficacious too.

The results of a multi-institutional parallel-group RCT of a cranially implanted responsive neurostimulator (RNS® System, NeuroPace, Mountain View, CA) were published in 2011[105]. All subjects (n=191) were adults (18-70 years) who had ≥ 3 disabling seizures per month (mean 1.2 seizures/day) which had been localized to 1 or 2 epileptogenic regions. Prior VNS (34%) or epilepsy surgery (32%) did not exclude patients from participation. As in the SANTE trial[49] an important postoperative prestimulation seizure reduction was observed, with subsequent further improvement from -34.2% (month 1) to -41.5% (month 3) after responsive stimulation of the ictal onset zone had been initiated but in contrast a

gradual return towards baseline in the control group (from -25.2% in month 1 to -9.4% in month 3). Differences were statistically significant from the second month on as well as for the entire blinded evaluation period as a whole (-37.9% vs -17.3%, p=0.012). Two subjects in the treatment group were seizure-free, compared to none in the sham group. Responder rates were very similar in both groups (29% vs 27%). Seizure reductions were sustained and even improved over time with responder rates of 43 and 46% after 1 and 2 years of open-label follow-up. Seven per cent of subjects had no seizures in the 3 months preceding their most recent visit. There were no significant differences in mild or serious adverse events in the blinded phase of the trial. Nine subjects had an intracranial haemorrhage (6/9 postoperative, 7/9 serious), but none of them had permanent neurologic sequelae. Implant or incision site soft tissue infections occurred in 5.2% of patients (no brain infections). Most commonly reported adverse events were related to the cranial implantation of the pulse generator and include implant site pain (15.7% in year 1), headache (10.5%) and dysesthesia (6.3%).

3. Conclusion and Future Perspectives

After pioneering work of Cooper and later Velasco and colleagues, many trials evaluating invasive brain stimulation have followed and different structures have been targeted often showing promising results. However, notwithstanding that at least some RCTs have demonstrated significant improvements with cerebellar, ATN, hippocampal and responsive ictal onset zone stimulation, results in those trials were in general quite moderate compared to the often very favourable outcomes reported in open-label trials. Besides the placebo effect, some other issues may have overestimated efficacy of stimulation *an sich* in open-label trials. These include an implantation effect[42,47,49,99,105], microlesions resulting from electrode insertion[61,106,107] and medication-induced and spontaneous improvements[108,109]. However, as a trend for increasing efficacy over time[46,49,62,93,94,105], results consistent with a possible outlasting effect after stimulation[44,47,60,63,75] and further improvement due to optimization of stimulation parameter settings[60,61,86] have been reported, efficacy may at the same time have been underestimated in RCTs due to their short duration, cross-over design and fixed stimulation protocol.

Apart from two large RCTs providing good evidence for ATN[49] and responsive ictal onset zone stimulation[105], a drawback of most trials is the small number of patients they included. More and large RCTs are certainly needed to fully appreciate efficacy and safety of intracranial stimulation and to define optimal stimulation targets and parameters. Furthermore, substantiating still poor but increasing knowledge about the mechanism of action of invasive brain stimulation in epilepsy may rationalize study designs in future.

Acknowledgments

Dr. M. Sprengers is supported by an FWO-aspirant grant. Prof. Dr. K. Vonck is supported by a BOF-ZAP grant from Ghent University Hospital. Prof. Dr. P. Boon is supported by grants from FWO-Flanders, grants from BOF and by the Clinical Epilepsy Grant from Ghent University Hospital.

References

1. Brown-Séquard CE. Research on epilepsy: its artificial production in animals, and its etiology, nature and treatment in man. Experimental and clinical researches applied to physiology and pathology. . Boston Medical and Surgical Journal 1856-1857;55-57.
2. Jackson H. National hospital for the epileptic and paralysed: case of convulsive attacks arrested by stopping the aura. Lancet 1868;91:618-619.
3. Gowers WR. Chapter 8: treatment Epilepsy and other chronic convulsive diseases: their causes, symptoms and treatment, William Wood and Company: New York; 1885:235-236.
4. Osorio I, Frei MG, Sunderam S, et al. Automated seizure abatement in humans using electrical stimulation. Ann Neurol 2005;57:258-268.
5. Heath RG. Electrical Self-Stimulation of Brain in Man. Am J Psychiatry 1963;120:571-&.
6. Cooke PM, Snider RS. Some cerebellar influences on electrically-induced cerebral seizures. Epilepsia 1955;4:19-28.
7. Cooper IS, Amin I, Gilman S. The effect of chronic cerebellar stimulation upon epilepsy in man. Trans Am Neurol Assoc 1973;98:192-196.
8. Davis R, Emmonds SE. Cerebellar stimulation for seizure control: 17-year study. Stereotact Funct Neurosurg 1992;58:200-208.
9. Cooper IS, Upton AR. Therapeutic implications of modulation of metabolism and functional activity of cerebral cortex by chronic stimulation of cerebellum and thalamus. Biol Psychiatry 1985;20:811-813.
10. Velasco F, Velasco M, Ogarrio C, et al. Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia 1987;28:421-430.
11. Gilman S, Dauth G, Tennyson VM, et al. Clinical, morphological, biochemical, and physiological effects of cerebellar stimulation. In Hambrecht FT, Reswick JB (Eds) Functional Electrical Stimulation: Applications in Neural Prosthesis, Marcel Dekker: New York / Basel; 1977:191-226.
12. Levy LF, Auchterlonie WC. Chronic cerebellar stimulation in the treatment of epilepsy. Epilepsia 1979;20:235-245.
13. Van Buren JM, Wood JH, Oakley J, et al. Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. J Neurosurg 1978;48:407-416.
14. Wright GD, McLellan DL, Brice JG. A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. J Neurol Neurosurg Psychiatry 1984;47:769-774.

15. Fisher RS, Uematsu S, Krauss GL, et al. Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 1992;33:841-851.
16. Okun MS. Deep-brain stimulation for Parkinson's disease. N Engl J Med 2012;367:1529-1538.
17. Shah RS, Chang SY, Min HK, et al. Deep brain stimulation: technology at the cutting edge. J Clin Neurol 2010;6:167-182.
18. Fountas KN, Kapsalaki E, Hadjigeorgiou G. Cerebellar stimulation in the management of medically intractable epilepsy: a systematic and critical review. Neurosurg Focus 2010;29:E8.
19. Halpern CH, Samadani U, Litt B, et al. Deep brain stimulation for epilepsy. Neurotherapeutics 2008;5:59-67.
20. Krauss GL, Koubeissi MZ. Cerebellar and thalamic stimulation treatment for epilepsy. Acta Neurochir Suppl 2007;97:347-356.
21. Mutani R, Bergamini L, Doriguzzi T. Experimental evidence for the existence of an extrarhinencephalic control of the activity of the cobalt rhinencephalic epileptogenic focus. Part 2. Effects of the paleocerebellar stimulation. Epilepsia 1969;10:351-362.
22. Dow RS, Fernandez-Guardiola A, Manni E. The influence of the cerebellum on experimental epilepsy. Electroencephalogr Clin Neurophysiol 1962;14:383-398.
23. Fridley J, Thomas JG, Navarro JC, et al. Brain stimulation for the treatment of epilepsy. Neurosurg Focus 2012;32:E13.
24. McIntyre CC, Savasta M, Kerkerian-Le Goff L, et al. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. Clin Neurophysiol 2004;115:1239-1248.
25. Laxer KD, Robertson LT, Julien RM, et al. Phenytoin: relationship between cerebellar function and epileptic discharges. Adv Neurol 1980;27:415-427.
26. Mutani R, Fariello R. Effect of low frequency caudate stimulation on the EEG of epileptic neocortex. Brain Res 1969;14:749-753.
27. Davis R. Cerebellar stimulation for cerebral palsy spasticity, function, and seizures. Arch Med Res 2000;31:290-299.
28. Velasco F, Carrillo-Ruiz JD, Brito F, et al. Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. Epilepsia 2005;46:1071-1081.
29. Velasco F, Carrillo-Ruiz JD, Brito F, et al. Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. Epilepsia 2005;46:1071-1081.
30. Davis R. Cerebellar stimulation for cerebral palsy spasticity, function, and seizures. Arch Med Res 2000;31:290-299.
31. Papez JW. A proposed mechanism of emotion. Arch Neur and Pscyh 1937;38:725-743.
32. Hamani C, Andrade D, Hodaie M, et al. Deep brain stimulation for the treatment of epilepsy. Int J Neural Syst 2009;19:213-226.

33. Mirski MA, Ferrendelli JA. Selective metabolic activation of the mammillary bodies and their connections during ethosuximide-induced suppression of pentylenetetrazol seizures. Epilepsia 1986;27:194-203.
34. Mirski MA, Ferrendelli JA. Interruption of the mammillothalamic tract prevents seizures in guinea pigs. Science 1984;226:72-74.
35. Kusske JA, Ojemann GA, Ward AA, Jr. Effects of lesions in ventral anterior thalamus on experimental focal epilepsy. Exp Neurol 1972;34:279-290.
36. Takebayashi S, Hashizume K, Tanaka T, et al. The effect of electrical stimulation and lesioning of the anterior thalamic nucleus on kainic acid-induced focal cortical seizure status in rats. Epilepsia 2007;48:348-358.
37. Hamani C, Ewerton FI, Bonilha SM, et al. Bilateral anterior thalamic nucleus lesions and high-frequency stimulation are protective against pilocarpine-induced seizures and status epilepticus. Neurosurgery 2004;54:191-195; discussion 195-197.
38. Mullan S, Vailati G, Karasick J, et al. Thalamic lesions for the control of epilepsy. A study of nine cases. Arch Neurol 1967;16:277-285.
39. Mirski MA, Rossell LA, Terry JB, et al. Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res 1997;28:89-100.
40. Hamani C, Hodaie M, Chiang J, et al. Deep brain stimulation of the anterior nucleus of the thalamus: effects of electrical stimulation on pilocarpine-induced seizures and status epilepticus. Epilepsy Res 2008;78:117-123.
41. Lado FA. Chronic bilateral stimulation of the anterior thalamus of kainate-treated rats increases seizure frequency. Epilepsia 2006;47:27-32.
42. Hodaie M, Wennberg RA, Dostrovsky JO, et al. Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 2002;43:603-608.
43. Kerrigan JF, Litt B, Fisher RS, et al. Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia 2004;45:346-354.
44. Andrade DM, Zumsteg D, Hamani C, et al. Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy. Neurology 2006;66:1571-1573.
45. Lee KJ, Jang KS, Shon YM. Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy. Operative Neuromodulation: Vol 2: Neural Networks Surgery 2006;99:87-91.
46. Osorio I, Overman J, Giftakis J, et al. High frequency thalamic stimulation for inoperable mesial temporal epilepsy. Epilepsia 2007;48:1561-1571.
47. Lim SN, Lee ST, Tsai YT, et al. Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. Epilepsia 2007;48:342-347.
48. Lee KJ, Shon YM, Cho CB. Long-term outcome of anterior thalamic nucleus stimulation for intractable epilepsy. Stereotact Funct Neurosurg 2012;90:379-385.
49. Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51:899-908.

50. Swanson TH. The pathophysiology of human mesial temporal lobe epilepsy. J Clin Neurophysiol 1995;12:2-22.
51. King D, Spencer S. Invasive electroencephalography in mesial temporal lobe epilepsy. J Clin Neurophysiol 1995;12:32-45.
52. Spencer SS, Guimaraes P, Katz A, et al. Morphological patterns of seizures recorded intracranially. Epilepsia 1992;33:537-545.
53. Wilson CL, Engel J, Jr. Electrical stimulation of the human epileptic limbic cortex. Adv Neurol 1993;63:103-113.
54. Spencer D, Burchiel K. Selective amygdalohippocampectomy. Epilepsy Res Treat 2012;2012:382095.
55. Wendling AS, Hirsch E, Wisniewski I, et al. Selective amygdalohippocampectomy versus standard temporal lobectomy in patients with mesial temporal lobe epilepsy and unilateral hippocampal sclerosis. Epilepsy Res 2012.
56. Tanriverdi T, Olivier A, Poulin N, et al. Long-term seizure outcome after mesial temporal lobe epilepsy surgery: corticalamygdalohippocampectomy versus selective amygdalohippocampectomy. J Neurosurg 2008;108:517-524.
57. Velasco AL, Velasco M, Velasco F, et al. Subacute and chronic electrical stimulation of the hippocampus on intractable temporal lobe seizures: preliminary report. Arch Med Res 2000;31:316-328.
58. Vonck K, Boon P, Achten E, et al. Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. Ann Neurol 2002;52:556-565.
59. Boon P, Vonck K, De Herdt V, et al. Deep brain stimulation in patients with refractory temporal lobe epilepsy. Epilepsia 2007;48:1551-1560.
60. Vonck K, Sprengers M, Carrette E, et al. A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. Int J Neural Syst 2013;23:1250034.
61. Boex C, Seeck M, Vulliemoz S, et al. Chronic deep brain stimulation in mesial temporal lobe epilepsy. Seizure 2011;20:485-490.
62. Velasco AL, Velasco F, Velasco M, et al. Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. Epilepsia 2007;48:1895-1903.
63. McLachlan RS, Pigott S, Tellez-Zenteno JF, et al. Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: impact on seizures and memory. Epilepsia 2010;51:304-307.
64. Tellez-Zenteno JF, McLachlan RS, Parrent A, et al. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. Neurology 2006;66:1490-1494.
65. Wiebe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 2001;345:311-318.
66. Engel J, Wiebe S, French J, et al. Practice parameter: Temporal lobe and localized neocortical resections for epilepsy - Report of the quality standards subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. Neurology 2003;60:538-547.

67. de Tisi J, Bell GS, Peacock JL, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet 2011;378:1388-1395.
68. Miatton M, Van Roost D, Thiery E, et al. The cognitive effects of amygdalohippocampal deep brain stimulation in patients with temporal lobe epilepsy. Epilepsy Behav 2011.
69. Penfield W. The cerebral cortex in man: I. the cerebral cortex and consciousness. Arch Neurol Psychiatr 1938;40:417-442.
70. Velasco M, Velasco F, Velasco AL, et al. Acute and chronic electrical stimulation of the centromedian thalamic nucleus: modulation of reticulo-cortical systems and predictor factors for generalized seizure control. Arch Med Res 2000;31:304-315.
71. Moruzzi G, Magoun HW. Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol 1949;1:455-473.
72. Miller JW, Ferrendelli JA. The central medial nucleus: thalamic site of seizure regulation. Brain Res 1990;508:297-300.
73. Velasco F, Velasco M, Velasco AL, et al. Effect of chronic electrical stimulation of the centromedian thalamic nuclei on various intractable seizure patterns: I. Clinical seizures and paroxysmal EEG activity. Epilepsia 1993;34:1052-1064.
74. Velasco F, Velasco M, Velasco AL, et al. Electrical stimulation of the centromedian thalamic nucleus in control of seizures: long-term studies. Epilepsia 1995;36:63-71.
75. Velasco F, Velasco M, Jimenez F, et al. Predictors in the treatment of difficult-to-control seizures by electrical stimulation of the centromedian thalamic nucleus. Neurosurgery 2000;47:295-304; discussion 304-295.
76. Velasco AL, Velasco F, Jimenez F, et al. Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox-Gastaut syndrome. Epilepsia 2006;47:1203-1212.
77. Chkhenkeli SA, Sramka M, Lortkipanidze GS, et al. Electrophysiological effects and clinical results of direct brain stimulation for intractable epilepsy. Clin Neurol Neurosurg 2004;106:318-329.
78. Cukiert A, Burattini JA, Cukiert CM, et al. Centro-median stimulation yields additional seizure frequency and attention improvement in patients previously submitted to callosotomy. Seizure 2009;18:588-592.
79. Loddenkemper T, Pan A, Neme S, et al. Deep brain stimulation in epilepsy. J Clin Neurophysiol 2001;18:514-532.
80. Lado FA, Velisek L, Moshe SL. The effect of electrical stimulation of the subthalamic nucleus on seizures is frequency dependent. Epilepsia 2003;44:157-164.
81. Vercueil L, Benazzouz A, Deransart C, et al. High-frequency stimulation of the subthalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. Epilepsy Res 1998;31:39-46.

82. Usui N, Maesawa S, Kajita Y, et al. Suppression of secondary generalization of limbic seizures by stimulation of subthalamic nucleus in rats. J Neurosurg 2005;102:1122-1129.
83. Chabardes S, Kahane P, Minotti L, et al. Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. Epileptic Disord 2002;4 Suppl 3:S83-93.
84. Handforth A, DeSalles AA, Krahl SE. Deep brain stimulation of the subthalamic nucleus as adjunct treatment for refractory epilepsy. Epilepsia 2006;47:1239-1241.
85. Alaraj A, Comair Y, Mikati M, et al. Subthalamic nucleus deep brain stimulation: a novel method for the treatment of non-focal intractable epilepsy. Presented as a poster at Neuromodulation: defining the future. Cleveland, OH. June 8-10, 2001.
86. Wille C, Steinhoff BJ, Altenmuller DM, et al. Chronic high-frequency deep-brain stimulation in progressive myoclonic epilepsy in adulthood--report of five cases. Epilepsia 2011;52:489-496.
87. Sramka M, Fritz G, Galanda M, et al. Some observations in treatment stimulation of epilepsy. Acta Neurochir (Wien) 1976:257-262.
88. Sramka M, Fritz G, Gajdosova D, et al. Central stimulation treatment of epilepsy. Acta Neurochir Suppl (Wien) 1980;30:183-187.
89. Chkhenkeli SA, Chkhenkeli IS. Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain in patients with intractable epilepsy. Stereotact Funct Neurosurg 1997;69:221-224.
90. Klee MR, Lux HD. Intracelluläre Untersuchungen über den Einfluß hemmender Potentiale im motorischen Cortex. II. Die Wirkungen electrischer Reizung des Nucleus caudatus. Arch Psychiatr Nervenkr 1962;203:667-689.
91. Elisevich K, Jenrow K, Schuh L, et al. Long-term electrical stimulation-induced inhibition of partial epilepsy - Case report. J Neurosurg 2006;105:894-897.
92. Velasco AL, Velasco F, Velasco M, et al. Neuromodulation of epileptic foci in patients with non-lesional refractory motor epilepsy. Int J Neural Syst 2009;19:139-147.
93. Franzini A, Messina G, Marras C, et al. Deep brain stimulation of two unconventional targets in refractory non-resectable epilepsy. Stereotact Funct Neurosurg 2008;86:373-381.
94. Khan S, Wright I, Javed S, et al. High frequency stimulation of the mamillothalamic tract for the treatment of resistant seizures associated with hypothalamic hamartoma. Epilepsia 2009;50:1608-1611.
95. Savard G, Bhanji NH, Dubeau F, et al. Psychiatric aspects of patients with hypothalamic hamartoma and epilepsy. Epileptic Disord 2003;5:229-234.
96. Marras CE, Rizzi M, Villani F, et al. Deep brain stimulation for the treatment of drug-refractory epilepsy in a patient with a hypothalamic hamartoma. Case report. Neurosurg Focus 2011;30:E4.
97. Kahane P, Ryvlin P, Hoffmann D, et al. From hypothalamic hamartoma to cortex: what can be learnt from depth recordings and stimulation? Epileptic Disord 2003;5:205-217.

98. Feinstein B, Gleason CA, Libet B. Stimulation of locus coeruleus in man. Preliminary trials for spasticity and epilepsy. Stereotact Funct Neurosurg 1989;52:26-41.
99. Marino Junior R, Gronich G. Corpus callosum stimulation and stereotactic callosotomy in the management of refractory generalized epilepsy. Preliminary communication. Arq Neuropsiquiatr 1989;47:320-325.
100. Cukiert A, Baumel SW, Andreolli M, et al. Effects of Corpus-Callosum Stimulation on the Morphology and Frequency of Epileptic Bursts in the Feline Topical Penicillin Generalized-Model. Stereotact Funct Neurosurg 1989;52:18-25.
101. Osorio I, Frei MG, Manly BF, et al. An introduction to contingent (closed-loop) brain electrical stimulation for seizure blockage, to ultra-short-term clinical trials, and to multidimensional statistical analysis of therapeutic efficacy. J Clin Neurophysiol 2001;18:533-544.
102. Kossoff EH, Ritzl EK, Politsky JM, et al. Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. Epilepsia 2004;45:1560-1567.
103. Anderson WS, Kossoff EH, Bergey GK, et al. Implantation of a responsive neurostimulator device in patients with refractory epilepsy. Neurosurg Focus 2008;25:E12.
104. Fountas KN, Smith JR, Murro AM, et al. Implantation of a closed-loop stimulation in the management of medically refractory focal epilepsy: a technical note. Stereotact Funct Neurosurg 2005;83:153-158.
105. Morrell MJ, Grp RSES. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 2011;77:1295-1304.
106. Schulze-Bonhage A, Dennig D, Wagner K, et al. Seizure control resulting from intrahippocampal depth electrode insertion. J Neurol Neurosurg Psychiatry 2010;81:352-353.
107. Katariwala NM, Bakay RA, Pennell PB, et al. Remission of intractable partial epilepsy following implantation of intracranial electrodes. Neurology 2001;57:1505-1507.
108. Neligan A, Bell GS, Elsayed M, et al. Treatment changes in a cohort of people with apparently drug-resistant epilepsy: an extended follow-up. J Neurol Neurosurg Psychiatry 2012;83:810-813.
109. Selwa LM, Schmidt SL, Malow BA, et al. Long-term outcome of nonsurgical candidates with medically refractory localization-related epilepsy. Epilepsia 2003;44:1568-1572.

Update 2013-2020

Since the publication of the review in 2013, several more recent articles on deep brain and cortical stimulation in epilepsy have been published. These articles will be summarized in this section.

1. Anterior thalamic nucleus (ATN) DBS

The most important publication with regard to anterior thalamic DBS in epilepsy since 2013 is the report of the long-term outcome of the SANTE trial patient cohort [16]. The median change in seizure frequency further increased from -41% at 1 year (n=105) to -69% at 5 years (n=83), with 43 and 68% corresponding 50% responder rates. Of notice are, however, 22 discontinuations by year 5 of the long-term follow-up phase (mean seizure reduction 'last observation carried forward' -44 and -65% respectively, 'worst case' -40 and -50%), and 61/110 implanted patients who received at least one additional anti-epileptic drug. At the 5-year assessment 11 out of 83 patients (13.2%) were seizure-free for at least six months. The median reduction was 44% at year 1 and 76% at year 5 for temporal lobe epilepsy, 53% at year 1 and 59% at year 5 for frontal lobe epilepsy and 34% at year 1 and 68% at year 5 for the remainder of seizure onset locations. Previous resective surgery or VNS was not associated with a worse response to ATN DBS. Futhermore, there were significant reductions in seizure severity, about half of patients showed a clinically significant improvement in quality of life and there was a gradual improvement from baseline in several neuropsychological composites (attention, executive function, depression, tension/anxiety, total mood disturbance, subjective cognitive function).

The most frequent device-related adverse events included implant site pain (20.9% in 5 years), paresthesias at the stimulator site (22.7%), implant site infection (12.7%), lead(s) not within target (8.2%), memory impairment (7.3%), extension fracture (5.5%) and neurostimulator migration (5.5%). Depression was reported in 32.7% at some time within the first 5 years, but only in 3 out of 41 this was considered as device-related. Sixty-six percent of these patients had a history of depression. Memory impairment was reported by 25.5% at some time during the first 5 years, 50% had a history of memory impairment and one third of these events were associated with a change from baseline in neuropsychological testing. SUDEP rate was 2.9 per 1000 patient-years, which was similar or lower than reported in literature [16].

A second but smaller (n=18) double-blind parallel-group RCT on ATN DBS in (multi)focal epilepsy was published in 2018 [17]. After six months of stimulation, the stimulation ON group (n=8) showed a statistically significant 23% reduction in seizure frequency, compared with a statistically non-significant 11% increase in the stimulation OFF group (n=10). The treatment effect (-34%) did not reach statistical significance but the study was probably underpowered. Two patients in the stimulation ON group showed a ≥50% seizure reduction (25%) compared with 1 in the stimulation OFF group (10%). None of patients were seizure-free and there was no change in seizure severity. No adverse event was reported by more than 1 patient, making it difficult to draw conclusions on this issue.

Seven smaller uncontrolled nonblinded trials have been published since 2013 and reported similar long-term outcomes as those that were found in previous studies. All included patients suffered from (multi)focal epilepsy. The 50% responder rates were 78% (7/9 patients), 40% (2/5), 67% (10/15), 69% (11/16), 55 (6/11) and 76% (22/29 patients), besides the successful use in one child (60% seizure

reduction) [18-24]. Two of these smaller open-label studies evaluated the neuropsychological outcome after long-term ATN DBS and observed improvements in word fluency and verbal memory, although at the same time 24% of patients in one of these trials reported subjective memory impairment at some time during follow-up [20, 23]. Finally, Lehtimaki and colleagues demonstrated that the contacts with an actual location at the anterior (and superior) aspect of ATN, as demonstrated by an ATN normalized and MRI-based coordinate system, were associated with a more favourable outcome [19].

2. Responsive stimulation of the ictal onset zone

As for the SANTE trial, the patients included in the Neuropace study were further followed in an open-label extension phase after the end of the blinded evaluation period. The median reduction in seizure frequency increased from -41.5% at the end of the blinded evaluation period to -53% after 2 years of responsive ictal onset zone stimulation, with a corresponding increase in the 50%-responder rate from 29% at 3 months to 55% at 2 years [25]. In 2015, Bergey and colleagues published the long-term outcome of 230 patients previously included in an initial open-label safety study or the Neuropace study. After 3 to 6 years of stimulation, median seizure reductions typically ranged between 60 and 65%, with a 55 to 60% 50%-responder rate [26]. Some improvement was observed in 84% of patients. Responses were similar in patients with seizure onset within or outside the mesial temporal lobe. Although 12.9% of patients had at least 1 seizure-free period of 1 year or longer, no participants were seizure-free over the entire follow-up. Sixty-three percent of the responders and 70% of the non-responders had a new antiepileptic drug added, compared to 9 and 8% with a reduction in the number or dosage of antiseizure medications. Overall, statistically significant increases in some measures of quality of life were reported at 1 year postimplant and maintained through year 5 [26].

The most important serious adverse events were related to the implanted device rather than to stimulation. The most frequent serious adverse event was implant site infection occurring in 9.4% of patients, either following the initial device implant, neurostimulator replacement or a seizure-related head trauma. About half of these had their device explanted. There were no infections of the brain or the subdural space. Other serious adverse events included medical device removal (5.5%, reasons: pursue other treatments, insufficient efficacy or participant elected), intracranial hemorrhage (4.7%, in the first days after the initial implant or associated with seizure-related head trauma), device lead damage (3.5%) and revision (3.1%) [26]. There was no deterioration in any of the neuropsychological measures at 1 and 2 years postimplant. Improvements in some measures of cognitive flexibility, visual spatial abilities and verbal learning were reported in patients with mesial temporal lobe epilepsy, whereas subjects with their seizure onset zone outside the mesial temporal lobe showed significant group improvements in some measures of language, naming, cognitive flexibility and general verbal ability. There was no negative effect on mood, and improvements were reported in mesial temporal lobe epilepsy patients [25, 27].

3. Hippocampal DBS

Since 2013 the two largest trials on hippocampal DBS have been published by Cukiert and colleagues. The results of an uncontrolled open-label trial with 9 patients suffering from drug-resistant temporal lobe epilepsy were published in 2014. After a mean follow-up of 30.1 months, a mean -58% seizure

reduction was observed, with 78% of patients showing a >50% reduction in seizure frequency and one patient (11%) achieving seizure freedom. Importantly, the absence of a beneficial effect on the number of interictal epileptiform discharges during the initial evalution period did not preclude long-term benefit [28]. The same research group conducted a parallel-group randomized double-blind controlled trial with 16 drug-resistant temporal lobe epilepsy patients. The blinded evaluation period lasted 6 months. In the active treatment group, a >50% reduction in focal impaired awareness and focal aware seizures was observed in 7/8 and 4/7 patients respectively, compared to 3/8 and 0/7 patients with sham stimulation. Four and two patients in the stimulation group were free of focal impaired awareness and focal aware seizures during the last two months of the blinded evaluation period, relative to none of the patients in the control group [29]. The presence of hippocampal sclerosis was not associated with a worse response to hippocampal DBS in both of these studies.

Two small uncontrolled nonblinded trials (n= 2 and 3) confirmed the promising results of previous trials, with mean reductions in seizure frequency of 78 and 93%, with all patients experiencing a >50% reduction in seizure frequency although none of the patients were completely seizure-free [30, 31]. Lim and colleagues reported for the first time the long-term outcome of low-frequency (5 Hz) DBS in 2 patients with hippocampal sclerosis. A 63% mean seizure reduction was shown in these patients, compared to a 33% decrease in 3 patients with MRI negative temporal lobe epilepsy treated with high-frequency (145 Hz) DBS. Overall, a 45% seizure reduction was reported and 3/5 patients were 50%-responders [32]. Adverse events or memory decline did not occur in any of these trials [30-32]. Finally, Bondallaz and colleagues investigated the relationship between the location of the active electrode contact and the effect of hippocampal DBS in eight drug-resistant medial temporal lobe epilepsy patients whose outcome had previously been reported by Boëx and colleagues [33, 34]. They did not observe a correlation between the distance to the ictal onset zone and the treatment effect. However, in the six 50%-responders the active contact was located <3 mm from the subiculum, compared to >3 mm in the two non-responding patients.

4. Centromedian thalamic nucleus (CMT) DBS

Valentin and colleagues reported their experience with centromedian thalamic DBS in a single-blind trial. At the end of the blinded phase of the trial, all six patients with generalized epilepsy (four of them with idiopathic generalized epilepsy) showed a >50% response (mean seizure reduction -77%) although two of these were seizure-free after electrode implantation without the need to activate the stimulator. This >50% seizure reduction was maintained in the ensuing open-label phase in 5 out of 6 patients (mean seizure reduction -81%). In contrast, only 1 and 2 out of 5 patients with frontal epilepsy showed a favourable response during the blinded and open-label phase, respectively (mean seizure reductions of 18 and 10%) [35].

Considerable seizure reductions were also observed by Son and colleagues in 10 patients with multilobar epilepsy and 4 patiens with Lennox-Gastaut syndrome. They reported a mean seizure reduction of 68% and a responder rate of 79%, with one patient (7%) being completely seizure-free. A correlation between the exact electrode location and the overall outcome could not be demonstrated [36]. In another study investigating DBS in a pediatric population, Valentin and colleagues found a beneficial effect of centromedian thalamic DBS in one of two children with generalized epilepsy (-60%) whereas the other did not respond to the treatment [22]. Sa and colleagues reported a >50% seizure

reduction in total seizure frequency and a suppression of generalized seizures in two pediactric patients with febrile infection-related epilepsy syndrome [37]. A temporary interruption of DBS was associated with a re-emergence of generalized seizures in both patients.

5. Nucleus accumbens DBS

A novel DBS target evaluated in an uncontrolled open-label and subsequently a double-blind randomized controlled trial is the nucleus accumbens. This structure plays an important role in both functional and anatomical connectivity between frontal and temporal lobes and has been shown to be involved in seizure propagation in rodents [38-40]. Anticonvulsant effects of dopamine agonist injections in the nucleus accumbens have been demonstrated in rodent models of both focal and generalized epilepsy [41, 42]. Furthermore, nucleus accumbens DBS has been suggested as a promising therapy for treatment-resistant depression, which could also be beneficial in drug-resistant epilepsy patients who are at high risk for comorbid depression [43-45].

An open-label pilot trial evaluated the safety and feasibility of nucleus accumbens DBS in 5 (multi)focal epilepsy patients [40]. Main findings were an unchanged psychiatric and neuropsychological assessment after 6 months of DBS, with a trend for increased quality of life. Furthermore, a median 37.5% reduction in disabling (focal impaired awareness and bilateral tonic-clonic seizures) seizure frequency was observed and there was a significant reduction in seizure severity. Two out of 5 patients showed a ≥50% reduction in seizure frequency. This pilot trial was followed by a cross-over RCT including 4 drug-resistant focal epilepsy patients [46]. Three months of nucleus accumbens stimulation resulted in a ≥50% reduction in seizure frequency in 3 out of 4 patients, whereas there were no 50%-responders during sham stimulation. Two patients reported worsening of seizure severity and 2 patients reported a slight improvement during active stimulation. Except for one patient feeling sad for two weeks during the active stimulation period after a close relative had died, there were no adverse events exclusively linked to the active stimulation period. One patient had an infection of the pulse generator and electrode leads requiring antibiotics and temporary removal of the stimulation system. Qualtiy of life, patient-reported outcome and neuropsychological testing remained unchanged. Complentary ANT DBS had no additional beneficial effect.

6. Open-loop cortical stimulation

Child and colleagues showed significant reductions in clinical and electroencephalographic seizure activity in three children (7-16 years old) by acute subtreshold stimulation of the seizure focus residing within eloquent cortex regions [47]. Chronic stimulation in 2 of these patients resulted into long-term seizure freedom (2 years) in one patient and a >99% reduction in seizure frequency (16 months) in the other patient. Stimulation parameters (high- versus low-frequency stimulation) needed to be individualized for optimal efficacy. There were no long-term side effects of stimulation.

Valentin and colleagues reported on three patients successfully treated with cortical stimulation [48, 49]. In 2015, they presented the results of chronic cortical stimulation of 2 patients (20-21 years old) with drug-resistant epilepsia partialis continua originating from or near the motor cortex precluding resective surgery. A >90% reduction in seizures and abolition of epilepsia partialis continua was shown in both patients after a follow-up of 22 months, with recurrence of epilepsia partialis continua upon

battery depletion [48]. In 2016, they reported on a 7-year old child with focal epilepsy where the epileptogenic focus was estimated to be in the lateral left temporal lobe. No clinical seizures were seen after starting subacute cortical stimulation of the epileptogenic region 4-6 hours per day for four days, and the child remained seizure-free for more than 20 months after electrode removal [49].

Kerezoudis and colleagues evaluated the safety, feasibility and efficacy of chronic subthreshold cortical stimulation in ten drug-resistant focal epilepsy patients for whom resective surgery was not possible as their seizure foci were located within eloquent cortex [50]. Intracranial pathologies included cortical dysplasia, encephalmalacia, cortical tubers, Rasmussen encephalitis and a linear migration anomaly. The seizure frequency and seizure severity improved in all patients. After a follow-up of 4 to 20 months, 2 patients were free of disabling seizures, 5 had only rare disabling seizures and 3 others showed a worthwile improvement. Complications did not occur in any of the patients.

Chang and colleagues demonstrated significant reductions in seizure frequency in 6 patients treated with cortical stimulation [51]. They suffered from drug-resistant epilepsy due to polymicrogyria, traumatic brain injury, periventricular heterotopia, encephalitis and familial lateral temporal lobe epilepsy. The mean reductions in seizure frequency were 61% at year 1, 68% at year 2 and 80% at the end of follow-up (36-156 months). Focal status epilepticus or epilepsia partialis continua was interrupted immediately in three patients, followed by a long-term >90% reduction of the seizure frequency. One patient required surgical hardware removal due to recurrent inflammation of the scalp but reported a sustained >90% improvement after explantation. There were no stimulation-related side effects.

7. Subthalamic nucleus (STN) DBS

Capecci and colleagues reported their experience with STN DBS in two patients (30-35 years old). One patient displayed a 65% decrease in focal motor seizures and a 85% decrease in generalized fits and falls [52]. In the other patient, however, bilateral tonic-clonic seizures subsided at the cost of a stimulation-associated atypical absence rate increase, eventually leading to DBS discontinuation after 18 months of follow-up. Side effects encountered in both patients included apathy, aboulia and mild balance impairment. In another case report, STN DBS in a 32-year old patient with progressive myoclonic epilepsy aggravated myoclonia, dyskinesia and gait problems [53]. DBS in the border zone between the STN and the reticular part of the substantia nigra, an approach that had previously been shown to decrease myoclonia and seizures in 5 patients with progressive myoclonic epilepsy, led to a slight improvement in myoclonia but also caused mild extrapyramidal symptoms [53, 54]. The most benefical effects were observed with low-amplitude DBS in the reticular part of the substantia nigra alone, resulting into a suppression of myoclonia and a significant amelioration of the gait [53].

Mechanism of action

DBS was initially developed as a less invasive and reversible alternative for ablative procedures to treat medically refractory movement disorders. Initial hypotheses about its mechanism of action were based on the observed similarity between the effects of DBS and the effects of lesions in the same region, such as pallidotomy for the treatment of Parkinson’s disease, thalamotomy for essential tremor and

capsulotomy for obsessive-compulsive disorder [14, 15]. DBS was thus thought to act as a reversible lesion. Over the years this view has been found too simplistic. For example, DBS of the external part of the globus pallidus (GPe) ameloriates motor symtoms in Parkinson's disease whereas GPe lesions have been found to worsen bradykinesia in parkinsonian monkeys [55]. Although the mechanism of action of DBS remains incompletely understood, various hypotheses on its mode of action have now been proposed based on extensive research. Most of this research has been performed in the basal ganglia network of which a schematic illustration is shown in figure 15. The purpose of this chapter is to give an overview of the most important hypotheses that I have encountered in the literature during my PhD.

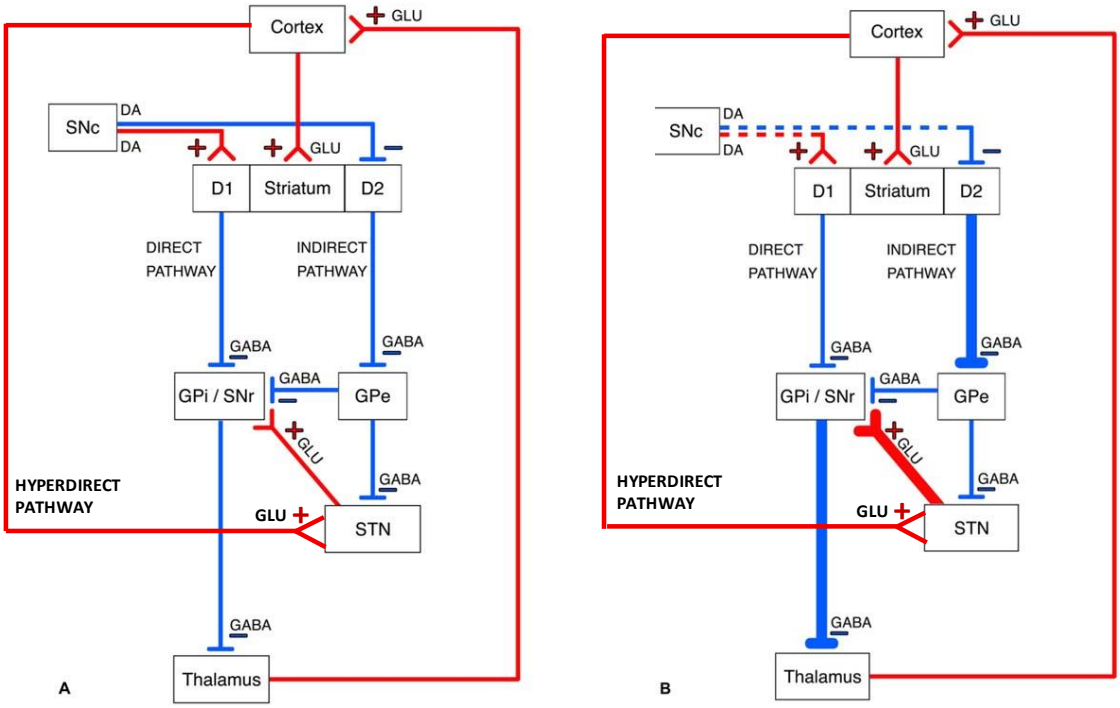


Figure 15. The basal ganglia network in healthy subjects (panel **A**) and in patients with Parkinson's disease (panel **B**). Both the direct and indirect pathway begin with glutamatergic (GLU) excitatory input from the cortex to the striatum (panel **A**). 1) In the *direct pathway*, GABAergic inhibitory neurons project directly to the internal globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). The inhibitory D1 receptor expressing striatal neurons of the direct pathway are *activated by the dopaminergic neurons of the substantia nigra pars compacta (SNc)*. 2) In the *indirect pathway*, the connection from to striatum to the GPi/SNr complex is indirect: D2 dopamine receptor expressing GABAergic inhibitory neurons from the striatum inhibit the external globus pallidus (GPe), which in its turn sends inhibitory projections to the subthalamic nucleus (STN). The STN eventually connects with the GPi/SNr complex via excitatory glutamatergic axons. The indirect pathway has *inhibitory input from the SNc* projecting to the D2 dopamine receptor expressing striatal neurons. The STN also receives direct excitatory input from the cortex via the *hyperdirect pathway*. The GPi and SNr are the output structures of the basal ganglia network and inhibit the excitatory connections from the thalamus to the cortex. Based on their effect on these thalamocortical connections, the direct and indirect pathway are considered to pro- and antikinetic, respectively. In Parkinson's disease (panel **B**), the loss of dopaminergic SNc neurons causes excessive activity in the antikinetic indirect pathway whereas it reduces the activity in the prokinetic direct pathway. Adapted from [56].

Inhibition versus excitation

Inspired by the original view of DBS acting as a 'reversible lesion' many of the initial studies have evaluated the effects of high-frequency stimulation on neuronal cell firing frequency in the basal ganglia network both locally in the stimulated structure and in downstream structures. Most of these electrophysiological studies found a decreased neuronal firing rate in the stimulated target. Reductions in firing rate have been shown in the STN in *in vitro* preparations [57-59], in the STN in both healthy and parkinsonian (e.g. in the 6-hydroxydopamine model) rats [60, 61], in the GPi in parkinsonian monkeys (e.g. in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model) [62, 63] and in the STN and GPi in patients with Parkinson's disease [64-67] and dystonia [68].

The observed decrease in neuronal firing in the stimulated target appeared to be in line with the 'reversible lesion' hypothesis. However, most of the trials evaluating the effect on firing rates in downstream structures within the basal ganglia network were consistent with an activation of the efferent axons. STN DBS has been found to increase firing rate in the GPi, substantia nigra pars reticulata (SNr) and GPe in rats, monkeys [69-71] and patients with Parkinson's disease [72]. Similarly, GPi DBS was associated with decreased neuronal activity in the thalamus in monkeys [73] and in patients with dystonia [74, 75]. These increases with STN DBS and decreases with GPi DBS are compatible with the activation of the efferent axons, as the efferent axons are mainly glutamatergic in the STN and GABAergic in the GPi. These electrophysiological studies were further supported by several metabolic studies. Windels showed increased levels of glutamate in the GPe analogue and SNr in rats after STN DBS [76]. In another study evaluating the effects of STN DBS in rats, increased levels of c-fos expression (a marker of neuronal activity) were found in various STN output structures [77]. Although no changes in glutamate levels were found in the GPi after perioperative STN DBS in patients with Parkinson's disease, the authors did report increased levels of cyclic guanosine monophosphate (a second messenger of glutamate).

Although the activation of efferent axons and inhibition of the targeted structure may appear paradoxical, modeling studies have shown that activation of efferent axons and inhibition of neuronal somata and dentrites can occur simultaneously [78, 79]. This phenomenon has been called 'axon-soma decoupling' and is an important concept in our current understandings of the mechanism of action of DBS.

It should be noted that not all studies are in line with local inhibition and efferent axon activation. Increased neuronal activity and increased levels of glutamate in the STN have been shown with STN DBS, as well as increased GPi activity with GPi DBS [58, 80, 81]. Various studies have also reported decreases in neuronal firing rate in the SNr with STN DBS [60, 61, 82, 83], seemingly contradictory to the activation of efferent axons. In addition, various studies found no or mixed changes in firing frequency [70, 83-87]. Some of the authors have tried to explain these discrepant results by the activation of fibers of passage or polysynaptic pathways [70, 83]. These studies highlight the importance of the experimental setup where different experimental conditions can be associated with seemingly contradictory results.

Synaptic inhibition

Many authors have suggested that the DBS-induced reductions in neuronal activity may be caused by GABAergic synaptic inhibition. As outlined above, the decrease in firing frequency of thalamic neurons during and 50 to 120 ms after GPi DBS is compatible with the activation of the GABAergic efferent axons of the GPi neurons [73]. Similarly, the observed reductions in firing rate in the STN/GPi during or after STN/GPi DBS have been attributed to the activation of GABAergic presynaptic terminals of afferent axons which are present in abundance in the STN and GPi. This mechanism was amongst others suggested because the observed reductions in firing frequency displayed a compatible time course (10 ms to < 1 second) and because it is plausible from a theoretical point of view. It should be noted, however, that most studies suggesting this mode of action did not perform futher experiments to confirm this hypothesis [62-65, 67, 88, 89]. Only Lee and colleagues reported that the decrease in firing frequency observed in 5/16 neurons in the STN during and after DBS disappeared in the presence of GABA antagonists [90].

Depolarization block

Some *in vitro* experiments observed complete neuronal silencing during or after STN DBS and suggested this was caused by a depolarization block [57, 59]. Beurrier and colleagues found a transient block of intrinsic voltage-gated currents including the persistent Na^+ current, T- and L-type Ca^{2+} currents, whereas the hyperpolarization-activated cation current (I_h) was little affected. In addition, the neuronal silencing was still observed in the presence of blockers of the ionotropic GABA and glutamate receptors and synaptic transmission [57]. Persistent postsynaptic depolarization and complete inhibition of spiking activity was found by Magarinos and Ascone with stimulation frequencies >100 Hz and durations >25 seconds. The persistence of a summated EPSP suggested a postsynaptic mechanism [59]. A similar sustained postsynaptic depolarization was reported by Bikson and colleagues, where it was associated with a complete suppression of epileptiform activity [91]. In contrast, the intrinsic voltage-gated currents were largely unaffected in another *in vitro* study by Anderson and colleagues [92].

Vesicle depletion

Paired-pulse depression is a phenomenon where two stimuli delivered at a short time interval lead to a transient decrease in synaptic strength [93, 94]. As outlined in Chapter 2, this is more likely to occur at synapses characterized by a high probability of stimulus-induced vesicle release and with higher frequency of activation. Various *in vitro* studies have reported reductions in excitatory post-synaptic currents and potentials during and after DBS [92, 95-98]. These reductions were input-specific in the studies of Iremonger and of Anderson [92, 95], could not entirely be explained by changes in the presynaptic fiber volley / axonal block in the studies of Iremonger and of Urbano [95, 98], and were not prevented by blocking postsynaptic desensitization in the studies of Anderson and of Iremonger [92, 95]. These *in vitro* studies therefore suggest that vesicle depletion and depression of synaptic transmission could be involved in the mechanism of action of DBS.

This hypothesis is also in line with the findings of Milosevic and colleagues in refractory tremor patients [99]. Following a transient driving response, they observed a strong suppression of thalamic neuronal fire rate during Vim stimulation. Interestingly, the degree of cell inhibition correlated with the degree of tremor reduction suggesting a causal relationship.

Axonal block

Kilgore [100] and Bhadra [101] showed that with appropriate stimulation parameters high-frequency stimulation of the sciatic nerve could prevent the contraction of the gastrocnemius muscle with a more proximal second stimulation electrode, thus demonstrating the presence of an axonal conduction block. Meeks and colleagues were one of the first to report the occurrence of axonal failure *in vitro* in the central nervous system during epileptiform activity or 10 Hz stimulation, although this only occurred with concomitant sustained depolarization [102]. Later studies showed that high-frequency stimulation can decrease the amplitude and increase the latency of the presynaptic fiber volley [103, 104]. The induction of axonal conduction failure by high-frequency DBS was further confirmed in a series of experiments of the group of Durand and colleagues. They observed a reduction in amplitude of the compound action potential measured along the alvear axon tract during high-frequency stimulation of the alveus *in vitro* [105], as well as a decrease in amplitude and an increase in latency of the antidromic population spike amplitude measured in the CA1 region upon high-frequency alvear stimulation both *in vitro* and *in vivo* in urethane-anesthetized rats [105-108]. The orthodromic population spike evoked by Schaffer collateral stimulation was unaffected, suggesting the presence of axonal failure. Vice versa, high-frequency stimulation of the Schaffer collaterals suppressed the orthodromic population spike with a preserved alvear stimulation-evoked antidromic population spike [106-108]. The axonal conduction failure recovered with two different time courses: a frequency-dependent recovery within 20 to 100 ms due to an extended axonal refractory period and a slower recovery phase lasting 2 to 3 minutes largely independent of the stimulation frequency [107].

Jamming of pathological neuronal firing activity

As outlined above, various studies have shown that DBS increases the firing frequency in downstream structures innervated by efferent axons leaving the stimulation target [69, 70, 72, 83, 106, 109, 110]. Time-locked activity to the DBS stimulation pulses was reported in most of these studies [69, 72, 106, 110]. Even in studies reporting a decrease in firing rate time-locked neuronal firing has been reported [84, 111]. The time-locked neuronal firing often showed polyphasic patterns with alternating periods of excitation and inhibition that in addition differed between different studies [69, 70, 81, 84, 110]. These polyphasic patterns probably originate from mono- and polysynaptic responses and/or changes in network activity.

This stimulus-locked evoked activity replaces spontaneous (pathological) neuronal activity which could be responsible for some of the beneficial effects of DBS. A computational model of Grill and colleagues showed that DBS can lead to a regular output with zero variance and hence a loss of information producing an ‘informational lesion’ [112]. This hypothesis was further supported by Gale and colleagues demonstrating inhibition of movement-related modulation of neuronal firing during STN DBS [71]. On the contrary, in the study of Zimnik and colleagus movement-related modulation of the firing rate of GPi neurons was not affected by STN DBS [87].

DBS-evoked activity has not only been demonstrated in the stimulation target [58] and downstream nuclei [69, 70, 72, 83, 106, 109, 110], but also in upstream structures including cortical neurons [71, 113-118]. This activity reflects the **antidromic activation** of afferent axons and likely also contributes to the effects of DBS. Although it does not necessarily implicate a causal relation, Dejean and colleagues showed that in rats the amplitude of the evoked activity in the frontal cortex during STN DBS correlated with the magnitude of clinical improvement [115].

Besides modulating the firing frequency and evoking activity time-locked to the stimulation pulses, various studies have also shown a suppression of burst firing with DBS [85, 86, 106, 111]. Although this was not the case in all studies [81], suppression of burst firing could also contribute to the clinical effects of DBS.

Desynchronization of neuronal activity

DBS-evoked activity could result into desynchronized activity as has been shown by Feng and colleagues [106]. High-frequency stimulation of the Schaffer collaterals evoked asynchronous firing of CA1 neurons. This activity was entrained and time-locked to the DBS pulses, but for each neuron only a minority of DBS pulses was followed by evoked activity thus leading to asynchronous neuronal activity. Desynchronization of hippocampal activity has also been observed during ATN DBS [119]. Furthermore, a decrease in oscillatory and correlated activity between pairs of neurons has been shown in the STN with STN DBS and in the GPi with GPi DBS [63, 81]. Desynchronization of neuronal activity rather than changes in firing frequency has therefore been hypothesized to be involved in the mechanism of action of DBS [63, 81, 106, 119-121]. In a rat model of epilepsy, DBS with a random interpulse interval caused a higher reduction in seizure frequency than DBS with a fixed interpulse interval [121]. On the contrary, irregular DBS was less efficacious than regular DBS to treat bradykinesia in patients with Parkinson's disease or tremor in essential tremor patients [122-124]. This reduced efficacy could be related to the occurrence of longer pauses with irregular DBS. When such pauses where prevented, irregular DBS outperformed regular DBS in the improvement of bradykinesia in a small trial with patients with Parkinson's disease [14, 125].

Suppression of pathological activity in specific frequency bands

Closely related to the previous section, the beneficial effect of DBS has been attributed to its ability to suppress pathological LFP oscillations in specific frequency bands (being a surrogate marker of local synchronization). Beta band oscillations and power are increased in patients with Parkinson's disease as well as in animal models of Parkinson's disease [115, 126-132]. Futhermore, these pathological oscillations seem to correlate with the degree of symptom severity [133]. STN DBS has been shown to suppress pathological beta oscillations both in the STN [134-138], the GPi[136, 139] and the motor cortex [128, 138, 140]. The reductions in beta oscillations correlated with clinical improvement in the studies of Kuhn and Little [129, 141], suggesting their involvement in the mechanism of action of DBS. Similarly, GPi DBS suppresses beta oscillations in Parkinson's disease both locally in the GPi [81, 84] and in the motor cortex [142].

Some remarks should be made with regards to the relationship between these DBS-induced beta power reductions and the mechanism of action of DBS. First, in various studies STN DBS was not

associated with a reduction in beta power [143-146]. Secondly, similar reductions in beta power have also been demonstrated with dopaminergic drugs [147-149]. Finally, DBS has been shown to induce different alterations in the power spectrum in other diseases. For example, reductions in the 4 to 12 Hz power and in the alfa and beta range have been shown with GPi DBS in patients with dystonia [138, 150]. In patients with Tourette's syndrome thalamic DBS increased thalamic gamma power, whereas in essential tremor patients it decreased alfa and theta power in the motor and sensory cortex, respectively [151, 152]. Instead of specifically reducing beta power, DBS thus rather seems to normalize disease-specific pathological changes in the power spectrum. Whether these normalizations are a direct consequence of DBS or only associated with the suppression of clinical symptoms as such needs further study.

Brain tissue damage

As DBS mimics the effects of ablative procedures, it has been argued that the beneficial effects of DBS could result from stimulation-induced damage to brain tissue. Various studies have therefore performed a detailed post-mortem histological analysis of the brain tissue around the electrode of patients with Parkinson's disease treated with DBS for months to many years. These studies observed mild gliosis around the electrode traject but the surrounding neural parenchyma was well-preserved [153-155]. This gliosis was identical for stimulated and non-stimulated locations around the electrode traject, compatible with reactive changes related to surgical placement of the electrode without evidence for further stimulation-related brain tissue damage [153-155]. This was further confirmed by the observation that these reactive changes were less pronounced after 12 compared to 3 months of stimulation [155].

Although the mechanism of action of DBS does not seem to result from stimulation-induced damage to brain tissue, microlesions resulting from electrode implantation can have clinically significant effects. For example, various studies have reported long-term seizure freedom in epilepsy patients after electrode insertion without any stimulation [156, 157]. These permanent microlesional effects should be discerned from temporary improvements associated with electrode implantation observed in epilepsy patients prior to any stimulation in many DBS trials [28, 35, 158-161]. These temporary effects are typically referred to as 'implantation effects' and could also be influenced by other factors related to the neurosurgical procedure such as the anesthesia.

Other mechanisms

Adenosine has been associated with seizure termination in a white farm swine acute model of epilepsy and in human epilepsy patients [162]. In addition, local infusion of adenosine in the hippocampus had antiseizure effects in a rat model of epilepsy with spontaneous seizures [163]. DBS has been shown to increase the release of ATP and its catabolic product adenosine, which contributed to the anti-tremor and anticonvulsant effects of DBS [164, 165]. Amongst others, adenosine is involved in heterosynaptic depression and increases homosynaptic depression [164].

In vitro experiments have shown **increased extracellular potassium concentrations** during or after DBS [91, 166, 167]. These increased concentrations were associated with suppression of epileptiform activity in hippocampal slices [91]. Furthermore, injection of KCl in the SNr or STN of hemiparkinsonian

rats improved forelimb akinesia [168]. Mechanisms via which increased potassium concentrations could be involved in the mechanism of action of DBS include depolarization block and axonal block [104, 167, 169].

Besides neurons, **astrocytes** also seem to be involved in the mechanism of action of DBS [170, 171]. DBS induced astrocytic vesicular release of glutamate and adenosine in slice preparations *in vitro*, which has been shown to have neuromodulatory properties and was associated with the abolishment of spontaneous spindle oscillations [170-172].

Various studies have reported a reduction of **neuroinlammation** after DBS in preclinical models of epilepsy, post-stroke depression and Alzheimer's disease, demonstrating decreased levels of inflammatory cytokines and microglial activation [173-176]. Given the bidirectional relationship between e.g. epilepsy / seizures and inflammation, however, more research is needed to define whether this reflects a primary DBS effect or rather is a consequence of the DBS-induced reductions in seizure frequency [177].

Long-term effects of DBS

Initiation of DBS is associated with nearly instantaneous tremor suppression in patients with Parkinson's disease and essential tremor. However, other symptoms such as rigidity, bradykinesia and especially axial symptoms may take minutes, hours or even weeks to months to achieve maximal improvement [14, 15, 178, 179]. Similarly, maximum symptom relief in many other neuropsychiatric diseases treated with DBS is often only observed after days to months of stimulation, for example in dystonia (in particular in tonic dysontia), epilepsy, obsessive-compulsive disorder, depression, Tourette's syndrome and cluster headache [14, 15, 158, 161, 180-185]. In addition to the delayed or increasing efficacy after DBS onset, outlasting effects after accidental or intentional cessation of DBS have been described in various disorders, including epilepsy, dystonia, Tourette's syndrome and for axial symptoms in Parkinson's disease [179, 180, 186-191]. Both the slower rates of improvement and the observed outlasting effects require longer-term mechanisms of action. In particular, neuroplasticity and neuroprotective / neurogenesis mechanisms have been hypothesized to explain these delayed and outlasting effects [14, 15]. The long-lasting neuroplasticity effects of DBS may, amongst others, be mediated by epigenetic changes [192, 193].

Multiple studies have reported long-term **neuroplasticity** induced by DBS. One minute of STN DBS *in vitro* caused long-term depression, short- and long-term potentiation in different subsets of STN neurons [194]. Long-term depression was observed *in vitro* after a couple of seconds of stimulation in the cortex or the white matter between the cortex and the striatum [195], after one second of DBS in the internal capsule in slices from dopamine-depleted but not from healthy rats [196] and after seconds of DBS in the medial prefrontal cortex in urethane-anesthetized rats [197]. In contrast, nucleus accumbens DBS for 90 minutes in urethane-anesthetized rats was associated with an LTP-like increase in evoked potentials in the orbitofrontal cortex whereas the EPs in the medial prefrontal cortex were unaffected [198, 199]. Although these studies did demonstrate DBS-induced long-term neuroplasticity effects that could be involved in the outlasting effects of DBS, it should be noted that they only evaluated the effects of relatively short DBS durations (most of them in the range of seconds). Therefore, they cannot explain the increasing efficacy reported with longer DBS durations in various clinical trials.

Several studies suggested that DBS may improve long-term outcome by the induction of **neurogenesis and neuroprotective effects**. Increased levels of brain-derived neurotrophic factor have been observed in the basal ganglia (substantia nigra, GPi, stiatum) and the primary motor cortex of STN-DBS treated animals, as well as in the prefrontal cortex and hippocampus following prefrontal cortex DBS [200-203]. In addition, long-term STN DBS (continuous for 2-4 weeks or intermittent 1 hour per day for 3 months) has been shown to increase the survival of dopaminergic neurons in the substantia nigra in rat and primate models of Parkinson's disease [202, 204-206]. Finally, various studies have also reported increased neurogenesis with DBS. Two weeks of one hour of STN DBS daily in rats increased the number of neural progenitor cells in the subthalamic region surrounding the electrode [207]. Up to 2 hours of entorhinal cortex DBS promoted cell proliferation in the dentate gyrus in mice resulting into differentiated neurons surviving for at least several weeks and increased performance in a memory task [208]. Similarly, 1 hour of perioperative ATN DBS also increased neurogenesis in the dentate gyrus of mice [209]. In a post-mortem study increased precursor cell proliferation was observed in the subventricular zone of the lateral ventricles, the third ventricle lining and the tissue surrounding the DBS lead of patients with Parkinson's disease treated STN DBS compared to healthy or Parkinson's disease patients not treated with DBS [210]. Clinical studies have also reported a greater clinical benefit when DBS is initiated earlier in the disease course [211, 212].

Notwithstanding the evidence for the occurrence of neuroprotective and neurogenesis changes in various (mainly animal) DBS studies, clear clinical evidence for STN-DBS-related neuroprotection in patients with Parkinson's disease is missing and considerable controversy about their clinical significance and specifity for DBS remains (similar changes have been observed in lesional studies) [14, 15, 206, 213, 214].

REFERENCES

[1] Arle J, Shils J. Essential neuromodulation. London, United Kingdom: Academic Press, Elsevier; 2011.
[2] Krames ES, Peckham PH, Rezai AR. Neuromodulation. London, United Kingdom: Academic Press, Elsevier; 2009.
[3] Temel Y, Leentjens AFG, de Bie RMA. Handboek diepe hersenstimulatie bij neurologische en psychiatrische aandoeningen. Houten, The Netherlands: Bohn Stafleu van Loghum; 2016.
[4] https://leapsmag.com/deep-brain-stimulation-mental-illnesses-raises-ethical-concerns. 19 January 2019.
[5] Hariz MI, Blomstedt P, Zrinzo L. Deep brain stimulation between 1947 and 1987: the untold story. Neurosurg Focus 2010;29(2):E1.
[6] Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol 1987;50(1-6):344-6.
[7] Coubes P, Echenne B, Roubertie A, Vayssiere N, Tuffery S, Humbertclaude V, et al. [Treatment of early-onset generalized dystonia by chronic bilateral stimulation of the internal globus pallidus. Apropos of a case]. Neurochirurgie 1999;45(2):139-44.
[8] Miocinovic S, Somayajula S, Chitnis S, Vitek JL. History, applications, and mechanisms of deep brain stimulation. JAMA neurology 2013;70(2):163-71.
[9] https://www.neuromodulation.com/deep-brain-stimulation. 16 February 2019.
[10] Okun MS. Deep-brain stimulation for Parkinson's disease. N Engl J Med 2012;367(16):1529-38.
[11] Perestelo-Perez L, Rivero-Santana A, Perez-Ramos J, Serrano-Perez P, Panetta J, Hilarion P. Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials. J Neurol 2014;261(11):2051-60.
[12] Larson PS. Deep brain stimulation for movement disorders. Neurotherapeutics 2014;11(3):465-74.
[13] Kisely S, Hall K, Siskind D, Frater J, Olson S, Crompton D. Deep brain stimulation for obsessive-compulsive disorder: a systematic review and meta-analysis. Psychol Med 2014;44(16):3533-42.
[14] Herrington TM, Cheng JJ, Eskandar EN. Mechanisms of deep brain stimulation. J Neurophysiol 2016;115(1):19-38.
[15] Udupa K, Chen R. The mechanisms of action of deep brain stimulation and ideas for the future development. Prog Neurobiol 2015;133:27-49.
[16] Salanova V, Witt T, Worth R, Henry TR, Gross RE, Nazzaro JM, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology 2015;84(10):1017-25.
[17] Herrman H, Egge A, Konglund AE, Ramm-Pettersen J, Dietrichs E, Tauboll E. Anterior thalamic deep brain stimulation in refractory epilepsy: A randomized, double-blinded study. Acta Neurol Scand 2019;139(3):294-304.
[18] Krishna V, King NK, Sammartino F, Strauss I, Andrade DM, Wennberg RA, et al. Anterior Nucleus Deep Brain Stimulation for Refractory Epilepsy: Insights Into Patterns of Seizure Control and Efficacious Target. Neurosurgery 2016;78(6):802-11.
[19] Lehtimaki K, Mottonen T, Jarventausta K, Katisko J, Tahtinen T, Haapasalo J, et al. Outcome based definition of the anterior thalamic deep brain stimulation target in refractory epilepsy. Brain Stimul 2016;9(2):268-75.
[20] Oh YS, Kim HJ, Lee KJ, Kim YI, Lim SC, Shon YM. Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients. Seizure 2012;21(3):183-7.
[21] Piacentino M, Durisotti C, Garofalo PG, Bonanni P, Volzone A, Ranzato F, et al. Anterior thalamic nucleus deep brain Stimulation (DBS) for drug-resistant complex partial seizures (CPS) with or without generalization: long-term evaluation and predictive outcome. Acta Neurochir (Wien) 2015;157(9):1525-32; discussion 32.

[22] Valentin A, Selway RP, Amarouche M, Mundil N, Ughratdar I, Ayoubian L, et al. Intracranial stimulation for children with epilepsy. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society 2017;21(1):223-31.
[23] Kim SH, Lim SC, Kim J, Son BC, Lee KJ, Shon YM. Long-term follow-up of anterior thalamic deep brain stimulation in epilepsy: A 11-year, single center experience. Seizure-Eur J Epilep 2017;52:154-61.
[24] Kulju T, Haapasalo J, Lehtimaki K, Rainesalo S, Peltola J. Similarities between the responses to ANT-DBS and prior VNS in refractory epilepsy. Brain Behav 2018;8(6).
[25] Heck CN, King-Stephens D, Massey AD, Nair DR, Jobst BC, Barkley GL, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. Epilepsia 2014;55(3):432-41.
[26] Bergey GK, Morrell MJ, Mizrahi EM, Goldman A, King-Stephens D, Nair D, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology 2015;84(8):810-7.
[27] Loring DW, Kapur R, Meador KJ, Morrell MJ. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. Epilepsia 2015;56(11):1836-44.
[28] Cukiert A, Cukiert CM, Burattini JA, Lima AM. Seizure outcome after hippocampal deep brain stimulation in a prospective cohort of patients with refractory temporal lobe epilepsy. Seizure 2014;23(1):6-9.
[29] Cukiert A, Cukiert CM, Burattini JA, Mariani PP, Bezerra DF. Seizure outcome after hippocampal deep brain stimulation in patients with refractory temporal lobe epilepsy: A prospective, controlled, randomized, double-blind study. Epilepsia 2017;58(10):1728-33.
[30] Jin H, Li W, Dong C, Wu J, Zhao W, Zhao Z, et al. Hippocampal deep brain stimulation in nonlesional refractory mesial temporal lobe epilepsy. Seizure 2016;37:1-7.
[31] Min B, Guoming L, Jian Z. Treatment of mesial temporal lobe epilepsy with amygdalohippocampal stimulation: A case series and review of the literature. Exp Ther Med 2013;5(4):1264-8.
[32] Lim SN, Lee CY, Lee ST, Tu PH, Chang BL, Lee CH, et al. Low and High Frequency Hippocampal Stimulation for Drug-Resistant Mesial Temporal Lobe Epilepsy. Neuromodulation 2016;19(4):365-72.
[33] Boex C, Seeck M, Vulliemoz S, Rossetti AO, Staedler C, Spinelli L, et al. Chronic deep brain stimulation in mesial temporal lobe epilepsy. Seizure 2011;20(6):485-90.
[34] Bondallaz P, Boex C, Rossetti AO, Foletti G, Spinelli L, Vulliemoz S, et al. Electrode location and clinical outcome in hippocampal electrical stimulation for mesial temporal lobe epilepsy. Seizure 2013;22(5):390-5.
[35] Valentin A, Garcia Navarrete E, Chelvarajah R, Torres C, Navas M, Vico L, et al. Deep brain stimulation of the centromedian thalamic nucleus for the treatment of generalized and frontal epilepsies. Epilepsia 2013;54(10):1823-33.
[36] Son BC, Shon YM, Choi JG, Kim J, Ha SW, Kim SH, et al. Clinical Outcome of Patients with Deep Brain Stimulation of the Centromedian Thalamic Nucleus for Refractory Epilepsy and Location of the Active Contacts. Stereotact Funct Neurosurg 2016;94(3):187-97.
[37] Sa M, Singh R, Pujar S, D'Arco F, Desai N, Eltze C, et al. Centromedian thalamic nuclei deep brain stimulation and Anakinra treatment for FIRES - Two different outcomes. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society 2019;23(5):749-54.
[38] Loscher W, Ebert U, Lehmann H. Kindling induces a lasting, regionally selective increase of kynurenic acid in the nucleus accumbens. Brain Res 1996;725(2):252-6.
[39] Lothman EW, Hatlelid JM, Zorumski CF. Functional mapping of limbic seizures originating in the hippocampus: a combined 2-deoxyglucose and electrophysiologic study. Brain Res 1985;360(1-2):92-100.
[40] Schmitt FC, Voges J, Heinze HJ, Zaehle T, Holtkamp M, Kowski AB. Safety and feasibility of nucleus accumbens stimulation in five patients with epilepsy. J Neurol 2014;261(8):1477-84.

[41] Deransart C, Riban V, Le B, Marescaux C, Depaulis A. Dopamine in the striatum modulates seizures in a genetic model of absence epilepsy in the rat. Neuroscience 2000;100(2):335-44.
[42] Wahnschaffe U, Loscher W. Anticonvulsant effects of ipsilateral but not contralateral microinjections of the dopamine D2 agonist LY 171555 into the nucleus accumbens of amygdala-kindled rats. Brain Res 1991;553(2):181-7.
[43] Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, et al. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. Biol Psychiatry 2010;67(2):110-6.
[44] Millet B, Jaafari N, Polosan M, Baup N, Giordana B, Haegelen C, et al. Limbic versus cognitive target for deep brain stimulation in treatment-resistant depression: accumbens more promising than caudate. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology 2014;24(8):1229-39.
[45] Zhou C, Zhang H, Qin Y, Tian T, Xu B, Chen J, et al. A systematic review and meta-analysis of deep brain stimulation in treatment-resistant depression. Prog Neuropsychopharmacol Biol Psychiatry 2018;82:224-32.
[46] Kowski AB, Voges J, Heinze HJ, Oltmanns F, Holtkamp M, Schmitt FC. Nucleus accumbens stimulation in partial epilepsy--a randomized controlled case series. Epilepsia 2015;56(6):e78-82.
[47] Child ND, Stead M, Wirrell EC, Nickels KC, Wetjen NM, Lee KH, et al. Chronic subthreshold subdural cortical stimulation for the treatment of focal epilepsy originating from eloquent cortex. Epilepsia 2014;55(3):e18-21.
[48] Valentin A, Ughratdar I, Cheserem B, Morris R, Selway R, Alarcon G. Epilepsia partialis continua responsive to neocortical electrical stimulation. Epilepsia 2015;56(8):e104-9.
[49] Valentin A, Ughratdar I, Venkatachalam G, Williams R, Pina M, Lazaro M, et al. Sustained Seizure Control in a Child with Drug Resistant Epilepsy after Subacute Cortical Electrical Stimulation (SCES). Brain Stimul 2016;9(2):307-9.
[50] Kerezoudis P, Grewal SS, Stead M, Lundstrom BN, Britton JW, Shin C, et al. Chronic subthreshold cortical stimulation for adult drug-resistant focal epilepsy: safety, feasibility, and technique. J Neurosurg 2018;129(2):533-43.
[51] Chang CW, Lee ST, Lim SN, Cheng MY, Lee CY, Wu T. Electrical cortical stimulation for refractory focal epilepsy: A long-term follow-up study. Epilepsy Res 2019;151:24-30.
[52] Capecci M, Ricciuti RA, Ortenzi A, Paggi A, Durazzi V, Rychlicki F, et al. Chronic bilateral subthalamic stimulation after anterior callosotomy in drug-resistant epilepsy: long-term clinical and functional outcome of two cases. Epilepsy Res 2012;98(2-3):135-9.
[53] di Giacopo A, Baumann CR, Kurthen M, Capecchi F, Surucu O, Imbach LL. Selective deep brain stimulation in the substantia nigra reduces myoclonus in progressive myoclonic epilepsy: a novel observation and short review of the literature. Epileptic Disord 2019;21(3):283-8.
[54] Wille C, Steinhoff BJ, Altenmuller DM, Staack AM, Bilic S, Nikkhah G, et al. Chronic high-frequency deep-brain stimulation in progressive myoclonic epilepsy in adulthood--report of five cases. Epilepsia 2011;52(3):489-96.
[55] Vitek JL. Mechanisms of deep brain stimulation: excitation or inhibition. Mov Disord 2002;17 Suppl 3:S69-72.
[56] Aum DJ, Tierney TS. Deep brain stimulation: foundations and future trends. Frontiers in bioscience (Landmark edition) 2018;23:162-82.
[57] Beurrier C, Bioulac B, Audin J, Hammond C. High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. J Neurophysiol 2001;85(4):1351-6.
[58] Garcia L, Audin J, D'Alessandro G, Bioulac B, Hammond C. Dual effect of high-frequency stimulation on subthalamic neuron activity. J Neurosc 2003;23(25):8743-51.
[59] Magarinos-Ascone C, Pazo JH, Macadar O, Buno W. High-frequency stimulation of the subthalamic nucleus silences subthalamic neurons: a possible cellular mechanism in Parkinson's disease. Neuroscience 2002;115(4):1109-17.

[60] Benazzouz A, Gao DM, Ni ZG, Piallat B, Bouali-Benazzouz R, Benabid AL. Effect of high-frequency stimulation of the subthalamic nucleus on the neuronal activities of the substantia nigra pars reticulata and ventrolateral nucleus of the thalamus in the rat. Neuroscience 2000;99(2):289-95.
[61] Tai CH, Boraud T, Bezard E, Bioulac B, Gross C, Benazzouz A. Electrophysiological and metabolic evidence that high-frequency stimulation of the subthalamic nucleus bridles neuronal activity in the subthalamic nucleus and the substantia nigra reticulata. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2003;17(13):1820-30.
[62] Boraud T, Bezard E, Bioulac B, Gross C. High frequency stimulation of the internal Globus Pallidus (GPi) simultaneously improves parkinsonian symptoms and reduces the firing frequency of GPi neurons in the MPTP-treated monkey. Neurosci Lett 1996;215(1):17-20.
[63] Meissner W, Leblois A, Hansel D, Bioulac B, Gross CE, Benazzouz A, et al. Subthalamic high frequency stimulation resets subthalamic firing and reduces abnormal oscillations. Brain 2005;128(Pt 10):2372-82.
[64] Dostrovsky JO, Levy R, Wu JP, Hutchison WD, Tasker RR, Lozano AM. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J Neurophysiol 2000;84(1):570-4.
[65] Filali M, Hutchison WD, Palter VN, Lozano AM, Dostrovsky JO. Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus. Exp Brain Res 2004;156(3):274-81.
[66] Milosevic L, Kalia SK, Hodaie M, Lozano AM, Fasano A, Popovic MR, et al. Neuronal inhibition and synaptic plasticity of basal ganglia neurons in Parkinson's disease. Brain 2018;141(1):177-90.
[67] Wu YR, Levy R, Ashby P, Tasker RR, Dostrovsky JO. Does stimulation of the GPi control dyskinesia by activating inhibitory axons? Mov Disord 2001;16(2):208-16.
[68] Liu LD, Prescott IA, Dostrovsky JO, Hodaie M, Lozano AM, Hutchison WD. Frequency-dependent effects of electrical stimulation in the globus pallidus of dystonia patients. J Neurophysiol 2012;108(1):5-17.
[69] Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. J Neurosc 2003;23(5):1916-23.
[70] Kita H, Tachibana Y, Nambu A, Chiken S. Balance of monosynaptic excitatory and disynaptic inhibitory responses of the globus pallidus induced after stimulation of the subthalamic nucleus in the monkey. J Neurosc 2005;25(38):8611-9.
[71] Montgomery EB, Jr., Gale JT. Mechanisms of action of deep brain stimulation(DBS). Neurosci Biobehav Rev 2008;32(3):388-407.
[72] Galati S, Mazzone P, Fedele E, Pisani A, Peppe A, Pierantozzi M, et al. Biochemical and electrophysiological changes of substantia nigra pars reticulata driven by subthalamic stimulation in patients with Parkinson's disease. Eur J Neurosci 2006;23(11):2923-8.
[73] Anderson ME, Postupna N, Ruffo M. Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. J Neurophysiol 2003;89(2):1150-60.
[74] Montgomery EB, Jr. Effects of GPi stimulation on human thalamic neuronal activity. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2006;117(12):2691-702.
[75] Pralong E, Debatisse D, Maeder M, Vingerhoets F, Ghika J, Villemure JG. Effect of deep brain stimulation of GPI on neuronal activity of the thalamic nucleus ventralis oralis in a dystonic patient. Neurophysiol Clin 2003;33(4):169-73.
[76] Windels F, Bruet N, Poupard A, Urbain N, Chouvet G, Feuerstein C, et al. Effects of high frequency stimulation of subthalamic nucleus on extracellular glutamate and GABA in substantia nigra and globus pallidus in the normal rat. Eur J Neurosci 2000;12(11):4141-6.
[77] Shehab S, D'Souza C, Ljubisavljevic M, Redgrave P. High-frequency electrical stimulation of the subthalamic nucleus excites target structures in a model using c-fos immunohistochemistry. Neuroscience 2014;270:212-25.
[78] McIntyre CC, Grill WM, Sherman DL, Thakor NV. Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. J Neurophysiol 2004;91(4):1457-69.

[79] McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2004;115(6):1239-48.
[80] Lee KH, Kristic K, van Hoff R, Hitti FL, Blaha C, Harris B, et al. High-frequency stimulation of the subthalamic nucleus increases glutamate in the subthalamic nucleus of rats as demonstrated by in vivo enzyme-linked glutamate sensor. Brain Res 2007;1162:121-9.
[81] McCairn KW, Turner RS. Deep brain stimulation of the globus pallidus internus in the parkinsonian primate: local entrainment and suppression of low-frequency oscillations. J Neurophysiol 2009;101(4):1941-60.
[82] Benazzouz A, Piallat B, Pollak P, Benabid AL. Responses of substantia nigra pars reticulata and globus pallidus complex to high frequency stimulation of the subthalamic nucleus in rats: electrophysiological data. Neurosci Lett 1995;189(2):77-80.
[83] Maurice N, Thierry AM, Glowinski J, Deniau JM. Spontaneous and evoked activity of substantia nigra pars reticulata neurons during high-frequency stimulation of the subthalamic nucleus. J Neurosc 2003;23(30):9929-36.
[84] Bar-Gad I, Elias S, Vaadia E, Bergman H. Complex locking rather than complete cessation of neuronal activity in the globus pallidus of a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primate in response to pallidal microstimulation. J Neurosc 2004;24(33):7410-9.
[85] Carlson JD, Cleary DR, Cetas JS, Heinricher MM, Burchiel KJ. Deep brain stimulation does not silence neurons in subthalamic nucleus in Parkinson's patients. J Neurophysiol 2010;103(2):962-7.
[86] Shi LH, Luo F, Woodward DJ, Chang JY. Basal ganglia neural responses during behaviorally effective deep brain stimulation of the subthalamic nucleus in rats performing a treadmill locomotion test. Synapse 2006;59(7):445-57.
[87] Zimnik AJ, Nora GJ, Desmurget M, Turner RS. Movement-related discharge in the macaque globus pallidus during high-frequency stimulation of the subthalamic nucleus. J Neurosc 2015;35(9):3978-89.
[88] Chan CS, Shigemoto R, Mercer JN, Surmeier DJ. HCN2 and HCN1 channels govern the regularity of autonomous pacemaking and synaptic resetting in globus pallidus neurons. J Neurosc 2004;24(44):9921-32.
[89] Lafreniere-Roula M, Kim E, Hutchison WD, Lozano AM, Hodaie M, Dostrovsky JO. High-frequency microstimulation in human globus pallidus and substantia nigra. Exp Brain Res 2010;205(2):251-61.
[90] Lee KH, Chang SY, Roberts DW, Kim U. Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. J Neurosurg 2004;101(3):511-7.
[91] Bikson M, Lian J, Hahn PJ, Stacey WC, Sciortino C, Durand DM. Suppression of epileptiform activity by high frequency sinusoidal fields in rat hippocampal slices. J Physiol 2001;531(Pt 1):181-91.
[92] Anderson TR, Hu B, Iremonger K, Kiss ZH. Selective attenuation of afferent synaptic transmission as a mechanism of thalamic deep brain stimulation-induced tremor arrest. J Neurosc 2006;26(3):841-50.
[93] Fioravante D, Regehr WG. Short-term forms of presynaptic plasticity. Curr Opin Neurobiol 2011;21(2):269-74.
[94] Zucker RS, Regehr WG. Short-term synaptic plasticity. Annu Rev Physiol 2002;64:355-405.
[95] Iremonger KJ, Anderson TR, Hu B, Kiss ZH. Cellular mechanisms preventing sustained activation of cortex during subcortical high-frequency stimulation. J Neurophysiol 2006;96(2):613-21.
[96] Schiller Y, Bankirer Y. Cellular mechanisms underlying antiepileptic effects of low- and high-frequency electrical stimulation in acute epilepsy in neocortical brain slices in vitro. J Neurophysiol 2007;97(3):1887-902.
[97] Shen KZ, Johnson SW. Complex EPSCs evoked in substantia nigra reticulata neurons are disrupted by repetitive stimulation of the subthalamic nucleus. Synapse 2008;62(4):237-42.
[98] Urbano F, Leznik E, Llinás R. Cortical activation patterns evoked by afferent axons stimuli at different frequencies: an in vitro voltage-sensitive dye imaging study. Thalamus Relat Syst 2002;1(4):371-8.

[99] Milosevic L, Kalia SK, Hodaie M, Lozano AM, Popovic MR, Hutchison WD. Physiological mechanisms of thalamic ventral intermediate nucleus stimulation for tremor suppression. Brain 2018;141(7):2142-55.
[100] Kilgore KL, Bhadra N. Nerve conduction block utilising high-frequency alternating current. Med Biol Eng Comput 2004;42(3):394-406.
[101] Bhadra N, Kilgore KL. High-frequency electrical conduction block of mammalian peripheral motor nerve. Muscle Nerve 2005;32(6):782-90.
[102] Meeks JP, Jiang X, Mennerick S. Action potential fidelity during normal and epileptiform activity in paired soma-axon recordings from rat hippocampus. J Physiol 2005;566(Pt 2):425-41.
[103] Kim E, Owen B, Holmes WR, Grover LM. Decreased afferent excitability contributes to synaptic depression during high-frequency stimulation in hippocampal area CA1. J Neurophysiol 2012;108(7):1965-76.
[104] Zheng F, Lammert K, Nixdorf-Bergweiler BE, Steigerwald F, Volkmann J, Alzheimer C. Axonal failure during high frequency stimulation of rat subthalamic nucleus. J Physiol 2011;589(Pt 11):2781-93.
[105] Jensen AL, Durand DM. High frequency stimulation can block axonal conduction. Exp Neurol 2009;220(1):57-70.
[106] Feng Z, Wang Z, Guo Z, Zhou W, Cai Z, Durand DM. High frequency stimulation of afferent fibers generates asynchronous firing in the downstream neurons in hippocampus through partial block of axonal conduction. Brain Res 2017;1661:67-78.
[107] Feng Z, Yu Y, Guo Z, Cao J, Durand DM. High frequency stimulation extends the refractory period and generates axonal block in the rat hippocampus. Brain Stimul 2014;7(5):680-9.
[108] Feng Z, Zheng X, Yu Y, Durand DM. Functional disconnection of axonal fibers generated by high frequency stimulation in the hippocampal CA1 region in-vivo. Brain Res 2013;1509:32-42.
[109] Ammari R, Bioulac B, Garcia L, Hammond C. The Subthalamic Nucleus becomes a Generator of Bursts in the Dopamine-Depleted State. Its High Frequency Stimulation Dramatically Weakens Transmission to the Globus Pallidus. Front Syst Neurosci 2011;5:43.
[110] Reese R, Leblois A, Steigerwald F, Potter-Nerger M, Herzog J, Mehdorn HM, et al. Subthalamic deep brain stimulation increases pallidal firing rate and regularity. Exp Neurol 2011;229(2):517-21.
[111] Maltete D, Jodoin N, Karachi C, Houeto JL, Navarro S, Cornu P, et al. Subthalamic stimulation and neuronal activity in the substantia nigra in Parkinson's disease. J Neurophysiol 2007;97(6):4017-22.
[112] Grill WM, Snyder AN, Miocinovic S. Deep brain stimulation creates an informational lesion of the stimulated nucleus. Neuroreport 2004;15(7):1137-40.
[113] Ashby P, Paradiso G, Saint-Cyr JA, Chen R, Lang AE, Lozano AM. Potentials recorded at the scalp by stimulation near the human subthalamic nucleus. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2001;112(3):431-7.
[114] Baker KB, Montgomery EB, Jr., Rezai AR, Burgess R, Luders HO. Subthalamic nucleus deep brain stimulus evoked potentials: physiological and therapeutic implications. Mov Disord 2002;17(5):969-83.
[115] Dejean C, Gross CE, Bioulac B, Boraud T. Dynamic changes in the cortex-basal ganglia network after dopamine depletion in the rat. J Neurophysiol 2008;100(1):385-96.
[116] Li S, Arbuthnott GW, Jutras MJ, Goldberg JA, Jaeger D. Resonant antidromic cortical circuit activation as a consequence of high-frequency subthalamic deep-brain stimulation. J Neurophysiol 2007;98(6):3525-37.
[117] Walker HC, Huang H, Gonzalez CL, Bryant JE, Killen J, Cutter GR, et al. Short latency activation of cortex during clinically effective subthalamic deep brain stimulation for Parkinson's disease. Mov Disord 2012;27(7):864-73.
[118] Walker HC, Huang H, Gonzalez CL, Bryant JE, Killen J, Knowlton RC, et al. Short latency activation of cortex by clinically effective thalamic brain stimulation for tremor. Mov Disord 2012;27(11):1404-12.

[119] Yu T, Wang XY, Li YJ, Zhang GJ, Worrell G, Chauvel P, et al. High-frequency stimulation of anterior nucleus of thalamus desynchronizes epileptic network in humans. Brain 2018;141:2631-43.
[120] Medeiros Dde C, Moraes MF. Focus on desynchronization rather than excitability: a new strategy for intraencephalic electrical stimulation. Epilepsy & behavior : E&B 2014;38:32-6.
[121] Wyckhuys T, Boon P, Raedt R, Van Nieuwenhuyse B, Vonck K, Wadman W. Suppression of hippocampal epileptic seizures in the kainate rat by Poisson distributed stimulation. Epilepsia 2010;51(11):2297-304.
[122] Birdno MJ, Kuncel AM, Dorval AD, Turner DA, Gross RE, Grill WM. Stimulus features underlying reduced tremor suppression with temporally patterned deep brain stimulation. J Neurophysiol 2012;107(1):364-83.
[123] Dorval AD, Kuncel AM, Birdno MJ, Turner DA, Grill WM. Deep brain stimulation alleviates parkinsonian bradykinesia by regularizing pallidal activity. J Neurophysiol 2010;104(2):911-21.
[124] Montgomery EB, Jr. Effect of subthalamic nucleus stimulation patterns on motor performance in Parkinson's disease. Parkinsonism Relat Disord 2005;11(3):167-71.
[125] Brocker DT, Swan BD, Turner DA, Gross RE, Tatter SB, Koop MM, et al. Improved efficacy of temporally non-regular deep brain stimulation in Parkinson's disease. Exp Neurol 2013;239:60-7.
[126] Avila I, Parr-Brownlie LC, Brazhnik E, Castaneda E, Bergstrom DA, Walters JR. Beta frequency synchronization in basal ganglia output during rest and walk in a hemiparkinsonian rat. Exp Neurol 2010;221(2):307-19.
[127] Brown P. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. Mov Disord 2003;18(4):357-63.
[128] de Hemptinne C, Ryapolova-Webb ES, Air EL, Garcia PA, Miller KJ, Ojemann JG, et al. Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease. Proc Natl Acad Sci U S A 2013;110(12):4780-5.
[129] Little S, Pogosyan A, Kuhn AA, Brown P. beta band stability over time correlates with Parkinsonian rigidity and bradykinesia. Exp Neurol 2012;236(2):383-8.
[130] Moran A, Stein E, Tischler H, Bar-Gad I. Decoupling neuronal oscillations during subthalamic nucleus stimulation in the parkinsonian primate. Neurobiol Dis 2012;45(1):583-90.
[131] Pollok B, Krause V, Martsch W, Wach C, Schnitzler A, Sudmeyer M. Motor-cortical oscillations in early stages of Parkinson's disease. J Physiol 2012;590(13):3203-12.
[132] Stein E, Bar-Gad I. beta oscillations in the cortico-basal ganglia loop during parkinsonism. Exp Neurol 2013;245:52-9.
[133] Kuhn AA, Tsui A, Aziz T, Ray N, Brucke C, Kupsch A, et al. Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. Exp Neurol 2009;215(2):380-7.
[134] Bronte-Stewart H, Barberini C, Koop MM, Hill BC, Henderson JM, Wingeier B. The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation. Exp Neurol 2009;215(1):20-8.
[135] Eusebio A, Thevathasan W, Doyle Gaynor L, Pogosyan A, Bye E, Foltynie T, et al. Deep brain stimulation can suppress pathological synchronisation in parkinsonian patients. Journal of neurology, neurosurgery, and psychiatry 2011;82(5):569-73.
[136] Kuhn AA, Kempf F, Brucke C, Gaynor Doyle L, Martinez-Torres I, Pogosyan A, et al. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. J Neurosc 2008;28(24):6165-73.
[137] Rosa M, Giannicola G, Servello D, Marceglia S, Pacchetti C, Porta M, et al. Subthalamic local field beta oscillations during ongoing deep brain stimulation in Parkinson's disease in hyperacute and chronic phases. Neurosignals 2011;19(3):151-62.
[138] Whitmer D, de Solages C, Hill B, Yu H, Henderson JM, Bronte-Stewart H. High frequency deep brain stimulation attenuates subthalamic and cortical rhythms in Parkinson's disease. Front Hum Neurosci 2012;6:155.

[139] Brown P, Mazzone P, Oliviero A, Altibrandi MG, Pilato F, Tonali PA, et al. Effects of stimulation of the subthalamic area on oscillatory pallidal activity in Parkinson's disease. Exp Neurol 2004;188(2):480-90.
[140] Devos D, Labyt E, Derambure P, Bourriez JL, Cassim F, Reyns N, et al. Subthalamic nucleus stimulation modulates motor cortex oscillatory activity in Parkinson's disease. Brain 2004;127(Pt 2):408-19.
[141] Kuhn AA, Kupsch A, Schneider GH, Brown P. Reduction in subthalamic 8-35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. Eur J Neurosci 2006;23(7):1956-60.
[142] McCairn KW, Turner RS. Pallidal stimulation suppresses pathological dysrhythmia in the parkinsonian motor cortex. J Neurophysiol 2015;113(7):2537-48.
[143] Foffani G, Ardolino G, Egidi M, Caputo E, Bossi B, Priori A. Subthalamic oscillatory activities at beta or higher frequency do not change after high-frequency DBS in Parkinson's disease. Brain Res Bull 2006;69(2):123-30.
[144] Giannicola G, Marceglia S, Rossi L, Mrakic-Sposta S, Rampini P, Tamma F, et al. The effects of levodopa and ongoing deep brain stimulation on subthalamic beta oscillations in Parkinson's disease. Exp Neurol 2010;226(1):120-7.
[145] Priori A, Ardolino G, Marceglia S, Mrakic-Sposta S, Locatelli M, Tamma F, et al. Low-frequency subthalamic oscillations increase after deep brain stimulation in Parkinson's disease. Brain Res Bull 2006;71(1-3):149-54.
[146] Rossi L, Marceglia S, Foffani G, Cogiamanian F, Tamma F, Rampini P, et al. Subthalamic local field potential oscillations during ongoing deep brain stimulation in Parkinson's disease. Brain Res Bull 2008;76(5):512-21.
[147] Brown P, Oliviero A, Mazzone P, Insola A, Tonali P, Di Lazzaro V. Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. J Neurosc 2001;21(3):1033-8.
[148] Brown P, Williams D. Basal ganglia local field potential activity: character and functional significance in the human. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2005;116(11):2510-9.
[149] Levy R, Ashby P, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO. Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. Brain 2002;125(Pt 6):1196-209.
[150] Barow E, Neumann WJ, Brucke C, Huebl J, Horn A, Brown P, et al. Deep brain stimulation suppresses pallidal low frequency activity in patients with phasic dystonic movements. Brain 2014;137(Pt 11):3012-24.
[151] Air EL, Ryapolova-Webb E, de Hemptinne C, Ostrem JL, Galifianakis NB, Larson PS, et al. Acute effects of thalamic deep brain stimulation and thalamotomy on sensorimotor cortex local field potentials in essential tremor. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2012;123(11):2232-8.
[152] Maling N, Hashemiyoon R, Foote KD, Okun MS, Sanchez JC. Increased thalamic gamma band activity correlates with symptom relief following deep brain stimulation in humans with Tourette's syndrome. PLoS One 2012;7(9):e44215.
[153] Haberler C, Alesch F, Mazal PR, Pilz P, Jellinger K, Pinter MM, et al. No tissue damage by chronic deep brain stimulation in Parkinson's disease. Ann Neurol 2000;48(3):372-6.
[154] Nielsen MS, Bjarkam CR, Sorensen JC, Bojsen-Moller M, Sunde NA, Ostergaard K. Chronic subthalamic high-frequency deep brain stimulation in Parkinson's disease--a histopathological study. Eur J Neurol 2007;14(2):132-8.
[155] Orlowski D, Michalis A, Glud AN, Korshoj AR, Fitting LM, Mikkelsen TW, et al. Brain Tissue Reaction to Deep Brain Stimulation-A Longitudinal Study of DBS in the Goettingen Minipig. Neuromodulation 2017;20(5):417-23.

[156] Katariwala NM, Bakay RA, Pennell PB, Olson LD, Henry TR, Epstein CM. Remission of intractable partial epilepsy following implantation of intracranial electrodes. Neurology 2001;57(8):1505-7.
[157] Schulze-Bonhage A, Dennig D, Wagner K, Cordeiro J, Carius A, Fauser S, et al. Seizure control resulting from intrahippocampal depth electrode insertion. J Neurol Neurosurg Psychiatry 2010;81(3):352-3.
[158] Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51(5):899-908.
[159] Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM. Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 2002;43(6):603-8.
[160] Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, Chen JL, et al. Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. Epilepsia 2007;48(2):342-7.
[161] Morrell MJ, Group RNSSiES. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 2011;77(13):1295-304.
[162] Van Gompel JJ, Bower MR, Worrell GA, Stead M, Chang SY, Goerss SJ, et al. Increased cortical extracellular adenosine correlates with seizure termination. Epilepsia 2014;55(2):233-44.
[163] Van Dycke A, Raedt R, Dauwe I, Sante T, Wyckhuys T, Meurs A, et al. Continuous local intrahippocampal delivery of adenosine reduces seizure frequency in rats with spontaneous seizures. Epilepsia 2010;51(9):1721-8.
[164] Bekar L, Libionka W, Tian GF, Xu Q, Torres A, Wang X, et al. Adenosine is crucial for deep brain stimulation-mediated attenuation of tremor. Nat Med 2008;14(1):75-80.
[165] Miranda MF, Hamani C, de Almeida AC, Amorim BO, Macedo CE, Fernandes MJ, et al. Role of adenosine in the antiepileptic effects of deep brain stimulation. Front Cell Neurosci 2014;8:312.
[166] Heinemann U, Lux HD. Ceiling of stimulus induced rises in extracellular potassium concentration in the cerebral cortex of cat. Brain Res 1977;120(2):231-49.
[167] Shin DS, Samoilova M, Cotic M, Zhang L, Brotchie JM, Carlen PL. High frequency stimulation or elevated K+ depresses neuronal activity in the rat entopeduncular nucleus. Neuroscience 2007;149(1):68-86.
[168] Sutton AC, Yu W, Calos ME, Mueller LE, Berk M, Shim J, et al. Elevated potassium provides an ionic mechanism for deep brain stimulation in the hemiparkinsonian rat. Eur J Neurosci 2013;37(2):231-41.
[169] Florence G, Sameshima K, Fonoff ET, Hamani C. Deep Brain Stimulation: More Complex than the Inhibition of Cells and Excitation of Fibers. Neuroscientist 2016;22(4):332-45.
[170] Fenoy AJ, Goetz L, Chabardes S, Xia Y. Deep brain stimulation: are astrocytes a key driver behind the scene? CNS Neurosci Ther 2014;20(3):191-201.
[171] Tawfik VL, Chang SY, Hitti FL, Roberts DW, Leiter JC, Jovanovic S, et al. Deep brain stimulation results in local glutamate and adenosine release: investigation into the role of astrocytes. Neurosurgery 2010;67(2):367-75.
[172] Kovacs A, Pal B. Astrocyte-Dependent Slow Inward Currents (SICs) Participate in Neuromodulatory Mechanisms in the Pedunculopontine Nucleus (PPN). Front Cell Neurosci 2017;11:16.
[173] Wang M, Guo J, Dong LN, Wang JP. Cerebellar Fastigial Nucleus Stimulation in a Chronic Unpredictable Mild Stress Rat Model Reduces Post-Stroke Depression by Suppressing Brain Inflammation via the microRNA-29c/TNFRSF1A Signaling Pathway. Med Sci Monit 2019;25:5594-605.
[174] Amorim BO, Covolan L, Ferreira E, Brito JG, Nunes DP, de Morais DG, et al. Deep brain stimulation induces antiapoptotic and anti-inflammatory effects in epileptic rats. J Neuroinflammation 2015;12:162.
[175] Leplus A, Lauritzen I, Melon C, Kerkerian-Le Goff L, Fontaine D, Checler F. Chronic fornix deep brain stimulation in a transgenic Alzheimer's rat model reduces amyloid burden, inflammation, and neuronal loss. Brain Struct Funct 2019;224(1):363-72.

[176] Chen YC, Zhu GY, Wang X, Shi L, Du TT, Liu DF, et al. Anterior thalamic nuclei deep brain stimulation reduces disruption of the blood-brain barrier, albumin extravasation, inflammation and apoptosis in kainic acid-induced epileptic rats. Neurol Res 2017;39(12):1103-13.
[177] Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. Nat Rev Neurol 2011;7(1):31-40.
[178] Fasano A, Aquino CC, Krauss JK, Honey CR, Bloem BR. Axial disability and deep brain stimulation in patients with Parkinson disease. Nature reviews Neurology 2015;11(2):98-110.
[179] Temperli P, Ghika J, Villemure JG, Burkhard PR, Bogousslavsky J, Vingerhoets FJ. How do parkinsonian signs return after discontinuation of subthalamic DBS? Neurology 2003;60(1):78-81.
[180] Johnson MD, Miocinovic S, McIntyre CC, Vitek JL. Mechanisms and targets of deep brain stimulation in movement disorders. Neurotherapeutics 2008;5(2):294-308.
[181] Krack P, Hariz MI, Baunez C, Guridi J, Obeso JA. Deep brain stimulation: from neurology to psychiatry? Trends Neurosci 2010;33(10):474-84.
[182] Pedersen JL, Barloese M, Jensen RH. Neurostimulation in cluster headache: a review of current progress. Cephalalgia : an international journal of headache 2013;33(14):1179-93.
[183] Sachdev PS, Mohan A, Cannon E, Crawford JD, Silberstein P, Cook R, et al. Deep brain stimulation of the antero-medial globus pallidus interna for Tourette syndrome. PLoS One 2014;9(8):e104926.
[184] Servello D, Porta M, Sassi M, Brambilla A, Robertson MM. Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation. Journal of neurology, neurosurgery, and psychiatry 2008;79(2):136-42.
[185] Yianni J, Bain PG, Gregory RP, Nandi D, Joint C, Scott RB, et al. Post-operative progress of dystonia patients following globus pallidus internus deep brain stimulation. Eur J Neurol 2003;10(3):239-47.
[186] Hebb MO, Chiasson P, Lang AE, Brownstone RM, Mendez I. Sustained relief of dystonia following cessation of deep brain stimulation. Mov Disord 2007;22(13):1958-62.
[187] Houeto JL, Karachi C, Mallet L, Pillon B, Yelnik J, Mesnage V, et al. Tourette's syndrome and deep brain stimulation. Journal of neurology, neurosurgery, and psychiatry 2005;76(7):992-5.
[188] Motlagh MG, Smith ME, Landeros-Weisenberger A, Kobets AJ, King RA, Miravite J, et al. Lessons Learned from Open-label Deep Brain Stimulation for Tourette Syndrome: Eight Cases over 7 Years. Tremor Other Hyperkinet Mov (N Y) 2013;3.
[189] Ruge D, Cif L, Limousin P, Gonzalez V, Vasques X, Coubes P, et al. Longterm deep brain stimulation withdrawal: clinical stability despite electrophysiological instability. J Neurol Sci 2014;342(1-2):197-9.
[190] Sprengers M, Vonck K, Carrette E, Marson AG, Boon P. Deep brain and cortical stimulation for epilepsy. Cochrane Database Syst Rev 2017;7:CD008497.
[191] Wyckhuys T, Raedt R, Vonck K, Wadman W, Boon P. Comparison of hippocampal Deep Brain Stimulation with high (130Hz) and low frequency (5Hz) on afterdischarges in kindled rats. Epilepsy Res 2010;88(2-3):239-46.
[192] Soreq L, Salomonis N, Bronstein M, Greenberg DS, Israel Z, Bergman H, et al. Small RNA sequencing-microarray analyses in Parkinson leukocytes reveal deep brain stimulation-induced splicing changes that classify brain region transcriptomes. Front Mol Neurosci 2013;6:10.
[193] Herre M, Korb E. The chromatin landscape of neuronal plasticity. Curr Opin Neurobiol 2019;59:79-86.
[194] Shen KZ, Zhu ZT, Munhall A, Johnson SW. Synaptic plasticity in rat subthalamic nucleus induced by high-frequency stimulation. Synapse 2003;50(4):314-9.
[195] Calabresi P, Maj R, Pisani A, Mercuri NB, Bernardi G. Long-term synaptic depression in the striatum: physiological and pharmacological characterization. J Neurosc 1992;12(11):4224-33.
[196] Yamawaki N, Magill PJ, Woodhall GL, Hall SD, Stanford IM. Frequency selectivity and dopamine-dependence of plasticity at glutamatergic synapses in the subthalamic nucleus. Neuroscience 2012;203:1-11.

[197] Braz BY, Belforte JE, Murer MG, Galinanes GL. Properties of the corticostriatal long term depression induced by medial prefrontal cortex high frequency stimulation in vivo. Neuropharmacology 2017;121:278-86.
[198] McCracken CB, Grace AA. High-frequency deep brain stimulation of the nucleus accumbens region suppresses neuronal activity and selectively modulates afferent drive in rat orbitofrontal cortex in vivo. J Neurosc 2007;27(46):12601-10.
[199] McCracken CB, Grace AA. Nucleus accumbens deep brain stimulation produces region-specific alterations in local field potential oscillations and evoked responses in vivo. J Neurosc 2009;29(16):5354-63.
[200] Fischer DL, Kemp CJ, Cole-Strauss A, Polinski NK, Paumier KL, Lipton JW, et al. Subthalamic Nucleus Deep Brain Stimulation Employs trkB Signaling for Neuroprotection and Functional Restoration. J Neurosc 2017;37(28):6786-96.
[201] Fischer DL, Sortwell CE. BDNF provides many routes toward STN DBS-mediated disease modification. Mov Disord 2019;34(1):22-34.
[202] Musacchio T, Rebenstorff M, Fluri F, Brotchie JM, Volkmann J, Koprich JB, et al. Subthalamic nucleus deep brain stimulation is neuroprotective in the A53T alpha-synuclein Parkinson's disease rat model. Ann Neurol 2017;81(6):825-36.
[203] Spieles-Engemann AL, Steece-Collier K, Behbehani MM, Collier TJ, Wohlgenant SL, Kemp CJ, et al. Subthalamic nucleus stimulation increases brain derived neurotrophic factor in the nigrostriatal system and primary motor cortex. J Parkinsons Dis 2011;1(1):123-36.
[204] Spieles-Engemann AL, Behbehani MM, Collier TJ, Wohlgenant SL, Steece-Collier K, Paumier K, et al. Stimulation of the rat subthalamic nucleus is neuroprotective following significant nigral dopamine neuron loss. Neurobiol Dis 2010;39(1):105-15.
[205] Temel Y, Visser-Vandewalle V, Kaplan S, Kozan R, Daemen MA, Blokland A, et al. Protection of nigral cell death by bilateral subthalamic nucleus stimulation. Brain Res 2006;1120(1):100-5.
[206] Wallace BA, Ashkan K, Heise CE, Foote KD, Torres N, Mitrofanis J, et al. Survival of midbrain dopaminergic cells after lesion or deep brain stimulation of the subthalamic nucleus in MPTP-treated monkeys. Brain 2007;130(Pt 8):2129-45.
[207] Vedam-Mai V, Baradaran-Shoraka M, Reynolds BA, Okun MS. Tissue Response to Deep Brain Stimulation and Microlesion: A Comparative Study. Neuromodulation 2016;19(5):451-8.
[208] Stone SS, Teixeira CM, Devito LM, Zaslavsky K, Josselyn SA, Lozano AM, et al. Stimulation of entorhinal cortex promotes adult neurogenesis and facilitates spatial memory. J Neurosc 2011;31(38):13469-84.
[209] Encinas JM, Hamani C, Lozano AM, Enikolopov G. Neurogenic hippocampal targets of deep brain stimulation. J Comp Neurol 2011;519(1):6-20.
[210] Vedam-Mai V, Gardner B, Okun MS, Siebzehnrubl FA, Kam M, Aponso P, et al. Increased precursor cell proliferation after deep brain stimulation for Parkinson's disease: a human study. PLoS One 2014;9(3):e88770.
[211] Merola A, Romagnolo A, Bernardini A, Rizzi L, Artusi CA, Lanotte M, et al. Earlier versus later subthalamic deep brain stimulation in Parkinson's disease. Parkinsonism Relat Disord 2015;21(8):972-5.
[212] Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013;368(7):610-22.
[213] Harnack D, Kupsch A. The impact of subthalamic deep brain stimulation on nigral neuroprotection-myth or reality? Neuromodulation 2010;13(3):160-7.
[214] Song S, Song S, Cao C, Lin X, Li K, Sava V, et al. Hippocampal neurogenesis and the brain repair response to brief stereotaxic insertion of a microneedle. Stem Cells Int 2013;2013:205878.

PART II:
RESULTS

CHAPTER 5

Hippocampal DBS in drug-resistant temporal lobe epilepsy: efficacy, adverse events and stimulation protocol in an uncontrolled open-label trial

International Journal of Neural Systems, Vol. 23, No. 1 (2013) 1250034 (13 pages)

DOI: 10.1142/S0129065712500347

World Scientific
www.worldscientific.com

A DECADE OF EXPERIENCE WITH DEEP BRAIN STIMULATION FOR PATIENTS WITH REFRACTORY MEDIAL TEMPORAL LOBE EPILEPSY

KRISTL VONCK*,§, MATHIEU SPRENGERS*, EVELIEN CARRETTE*, INE DAUWE*, MARIJKE MIATTON*, ALFRED MEURS*, LUT GOOSSENS*, VEERLE DE HERDT*, RIK ACHTEN†, EVERT THIERY*, ROBRECHT RAEDT*, DIRK VAN ROOST‡ and PAUL BOON*

*Department of Neurology
Reference Center for Refractory Epilepsy

†Department of Neuroradiology
Ghent University Hospital — Institute for Neuroscience
De Pintelaan 185, 9000 Gent, Belgium

‡Department of Neurosurgery
Ghent University Hospital — Institute for Neuroscience
De Pintelaan 185, 9000 Gent, Belgium
§Kristl.Vonck@UGent.be

Accepted 19 September 2012
Published Online 7 December 2012

In this study, we present long-term results from patients with medial temporal lobe (MTL) epilepsy treated with deep brain stimulation (DBS). Since 2001, 11 patients (8M) with refractory MTL epilepsy underwent MTL DBS. When unilateral DBS failed to decrease seizures by $>90\%$, a switch to bilateral MTL DBS was proposed. After a mean follow-up of 8.5 years (range: 67–120 months), 6/11 patients had a $\geq 90\%$ seizure frequency reduction with 3/6 seizure-free for >3 years; three patients had a 40%–70% reduction and two had a $<30\%$ reduction. In 3/5 patients switching to bilateral DBS further improved outcome. Uni- or bilateral MTL DBS did not affect neuropsychological functioning. This open study with an extended long-term follow-up demonstrates maintained efficacy of DBS for MTL epilepsy. In more than half of the patients, a seizure frequency reduction of at least 90% was reached. Bilateral MTL DBS may herald superior efficacy in unilateral MTL epilepsy.

Keywords: Neurostimulation; refractory epilepsy; deep brain stimulation; medial temporal lobe.

1. Introduction

Epilepsy is one of the most common neurological disorders, affecting 0.5%–1% of the population.[1,2] Uncontrolled epilepsy is associated with excess injury and mortality and increased adverse psychosocial, behavioral and cognitive consequences, resulting in a low quality of life and an enormous burden of both direct and indirect economic costs.[3–6] Despite appropriate drug treatment, 30% of all epilepsy patients continue to have uncontrolled seizures or unacceptable medication-related side effects.[7] Modern anti-epileptic drugs (AEDs) achieve seizure freedom in 6% of these patients and 50% seizure frequency reduction in 21%.[8] Epilepsy surgery is a successful treatment for patients with focal epilepsy with long-term seizure freedom of 40%–75%.[9–12] Many refractory epilepsy patients turn out to be unsuitable epilepsy surgery candidates or are reluctant to undergo brain surgery. In the past decade,

interest in the efficacy, side effects and mechanism of action of various neurostimulation modalities for epilepsy has grown steadily. Vagus nerve stimulation (VNS) is now an established epilepsy treatment available in epilepsy centers worldwide. Ongoing research and improved biomedical technology will further improve its efficacy and clinical applicability.[13–15] Deep brain stimulation for epilepsy of various intracranial targets has been studied, including the anterior and centromedian thalamic nucleus, the subthalamic nucleus, the caudate nucleus, the motor cortex, the cerebellum and the hippocampus.[16,17] For most investigated DBS targets the current evidence for clinical efficacy in refractory epilepsy is limited to open-label pilot studies and small double-blind clinical trials.[18] In 2010, a first large randomized clinical trial (RCT) (110 patients) was published showing a 40% reduction in seizure frequency using bilateral anterior thalamic nucleus (ATN) DBS.[19] In an open-label follow-up study, after two years, seizure frequency reduction further increased up to 56%. A second large DBS RCT (191 patients) reported on the efficacy of responsive neurostimulation in the seizure focus showing a 38% seizure frequency reduction during the three months blinded phase.[20] While most centers investigated subcortical structures with a presumed crucial role in the epileptogenic network, in 2001 we initiated a prospective open-label clinical trial to study the efficacy and safety of medial temporal lobe (MTL) DBS for patients with MTL epilepsy directly stimulating in the vicinity of the ictal onset zone itself. Animal experiments and *in vitro* hippocampal slice work support the efficacy of MTL DBS for epilepsy.[21–24] A first report on three patients with a mean follow-up of 4.5 months showed encouraging results, with a $>95\%$, a 75% and a 50% seizure frequency reduction.[25] Long-term results in 10 patients (mean follow-up 2.5 years) showed seizure freedom in 1/10 patients, a $>90\%$ reduction in another patient, a 50%–90% reduction in 5/10 patients, a 30%–49% reduction in 2/10 patients and 1/10 patients was considered a nonresponder.[26] Detailed neuropsychological evaluations before and six months after initiation of MTL DBS showed no major adverse neuropsychological consequences and enhanced emotional well-being.[27] After a decade of experience with MTL DBS, we now report on our extended long-term FU results in 11 patients with a mean follow-up of 8.5 years. This seems particularly interesting because evidence has emerged that favorable outcome after DBS may further increase over time after stimulation initiation.[19,24,28–34] Extended long-term follow-up results of MTL DBS have not been published before. Moreover, we report on a subgroup of patients in whom we investigated the efficacy of bilateral versus unilateral DBS for unilateral MTL epilepsy.

2. Patients and Methods

Patient selection, the surgical procedure and recording and stimulation paradigm have been described in detail in previously published reports.[25,26]

2.1. *Patient selection*

Patients with refractory epilepsy were enrolled in a presurgical evaluation protocol at the Reference Centre for Refractory Epilepsy at Ghent University Hospital, a tertiary neurological referral center in Belgium. Thirteen patients with refractory epilepsy were included in the study. Inclusion criteria consisted of (i) a suspicion of temporal lobe epilepsy on the basis of video-EEG monitoring; (ii) seizure frequency of at least one complex partial seizure per month, confirmed during a prospective pre-intervention baseline period of six months; and (iii) indication for invasive video-EEG monitoring in the bilateral MTL area and other subdural areas because of incongruent findings during noninvasive presurgical evaluations to localize the ictal onset zone. Two patients who were suitable surgical candidates on the basis of invasive video-EEG monitoring preferred to undergo selective amygdalohippocampectomy and are not considered in this study.[26]

2.2. *Surgical procedure and stimulation paradigm*

The most anterior electrode on each side was placed in the amygdala, the second in the anterior part of the hippocampus. Postoperatively, the precise location of the intracranial electrode contacts was assessed using an MPRAGE MRI sequence. Four days after electrode implantation, antiepileptic drugs (AED) were gradually tapered until habitual seizures were recorded (AED tapering condition). Patients

with a unilateral or bilateral focal or regional MTL ictal onset were offered the choice to undergo continuous MTL DBS. At any time during the study, patients could make the choice of interrupting the ongoing stimulation treatment to undergo resective surgery, when indicated. Focal ictal EEG onset involved one or more electrode contacts on a single recording electrode and regional ictal EEG onset involved early changes in several electrode contacts on one or more recording electrodes. Patients with unilateral MTL seizure onset were stimulated using the ipsilateral amygdalar and hippocampal DBS electrodes; patients with bilateral MTL onset received bilateral hippocampal stimulation. Stimulation parameters were set at a frequency of 130 Hz with a 450 μs pulse width, based on earlier experience with DBS in the MTL by Velasco *et al.*[35] Pairs of adjacent electrode contacts were continuously stimulated in a bipolar way. During follow-up, gradual increase of stimulation output current in patients who were not seizure-free was allowed. When unilateral DBS failed to decrease seizure frequency by more than 90% after 2.5–3 years of follow-up, bilateral hippocampal stimulation was proposed at the time of an upcoming battery replacement. As the contralateral depth electrode had remained in place after the initial invasive video-EEG monitoring, this did not require an additional intracranial surgery. To prolong battery life, day-night cycling (stimulation to be turned off between midnight and 6 am) was proposed to patients after a stable seizure frequency had been reached.

2.3. *AEDs*

During the first 12 months, the aim was to keep patients on the tapered AED regimen. In case of an acute increase in seizure frequency, reinstallation of AEDs at the baseline dosage and/or escape medication was planned. After 12 months of DBS, the AED regimen could be changed according to best medical practice.

2.4. *Follow-up and data analysis*

After the first year during which patients were seen at regular two-week intervals, patients were followed on an outpatient basis every three months, or more frequently when indicated. Seizure frequency, adverse events and concomitant AEDs were carefully monitored using a seizure diary. With regards to changes in the chronic stimulation protocol during long-term follow-up, four relevant assessments were made: (i) the influence of changing the stimulation output voltage, (ii) the impact of switching from unilateral amygdalohippocampal to uni- or bilateral hippocampal stimulation, (iii) the effect of discontinuation of DBS and (iv) the effect of day-night cycling.

3. Results

Between 2001 and 2006, DBS was initiated in 11 patients (eight male) suffering from refractory complex partial seizures with (4/11) or without (7/11) occasional secondary generalization. Results of neuroimaging and invasive video-EEG monitoring are presented in Table 1. In nine patients the seizure onset was localized unilaterally in the MTL (4/11 focal and 5/11 regional) and in two patients seizures started bilaterally in the MTL. In three patients MRI showed typical findings for hippocampal sclerosis. The mean number of anti-epileptic drugs taken during the pre-intervention baseline period was three and decreased to two during the tapering period. The mean follow-up in these patients was 8.5 years (range: 67–120 months). Changes in seizure frequency, stimulation protocol and AED treatment during follow-up are summarized in Table 2. Comparing mean monthly seizure frequency before DBS and at maximum follow-up shows excellent outcome ($\geq 90\%$ seizure frequency reduction) in 6/11 patients, half of them being seizure-free for more than three years (1/3 with DBS off, see below). Three patients showed a moderate response (40%–70% seizure frequency reduction) while two patients were considered nonresponders with changes in mean monthly seizure frequency of $< 30\%$.

In all patients with a focal unilateral ictal onset based on invasive video-EEG monitoring data (4/11) a $\geq$ 90% seizure frequency reduction was found; two of them are seizure-free. One in five patients with a regional unilateral ictal onset has become seizure-free for more than five years, 1/5 has a $\geq$ 90% seizure frequency reduction, another has a 70% seizure frequency reduction and 2/5 are nonresponders. Patients with bilateral ictal onset (2/11) responded moderately to the MTL DBS treatment

Table 1. Results of neuroimaging, invasive video-EEG recording and overview of changes in antiepileptic drug treatment.

Pt	FU	MRI	Ictal onset (invasive video-EEG recording)	AED pre-DBS	AED tapering period	AED at maximal FU	Seizure frequency reduction
1	117	Normal	L focal MT	PHT 300, CZP 3, CBZ 1000, LTG 100	PHT 300, CZP 3	LEV 4000, CZP 3, PHT 300, LAC 400	$\geq$ 90%
2	120	Normal	L focal MT	VPA 1600, GBP 2800, TGB 10	VPA 1000	VPA 1750, PB 75, LEV 2500, CLB 5	$\geq$ 90%
3	115	Normal	R regional MT	PHT 300, CBZ 1600, PRM 375	PHT 300, CBZ 1600	CBZ 1600, PB 60, LEV 2000	NR
4	111	Normal	R regional MT	VPA 1000, LEV 2000, CLB 10	VPA 500, LEV 2000	LEV 2000, VPA 500, PGB 600	$\geq$ 90%
5	110	Normal	L regional MT with early right-sided involvement	CBZ 1200, GBP 900, PHT 300	CBZ 1200, PHT 300	CZP 0,25, LEV 3000, PGB 600, LCM 400	70%
6	106	L HS and ant neocortical T scl	L regional MT	CBZ 1000, LTG 200, VGB 2000	LTG 450	LEV 2000, LTG 450, CZP 1	100%
7	106	Normal	R regional MT	LTG 400, TPM 400	LTG 300	LEV 2000, PGB 900, LTG 400	NR
8	92	L HS	L focal MT	VPA 1500, LTG 400, LEV 3000	LTG 400, LEV 3000	LEV 3000, LTG 400	100%
9	86	Normal	B focal MT (L > R)	CBZ 800, VPA 1000, CZP 1	CBZ 800	LTG 400, CBZ 800	40%
10	86	B P WML	L focal MT	CBZ 900, GBP 1200, PHT 300, LEV 1000	CBZ 600, PHT 450	CBZ 600, PHT 450, CZP 2	100%
11	67	R HS	B regional	CBZ 1000, LEV 3000, PGB 600	CBZ 800, LEV 2500, PGB 600	PGB 600, CBZ 800, LEV 2500	50%

Note: Pt: patient number; MRI: magnetic resonance imaging; FU: follow-up; AED: antiepileptic drug treatment; pre-DBS: during the pre-intervention baseline period; HS: hippocampal sclerosis; L: left; R: right; P WML: parietal white matter lesions; MT: medial temporal; PHT: phenytoin; CZP: clonazepam; CBZ: carbamazepine; LTG: lamotrigine; VPA: valproic acid; GBP: gabapentin; TGB: tiagabine; PRM: primidone; LEV: levetiracetam; CLB: clobazam: VGB: vigabatrin; TPM: topiramate; PB: phenobarbital; PGB: pregabalin; LCM: lacosamide.

Table 2. Overview of changes in mean monthly seizure frequency, stimulation protocol and antiepileptic drug treatment during follow-up.

Pt	**PRE**	**Yr 1**	St P	**Yr 2**	St P	**Yr 3**	St P	**Yr 4**	St P	**Yr 5**	St P	**Yr 6**	St P	**Yr 7**	St P	**Yr 8**	St P	**Yr 9**	St P	**Yr 10**	St P	**SFR**	**Off**	Durat	Yr
1	**30/4**	**1/0,5**	1,5 ah	**1,5/0** i	1,5 ah	**0,5/0**	2,5 ah	**0,5/0**	2,5 ah	**0,5/0**	2,5 ah	**0,5/0**	2,5 ah	**0,5/0**	2,5 ah	**1/0**	2,5 ah	**1/0** i	2,5 ah	**0,5/0**	2,5 ah	**≥ 90%**			
2	**30/0**	**6,5/0**	1,5 ah	**5/0** i, i	1,6 ah	**5/0**	rm	**5/0**	rm	**10/0** D+	rm	**7/0** D-	2,0 BH	**2/0** d+	2,4c bh	**1,5/0** d+	1,0c bh	**3/0**	1,4c bh	**2,5/0** I	2,5c bh	**≥ 90%**	**7,5/0**	33	3–5
3	**4/0**	**3,5/0**	1,0 ah	**4/0**	1,5 ah	**7/0** i	2,0 ah	**3/0**	2,0 ah	**2/0**	0,0 ah	**4/0**	1,5 BH	**5,5/0** i	2,0 bh	**5/0** D+, d-	2,0 bh	**5/0** d-	2,0 bh	**7/0** t, s, d+	2,0 bh	**< 30%**	**2,5/0**	8	5–6
4	**20/0**	**15/0**	1,0 ah	**15/0**	2,2 ah	**15/0**	2,5 ah	**14/0** i	2,0 BH	**6/0**	2,4 bh	**1/0**	2,2c bh	**2/0**	2,2c bh	**0*/0** D+	2,2c bh	**0,5/0**	2,2c bh	**1/0**	2,2c bh	**≥ 90%**	**24,0**	3	3
5	**8/2**	**2,5/2**	1,5 ah	**3/2,5**	2,0 ah	**2,5/1** i	2,5 H	**3/1**	3,0 h	**7/2**	1,5 BH	**3,5/1** i	2,0 bh	**4/0,5** i	2,0 bh	**3/0,5** D+, r	2,0 bh	**3/0,5** D-, s	2,4 bh	**2,5/1** d-	2,6 bh	**70%**	**3/5**	3	2
																							9,5/1	6	5
6	**12/0**	**7/0**	1,2 ah	**8/0**	2,0 ah	**7/0** i	2,2 ah	**4/0**	0,0 ah	**0/0**	0,0 ah	**0/0**	0,0 ah	**0/0**	0,0 ah	**0/0**	0,0 ah	**0/0**	0,0 ah			**100%**	**0/0**	61	4–9
7	**2/0**	**2/0**	1,7 ah	**1/0** i	2,8 ah					**1,5/0**	0,0 ah	**1,5/0** d+	1,0 H	**1,5/0** i	3,0c h	**2/0** r	3,0c h	**2,5/0** r	3,0c h			**< 30%**	**1,5/0**	>22	5–6
8	**8/0**	**3,5/0**	2,5 ah	**1/0**	3,0 ah	**0/0**	3,0 ah	**0/0**	3,0c H	**0/0**	3,0c h	**0/0**	3,0c h	**0/0**	3,0c h	**0/0**	3,0c h					**100%**	**0/0**	2	3
9	**10/0**	**8/0**	1,0 bh	**7/0** i	1,5 bh	**12/0** d+, t	1,5 bh	**6/0** t	0,0 bh	**6/0**	1,0 H	**6/0**	1,0 h	**6/0** d+	1,0 h	**6/0**	1,0 h					**40%**	**7.5/0**	(5+)6	4
10	**2/2**	**0,5/0,5**	2,0 ah	**0,5/0,5** i	2,0 ah	**1/1**	1,0 BH	**1/1**	1,0 bh	**0*/ 0***	1,5 bh	**0/0**	1,5 bh	**0/0**	1,5 bh	**0/0**	1,5 bh					**100%**	**1,5/1,5**	5	3
11	**11/0***	**6,5/0**	3,0 bh	**7/0***	3,1c bh	**8/0,5**	3,1c bh	**4/0***	3,1 bh	**5,5/0,5**	3,1 bh	**5/0,5** d+	3,1 bh									**50%**			

Note: 1. Pt: patient number; 2. PRE: preintervention *baseline seizure frequency* (complex partial seizures/generalized tonic-clonic seizures); 3. **Yr** #: *mean monthly seizure frequency* during year # (with 0^* meaning 1 or 2 seizures that year) with the *anti-epileptic drug adaptations* during that year below (i: initiation of a new anti-epileptic drug (AED); s: stop intake of one AED; t: short trial of an AED; r: replacement of one AED by another; D+/D−: major increase (> x2) or decrease (> 1/2) of the dose of one or more AEDs; d+/d-: minor increase or decrease of the dose of one AED); 4. St P: stimulation parameters at the end of the previously mentioned year, with the *output voltage in Volt* (every first row; "c" meaning day-night cycling activated; rm: pulse generator removed, no simulation) and *the stimulated sites* (every second row; ah: unilateral amgydalohippocampal; h: unilateral hippocampal; bh: bilateral hippocampal; CAPITALS indicate recent change of stimulation site); 5. SFR: *seizure frequency reduction at last six months of follow-up* compared to preintervention baseline seizure frequency; 6. Off: *mean monthly seizure frequency when DBS was discontinued* (accidentally or intentionally, see text); 7. Durat: time in months during which DBS was discontinued; 8. Yr (the far right column in the Table): year during which DBS was accidentally or intentionally discontinued.

and have a 40% (bilateral focal onset) to 50% (bilateral regional onset) seizure frequency reduction. Of the three patients with an MRI indicative of hippocampal sclerosis, 2/3 became seizure-free and 1/3 had a 50% seizure frequency reduction.

3.1. *Stimulation output, duty cycle and other stimulation parameters*

There was no correlation between outcome and *output voltage* at maximum follow-up. Adjustments in output voltage per patients per year are described in Table 2. In the majority of patients, changing the stimulation output was not intimately associated with changes in seizure frequency. Two patients however (patients 8, 10) became seizure-free shortly after output voltage increments from 1 to 1.5 and from 2.5 to 2.7, respectively. In patient 9, seizures could be provoked by augmenting the stimulation output from 1.5 to 1.6 V (5–6 seizures daily). This finding was confirmed by video-EEG monitoring during which seizures increased almost immediately after stimulation was programmed to 1.6 V, even when the patient was blinded for output voltage. In this patient DBS was discontinued for one year and a trial drug (E2007 study) was given during a five-month period. Seizure frequency was reduced from 12 to 3 per month but the trial drug was discontinued due to intolerable side effects. DBS was reinitiated at 1 V in the right medial temporal lobe where the majority of seizures (5/6) were recorded during invasive video-EEG monitoring. At maximum follow-up, seizure frequency in this patient was reduced by 40% compared to baseline.

In nine patients, MTL DBS was initiated unilaterally. In 6/9 in whom DBS failed to decrease seizures by $\geq$ 90% after 2.5–3 years, *bilateral DBS* was proposed at the time of an upcoming battery replacement and 5/6 patients consented to this change (patient 7 refused). This resulted in improved seizure control in 3/5 patients. One patient became seizure-free for more than three years (patient 10, 75% reduction with unilateral DBS) and two patients who previously had a stable 83% (patient 2) and 25% (patient 4) seizure frequency reduction achieved a steady $\geq$ 90% reduction after switching to bilateral DBS. Two patients were treated with bilateral MTL DBS from the beginning due to bilateral MTL involvement in ictal onset. One patient (patient 11) achieved a 50% reduction at maximum follow-up compared to baseline. The complicated course of patient 9 has been described above.

In 9/11 patients (seven responders and two non-responders) DBS was *discontinued* for at least one month, either intentional (patient 9, initiation of drug trial, see above), due to complications (patient 2), accidentally (patient 5 and 8) or due to an end of battery life (all other patients) (see also Table 2). Discontinuation of DBS resulted into an immediate (patient 4 and 5) or delayed (patient 2, see below) significant increase in seizure frequency in 3/7 patients, an immediate but more subtle increase in seizure frequency in 1/7 patients (patient 10), did not affect outcome in 2/7 patients (patient 8 and 9) or coincided with seizure freedom in 1/7 patients (patient 6, see below). An interesting case is patient 2 whose seizure frequency did not increase for 21 months after his battery had been removed due to local infection at the time of battery replacement. From the 17th month after battery removal on, however, he reported an increase in severity of the postictal period and after 21 months monthly seizure frequency gradually increased up to 12–18 seizures per month. Upon reinstallation of DBS, seizure frequency decreased for a second time. In 1 seizure-free patient unilateral DBS was interrupted after 46 months due to seizure freedom when end of battery life was reached with continued seizure freedom at maximum follow-up.

Day-night cycling (i.e. stimulation turned off 12 pm until 6 am) was initiated in five patients to prolong battery life after a stable seizure frequency had been reached (see also Table 2,c). In 4/5 patients, including one patient with nightly seizures this did not affect seizure frequency. In patient 11 cycling seemed to be associated with an increase in seizure frequency upon which continuous MTL DBS was successfully reinstalled.

3.2. *Anti-epileptic drugs*

During the first year of MTL DBS the aim was to keep AEDs unchanged. After the first year changes in the AED regimen were allowed according to best medical practice. Most adaptations did not seem to clearly affect seizure frequency. The mean number of AEDs during the pre-intervention baseline period and at maximum follow-up remained the same ($n = 3$). In some patients, however, altering AED

treatment did or could have had an impact on seizure frequency. In patient 4, a switch from uni- to bilateral DBS was implemented at the same time of initiation of pregabaline, whereafter seizure frequency significantly improved. This reduction in seizure frequency increased gradually over time and became maximal only 18 months after initiation of bilateral DBS and pregabaline, which may suggest a dominant effect of bilateral DBS. Second, secondary generalization seemed to occur less frequently in patient 5 after adding levetiracetam to the treatment regimen in year 7, although this could also represent a delayed effect of a switch to bilateral DBS in year 5. Third, when the battery reached end of life in patient 6, clonazepam 0.5 mg daily was initiated in expectation of battery replacement. Four months later (with unchanged seizure frequency) his battery had become completely empty and clonazepam was augmented to 1 mg daily. He became immediately seizure-free and remained so until maximum follow-up. Finally, in year 4, patient 9 participated in a new AED (E2007) trial for which DBS was turned off. Although the patient seemed to benefit from this new AED (mean seizure frequency decreased to three per month), the AED trial was stopped due to intolerable side effects after five months.

3.3. *Side effects*

Complications occurred rarely. One patient had an asymptomatic intracranial haemorrhage during the insertion of the deep brain electrodes. In one patient a cable revision was performed. As already mentioned above, one patient suffered from acute seizure induction upon output voltage increase and the implantable pulse generator had to be removed in another patient because of local infection after battery replacement that could not be resolved by systemic administration of antibiotics. Finally, none of the patients showed changes in neuropsychological testing as performed during the pre-intervention baseline period and after initiation of MTL DBS. Repeated testing in 4/5 patients who were switched from uni- to bilateral MTL DBS yielded the same conclusion.

4. Discussion

This open prospective cohort study demonstrates a long-term beneficial effect of MTL DBS in the majority of our patients. Three patients are seizure-free for more than three years, three patients have a $\geq$ 90% reduction in seizure frequency and three others have a moderate response with a seizure frequency reduction of 40%–70%.

Because this was an open trial, adaptations of the AED regimen were allowed after the first DBS year. As often in refractory epilepsy patients, this did not seem to affect seizure frequency in most patients. It should however be noted that a substantial pharmacological effect cannot be excluded in two of our patients with excellent outcome.

In the past decade no more than four epilepsy groups have reported on the efficacy of MTL DBS for MTL epilepsy.[26,30,36–38] Two studies describing results in patients treated continuously for at least one year reported outcomes comparable to the results in our patient group. Velasco *et al.* reported seizure freedom in 4/9 patients, a $\geq$ 90% reduction in one patient and a moderate response (50%–70% reduction) in four patients after a mean follow-up of three years.[30] Boëx *et al.* reported seizure freedom in 2/8 patients, a 60%–90% seizure frequency reduction in four patients and two nonresponders.[36] Two RCTs have been performed in small patient groups. Outcome was less favorable in these studies, with a mean seizure frequency reduction of 33% in two patients and a median reduction of 26% in four patients.[37,38] Apart from differences in ictal onset zone, neuroimaging findings and applied stimulation parameters, a reason for less favorable outcome may be due to the crossover design of these studies. DBS in these patients was frequently interrupted after relatively short treatment periods. Several studies have shown increased efficacy of DBS over time during the first months and years after DBS initiation.[19,28–34] This delayed efficacy was also observed in several of our patients. After 18 to 24 months of stimulation in a specific stimulation target, further improvement of seizure control is less likely to occur. In contrast to many other antiepileptic treatments, established effect is rarely lost even after years of follow-up.

When comparing the efficacy of MTL DBS (= ictal onset zone DBS) and ANT DBS, the most common form of "epileptic network DBS", overall efficacy seems to be comparable for both targets. MTL DBS ($n = 34$) resulted in a mean seizure frequency reduction of 59% (71% responders, meaning a $\geq$ 50 % reduction).[30,36–38] ANT DBS resulted in a mean 56%

reduction in small open trials ($n = 27$) (64% responders) and a median 56% reduction after two years in a large RCT[15] (responder rate 54%).[19,31,39–42] Seizure freedom is remarkably more frequent in MTL DBS (27%) compared to ANT DBS (0% in small open trials and 7% in the RCT). This may reflect differences in the treated patient populations in trials with MTL DBS compared to epileptic network stimulation trials such as the SANTE-trial in which patients with multifocal epilepsy, previous unsuccessful epilepsy surgery and/or VNS have been included and may represent a relatively more severe epilepsy population compared to patients with MTL epilepsy. In the SANTE-trial patients with MTL epilepsy were identified as a subpopulation with optimal ANT DBS efficacy.[19]

In a large RCT, responsive neurostimulation (another type of ictal onset DBS) shows a 46% responder rate after two years, which seems slightly inferior compared to responder rates in MTL DBS studies although these were almost never randomized studies and included far less patients.[20] Seizure freedom was observed in a small percentage of patients (7% seizure-free for $\geq$ 3 months). In this specific unique trial that investigated a closed-loop paradigm, these findings may be the reflection of the fact that in an individual patient responsive DBS is able to block many but not all seizures. In some cases full seizure control may not be reached not due to lack of DBS efficacy but rather due to false negative seizure detections. Increased experience of physicians in the optimization of seizure detection algorithm settings may further improve results with closed-loop systems.[43–45]

In our study, patients with a unilateral focal ictal onset showed optimal response to MTL DBS, which seems logical from a theoretical point of view. Three out of five patients with a unilateral regional onset showed seizure frequency reductions between 70 and 100%, while two were nonresponders. Regional ictal onset is defined as a more widespread distribution of early invasive EEG changes involving different electrodes. Hence, electrodes could have been implanted relatively more distant from the epileptic focus or unable to completely encompass the focus due to the limited size of the implanted electrodes.

We found less favorable outcome in patients with bilateral ictal onset. This is in contrast with findings from other studies that included slightly larger number of bilateral MTL epilepsy patients, so it seems premature to draw any conclusions on this issue.[30,36]

Due to the nature of routine clinical practice during a time span of 10 years changes in DBS regimens with intentional or accidental DBS discontinuation occurred that may reveal interesting clues toward the mechanism of action of DBS in epilepsy. Beneficial effect may be due to localized action of DBS, mimicking the effect of epilepsy surgery, or stimulation-induced modification of network activity as reflected by efficacy of DBS of remote network structures, either by neuronal inhibition or activation.[46–48] Several authors have reported immediate increases in seizure frequency after DBS discontinuation in line with findings in some of our patients.[30,34,38–40] This suggests a direct and immediate effect of DBS. In contrast, other studies have shown that in some patients, including in some of our own series, seizure frequency did not increase instantaneously following DBS discontinuation.[30,37,40,41,46,49] Besides direct stimulation-dependent effects of DBS, long-lasting neuromodulatory changes seem to play an important role, either at a molecular level or by reorganization of brain circuitry. The delayed DBS efficacy in some of our patients and in other series also fits into this neuromodulation model. The possible reversibility of these changes was illustrated in one of our patients with an increase in seizure frequency 21 months after battery removal. Similar findings have been described previously by McLachlan *et al.* and Velasco *et al.*[30,37] In some cases, the effect of DBS may be related to a microlesional effect as continued seizure freedom has been reported in individual cases after electrode implantation without any electrical stimulation.[36,50,51] Different studies have shown a substantial seizure frequency reduction after electrode implantation prior to electrical stimulation.[19,20,40,41] Two large RCT with a longer post-implantation pre-stimulation period, however, have demonstrated that this implantation effect is temporary.[19,20] Furthermore, it has been suggested that this effect is nonspecific with regard to localization in the brain.[52]

We report our findings on day-night cycling as it may provide a strategy to increase battery life after stable seizure frequency control has been reached. To our knowledge this type of cycling with the stimulator turned off between midnight and six am was

applied for the first time in this patient series. In the majority of our patients this strategy did not affect seizure control; in one patient it potentially did and returning back to continuous stimulation reinstalled previous seizure frequency. Other duty cycles mainly alternate between one minute of stimulation "on" and four to eight minutes of stimulation "off" among which one MTL DBS study.[29–31,39–41,49] One study comparing continuous and intermittent stimulation found no differences in efficacy.[40] Prospective randomized trials comparing various duty cycles in various stimulation targets are required to evaluate the full potential and practical applications of cycling.

No permanent symptomatic complications occurred during more than 93 person-years of follow-up, which is in accordance with previously published studies. In particular no major neuropsychological adverse effects occurred, even in patients undergoing bilateral MTL DBS. In previously published studies of MTL DBS, only Boëx *et al.* reported a reversible neuropsychological deterioration in two of five patients when output parameters were set too high.[36] In one of our patients increasing stimulation output consistently provoked seizures as has also been reported before.[36]

The unaffected neuropsychological performance in MTL DBS offers new treatment options especially for those patients in whom resective surgery is contra-indicated due to concerns about possible neuropsychological decline.[53–55]

Although we stated above that seizure frequency tends to remain stable after 18 to 24 months of DBS, the outcomes reported have improved considerably since our initial long-term follow-up results (mean follow-up 2.5 years).[26] This may reflect the initiation of bilateral DBS for unilateral MTL epilepsy in some of our patients who had not reached full seizure control after 2–3 years. A significant further improvement in the majority of these patients was found without additional side effect. In unilateral MTL epilepsy structural, metabolic/functional and nonepileptic clinical involvement of the contralateral MTL has been demonstrated (mainly in the hippocampus, but also in the parahippocampal gyrus, the entorhinal cortex, the temporal pole and the white matter) and is related to epilepsy duration.[56–65] Although seizure spread to the contralateral MTL often occurs in MTL epilepsy, the pathways responsible for this remain poorly understood. Multiple electrophysiological studies (mainly invasive EEG-recordings) have suggested an indirect pathway and evidence has emerged for contralateral seizure spread via the frontal lobes.[66–74] Other studies, however, are in accordance with direct interhippocampal seizure propagation in at least a substantial part of patients,[75–79] which would also be the cause of pure anamnestic seizures.[76] Studies focusing on brain anatomy have identified various potential anatomical correlates, among which the dorsal hippocampal commissure, the anterior commissure and the corpus callosum.[80–83] Although controversy about their pathophysiological role remains, these commissural structures could reflect a possible pathway of action of contralateral MTL DBS. An interesting study by Chkhenkeli *et al.* reported mutually suppressive effects of bitemporal epileptic foci and therefore suggested contralateral MTL DBS as a treatment option for MTL epilepsy.[84] They supported this hypothesis by demonstrating that MTL seizure termination occurs through acute contralateral stimulation. This result is consistent with the contralateral interictal spike rate reduction found by Boëx *et al.* during acute unilateral stimulation.[85] In conclusion, evidence exists that the contralateral MTL is involved in the MTL epileptogenic network. To our knowledge, we here reported for the first time that combined stimulation of the ictal onset zone and a remote network structure may further increase efficacy of DBS in epilepsy patients.

5. Conclusion

Our extended long-term follow-up results demonstrate that MTL DBS is a safe and efficacious treatment strategy in MTL epilepsy patients, leading to a significant and sustained seizure frequency reduction. This study is limited by the small patient number and open design preventing any relevant statistical analysis. On the other hand the careful prospective and detailed data collection over a full follow-up period of 5.5–10 years did allow to draw relevant conclusions on DBS effects over time. When comparing results in this patient series after a 2.5 year follow-up and an 8.5 year follow-up a significant number of patients gained additional seizure control. These effects may be partially due to longer DBS treatment and relevant treatment changes such as output current increases and bilateral instead

of unilateral treatment. After 18 to 24 months of stimulation with a specific stimulation protocol, further significant improvement of seizure control is less likely to occur.

With 47% of patients remaining seizure-free ten years after surgery,[12] resective surgery still performs better. Nevertheless, surgery is more invasive and contra-indicated or refused in many cases. For those patients as well as for those in whom surgery failed to improve outcome, MTL DBS seems to be a valuable alternative. This tends to be especially true for those with a focal ictal onset. Furthermore, day-night cycling does not seem to affect seizure control in the majority of patients once a stable seizure control has been reached and therefore should be tried to prolong battery life. Finally, we demonstrated further seizure frequency reduction after initiation of bilateral MTL DBS for unilateral MTL epilepsy. Future studies should investigate whether such improved outcome can also be achieved by other DBS strategies combining ictal onset zone and network structure stimulation.

Acknowledgments

Prof. Dr. K. Vonck is supported by a BOF-ZAP grant from Ghent University Hospital. Prof. Dr. P. Boon is supported by grants from FWO-Flanders; grants from BOF and by the Clinical Epilepsy Grant from Ghent University Hospital. Dr. M. Sprengers is supported by an "FWO-aspirant" grant. Marijke Miatton is supported by an FWO grant.

References

1. D. Hirtz, D. J. Thurman, K. Gwinn-Hardy, M. Mohamed, A. R. Chaudhuri and R. Zalutsky, How common are the "common" neurologic disorders? *Neurology* **68** (2007) 326–337.
2. W. A. Hauser, J. F. Annegers and L. T. Kurland, Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984, *Epilepsia* **34**(3) (1993) 453–468.
3. E. C. Wirrell, Epilepsy-related injuries, *Epilepsia* **47** (2006) 79–86.
4. T. Tomson, E. Beghi, A. Sundqvist and S. I. Johannessen, Medical risks in epilepsy: A review with focus on physical injuries, mortality, traffic accidents and their prevention, *Epilepsy Res.* **60**(1) (2004) 1–16.
5. C. W. Bazil, Comprehensive care of the epilepsy patient–control, comorbidity, and cost, *Epilepsia* **45**(6) (2004) 3–12.
6. W. J. Cardarelli and B. J. Smith, The burden of epilepsy to patients and payers, *Am. J. Manag. Care* **16**(12) (2010) S331–S336.
7. P. Kwan, S. C. Schachter and M. J. Brodie, Drug-resistant epilepsy, *N. Engl. J. Med.* **365**(10) (2011) 919–926.
8. S. Beyenburg, K. Stavem and D. Schmidt, Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: Systematic review and meta-analysis, *Epilepsia* **51**(1) (2010) 7–26.
9. S. Wiebe, W. T. Blume, J. P. Girvin and M. Eliasziw, A randomized, controlled trial of surgery for temporal-lobe epilepsy, *N. Engl. J. Med.* **345**(5) (2001) 311–318.
10. J. Engel, S. Wiebe, J. French, M. Sperling, P. Williamson, D. Spencer, R. Gumnit, C. Zahn, E. Westbrook and B. Enos, Practice parameter: Temporal lobe and localized neocortical resections for epilepsy — Report of the quality standards subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons, *Neurology* **60**(4) (2003) 538–547.
11. A. A. Cohen-Gadol, B. G. Wilhelmi, F. Collignon, J. B. White, J. W. Britton, D. M. Cambier, T. J. H. Christianson, W. R. Marsh, F. B. Meyer and G. D. Cascino, Long-term outcome of epilepsy surgery among 399 patients with nonlesional seizure foci including mesial temporal lobe sclerosis, *J. Neurosurg* **104**(4) (2006) 513–524.
12. J. de Tisi, G. S. Bell, J. L. Peacock, A. W. McEvoy, W. F. Harkness, J. W. Sander and J. S. Duncan, The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: A cohort study, *Lancet* **378**(9800) (2011) 1388–1395.
13. S. C. Schachter, Vagus nerve stimulation therapy summary: Five years after FDA approval, *Neurology* **59**(6 Suppl 4) (2002) S15–S20.
14. A. Shoeb, J. Guttag, T. Pang and S. Schachter, Non-invasive computerized system for automatically initiating vagus nerve stimulation following patient-specific identification of seizures or epileptiform discharges, *Int. J. Neural Syst.* **19** (2009) 157–172.
15. R. El Tahry, V. De Herdt, R. Raedt, A. Van Dycke, A. Meurs, F. Dewaele, P. Boon, D. Van Roost and K. Vonck, Evolution in VNS therapy for refractory epilepsy, experience with demipulse devices at Ghent University Hospital, *Seizure* **19** (2010) 531–535.
16. C. Hamani, D. Andrade, M. Hodaie, R. Wennberg and A. Lozano, Deep brain stimulation for the treatment of epilepsy, *Int. J. Neural Syst.* **19** (2009) 213–226.
17. A. Velasco, F. Velasco, M. Velasco, J. Nunez, D. Trejo and I Garcia, Neuromodulation of epileptic foci in patients with non-lesional refractory motor epilepsy, *Int. J. Neural Syst.* **19** (2009) 139–147.

18. C. H. Halpern, U. Samadani, B. Litt, J. L. Jaggi and G. H. Baltuch, Deep brain stimulation for epilepsy, *Neurotherapeutics* **5**(1) (2008) 59–67.
19. R. Fisher, V. Salanova, T. Witt, R. Worth, T. Henry, R. Gross, K. Oommen, I. Osorio, J. Nazzaro, D. Labar, M. Kaplitt, M. Sperling, E. Sandok, J. Neal, A. Handforth, J. Stern, A. DeSalles, S. Chung, A. Shetter, D. Bergen, R. Bakay, J. Henderson, J. French, G. Baltuch, W. Rosenfeld, A. Youkilis, W. Marks, P. Garcia, N. Barbaro, N. Fountain, C. Bazil, R. Goodman, G. McKhann, K. B. Krishnamurthy, S. Papavassiliou, C. Epstein, J. Pollard, L. Tonder, J. Grebin, R. Coffey, N. Graves and S. S. Grp, Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy, *Epilepsia* **51**(5) (2010) 899–908.
20. M. J. Morrell and R. S. E. S. Grp, Responsive cortical stimulation for the treatment of medically intractable partial epilepsy, *Neurology* **77**(13) (2011) 1295–1304.
21. T. Wyckhuys, P. Boon, R. Raedt, B. Van Nieuwenhuyze, K. Vonck and W. Wadman, Suppression of hippocampal epileptic seizures in the kainate rat by Poisson distributed stimulation, *Epilepsia* **51** (2010) 2297–2304.
22. T. Wyckhuys, S. Staelens, B. Van Nieuwenhuyze, S. Deleye, H. Hallez, K. Vonck, R. Raedt, W. Wadman and P. Boon, Hippocampal deep brain stimulation induces decreased rCBF in the hippocampal formation of the rat, *Neuroimage* **52** (2010) 55–61.
23. A. F. Jahangiri and D. M. Durand, Phase resetting of spiking epileptiform activity by electrical stimulation in the CA3 region of the rat hippocampus, *Int. J. Neural. Syst.* **21** (2011) 127–138.
24. L. B. Good, S. Sabesan, S. T. Marsh, K. S. Tsakalis and L. D. Iasemidis, Control of synchronization of brain dynamics leads to control of epileptic seizures in rodents, *Int. J. Neural. Syst.* **19** (2009) 173–196.
25. K. Vonck, P. Boon, E. Achten, J. De Reuck and J. Caemaert, Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy, *Ann. Neurol.* **52**(5) (2002) 556–565.
26. P. Boon, K. Vonck, V. De Herdt, A. Van Dycke, M. Goethals, L. Goossens, M. Van Zandijcke, T. De Smedt, I. Dewaele, R. Achten, W. Wadman, F. Dewaele, J. Caemaert and D. Van Roost, Deep brain stimulation in patients with refractory temporal lobe epilepsy, *Epilepsia* **48**(8) (2007) 1551–1560.
27. M. Miatton, D. Van Roost, E. Thiery, E. Carrette, A. Van Dycke, K. Vonck, A. Meurs, G. Vingerhoets and P. Boon, The cognitive effects of amygdalohippocampal deep brain stimulation in patients with temporal lobe epilepsy, *Epilepsy. Behav.* **22** (2011) 759–764.
28. F. Velasco, J. D. Carrillo-Ruiz, F. Brito, M. Velasco, A. L. Velasco, I. Marquez and R. Davis, Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures, *Epilepsia* **46**(7) (2005) 1071–1081.
29. A. L. Velasco, F. Velasco, F. Jimenez, M. Velasco, G. Castro, J. D. Carrillo-Ruiz, G. Fanghanel and B. Boleaga, Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox-Gastaut syndrome, *Epilepsia* **47**(7) (2006) 1203–1212.
30. A. L. Velasco, F. Velasco, M. Velasco, D. Trejo, G. Castro and J. D. Carrillo-Ruiz, Electrical stimulation of the hippocampal epileptic foci for seizure control: A double-blind, long-term follow-up study, *Epilepsia* **48**(10) (2007) 1895–1903.
31. I. Osorio, J. Overman, J. Giftakis and S. B. Wilkinson, High frequency thalamic stimulation for inoperable mesial temporal epilepsy, *Epilepsia* **48**(8) (2007) 1561–1571.
32. J. Vesper, B. Steinhoff, S. Rona, C. Wille, S. Bilic, G. Nikkhah and C. Ostertag, Chronic high-frequency deep brain stimulation of the STN/SNr for progressive myoclonic epilepsy, *Epilepsia* **48**(10) (2007) 1984–1989.
33. S. Khan, I. Wright, S. Javed, P. Sharples, P. Jardine, M. Carter and S. S. Gill, High frequency stimulation of the mamillothalamic tract for the treatment of resistant seizures associated with hypothalamic hamartoma, *Epilepsia* **50**(6) (2009) 1608–1611.
34. A. Franzini, G. Messina, C. Marras, F. Villani, R. Cordella and G. Broggi, Deep brain stimulation of two unconventional targets in refractory non-resectable epilepsy, *Stereotact. Funct. Neurosurg.* **86**(6) (2008) 373–381.
35. M. Velasco, F. Velasco and A. L. Velasco, Centromedian-thalamic and hippocampal electrical stimulation for the control of intractable epileptic seizures, *J. Clin. Neurophysiol.* **18**(6) (2001) 495–513.
36. C. Boex, M. Seeck, S. Vulliemoz, A. O. Rossetti, C. Staedler, L. Spinelli, A. J. Pegna, E. Pralong, J. G. Villemure, G. Foletti and C. Pollo, Chronic deep brain stimulation in mesial temporal lobe epilepsy, *Seizure* **20**(6) (2011) 485–490.
37. R. S. McLachlan, S. Pigott, J. F. Tellez-Zenteno, S. Wiebe, A. Parrent, Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: Impact on seizures and memory, *Epilepsia* **51**(2) (2010) 304–307.
38. J. F. Tellez-Zenteno, R. S. McLachlan, A. Parrent, C. S. Kubu and S. Wiebe, Hippocampal electrical stimulation in mesial temporal lobe epilepsy, *Neurology* **66**(10) (2006) 1490–1494.
39. J. F. Kerrigan, B. Litt, R. S. Fisher, S. Cranstoun, J. A. French, D. E. Blum, M. Dichter, A. Shetter, G. Baltuch, J. Jaggi, S. Krone, M. Brodie, M. Rise and N. Graves, Electrical stimulation of the anterior nucleus of the thalamus for the treatment

of intractable epilepsy, *Epilepsia* **45**(4) (2004) 346–354.
40. S. N. Lim, S. T. Lee, Y. T. Tsai, I. A. Chen, P. H. Tu, J. L. Chen, H. W. Chang, Y. C. Su and T. Wu, Long-term anterior thalamus stimulation for intractable epilepsy, *Chang Gung. Med. J.* **31**(3) (2008) 287–296.
41. D. M. Andrade, D. Zumsteg, C. Hamani, M. Hodaie, S. Sarkissian, A. M. Lozano and R. A. Wennberg, Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy, *Neurology* **66**(10) (2006) 1571–1573.
42. K. J. Lee, K. S. Jang and Y. M. Shon, Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy, *Acta. Neurochir.* **Suppl 99** (2006) 87–91.
43. S. Ghosh-Dastidar and H Adeli, Spiking neural networks, *Int. J. Neural. Syst.* **19** (2009) 295–308.
44. P. Rajdev, M. Ward and P. Irazoqui, Effect of stimulation parameters on seizure treatment in the kainate animal model, *Int. J. Neural Syst.* **21** (2011) 151–162.
45. T. S. Nelson, C. L. Suhr, D. R. Freestone, A. Lai, A. J. Halliday, K.J. McLean, A. N. Burkitt and M. J. Cook, Closed-loop seizure control with very high frequency electrical stimulation a seizure onset in the GAERS model of absence epilepsy, *Int. J. Neural Syst.* **21** (2011) 163–173.
46. A. L. Velasco, M. Velasco, F. Velasco, D. Menes, F. Gordon, L. Rocha, M. Briones and I. Marquez, Subacute and chronic electrical stimulation of the hippocampus on intractable temporal lobe seizures: Preliminary report, *Arch. Med. Res.* **31**(3) (2000) 316–328.
47. C. C. McIntyre, M. Savasta, L. Kerkerian-Le Goff and J. L. Vitek, Uncovering the mechanism(s) of action of deep brain stimulation: Activation, inhibition, or both, *Clin. Neurophysiol.* **115**(6) (2004) 1239–1248.
48. P. Jiruska, A. D. Powell, J. K. Deans and J. G. Jefferys, Effects of direct brain stimulation depend on seizure dynamics, *Epilepsia* **51**(3) (2010) 93–97.
49. R. Davis, Cerebellar stimulation for cerebral palsy spasticity, function, and seizures, *Arch. Med. Res.* **31**(3) (2000) 290–299.
50. A. Schulze-Bonhage, D. Dennig, K. Wagner, J. Cordeiro, A. Carius, S. Fauser and M. Trippel, Seizure control resulting from intrahippocampal depth electrode insertion, *J. Neurol. Neurosurg. Psychiatry* **81**(3) (2010) 352–353.
51. N. M. Katariwala, R. A. Bakay, P. B. Pennell, L. D. Olson, T. R. Henry and C. M. Epstein, Remission of intractable partial epilepsy following implantation of intracranial electrodes, *Neurology* **57**(8) (2001) 1505–1507.
52. R. P. Lesser, Remission of intractable partial epilepsy following implantation of intracranial electrodes, *Neurology* **58**(8) (2002) 1317.
53. W. B. Scoville and B. Milner, Loss of recent memory after bilateral hippocampal lesions, *J. Neurol. Neurosurg. Psychiatry* **20**(1) (1957) 11–21.
54. S. B. Bonelli, R. H. Powell, M. Yogarajah, R. S. Samson, M. R. Symms, P. J. Thompson, M. J. Koepp and J. S. Duncan, Imaging memory in temporal lobe epilepsy: Predicting the effects of temporal lobe resection, *Brain* **133**(Pt 4) (2010) 1186–1199.
55. F. Rosenow and H. Luders, Presurgical evaluation of epilepsy, *Brain* **124**(Pt 9) (2001) 1683–1700.
56. H. Jokeit, A. Ebner, S. Arnold, M. Schuller, C. Antke, Y. Huang, H. Steinmetz, R. J. Seitz and O. W. Witte, Bilateral reductions of hippocampal volume, glucose metabolism, and wada hemispheric memory performance are related to the duration of mesial temporal lobe epilepsy, *J. Neurol.* **246**(10) (1999) 926–933.
57. D. Araujo, A. C. Santos, T. R. Velasco, L. Wichert-Ana, V. C. Terra-Bustamante, V. Alexandre, C. G. Carlotti, J. A. Assirati, H. R. Machado, R. Walz, J. P. Leite and A. C. Sakamoto, Volumetric evidence of bilateral damage in unilateral mesial temporal lobe epilepsy, *Epilepsia* **47**(8) (2006) 1354–1359.
58. S. Knake, D. H. Salat, E. Halgren, M. A. Halko, D. N. Greve and P. E. Grant, Changes in white matter microstructure in patients with TLE and hippocampal sclerosis, *Epilept. Disord.* **11**(3) (2009) 244–250.
59. F. Zubler, M. Seeck, T. Landis, F. Henry and F. Lazeyras, Contralateral medial temporal lobe damage in right but not left temporal lobe epilepsy: A (1)H magnetic resonance spectroscopy study, *J. Neurol. Neurosurg. Psychiatry* **74**(9) (2003) 1240–1244.
60. M. Seeck, F. Lazeyras, K. Murphy, A. Naimi, G. P. Pizzolatto, N. de Tribolet, J. Delavelle, J. G. Villemure and T. Landis, Psychosocial functioning in chronic epilepsy: Relation to hippocampal volume and histopathological findings, *Epilept. Disord.* **1**(3) (1999) 179–185.
61. S. Dupont, Y. Samson, P. F. Van de Moortele, S. Samson, J. B. Poline, D. Hasboun, D. Le Bihan and M. Baulac, Bilateral hemispheric alteration of memory processes in right medial temporal lobe epilepsy, *J. Neurol. Neurosurg. Psychiatry* **73**(5) (2002) 478–485.
62. J. W. Lee, F. Andermann, F. Dubeau, A. Bernasconi, D. MacDonald, A. Evans and D. C. Reutens, Morphometric analysis of the temporal lobe in temporal lobe epilepsy, *Epilepsia* **39**(7) (1998) 727–736.
63. N. Bernasconi, A. Bernasconi, F. Andermann, F. Dubeau, W. Feindel and D. C. Reutens, Entorhinal cortex in temporal lobe epilepsy: A quantitative MRI study, *Neurology* **52**(9) (1999) 1870–1876.

64. W. B. Barr, M. Ashtari and N. Schaul, Bilateral reductions in hippocampal volume in adults with epilepsy and a history of febrile seizures, *J. Neurol. Neurosurg. Psychiatry* **63**(4) (1997) 461–467.
65. L. Bonilha, J. J. Halford, P. S. Morgan and J. C. Edwards, Hippocampal atrophy in temporal lobe epilepsy: The 'generator' and 'receiver', *Acta Neurol. Scand.* **125**(2) (2012) 105–110.
66. S. S. Spencer, D. D. Spencer, P. D. Williamson and R. Mattson, Combined depth and subdural electrode investigation in uncontrolled epilepsy, *Neurology* **40**(1) (1990) 74–79.
67. C. L. Wilson, M. Isokawa, T. L. Babb and P. H. Crandall, Functional connections in the human temporal lobe. I. Analysis of limbic system pathways using neuronal responses evoked by electrical stimulation, *Exp. Brain Res.* **82**(2) (1990) 279–292.
68. C. L. Wilson, M. Isokawa, T. L. Babb, P. H. Crandall, M. F. Levesque and J. Engel Jr., Functional connections in the human temporal lobe. II. Evidence for a loss of functional linkage between contralateral limbic structures, *Exp. Brain Res.* **85**(1) (1991) 174–187.
69. C. L. Wilson and J. Engel Jr., Electrical stimulation of the human epileptic limbic cortex, *Adv. Neurol.* **63** (1993) 103–113.
70. M. E. Lacruz, J. J. Garcia Seoane, A. Valentin, R. Selway and G. Alarcon, Frontal and temporal functional connections of the living human brain, *Eur. J. Neurosci.* **26**(5) (2007) 1357–1370.
71. C. E. Napolitano and M. A. Orriols, Graduated and sequential propagation in mesial temporal epilepsy: Analysis with scalp ictal EEG, *J. Clin. Neurophysiol.* **27**(4) 285–291.
72. H. Catenoix, M. Magnin, M. Guenot, J. Isnard, F. Mauguiere and P. Ryvlin, Hippocampal-orbitofrontal connectivity in human: An electrical stimulation study, *Clin. Neurophysiol.* **116**(8) (2005) 1779–1784.
73. J. P. Lieb, R. M. Dasheiff and J. Engel Jr., Role of the frontal lobes in the propagation of mesial temporal lobe seizures, *Epilepsia* **32**(6) (1991) 822–837.
74. K. M. Bertashius, Propagation of human complex-partial seizures: A correlation analysis, *Electroencephalogr Clin. Neurophysiol.* **78**(5) (1991) 333–340.
75. L. Eross, L. Entz, D. Fabo, R. Jakus, A. Szucs, G. Rasonyi, A. Kelemen, G. Barcs, V. Juhos, A. Balogh, P. Barsi, Z. Clemens and P. Halasz, Interhemispheric propagation of seizures in mesial temporal lobe epilepsy, *Ideggyogy Sz* **62**(9–10) (2009) 319–325.
76. A. L. Palmini, P. Gloor and M. Jones-Gotman, Pure amnestic seizures in temporal lobe epilepsy. Definition, clinical symptomatology and functional anatomical considerations, *Brain* **115**(Pt 3) (1992) 749–769.
77. D. King and S. Spencer, Invasive electroencephalography in mesial temporal lobe epilepsy, *J. Clin. Neurophysiol.* **12**(1) (1995) 32–45.
78. S. S. Spencer, P. D. Williamson, D. D. Spencer and R. H. Mattson, Human hippocampal seizure spread studied by depth and subdural recording: The hippocampal commissure, *Epilepsia* **28**(5) (1987) 479–489.
79. I. Rosenzweig, S. Beniczky, F. Brunnhuber, G. Alarcon and A. Valentin, The dorsal hippocampal commissure: When functionality matters, *J. Neuropsychiatry. Clin. Neurosci.* **23**(3) (2011) E45–E48.
80. C. Adam, How do the temporal lobes communicate in medial temporal lobe seizures? *Rev. Neurol. (Paris)* **162**(8–9) (2006) 813–818.
81. M. Sindou and M. Guenot, Surgical anatomy of the temporal lobe for epilepsy surgery, *Adv. Tech. Stand. Neurosurg.* **28** (2003) 315–343.
82. P. Gloor, V. Salanova, A. Olivier and L. F. Quesney, The human dorsal hippocampal commissure. An anatomically identifiable and functional pathway, *Brain* **116**(Pt 5) (1993) 1249–1273.
83. S. Colnat-Coulbois, K. Mok, D. Klein, S. Penicaud, T. Tanriverdi and A. Olivier, Tractography of the amygdala and hippocampus: Anatomical study and application to selective amygdalohippocampectomy, *J. Neurosurg.* **113**(6) (2010) 1135–1143.
84. S. A. Chkhenkeli, V. L. Towle, G. S. Lortkipanidze, J. P. Spire, E. Bregvadze, J. D. Hunter, M. Kohrman and D. M. Frim, Mutually suppressive interrelations of symmetric epileptic foci in bitemporal epilepsy and their inhibitory stimulation, *Clin. Neurol. Neurosurg.* **109**(1) (2007) 7–22.
85. C. Boex, S. Vulliemoz, L. Spinelli, C. Pollo and M. Seeck, High and low frequency electrical stimulation in non-lesional temporal lobe epilepsy, *Seizure* **16**(8) (2007) 664–669.

CHAPTER 6

Systematic review and meta-analysis on DBS and cortical stimulation in drug-resistant epilepsy

Cochrane Library

Cochrane Database of Systematic Reviews

Deep brain and cortical stimulation for epilepsy (Review)

Sprengers M, Vonck K, Carrette E, Marson AG, Boon P

Sprengers M, Vonck K, Carrette E, Marson AG, Boon P.
Deep brain and cortical stimulation for epilepsy.
Cochrane Database of Systematic Reviews 2017, Issue 7. Art. No.: CD008497.
DOI: 10.1002/14651858.CD008497.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Deep brain and cortical stimulation for epilepsy

Mathieu Sprengers[1], Kristl Vonck[1], Evelien Carrette[1], Anthony G Marson[2], Paul Boon[1]

[1]Department of Neurology, Ghent University Hospital, Ghent, Belgium. [2]Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK

Contact address: Paul Boon, Department of Neurology, Ghent University Hospital, 1K12, 185 De Pintelaan, Ghent, B-9000, Belgium. Paul.Boon@UGent.be.

Editorial group: Cochrane Epilepsy Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 7, 2017.

Citation: Sprengers M, Vonck K, Carrette E, Marson AG, Boon P. Deep brain and cortical stimulation for epilepsy. *Cochrane Database of Systematic Reviews* 2017, Issue 7. Art. No.: CD008497. DOI: 10.1002/14651858.CD008497.pub3.

ABSTRACT

Background

Despite optimal medical treatment, including epilepsy surgery, many epilepsy patients have uncontrolled seizures. Since the 1970s interest has grown in invasive intracranial neurostimulation as a treatment for these patients. Intracranial stimulation includes both deep brain stimulation (DBS) (stimulation through depth electrodes) and cortical stimulation (subdural electrodes). This is an updated version of a previous Cochrane review published in 2014.

Objectives

To assess the efficacy, safety and tolerability of DBS and cortical stimulation for refractory epilepsy based on randomized controlled trials (RCTs).

Search methods

We searched the Cochrane Epilepsy Group Specialized Register on 29 September 2015, but it was not necessary to update this search, because records in the Specialized Register are included in CENTRAL. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2016, Issue 11, 5 November 2016), PubMed (5 November 2016), ClinicalTrials.gov (5 November 2016), the WHO International Clinical Trials Registry Platform ICTRP (5 November 2016) and reference lists of retrieved articles. We also contacted device manufacturers and other researchers in the field. No language restrictions were imposed.

Selection criteria

RCTs comparing deep brain or cortical stimulation versus sham stimulation, resective surgery, further treatment with antiepileptic drugs or other neurostimulation treatments (including vagus nerve stimulation).

Data collection and analysis

Four review authors independently selected trials for inclusion. Two review authors independently extracted the relevant data and assessed trial quality and overall quality of evidence. The outcomes investigated were seizure freedom, responder rate, percentage seizure frequency reduction, adverse events, neuropsychological outcome and quality of life. If additional data were needed, the study investigators were contacted. Results were analysed and reported separately for different intracranial targets for reasons of clinical heterogeneity.

Main results

Twelve RCTs were identified, eleven of these compared one to three months of intracranial neurostimulation with sham stimulation. One trial was on anterior thalamic DBS (n = 109; 109 treatment periods); two trials on centromedian thalamic DBS (n = 20; 40 treatment periods), but only one of the trials (n = 7; 14 treatment periods) reported sufficient information for inclusion in the quantitative meta-analysis; three trials on cerebellar stimulation (n = 22; 39 treatment periods); three trials on hippocampal DBS (n = 15; 21 treatment periods); one trial on nucleus accumbens DBS (n = 4; 8 treatment periods); and one trial on responsive ictal onset zone stimulation (n = 191; 191 treatment periods). In addition, one small RCT (n = 6) compared six months of hippocampal DBS versus sham stimulation. Evidence of selective reporting was present in four trials and the possibility of a carryover effect complicating interpretation of the results could not be excluded in five cross-over trials without any or a sufficient washout period.

Moderate-quality evidence could not demonstrate statistically or clinically significant changes in the proportion of patients who were seizure-free or experienced a 50% or greater reduction in seizure frequency (primary outcome measures) after one to three months of anterior thalamic DBS in (multi)focal epilepsy, responsive ictal onset zone stimulation in (multi)focal epilepsy patients and hippocampal DBS in (medial) temporal lobe epilepsy. However, a statistically significant reduction in seizure frequency was found for anterior thalamic DBS (mean difference (MD), -17.4% compared to sham stimulation; 95% confidence interval (CI) -31.2 to -1.0; high-quality evidence), responsive ictal onset zone stimulation (MD -24.9%; 95% CI -40.1 to -6.0; high-quality evidence) and hippocampal DBS (MD -28.1%; 95% CI -34.1 to -22.2; moderate-quality evidence). Both anterior thalamic DBS and responsive ictal onset zone stimulation do not have a clinically meaningful impact on quality life after three months of stimulation (high-quality evidence).

Electrode implantation resulted in postoperative asymptomatic intracranial haemorrhage in 1.6% to 3.7% of the patients included in the two largest trials and 2.0% to 4.5% had postoperative soft tissue infections (9.4% to 12.7% after five years); no patient reported permanent symptomatic sequelae. Anterior thalamic DBS was associated with fewer epilepsy-associated injuries (7.4 versus 25.5%; P = 0.01) but higher rates of self-reported depression (14.8 versus 1.8%; P = 0.02) and subjective memory impairment (13.8 versus 1.8%; P = 0.03); there were no significant differences in formal neuropsychological testing results between the groups. Responsive ictal-onset zone stimulation seemed to be well-tolerated with few side effects.The limited number of patients preclude firm statements on safety and tolerability of hippocampal DBS.

With regards to centromedian thalamic DBS, nucleus accumbens DBS and cerebellar stimulation, no statistically significant effects could be demonstrated but evidence is of only low to very low quality.

Authors' conclusions

Except for one very small RCT, only short-term RCTs on intracranial neurostimulation for epilepsy are available. Compared to sham stimulation, one to three months of anterior thalamic DBS ((multi)focal epilepsy), responsive ictal onset zone stimulation ((multi)focal epilepsy) and hippocampal DBS (temporal lobe epilepsy) moderately reduce seizure frequency in refractory epilepsy patients. Anterior thalamic DBS is associated with higher rates of self-reported depression and subjective memory impairment. There is insufficient evidence to make firm conclusive statements on the efficacy and safety of hippocampal DBS, centromedian thalamic DBS, nucleus accumbens DBS and cerebellar stimulation. There is a need for more, large and well-designed RCTs to validate and optimize the efficacy and safety of invasive intracranial neurostimulation treatments.

PLAIN LANGUAGE SUMMARY

Electrical stimulation through implanted electrodes in contact with the brain to treat drug-resistant epilepsy

Background

Despite many antiepileptic drugs being available, about 30% of epilepsy patients are not seizure-free. Electrical stimulation through implanted electrodes in contact with the brain (i.e. intracranial electrical stimulation, referring to 'deep brain stimulation' and 'cortical brain stimulation') has been proposed as an alternative treatment for these patients. This review aimed to evaluate its efficacy, safety and tolerability.

Results

Various brain structures have been targeted with scheduled (that is seizure-independent) stimulation, including the anterior thalamic nucleus (one trial, 109 participants), the centromedian thalamic nucleus (two trials, 20 participants), the cerebellar cortex (three trials, 22 participants), the hippocampus (four trials, 21 participants) and the nucleus accumbens (one trial; 4 participants). In addition, one trial (191 participants) studied responsive stimulation (that is only upon seizure detection) of the seizure onset zone. There is evidence for a moderate (15% to 30%) seizure frequency reduction after short-term (one to three months) anterior thalamic nucleus stimulation in (multi)focal epilepsy, hippocampal stimulation in temporal lobe epilepsy and responsive seizure onset zone stimulation in (multi)focal epilepsy. However, there is no evidence for significant impact on seizure freedom, the proportion of patients with a greater than 50% seizure frequency reduction, or quality of life.

Adverse effects of anterior thalamic stimulation include self-reported depression and subjective memory impairment, and possibly anxiety and confusional state. Responsive seizure onset zone stimulation seemed to be well-tolerated with few side effects.

Evidence on anterior thalamic and responsive ictal onset zone stimulation is of moderate to high quality, whereas the evidence on hippocampal stimulation is of low to moderate quality. There is insufficient evidence to make firm conclusive statements on the efficacy or side effects of hippocampal, centromedian thalamic, cerebellar cortical and nucleus accumbens stimulation. Intracranial implantation of the electrodes was relatively safe without permanent symptomatic sequelae in the patients included in the trials.

Conclusions

More, larger and well-designed trials on intracranial electrical stimulation treatments are needed to validate and optimize its efficacy and safety and to compare this treatment to currently available treatments (for example, antiepileptic drugs or vagus nerve stimulation).

The evidence is current to 5 November 2016.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Anterior thalamic nucleus stimulation for refractory epilepsy

Patient or population: adults with IQ > 70 with refractory focal epilepsy
Settings: epilepsy centres in the USA
Intervention: anterior thalamic nucleus stimulation
Comparison: sham stimulation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Sham stimulation	Anterior Thalamic Nucleus stimulation				
Seizure freedom (3-month blinded evaluation period)	**Observed in** Fisher 2010		**OR 0.33** (0.01 to 8.36)	109 (1)	⊕⊕⊕◯ **moderate**[2]	
	1 per 55	**0 per 54** (0 to 7)				
	Low risk population[1]					
	1 per 1000	**0 per 1000** (0 to 8)				
	High risk population[1]					
	15 per 1000	**5 per 1000** (0 to 113)				
Responder rate (3-month blinded evaluation period)	**26 per 100**	**30 per 100** (15 to 49)	**OR 1.20** (0.52 to 2.80)	108 (1)	⊕⊕⊕◯ **moderate**[2]	

Seizure frequency reduction (%) (3-month blinded evaluation period)	Median monthly seizure frequency reductions ranged from **-14.5 to -28.7%**	The mean seizure frequency in the intervention group was **-17.4% lower** (-31.2 to -1.0% lower)	108 (1)	⊕⊕⊕⊕ **high**[3]	A trend for increasing efficacy over time was observed during the blinded evaluation period and could result into an underestimation of the treatment effect (treatment effect of month 3: -29%)
Adverse events	See comment	See comment	109 (1)	⊕⊕⊕○ **moderate**[2]	Stimulation-related adverse events during the blinded evaluation period include (stimulation versus control): depression (14.8 versus 1.8%, P = 0.02), subjective memory impairment (13.8 versus 1.8%, P = 0.03) and epilepsy-related injuries (7.4 versus 25.5%, P = 0.01). Standard stimulation parameters could be inappropriate and increase seizure frequency in a small minority of patients.[4] Asymptomatic intracranial haemorrhages occurred in 3.7% of participants after the initial implant procedure. In 8.2%of participants leads had to be replaced after

					initial implantation outside the target. Postoperative implant site infections occurred in 4.5% of participants, increasing to 12.7% after 5 years of follow-up urging (temporary) hardware removal in 8.2% of participants. Implant site pain was not uncommon (year 1: 10.9%, year 5: 20.9%). SUDEP rate during long-term (including open-label) follow-up was 2.9 per 1000 p-y which is comparable to rates reported in refractory epilepsy populations (2.2-10 per 1000 p-y) (Tellez-Zenteno 2005; Tomson 2008).
Neuropsychological outcome (3 months)	See comment	See comment	96-100 (1)	⊕⊕⊕○ **moderate**[5]	Changes in neuropsychological test scores for cognition and mood were very similar in the treatment and control group and not significantly different. Individual patient data show worsening (> 1 SD) of Profile of Mood States Depression subscale (POMS-D) in 3/8 stimulated partici-

					pants with self-reported depression and 0/7 patients with subjective memory impairment showed worsening (> 1 SD) of verbal or visual memory scores
Quality of life (QOLIE-31) (3 months)	The mean improvement of the QOLIE-31 score in the control group was **+2.8 higher**	The mean improvement in QOLIE-31 score in the intervention group was **-0.30 lower** (-3.50 lower to +2.90 higher)	105 (1)	⊕⊕⊕⊕ **high**	Positive changes in QOLIE-31 (quality of life in epilepsy 31) scores indicate improvement. Changes of 5-11.7 have been defined in literature as being clinically meaningful (Borghs 2012; Cramer 2004; Wiebe 2002).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **SUDEP:** sudden unexpected death in epilepsy patients; **p-y:** patient-years; **SD:** standard deviation

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The assumed risks (low and high) are based on the range of the number of events observed in the sham stimulation control groups of all RCTs evaluating deep brain and cortical stimulation in refractory epilepsy patients
[2] More trials and patients are needed to allow more precise estimation of stimulation effects (including more rare adverse effects) (GRADE -1).
[3] The confidence interval includes clinically non-significant changes (GRADE -1), however, the observed trend for increasing efficacy over time probably underestimates the treatment effect (GRADE +1).
[4] One participant experienced a spectacular seizure frequency increase after initiation of stimulation, which was reversible after lowering output voltage. New or worse seizures occurred more frequently in the stimulation group compared to the control group but differences did not reach statistical significance.

[5] Although clinically meaningful differences in formal neuropsychological testing results seem unlikely on the group level, the discrepancy between objective and subjective measures needs further clarification (GRADE -1).

BACKGROUND

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews (the Cochrane Library, 2014, Issue 6; Sprenger 2014).

Description of the condition

Epilepsy is a common neurological disorder affecting 0.5% to 1% of the population (Forsgren 2005). More than 30% of all patients with epilepsy suffer from uncontrolled seizures or have unacceptable medication-related side effects (Kwan 2000). Alternative treatment options are available for patients with refractory seizures. Addition of newly developed antiepileptic drugs to the treatment regimen may result in freedom from seizures in this population group. However, the chance of becoming seizure-free with this strategy is limited and estimated to be around 6% when compared to placebo (Beyenburg 2009). Surgery for epilepsy leads to long-term freedom from seizures in approximately 58% to 65% of suitable surgery candidates (Engel 2003; West 2015). For the remainder, few options are left and neurostimulation may provide an alternative treatment (Engel 2003).

Description of the intervention

Both extracranial (vagus nerve stimulation) and intracranial (deep brain stimulation (DBS) and cortical (neocortex and cerebellar cortex) stimulation) neurostimulation have been used as treatments for epilepsy (Boon 2007a). Intracranial stimulation is the direct application of an electrical current to central nervous system structures by means of implanted (DBS) or subdural (cortical stimulation) electrodes connected to an implantable pulse generator.

How the intervention might work

The precise mechanism of action of DBS still needs to be elucidated. Several mechanisms of action have been proposed. By continuous application of current via the electrodes, the targeted brain structures may be (functionally) inhibited. This is done in a reversible manner since the stimulation can be stopped at any time. The effect of the inhibition depends on the targeted structures, thus depending on the location of the implanted electrodes in the brain. Stimulation of electrodes placed in the epileptic onset region (for example, the hippocampus) may lead to 'local' inhibition of the hyperexcitable region and to seizure suppression. Stimulation of electrodes placed in key structures responsible for seizure propagation (for example, the thalamus) may additionally lead to suppression of seizure spread, based on the connections between the area of stimulation and other parts of the central nervous system. This may provide a likely hypothesis when crucial structures in the epileptogenic networks are involved (Boon 2007a).

Why it is important to do this review

For both deep brain and cortical stimulation, several uncontrolled and unblinded trials with discongruent results and high risk of bias exist. Randomized controlled trials have been performed but not systematically reviewed. Until now, no clear descriptions of the outcomes and side effects have been available. The aim of this systematic review is to give an overview of the current evidence for the use of DBS and cortical stimulation as treatments for refractory epilepsy.

OBJECTIVES

To assess the efficacy, safety and tolerability of deep brain and cortical stimulation for refractory epilepsy based on randomized controlled trials.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) investigating deep brain or cortical stimulation in patients with refractory epilepsy were selected. Blinded as well as unblinded studies were considered for inclusion in this review.

Types of participants

Patients with refractory epilepsy with partial or generalized seizures, or both. Partial seizures are found in a localization-related form of epilepsy in which seizure semiology or findings from investigations disclose a localized origin of the seizures. With generalized seizures the first clinical changes indicate involvement of both hemispheres (ILAE classification). Patients are considered to be refractory if they suffer from uncontrolled seizures despite adequate treatment with at least two first-line antiepileptic drugs (either as monotherapy or in combination) that are appropriate for the epileptic syndrome, or they experience unacceptable medication-related side effects. In adults, at least two years of treatment is recommended before drug-resistant epilepsy can be diagnosed (Kwan 2010; Kwan 2009).

Both patients with normal and abnormal magnetic resonance imaging (MRI) were included. Patients who had undergone other treatments besides antiepileptic drugs (for example, resective surgery or vagus nerve stimulation) were also included.

Types of interventions

Deep brain stimulation (DBS) (in different intracranial regions) or cortical (neocortex or cerebellar cortex) stimulation. Both treatments could have been compared to a control patient group: 1) receiving sham stimulation, 2) undergoing resective surgery, 3) being further treated with antiepileptic drugs, or 4) other neurostimulation treatments (including vagus nerve stimulation), depending on the study protocol.

Types of outcome measures

Primary outcomes

(1) Seizure freedom: the proportion of participants that was free of seizures (complete absence of seizures, comparable with Engel classification class I (Jehi 2008)) during the randomized period, i.e. the phase of the trial during which, according to treatment allocation, one group of patients received the intracranial neurostimulation treatment and the other group the control treatment (in contrast to open-label follow-up periods of the same trials during which (nearly) all patients received the neurostimulation treatment under investigation in an unblinded manner, without any control group).
(2) Responder rate: proportion of patients with at least a 50% seizure frequency reduction, compared to the baseline period, throughout the randomized period.

Secondary outcomes

(1) Seizure frequency reduction: percentage reduction in seizure frequency during the randomized phase of the trial compared to baseline. When the needed data were not presented in the respective article, they were calculated (if raw data were present) or the authors were contacted. When necessary to avoid treatment effects > 100%, we directly compared 'on' to 'off' stimulation periods instead of referring to baseline seizure frequency (as for Van Buren 1978, see also Appendix 1).
(2) Adverse events: adverse events occurring throughout the randomized period; the primary focus is on the comparison of the different randomized groups; to inform the reader adverse events related to the surgical procedure or the chronic presence of an implanted device (e.g. infection, haemorrhage) occurring in trials comparing active to sham stimulation (and thus in both groups) are also reported (including open-label data, if applicable).
(3) Neuropsychological testing: results of neuropsychological testing during or at the end of the randomized period.
(4) Quality of life: results of questionnaires concerning quality of life that were completed during or at the end of the randomized period.

Search methods for identification of studies

Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 1) in the Cochrane Library (searched 10 February 2015);

Electronic searches

We searched the following electronic databases, without any language restrictions:
(1) Cochrane Epilepsy Group Specialized Register (29 September 2015), using the search strategy outlined in Appendix 2. It is not necessary to update this search, because records in the Specialized Register are included in CENTRAL;
(2) Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 11), in the Cochrane Library2016, Issue 11 (searched 5 November 2016), using the search strategy outlined in Appendix 2;
(3) PubMed (5 November 2016), using the search strategy outlined in Appendix 2;
(4) ClinicalTrials.gov (5 November 2016), using the search strategy outlined in Appendix 2; and
(5) the WHO International Clinical Trials Registry Platform ICTRP (5 November), using the search strategy outlined in Appendix 2.

Searching other resources

We reviewed the reference lists of retrieved studies to search for additional reports of relevant studies.
We contacted authors of relevant trials identified by our search, other researchers in the field, and manufacturers of the devices to identify unpublished or ongoing studies, or studies published in non-English journals.

Data collection and analysis

Selection of studies

Four review authors (Mathieu Sprengers (MS), Kristl Vonck (KV), Evelien Carrette (EC) and Paul Boon (PB)) independently assessed the identified trials for inclusion. Any disagreements were resolved by discussion and by involving another review author (Anthony Marson (AM)).

Data extraction and management

Relevant data were extracted into a prespecified data extraction form by two review authors (MS and KV). If additional data were needed, we contacted the investigators of the studies. Disagreements were resolved by discussion.
The following data were extracted.

(1) Methodological and trial design:

(a) method of randomization and sequence generation;
(b) method of allocation concealment;
(c) blinding methods (patient, physician, outcome assessor);
(d) information about sponsoring;
(e) whether any participants had been excluded from reported analyses;
(f) duration of period between implantation and start of the treatment period;
(g) duration of treatment period and, in the case of a cross-over design, washout period;
(h) antiepileptic drug (AED) policy.

(2) Participants and demographic information:

(a) number of participants allocated to each treatment group;
(b) age and sex;
(c) information about type of epilepsy and seizures types;
(d) duration of epilepsy;
(e) additional information if applicable and available (intellectual capacities, neuroimaging results).

(3) Intervention:

(a) stimulation target;
(b) output voltage and current;
(c) stimulation frequency;
(d) pulse width;
(e) continuous, intermittent or responsive ('closed-loop') stimulation.

(4) Outcomes:

(a) seizure freedom;
(b) responder rate;
(c) seizure frequency reduction;
(d) adverse events;
(e) neuropsychological outcome;
(f) quality of life.

Assessment of risk of bias in included studies

The methodological quality of the studies was independently evaluated by two review authors (MS and KV) according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)

1. The risk of bias was assessed for each individual study using the Cochrane Collaboration's tool for assessing risk of bias.

2. Randomization: only RCTs were included in this review. We planned to exclude studies with inadequate methods of allocation concealment.

3. Blinding of participants, personnel and outcome assessors: double-blind studies were preferred but single-blind and even unblinded (comparison to resective surgery or antiepileptic drugs) studies were also eligible for inclusion in the review.

4. Incomplete outcome data: this was evaluated separately for each study. We planned to exclude studies where losses to follow-up differed significantly between the treatment and control groups.

5. Selective reporting: this was evaluated separately for each study (selective outcome reporting) and, furthermore, if sufficient studies were identified, we planned to explore if there was any evidence of publication bias using funnel plots.

Several studies have reported results that may be consistent with an outlasting effect after intracranial stimulation (Andrade 2006; Lim 2007; McLachlan 2010; Velasco 2007). Such an effect could mask or reduce any treatment effect if seizure frequency in the control group is evaluated after previous stimulation without an adequate washout period. As there is no general consensus concerning this outlasting effect, we judged the risk of bias in such studies as 'uncertain', whereas studies without prior stimulation or with an adequate washout period were classified as 'at low risk of bias'. Finally, we also made judgements if antiepileptic drugs were changed during the trial as this could also influence observed treatment effects.

Measures of treatment effect

We planned to express results of categorical outcomes as risk ratios (RR) with 95% confidence intervals (CIs). However, to combine results from parallel-group (unpaired data) and cross-over trials (paired data), we used the method described by Curtin 2002, Elbourne 2002 and Stedman 2011. This method makes use of maximum likelihood estimate odds ratios (OR) (Mantel-Haenszel ORs) for parallel trials and marginal Becker-Balagtas ORs (Becker 1993) for cross-over trials. Treatment effects of continuous outcomes were expressed as mean differences (MDs) with 95% CIs. Although quality of life was evaluated using the QOLIE-89, QOLIE-31 (abbreviated version of QOLIE-89) and QOLIE-31-P (slightly modified version of QOLIE-31) questionnaires in different trials, we chose the MD approach instead of the standardized mean difference (SMD) approach. Firstly, all questionnaires have the same range, and for the QOLIE-31 and QOLIE-89 questionnaires, very similar means, standard deviations(SDs) and minimally clinically important change values in the same population have been reported (Cramer 1998; Devinsky 1995; Wiebe 2002); although we could not find similar studies also incorporating QOLIE-31-P scores, the QOLIE-31-P is an only slightly modified version of the QOLIE-31 questionnaire. Secondly, we thought the MD approach would introduce less error then the SMD approach, which attributes differences in SDs entirely to differences in measurement scales and ignores real differences in variability among study populations. Finally, unlike the SMD approach, the MD approach allows us to combine final values and change scores. In view of the difficulty in combining neuropsychological data from various studies, we summarized the data for

this outcome only qualitatively in the text. The same was true for adverse events, due to their diverse nature.

Unit of analysis issues

Results from cross-over trials were analysed and incorporated in the meta-analysis as paired data, using the approach proposed by Curtin 2002.

Dealing with missing data

Where data for our chosen outcomes were not provided in trial reports, we contacted the original investigators and further data were requested. If raw data were available, missing outcomes were calculated, if possible (for example, seizure frequency reduction). When losses to follow-up differed significantly between the treatment and control groups and if sufficient individual patient data were available, we planned to perform sensitivity analyses using 'best case scenario' (treatment group: not seizure-free, responder, 95% seizure frequency reduction, QOLIE-score +20; control group: not seizure-free, no responder, 95% seizure frequency increase, QOLIE-score -20), 'worst case scenario' (the opposite of the best case scenario) and 'last observation carried forward' LOCF) data imputation.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the clinical and trial characteristics, and a judgement was made as to whether significant clinical heterogeneity was present. Statistical inconsistency was assessed by visual inspection of the forest plots and by using the I^2 statistic (with an I^2 statistic of 30% or higher representing substantial heterogeneity) and the Chi^2 test (Q test, significance level set at a P value of 0.10).

Data synthesis

If neither clinical nor statistical heterogeneity were found, results were pooled using a fixed-effect model. We planned to use the Mantel-Haenszel method for dichotomous outcomes and the inverse variance method for continuous outcomes. However, to combine data from parallel and cross-over trials we had to use the generic inverse variance method. This approach also allowed incorporation of treatment effects estimated by regression and other models.

Subgroup analysis and investigation of heterogeneity

Stimulation of different intracranial structures may not be equally effective and lead to different adverse events. Therefore, results were not pooled across different targets but were presented per individual target for reasons of clinical heterogeneity.

As there is some evidence that the efficacy of deep brain and cortical stimulation treatments may increase over time (see also Discussion), results were pooled per three-month stimulation epochs (one to three months of stimulation, four to six months of stimulation etc) as planned in the previous version of this review.

Sensitivity analysis

Various sensitivity analyses were planned before any trial had been identified. First, if sufficient studies were found, we planned to assess the effect of study quality on the outcome. Second, because we initially planned to express results of categorical outcomes as RR instead of OR, we performed a sensitivity analysis using RR as described by Zou 2007. In summary, they show that, while two odds ratios (ORs) can be calculated in a pair-matched study with binary outcome data (the conditional and the marginal OR), there is only one RR for such design. In their article, they provide formulae to directly estimate the RR and its variance from the raw data (instead of obtaining these by conversion of ORs). Third, an increasing efficacy over time has been suggested for various neurostimulation treatments, including intracranial cortical and DBS. Therefore we planned to analyze and pool the outcome data per three-month stimulation epochs (see above). As separate data per three-month epoch are not always available in trials with a longer duration of follow-up, we planned to perform a sensitivity analysis pooling outcome data obtained after different durations of follow-up, but only if there was no evidence of clinical heterogeneity. Fourth, if different strategies could be followed, we planned to analyse their consequences in a sensitivity analysis.

Some sensitivity analysis were planned in the context of general foreseeable problems after study identification but before any data analysis was done. First, empty cells hinder calculation of ORs or RRs. In these situations, it is customary to add +0.5 to each cell (Deeks 2011). Given the small number of included patients in most trials, we examined in a sensitivity analysis if adding + 0.25 instead of +0.5 would change our conclusions. Second, when necessary to avoid treatment effects > 100%, we directly compared 'on' to 'off' stimulation periods instead of referring to baseline seizure frequency (see above and see Appendix 1). We therefore performed an analysis taking baseline seizure frequency as a reference (and thus allowing treatment effects > 100%) as a sensitivity analysis.

Finally, several post-hoc sensitivity analyses were only made after encountering some specific problems associated with particular trials or meta-analyses: as the two participants in McLachlan 2010 experienced very similar treatment effects, the standard error (SE) associated with the MD in seizure frequency in this study was the lowest among all trials on hippocampal stimulation. In this way, this very small cross-over study (n = 2) substantially influenced the pooled mean treatment effect. As its weight in the standard analysis appeared disproportionally high (94%), we checked the robustness of the conclusions to the other extreme situation in which the SE of this trial would be (equal to) the highest of all trials on hippocampal DBS.

In Fisher 1992 there was one patient who seemed to benefit from the stimulation but who was dropped from the blinded protocol due to a seizure frequency increase during the washout period. The absence of stimulation OFF data therefore prevented inclusion of the stimulation ON data of this patient in the paired data analysis. Besides 'best and worst case scenario' sensitivity analyses (see above), we also performed a sensitivity analysis with unpaired data analysis allowing us to include all available data, but without any data imputation.

'Summary of findings' tables

The data are summarized per stimulation target in 'Summary of findings' tables. All outcome parameters investigated in the review are incorporated into the tables. The quality of evidence contributing to these outcomes was judged using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria (Guyatt 2008).

RESULTS

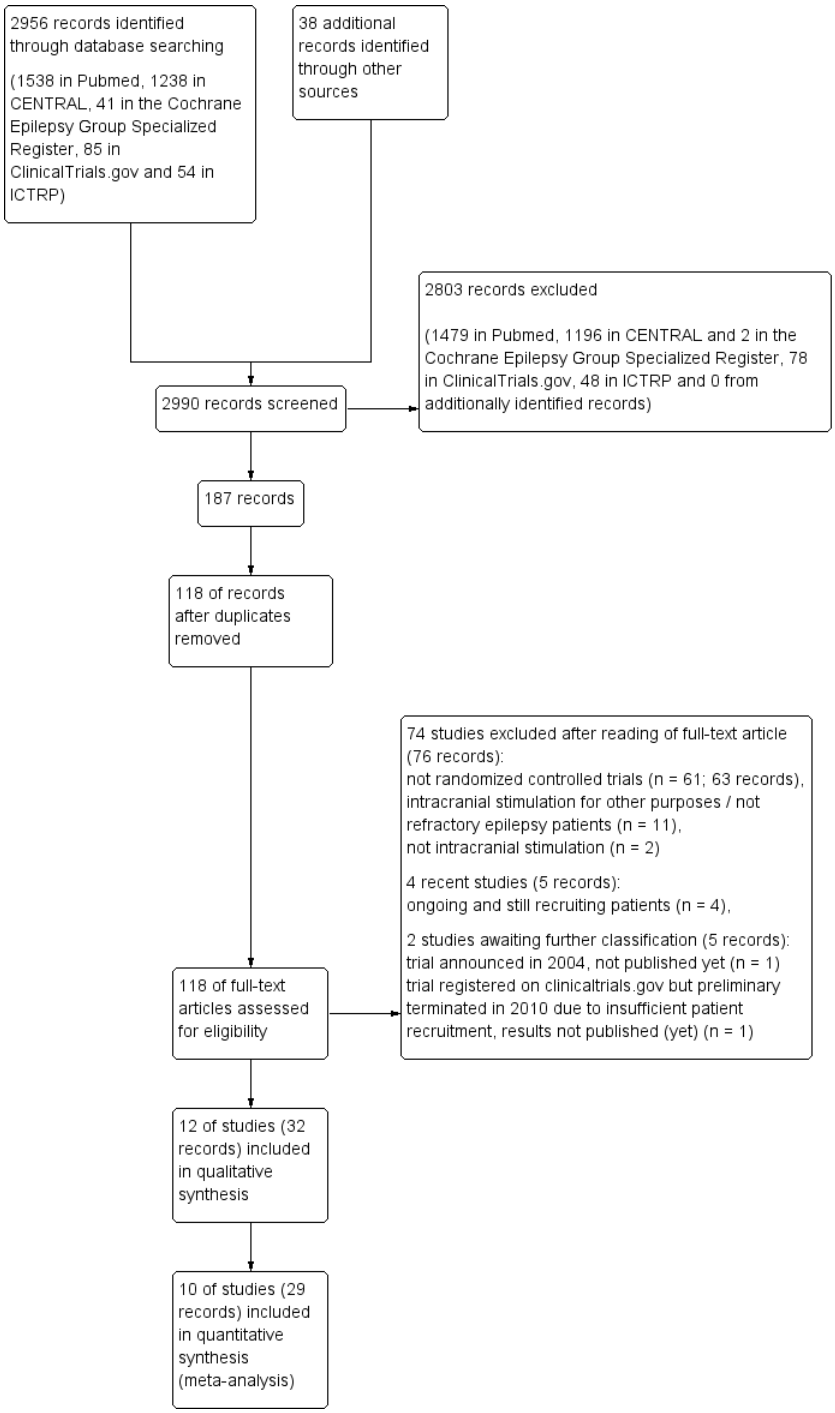
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

See Figure 1 for a flow-diagrammatic summary of the search results. One hundred and eighteen records were identified as potentially eligible for inclusion in this review. Seventy-six records were excluded as they did not meet the eligibility criteria: 63 records were not randomized controlled trials (RCTs), 11 assessed intracranial stimulation for other purposes than treating refractory epilepsy, and in two articles, the efficacy of another intervention (transcranial direct current stimulation) was evaluated.

Figure 1. Study flow diagram.



Five records described four recent parallel-group RCTs still recruiting participants. Boon 2007b is a trial comparing hippocampal stimulation, sham stimulation and amygdalohippocampectomy in refractory temporal lobe epilepsy patients. Chabardes 2014 aims to compare anterior thalamic nucleus stimulation to 'usual treatment'. Koubeissi 2015 is investigating 1 Hz versus 5 Hz low-frequency stimulation of the fornix in patients with refractory medial temporal lobe epilepsy and in Zhang 2015, refractory focal epilepsy patients are randomized to anterior thalamic nucleus deep brain stimulation (DBS) or vagus nerve stimulation.

Two trials are still awaiting classification. Four records mentioned an RCT evaluating the efficacy and safety of DBS of the mammillary bodies and mammillothalamic tracts (van Rijckevorsel 2004). However, up to now the results have not been published. As for the previous version of this review, we again tried to contact the authors but additional information could not be gained. Chabardes 2005 was registered on ClinicalTrials.gov as a cross-over trial evaluating subthalamic nucleus DBS in refractory focal epilepsy patients but had to be preliminarily terminated in 2010 due to insufficient patient recruitment (n = 4). As the preliminary results have not been published yet, we in vain tried to contact the authors. Further efforts to acquire these data will be undertaken by the next update of this review.

Thirty-two records describing 12 studies fulfilled the criteria for inclusion in this review. As the results of two of these studies were only presented in a graph (no exact figures) (Velasco 2000a), or as an abstract (Wiebe 2013), and additional data could not be obtained, only 10 studies were fully included in the quantitative synthesis (meta-analysis).

Included studies

See: Characteristics of included studies.

Eleven out of 12 included studies evaluated the safety and efficacy of open-loop (scheduled) stimulation, the remaining study concerned closed-loop (responsive) stimulation. Stimulation of the ictal onset zone (including the hippocampus (four studies) and the trial on responsive stimulation) as well as of more remote network structures has been studied. The latter included the cerebellar cortex (three studies), the anterior (one study) and centromedian (two studies) thalamic nucleus and the nucleus accumbens (one study).

1. Anterior thalamic nucleus stimulation

Fisher 2010, also known as the SANTE trial, is a parallel-group RCT evaluating the efficacy and safety of bilateral anterior thalamic nucleus DBS in 109 patients (age 18 to 65 years) with refractory partial-onset epilepsy (mean duration of epilepsy: 22.3 years, median baseline seizure frequency: 19.5 per month). After one month of postoperative recovery, patients entered a three-month blinded randomized phase during which half of the participants received stimulation and half did not. This was followed by a nine-month open-label period during which all patients received stimulation in an unblinded way and stimulation parameters could be programmed on an individual basis but antiepileptic drugs (AED) were still kept constant. From the 13th month on, AEDs could vary freely ('long-term follow-up'). All outcomes considered for this review were examined.

2. Centromedian thalamic nucleus stimulation

1. Fisher 1992 is a cross-over randomized trial in seven patients (age 16 to 41 years) who were found to be poor candidates for epilepsy surgery, two of them having (multi)focal epilepsy and five generalized epilepsy (2/5 had Lennox-Gestaut syndrome). The patients had been suffering from epilepsy for 14 to 29 years and had a mean monthly baseline seizure frequency of 23.4 seizures. Patients were randomized one to two months postoperatively to first receive either bilateral centromedian thalamic nucleus (two hours per day) or sham stimulation. The two treatment blocks lasted three months with a three-month washout phase between them. After this nine-month randomized and blinded period, all patients were stimulated during the long-term open-label follow-up period. All outcomes considered for this review were studied and reported except for quality of life.

2. Velasco 2000a is a cross-over randomized trial in 13 patients (age 4 to 31 years) with refractory epilepsy for 4 to 33 years (eight with Lennox-Gestaut syndrome and five with localization-related epilepsy) and a median baseline seizure frequency of 119 seizures per month. After six to nine months of stimulation in all participants, patients entered a six-month randomized double-blind cross-over protocol. In half of the patients, the stimulator was turned off for three months, between months six and nine, the other half underwent the same manoeuvre nine to 12 months postoperatively. Between months 13 and 15, stimulation was restarted in all patients in an unblinded manner. Two of the original 15 patients were explanted before initiation of the randomized double-blind period due to skin erosions. Seizure frequency during the blinded three-month period without stimulation was presented in a graph and compared to the preceding three months (with stimulation). As these three months only coincided with the three-month stimulation 'on' period of the double-blind protocol in half of patients, and furthermore no exact figures were provided, this study could not be included in the meta-analysis but only in the qualitative synthesis.

3. Cerebellar stimulation

1. Van Buren 1978 reported their results of cerebellar stimulation (superior surface of the cerebellum parallel to and about 1

cm from either side of the midline) in five patients (age 18 to 34 years) with refractory epilepsy for eight to 23 years, with a mean baseline seizure frequency of 5.1 seizures per day. Presumably four had (multi)focal epilepsy and one had generalized epilepsy. Stimulation was initiated as soon as preoperative seizure frequency had resumed after electrode implantation. Over the ensuing 15 to 21 months, patients were hospitalized three or four times for four to six weeks. During these admissions, seizure frequency was evaluated with and without stimulation. This was performed in a blinded as well as an unblinded way. For this review, only the double-blind data were considered (in total 26 days 'on' and 26 days 'off'). As four out of five patients' seizure frequency increased during the trial (with as well as without stimulation), we decided to directly compare seizure frequency during the stimulation 'on' and 'off' periods to avoid treatment effects with > 100% reductions in seizure frequency (see Appendix 1). The analysis expressing treatment effects with regard to baseline seizure frequency was performed as a sensitivity analysis.

2. Wright 1984 is a cross-over randomized trial in 12 patients (age 20 to 38 years) who had had epilepsy for 10 to 32 years. Five patients had only generalized seizures, one only partial seizures, four partial and generalized seizures, and in two patients seizures were difficult to classify (complex partial seizures versus complex absences). The type of epilepsy was not reported. The six-month randomized phase started several months after electrode implantation, after the patient had returned to his preoperative seizure frequency, and consisted of three two-month periods: continuous, contingent (that is, patients received only stimulation when the 'seizure button' was depressed (during an aura or seizure) and for two minutes after it was released) and sham stimulation of the upper surface of the cerebellum (electrodes ± 2 cm parasagittally from the midline). As there was no baseline period, the sham stimulation period seizure frequency (mean: 62 seizures per month) served as reference data for the meta-analysis. Apart from quality of life, all outcomes considered for this review were evaluated.

3. Velasco 2005 studied the efficacy and safety of bilateral stimulation of the superomedial surface of the cerebellum in five patients (age 16 to 35 years) with generalized (n = 3) or (multi)focal frontal lobe epilepsy (n = 2) for 11 to 27 years (mean baseline seizure frequency: 14.1 seizures per month). All patients had generalized tonic-clonic seizures and 4/5 had tonic seizures. The three-month parallel-group randomized phase was initiated one month after electrode implantation and was followed by unblinded stimulation in all patients for 21 months. Seizure frequency and adverse events were evaluated.

4. Hippocampal stimulation

1. Tellez-Zenteno 2006 is a multiple cross-over RCT in four patients (age 24 to 37 years) with refractory left medial temporal lobe epilepsy with mesial temporal sclerosis on magnetic resonance imaging (MRI) whose risk of postoperative memory deficits prevented resective surgery. Duration of epilepsy ranged from 16 to 24 years and the mean monthly baseline seizure frequency was between two and four in three participants and 25 in another. Left hippocampal stimulation was compared to sham stimulation in three two-month treatment pairs, each containing one month with and one month without stimulation. All outcomes considered for this review were studied. With regards to quality of life, see Appendix 3.

2. Velasco 2007 reported their results of uni- or bilateral hippocampal stimulation (according to seizure focus) in nine patients (age 14 to 43 years) with intractable temporal lobe epilepsy for three to 37 years (mean baseline seizure frequency: 37.9 seizures per month) who were poor surgery candidates. Five had a normal MRI and four had hippocampal sclerosis. Seizure frequency and adverse events were assessed in a double-blind manner during the first postoperative month during which half of the participants received stimulation and half did not. After this, randomized one-month period stimulation was turned on in all patients (follow-up: 18 to 84 months).

3. McLachlan 2010 is another study evaluating hippocampal stimulation as a treatment for medically intractable epilepsy in two patients (age 45 to 54 years) with independent bitemporal originating seizures for 15 to 29 years (with 32 and 16 seizures per month, respectively). MRI was normal in one and showed bilateral hippocampal sclerosis in the other patient. A three-month postoperative baseline period was followed by a cross-over protocol which contained three months of bilateral hippocampal stimulation followed by a three-month washout period and three months of sham stimulation (control). All outcomes considered for this review were evaluated except for quality of life.

4. Wiebe 2013 is a parallel-group RCT in six patients (age 30 to 46 years) with uni- or bilateral drug-resistant medial temporal lobe epilepsy treated with uni- or bilateral hippocampal stimulation, respectively (median baseline seizure frequency of 10 to 12 seizures per month). After hippocampal electrode implantation and one month for 'adjustments of interventions', patients were randomized to six months active or sham stimulation. The initial target sample of 57 participants could not be reached due to difficulties in patient recruitment despite the five-centre participation.The results collected in these six patients (active stimulation n = 2; sham stimulation n = 4) have been published as an abstract. Many details on the methodology, participants, interventions and outcomes needed for a complete judgement of the methodology or for full incorporation into this review are missing. We tried to contact the authors but could not obtain additional information or data yet. Another attempt will be made by the next update of this review. Meanwhile, this trial is mainly incorporated into the qualitative (and not quantitative) synthesis.

5. Nucleus accumbens stimulation

Kowski 2015 is a cross-over RCT in four patients (age 28 to 44

years) with pharmaco-resistant partial-onset epilepsy for nine to 15 years. The mean baseline frequency of 'disabling' seizures (complex partial or generalized tonic-clonic seizures) ranged between four and 20 seizures per month, one patient additionally reported 99 simple partial seizures per month. Resection or further invasive assessment had been dismissed or surgery had been unsuccessful and patients preferred participation in the study above vagus nerve stimulation or standard anterior thalamic DBS treatment. After a three-month baseline period, depth electrodes were bilaterally implanted in the nucleus accumbens and the anterior nucleus of the thalamus. One month after surgery, patients were randomized to receive first either nucleus accumbens stimulation or sham stimulation. These two treatment blocks lasted three months each and were both followed by a one-month washout period. The blinded evaluation period (BEP) was followed by a three-month open-label period during which nucleus accumbens DBS was continued only in those patients who had experienced a $\geq$ 50% reduction in frequency of disabling seizures. Additionally, anterior thalamic DBS was switched on in all patients. All outcomes considered for this review were evaluated.

6. Closed-loop ictal onset zone stimulation

Morrell 2011, also known as the Neuropace study, was a parallel-group RCT in 191 patients (age 18 to 66 years) with intractable partial-onset seizures for two to 57 years with one (45%) or two (55%) seizure foci. The mean daily baseline seizure frequency was 1.2. After a 12-week baseline period, one or two recording and stimulating depth or subdural cortical strip leads, or both, were surgically placed in the brain according to the seizure focus or foci. A four-week postoperative stabilization period (neurostimulator programmed to sense and record the electrocorticogram; all patients) and a four-week stimulation optimization period (optimization of stimulation parameters; only patients randomized to treatment group) preceded the 12-week BEP during which, in half of the participants, the seizure focus was stimulated in response to epileptiform electrographic events. This was followed by an open-label evaluation period with stimulation 'on' in all patients. All outcomes considered for this review were evaluated in this trial. For the adverse events related to the surgical procedure, the permanent presence of an implanted device (e.g. infection) and sudden unexpected death in epilepsy patients (SUDEP) rate (adverse events for which the long-term open-label data were also taken into account), long-term results in the published articles were often only reported together with those of a preceding open-label trial (n = 65, for more details see Bergey et al. 2015 in Morrell 2011).

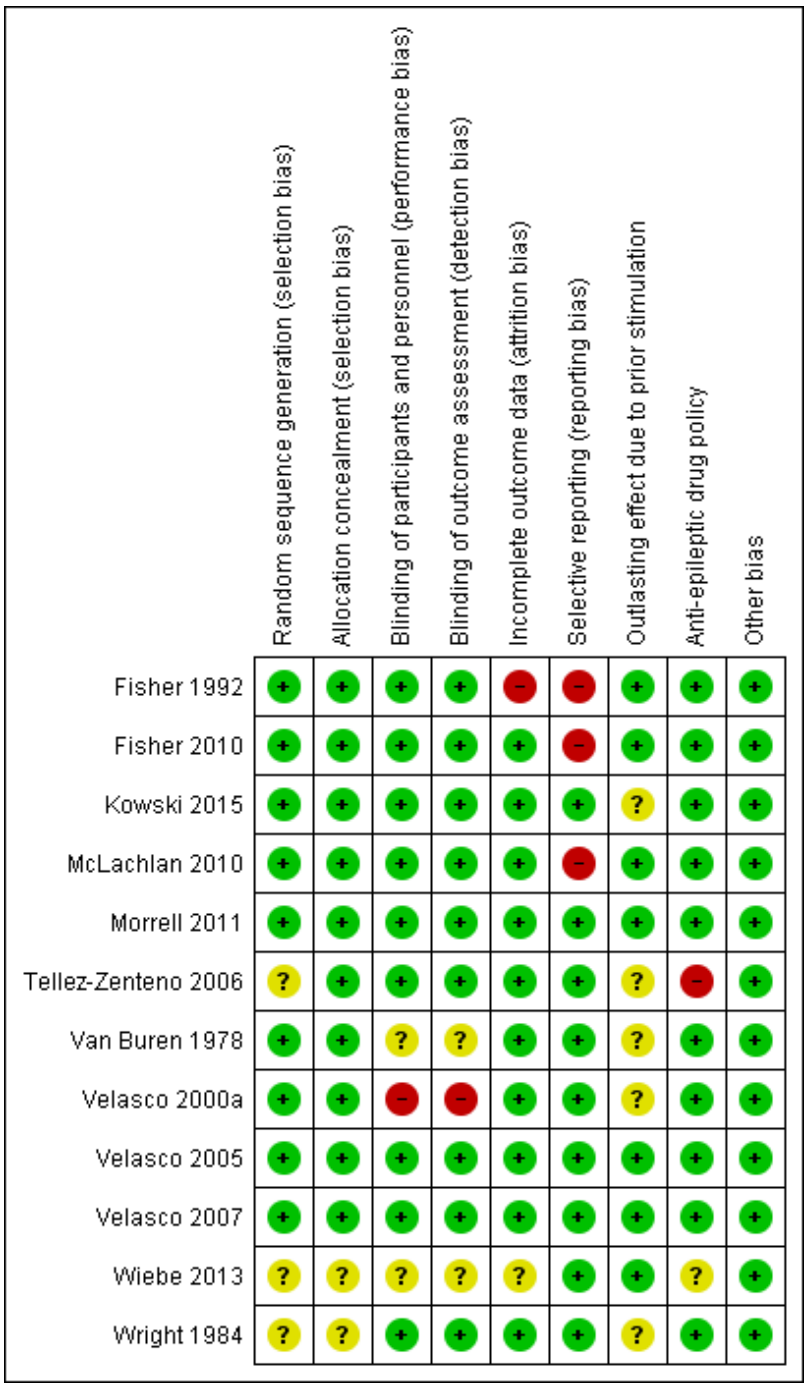
Excluded studies

Sixty-one trials (63 records) were excluded because they were not randomized controlled trials. In 11 trials intracranial stimulation was not used to treat refractory epilepsy patients but served other purposes (Brown 2006; Esteller 2004; Fell 2013; Galvez-Jimenez 1998; Huang 2008; Levy 2008; Miller 2015; Nguyen 1999; Pahwa 1999; Tanriverdi 2009; Torres 2013). Finally, Fregni and colleagues evaluated transcranial direct current stimulation instead of intracranial stimulation (Fregni 2005; Fregni 2006).

Risk of bias in included studies

Detailed assessments of each 'Risk of bias' item for each included study can be found in the 'Risk of bias' tables in the section 'Characteristics of included studies'. A summary of the review authors' judgements is shown in Figure 2.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Methods for random sequence generation and treatment allocation concealment (selection bias) were often poorly described in the published articles. After personal communication with the authors, however, these were found to be adequate in all trials for which such additional information could be obtained. As some authors could not be contacted or provide any further explanation, there remained some uncertainty about three trials (Tellez-Zenteno 2006; Wiebe 2013; Wright 1984).

Blinding

All 12 trials were reported to be double-blind RCTs. However, only for nine out of the 12 included trials was the blinding of patients, personnel and outcome assessors assessed as adequate.Some uncertainty remained with regards to Van Buren 1978. For this RCT (which contained both double-blind and unblinded evaluation periods, see above), it was not reported whether neuropsychological testing was performed during the blinded or unblinded evaluation period and if the sealed notes containing the treatment code for the double-blind evaluation period were double-opaque and by whom they were handled (for more details: see Characteristics of included studies). Although the double-blinding procedure in Velasco 2000a seemed adequate, the authors compared seizure frequency between stimulation 'off' periods (blinded) and the three-month periods preceding these. Only in about 50% of participants, these latter periods coincided with blinded stimulation 'on' periods. For the other half, these three months corresponded to unblinded stimulation 'on' periods, which could have resulted in performance or detection bias (the seizure frequency during blinded stimulation 'on' periods could not be obtained from the authors). Both the protocol and abstract of Wiebe 2013 described the trial to be double-blind but the lack of further details hindered a more in-depth judgement of the blinding procedure.
Morrell 2011 was the sole study where patients were asked at the end of the BEP if they knew or could guess if they had received 'real' or sham stimulation. This was of particular importance in this trial as stimulation parameters were determined individually after randomization and only in patients allocated to the stimulation group (for more details: see Characteristics of included studies).

Incomplete outcome data

Risk of bias arising from incomplete outcome data was assessed as high for Fisher 1992. In this study, one of the two patients who improved noticeably with stimulation experienced a marked seizure frequency increase in the washout period and, therefore, was dropped from the blinded protocol, after which stimulation was successfully reinstalled. As there were only seven patients (two responders), this one patient represented a significant proportion, especially when taking into consideration the reason for dropout and the fact that a paired analysis of outcome data did not allow inclusion of this patient in the (default) meta-analysis. Although there is no evidence for incomplete outcome data leading to attrition bias in Wiebe 2013, insufficient details prevented full appreciation.

Selective reporting

Evidence suggesting selective reporting was present for a number of trials. Statistical analysis included only a subgroup of patients in Fisher 1992 (only patients with generalized tonic-clonic seizures, not prespecified in the 'Methods' section), or a subset of available data in McLachlan 2010 (median monthly seizure frequency instead of total number of seizures). As raw data were published in the original articles or provided upon our request, this had no influence on the review.
Fisher 2010 did not report on or mention all available outcome measures in the published paper (for example, seizure-free days and seizure-free intervals), but only reported that 'changes in additional outcome measures did not show significant differences'. Again, this had no direct consequences for this review as these outcome variables were not taken into consideration.
Only for Kowski 2015 was a detailed study protocol available as the study had been registered beforehand in the German Trial Registry. All outcomes mentioned in the protocol were reported on in the published paper in a very detailed and extensive way. Such a detailed study protocol was not available for the other trials. However, as it is unusual for trial protocols to be available unless the trial is very recent, risk of reporting bias was judged as low when there was no strong evidence of selective reporting.
In various trials results were incompletely reported, however without strong evidence of selective reporting.

1. As mentioned above, the results of Wiebe 2013 were only published as an abstract, inherently associated with many missing details. This prevented full inclusion in our meta-analysis so results were mainly incorporated in the qualitative synthesis.
2. Seizure frequency reduction in Velasco 2000a and Velasco 2007 was only presented in graphs. As exact figures could only be provided by Velasco 2007, this prevented inclusion of Velasco 2000a in our meta-analysis.
3. Neuropsychological testing results were often only reported to be non-significant (Fisher 1992; Wright 1984) or were incompletely published (Tellez-Zenteno 2006). However, as: 1) neuropsychological testing yields too abundant data for publication in a journal article (and therefore not entirely reporting them does not necessarily reflect study quality), and 2) we did not attempt to incorporate these results into a meta-

analysis, but rather described them in a qualitative way; we think this is of less concern for this review.

4. Finally, as not all exact figures with regards to adverse events, neuropsychological outcome and quality of life could be reported in Morrell 2011 (too much data), the authors provided us with these data.

Outlasting effect after prior stimulation

Five trials with a parallel-group design (Fisher 2010; Morrell 2011; Velasco 2005; Velasco 2007; Wiebe 2013) and two cross-over trials with a three-month washout period (Fisher 1992; McLachlan 2010) were judged as being at low risk of bias. Two cross-over trials (Tellez-Zenteno 2006; Wright 1984) did not contain any washout period, which could mask or reduce any treatment effect if stimulation had an outlasting effect. This was even more true for Van Buren 1978 and Velasco 2000a, two cross-over trials for which the randomized evaluation took place only after six to 21 months of stimulation, without any washout period. Kowski 2015 was a cross-over study with a one-month washout period after three months of stimulation which might be too short, although we recognize that clear judgements on this issue are difficult to make and arbitrary (unclear risk of bias).

Antiepileptic drug (AED) policy

In all trials providing details on the AED policy, the AED regimen was kept unchanged except for Tellez-Zenteno 2006 in which it was changed in three out of four patients during the trial. Morrell 2011 allowed benzodiazepines for seizure clusters or prolonged seizures, but it was unlikely this significantly influenced the reported results. Only for Wiebe 2013 were details on the AED policy not available.

Effects of interventions

See: **Summary of findings for the main comparison** Anterior thalamic nucleus stimulation; **Summary of findings 2** Centromedian thalamic nucleus stimulation; **Summary of findings 3** Cerebellar stimulation; **Summary of findings 4** Hippocampal stimulation; **Summary of findings 5** Nucleus accumbens stimulation; **Summary of findings 6** Responsive ictal onset zone stimulation

See: Figure 3; Figure 4; Figure 5; Figure 6.

Figure 3. Forest plot of comparison: 1 Stimulation versus sham stimulation, outcome: 1.1 Seizure freedom.

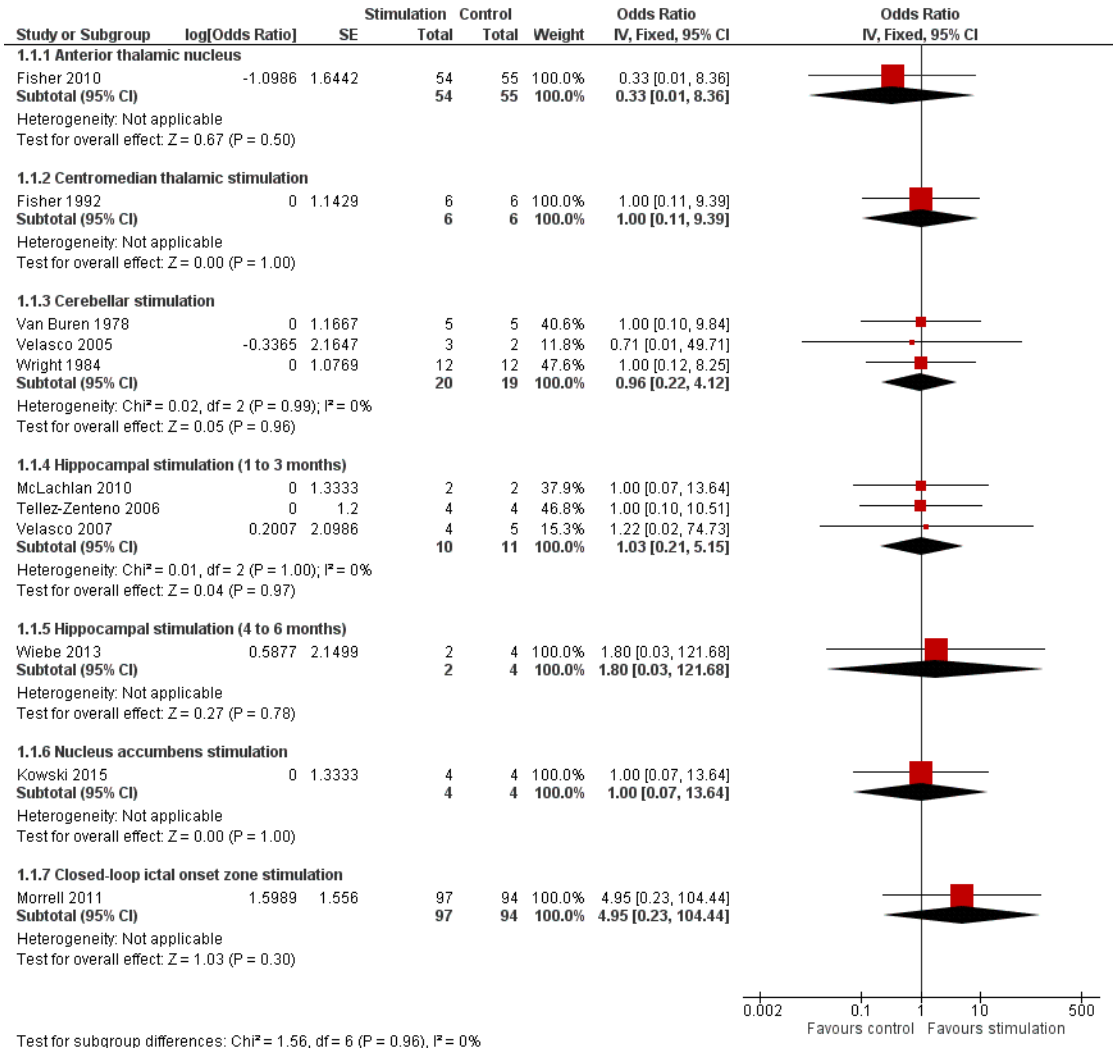


Figure 4. Forest plot of comparison: 1 Stimulation versus sham stimulation, outcome: 1.2 Responder rate.

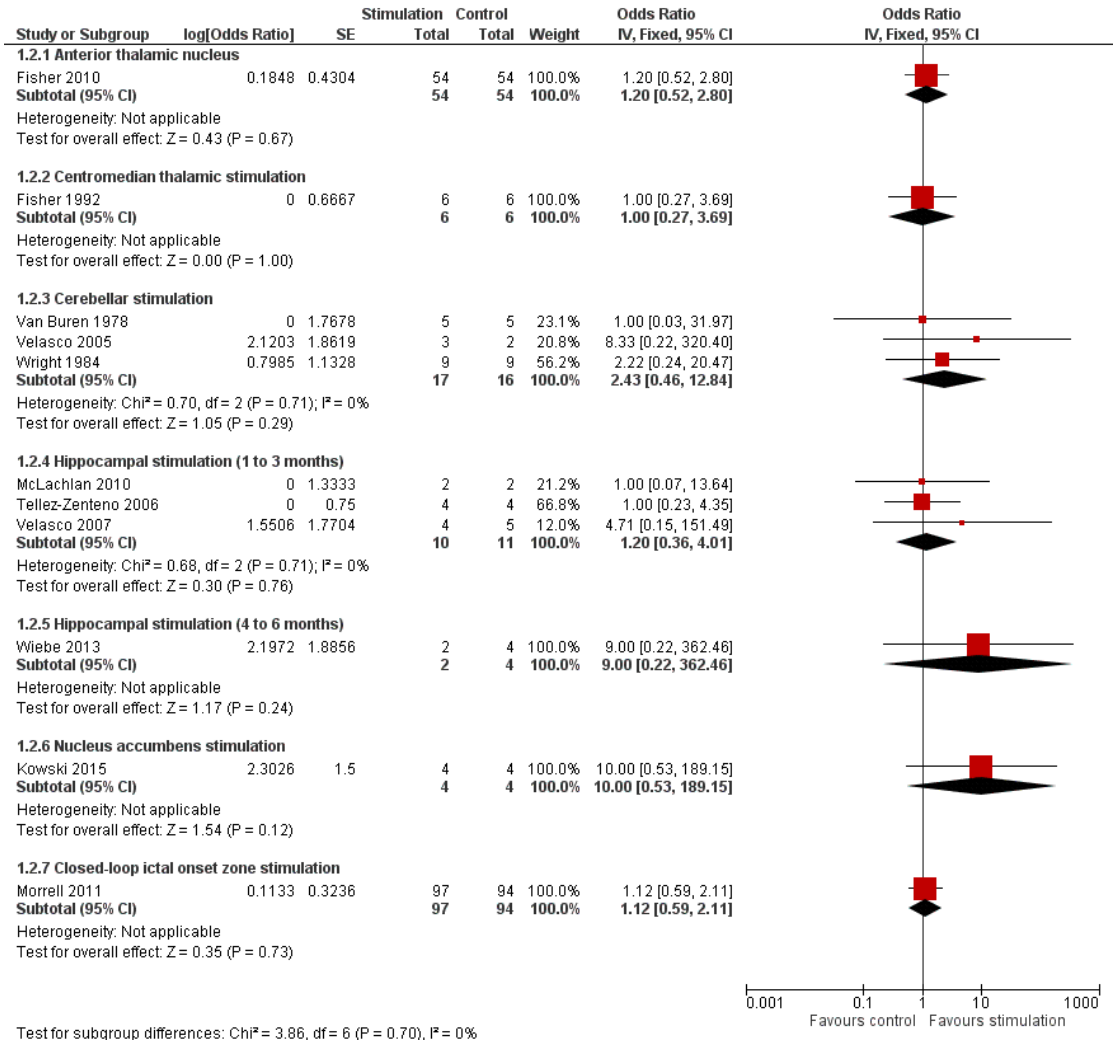


Figure 5. Forest plot of comparison: 1 Stimulation versus sham stimulation, outcome: 1.3 Seizure frequency reduction.Note: Fisher 2010 (anterior thalamic nucleus stimulation) and Morrell 2011 (closed-loop ictal onset zone stimulation) estimated the treatment effect and its standard error on a logarithmic scale, using the generalized estimating equation (GEE) model. As in this figure standard errors could not be inputted on the logarithmic scale, the values for the 95% confidence interval presented here differ slightly from the (more correct) values mentioned in the text. These correct values are -17.4% with 95% CI [-31.2;-1.0] for Fisher 2010 and -24.9% with 95% CI [-40.1;-6.0] for Morrell 2011.

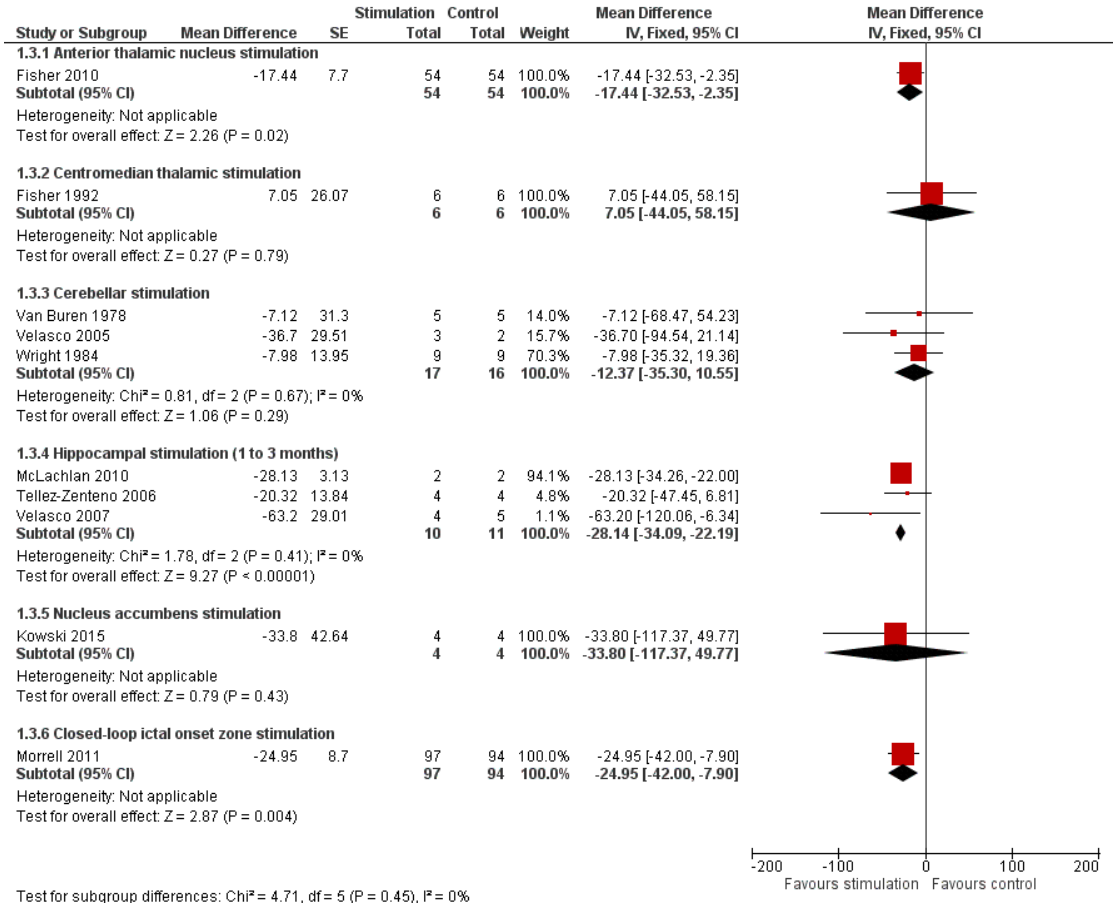
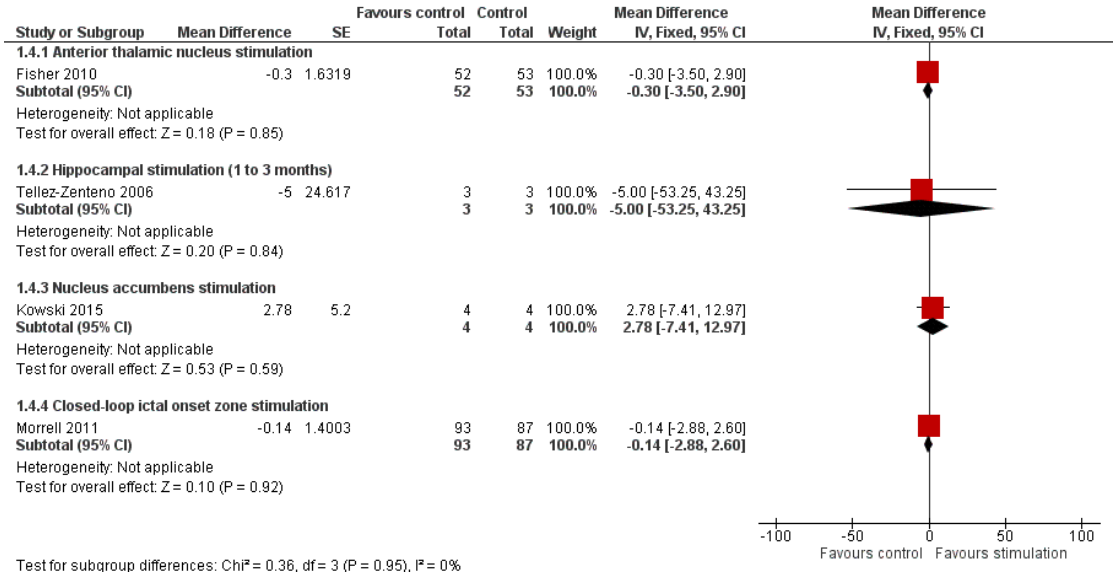


Figure 6. Forest plot of comparison: 1 Stimulation versus sham stimulation, outcome: 1.4 Quality of Life. To measure quality of life, Tellez-Zenteno 2006 and Morrell 2011 used the QOLIE-89 questionnaire, Fisher 2010 used the QOLIE-31 questionnaire (= abbreviated form of the QOLIE-89 questionnaire) and Kowski 2015 usde the QOLIE-31-P questionnaire (slightly modified version of the QOLIE-31 questionnaire). These questionnaires have the same range and for the QOLIE-89 and QOLIE-31 questionnaires very similar means, standard deviations and minimum clinically important change values in the same population have been reported (Cramer 1998; Devinsky 1995; Wiebe 2002). For this reason results from the different trials are presented in one forest plot (see also Methods section). For the QOLIE-89 and QOLIE-31 questionnaires, improvements of 5-11.7 have been defined in literature (Borghs 2012; Cramer 2004; Wiebe 2002) as being clinically meaningful, positive is better.



1. Anterior thalamic nucleus stimulation

a. Seizure freedom

During the three-month blinded randomized phase of Fisher 2010 1/55 patients in the control group was seizure-free versus 0/54 in the stimulated group (odds ratio (OR) 0.33; 95% confidence interval (CI) 0.01 to 8.36; one study, 109 participants; moderate-quality evidence) (Analysis 1.1).

b. Responder rate

Responder rate was not significantly different in the stimulated (29.6%) compared to the control (25.9%) group (OR 1.20; 95% CI 0.52 to 2.80; one study, 108 participants; moderate-quality evidence) (Analysis 1.2).

c. Seizure frequency reduction

Over the entire blinded randomized period anterior thalamic nucleus stimulation resulted in a significantly (mean difference (MD), -17.4%; 95% CI -31.2 to -1.0; one study, 108 participants; high-quality evidence) higher seizure frequency reduction compared to sham stimulation (Analysis 1.3). The authors reported a trend for increasing differences in median monthly seizure frequency reduction over time between the groups (stimulation versus control: month one: -33.9% versus -25.3%, month two: -42.1% versus -28.7% and month three: -40.4% versus -14.5%; the adjusted treatment effects being -10% (P = 0.37), -11% (P = 0.34) and -29% (P = 0.002), respectively).

d. Adverse events

Adverse events were evaluated in one trial (109 participants, moderate-quality evidence). During the blinded evaluation period (BEP), two self-reported adverse events occurred significantly more frequently in the stimulated group compared to the control group: depression (14.8% versus 1.8%; P = 0.02, Fisher's Exact Test) and subjective memory impairment (13.0% versus 1.8%; P

= 0.03). On the contrary, there were significantly fewer epilepsy-related injuries (7.4% versus 25.5%; P = 0.01). Differences for other adverse events were not statistically significant and included: confusional state (7.4% versus 0.0%; P = 0.06), anxiety (9.3% versus 1.8%; P = 0.11), paraesthesia (9.3% versus 3.6%; P = 0.27), new or worse partial seizures with secondary generalization (9.3% versus 5.5%; P = 0.48) and new or worse simple (5.6% versus 1.8%; P = 0.36) or complex (9.3% versus 7.3%; P=0.74) partial seizures. One patient experienced 210 complex partial seizures in the three days after turning on the stimulator (baseline seizure frequency of 19 seizures per month), resolving with reprogramming of the stimulator.

Within the first year after implantation, five (4.5%) asymptomatic haemorrhage events were reported (four after the initial implant procedure, one following a seizure and a fall and remote from the lead tract). All were asymptomatic. Ten participants (9.1%; 4.5% within first postoperative month) developed implant site infections (12.7% after five years of follow-up). There were no parenchymal brain infections. In five patients (4.5%), this eventually led to (temporary) hardware removal (8.2% after five years). Leads initially implanted outside the target structure had to be replaced in 8.2% of participants. Implant site pain was reported by 10.9% of participants during the first year of the trial (20.9% after five years). Five participants (4.5%) experienced status epilepticus during the first year after electrode implantation, two of them with stimulation 'on': one during month two of the blinded phase (complex partial status), and one when the stimulator was turned on after the blinded phase (complex partial status, resolving within five days after switching stimulation off) (6.4% after five years, 3.6% with stimulation ON). The first reported SUDEP (sudden unexpected death in epilepsy patients) rate during stimulation (two SUDEPs over 325 patient-years with stimulation = 6.2 per 1000 patient-years) fell within the range reported in comparable refractory epilepsy populations (2.2 to 10 per 1000 patient-years) (Tellez-Zenteno 2005; Tomson 2008) and long-term open-label follow-up has now recently reported a SUDEP rate of 2.9 per 1000 patient-years (95% CI 0.3 to 10.4).

e. Neuropsychological outcome

Although self-reported depression and subjective memory impairment occurred significantly more frequently in the stimulated group (see above), changes in neuropsychological test scores for cognition and mood were very similar in the treatment and control groups and were not significantly different (one study, 96 to 100 participants; moderate-quality evidence). The evaluated items can be found in Characteristics of included studies. Looking at the individual patients, worsening (> 1 standard deviation change (SD)) of Profile of Mood States Depression subscale (POMS-D) was present in 3/8 stimulated participants with self-reported depression. None of the seven patients with subjective memory impairment showed worsening (> 1 SD) of verbal or visual memory scores.

f. Quality of life

Changes from baseline in overall QOLIE-31 scores were comparable for the treatment (+ 2.5) and control (+ 2.8) group. The MD in change score (-0.30) was neither statistically (95% CI -3.50 to 2.90; one study, 105 participants; high-quality evidence) nor clinically significant (positive is better, improvements of 5 to 11.7 have been defined in the literature (Borghs 2012; Cramer 2004; Wiebe 2002) as being clinically meaningful) (Analysis 1.4).

2. Centromedian thalamic nucleus stimulation

a. Seizure freedom

None of the patients in the Fisher 1992 trial (two hours of intermittent stimulation per day) achieved seizure freedom, neither with nor without stimulation (OR 1.00; 95% CI 0.11 to 9.39; one cross-over trial, 12 treatment periods; very low-quality evidence) (Analysis 1.1).

Although one patient was completely seizure-free at the maximum open-label follow-up (minimum follow-up of one year, mean 41.2 months), Velasco 2000a (24 hours of intermittent stimulation per day) did not report on differences in seizure freedom between stimulation 'on' versus 'off' periods in the double-blind protocol performed between month six and month 12 of the trial. However, as mean seizure frequency reductions were very similar in both groups, major differences in seizure freedom seem unlikely.

b. Responder rate

Statistically significant differences in responder rate, favouring either the stimulation or the control group, could not be demonstrated by Fisher 1992 (OR 1.00; 95% CI 0.27 to 3.69; one cross-over trial, 12 treatment periods; very low-quality evidence) (Analysis 1.2). Two patients did experience ≥ 50% seizure frequency reductions with stimulation 'on' compared to baseline, but one of them had a similar reduction without stimulation and the other could not be included in a paired analysis as he was dropped from the blinded protocol due to a seizure frequency increase during the washout period (see also 'Sensitivity analyses').

Eleven out of 13 patients showed ≥ 50% seizure reductions at maximum follow-up in Velasco 2000a, but again the authors did not report on differences in responder rates between stimulation 'on' versus 'off' periods. As for seizure freedom, however, important differences in responder rate were improbable as mean seizure frequency reductions were comparable for stimulation 'on' and 'off' periods.

c. Seizure frequency reduction

Paired analysis (thus excluding one patient) revealed a non-significant 7.1% seizure frequency increase during stimulation 'on' compared to stimulation 'off' periods in Fisher 1992 (95% CI -44.1 to 58.2; one cross-over trial, 12 treatment periods; very low-quality evidence) (Analysis 1.3). Successive months of stimulation were not associated with a clear trend for increasing efficacy over time during the three-month stimulation 'on' period.

Velasco 2000a found very similar and statistically not significantly different reductions in seizure frequency during stimulation 'off' periods in the double-blind phase of the trial and the three-month period preceding it (with stimulation 'on'). Graphs showed approximately a mean 75% reduction in total seizure frequency during stimulation 'on' as well as stimulation 'off' periods (P = 0.23).

Some open-label trials have reported that complex partial seizures may be less prone to centromedian thalamic nucleus stimulation (Velasco 1993; Velasco 1995). Excluding patients with only complex partial seizures (n = 1) in a subgroup analysis of Fisher 1992 showed a non-significant -8.9% MD in seizure frequency reduction (95% CI -79.0 to 61.3%). Although, compared to baseline seizure frequency, reductions in generalized tonic-clonic seizures and atypical absences in Velasco 2000a were more pronounced than those found for complex partial seizures, very similar reductions in seizure frequency were found for any seizure type during stimulation 'on' and 'off' periods and statistically significant differences could not be demonstrated (P values being 0.27, 0.29 and 0.72, respectively).

d. Adverse events

Stimulation-related side effects did not occur in Fisher 1992 or Velasco 2000a (two cross-over trials, 38 treatment periods; low-quality evidence). Fisher 1992 explicitly reported that no single patient had new seizures or worsening of seizures after initiation of stimulation.

However, various patients in both trials experienced some device- or procedure-related adverse events (two cross-over trials, 21 participants; low-quality evidence). One patient in Fisher 1992 required repair of the connection to the pulse generator on one side because no stimulation effect was evident at any intensity, either behaviourally or by electroencephalogram (EEG) monitoring. A post implantation computed tomography (CT) scan in another patient revealed an asymptomatic and minimal haemorrhage in the vicinity of one depth electrode. Skin erosion forced explantation in three patients of the Velasco 2000a trial, including two children (five and six years old) whose stimulators had to be removed before the double-blind protocol took place. Young children seemed particularly vulnerable to skin erosions because of the size of the hardware, which is designed for an adult population.

e. Neuropsychological outcome

Multivariate analysis with repeated measures showed no significant differences in any of the neuropsychological tests between baseline and stimulation 'on' and 'off' periods in Fisher 1992 (one cross-over trial, 12 treatment periods; very low-quality of evidence). The cognitive assessment battery can be found in Characteristics of included studies.

f. Quality of life

Neither of the two studies evaluated the impact of centromedian thalamic stimulation on quality of life.

3. Cerebellar stimulation

a. Seizure freedom

Regardless of stimulation status, seizure freedom could not be achieved in any of the trials evaluating cerebellar stimulation (pooled OR 0.96; 95% CI 0.22 to 4.12; three trials, 39 treatment periods; moderate-quality evidence) (Analysis 1.1).

b. Responder rate

Cerebellar stimulation did not result in a statistically significantly higher responder rate compared to sham stimulation (pooled OR 2.43; 95% CI 0.46 to 12.84; three trials, 33 treatment periods; low-quality evidence) (Analysis 1.2). In the treatment groups, there were 1/5 (Van Buren 1978), 1/9 (Wright 1984) and 2/3 (Velasco 2005) responders, whereas sham stimulation was associated with a $\geq$ 50% reduction in seizure frequency in 1/5, 0/9 and 0/2 patients, respectively.

There were no responders with contingent stimulation in Wright 1984 (OR 1.00; 95% CI 0.12 to 8.64).

c. Seizure frequency reduction

The pooled mean treatment effect was a MD -12.4% change in seizure frequency in favour of cerebellar stimulation, but this effect did not reach statistical significance (95% CI -35.3 to 10.6; three trials, 33 treatment periods; low-quality evidence) (Analysis 1.3). Only Velasco 2005 reported enough details to evaluate a possible trend for increasing efficacy over successive months of stimulation. Although the treatment effect was most pronounced in the third month of stimulation (month one: -54% versus -29%, month two: -31% versus -14%, month three: -82% versus -14%), the small number of patients and the observed variability make it premature to draw any conclusions on this issue. Finally, Van Buren 1978 stated that no slow trends toward improvement could be noticed. Contingent stimulation was not associated with changes in seizure frequency in Wright 1984 (treatment effect +0.9%; 95% CI -23.2 to 24.9%).

d. Adverse events

Stimulation-related side effects were not reported in any of the trials (three trials, 39 treatment periods; low-quality evidence). Psychiatric evaluation after completion of the Wright 1984 trial did not detect adverse psychiatric sequelae as a result of the stimulation trial.

In contrast, device- or procedure-related adverse events were not uncommon (three trials, 22 participants; low-quality evidence). Electrode migration necessitating repeated surgery occurred in 3/12 and 3/5 patients in Wright 1984 and Velasco 2005, respectively. An electrode lead causing pain needed to be repositioned in one patient and a receiver pocket that had burst open had to be resutured in another (Wright 1984). Leakage of cerebrospinal fluid into the subcutaneous apparatus tracts required resuturing in 3/5 patients of Van Buren 1978, and Wright 1984 reported that most patients experienced temporary swelling over one or both receiver sites, presumably due to cerebrospinal fluid accumulation, but that this spontaneously resolved. A subcutaneous seroma had to be drained in one of the patients in Velasco 2005. Wound infections could be settled with antibiotics in two patients but required total hardware removal in one patient (Velasco 2005; Wright 1984). Finally, repeated surgery was performed in another two patients due to a defective receiver and abdominal wound erosion (Wright 1984). Taken all together, in every trial about half of the patients required repeated surgery (3/5 in Van Buren 1978, 6/12 in Wright 1984 and 3/5 in Velasco 2005).

e. Neuropsychological outcome

Neuropsychological outcome was assessed in two cross-over trials (32 treatment periods; very low-quality evidence). Each patient in Wright 1984 was assessed by a clinical psychologist in every phase of the trial but 'psychometry' could not reveal any major change in any of the patients. More details were provided by Van Buren 1978. Consistent changes in full scale intelligence or memory quotients could not be detected, nor were there any significant changes in subtests (performance and oral intelligence quotient). Comparing 'on' to 'off' stimulation, the test scores of the four individuals they evaluated showed very similar results in two participants, a moderate increase in one patient, and a moderate decrease in another.

f. Quality of life

None of the trials on cerebellar stimulation formally evaluated impact on quality of life (very low-quality evidence). However, Wright 1984 reported that all his patients but one felt better for cerebellar stimulation, thought it had helped them, and wished to continue it after completion of the trial. However, only five patients chose one phase of the trial as being different from the others: two singled out the continuous, one the contingent, and two others the no-stimulation phase. Moreover, only one patient's subjective impression agreed with the authors' assessment and in this patient the no-stimulation period was his best. Finally, one patient reported a reduction of episodes of incontinence with contingent but not continuous stimulation, which beneficially affected his social possibilities.

4. Hippocampal stimulation

Four trials evaluated hippocampal stimulation, three of these had a BEP with one to three months of active stimulation and one parallel-group RCT (Wiebe 2013) had a six-month BEP. As results of the first three-month epoch of the latter were not reported and could not be obtained, we could not include this trial into the analyses on the effect of one to three months of hippocampal stimulation.

4.1 Hippocampal stimulation (one to three months of stimulation)

a. Seizure freedom

No single patient was seizure-free for the duration of the RCT they had been included in (pooled OR 1.03; 95% CI 0.21 to 5.15; three trials, 21 treatment periods; moderate-quality evidence) (Analysis 1.1).

b. Responder rate

Hippocampal stimulation was not associated with significantly higher responder rates compared to sham stimulation (pooled OR 1.20; 95% CI 0.36 to 4.01; three trials, 21 treatment periods; low-quality evidence) (Analysis 1.2). There were no responders in McLachlan 2010, 1/4 patient experienced a $\geq$ 50% reduction in seizure frequency with as well as without stimulation in Tellez-Zenteno 2006, and Velasco 2007 reported 1/4 responder in the treatment group compared to 0/5 in the control group.

c. Seizure frequency reduction

Hippocampal stimulation significantly reduced seizure frequency with a pooled mean treatment effect of -28.1% (95% CI -34.1 to -22.2; three trials, 21 treatment periods; moderate-quality evidence) (Analysis 1.3). None of the authors provided enough data to allow evaluation for trends of increasing efficacy over time.

d. Adverse events

No adverse events occurred in relation to stimulation and there were no early surgical complications in any of the trials (McLachlan 2010; Tellez-Zenteno 2006; Velasco 2007; 15 participants, 21 treatment periods; low-quality evidence). However, skin erosion

and local infection 24 months after implantation required explantation in 3/9 patients in Velasco 2007.

e. Neuropsychological outcome

Neuropscychological outcome was assessed in two cross-over trials (12 treatment periods; very low- quality evidence). Neuropsychological testing in Tellez-Zenteno 2006 could not reveal significant differences between baseline, 'on' and 'off' periods in any of the formal or subjective measures (see Characteristics of included studies for the different tests they performed). Moreover, reported mean scores were exactly or nearly the same for the 'on' and 'off' periods. Of particular interest was a patient who previously had a right temporal lobectomy and whose memory scores were not influenced by left hippocampal stimulation. The Center for Epidemiologic Studies Depression (CES-D) scale could not demonstrate meaningful changes in mood states during baseline (19), 'on' (20) and 'off' (18) stimulation periods.
McLachlan 2010 assessed the objective and subjective memory of their two patients during baseline, 'on', washout and 'off' periods. They found no changes in one participant and contradictory results in the other. This latter patient reported improved subjective memory during the stimulation 'on' period (baseline second, 'off' third to sixth and 'on' 12th to 13th percentile (pc), higher was better) but formal testing pointed towards worsening of verbal (baseline first, 'off' 14th and 'on' second pc) as well as visuospatial (baseline 21st, 'off' 42nd and 'on' first pc) memory.

f. Quality of life

Only Tellez-Zenteno 2006 evaluated the impact of hippocampal DBS on quality of life (six treatment periods; very low-quality evidence). Repeated (once per month) testing in three patients could not demonstrate statistically significant differences between QOLIE-89 scores during baseline (57), 'on' (55) and 'off' (60) periods (treatment effect -5.0; 95% CI -53.3 to 43.3), which was obviously not surprising given the small number of patients (Analysis 1.4). This five-point difference was clinically of borderline significance (positive was better, improvements of 5 to 11.7 have been defined in the literature (Borghs 2012; Cramer 2004; Wiebe 2002) as being clinically meaningful).

4.2 Hippocampal stimulation (four to six months of stimulation)

a. Seizure freedom

None of the patients were seizure-free during either sham (n = 0/4) or hippocampal (n = 0/2) stimulation (OR 1.80; 95% CI 0.03 to 121.68; one study, six participants; very low-quality evidence) (Analysis 1.1).

b. Responder rate

One out of two patients in the active stimulation group experienced a ≥50% reduction in seizure frequency compared to 0/4 in the sham group (OR 9.00; 95% CI 0.22 to 362.46; one study, six participants; very low-quality evidence) (Analysis 1.2).

c. Seizure frequency reduction

The sham stimulation group reported a median seizure frequency increase of 60% compared to a 45% decrease in the stimulation group (P > 0.05, no information on statistical dispersion available; one study, six participants; very low-quality evidence). When only counting complex partial and generalized tonic-clonic seizures, the sham stimulation group experienced a 31.3% increase compared to a 50% increase in the stimulation group.

d. Adverse events

Adverse events were not reported (one study, six participants; very low-quality evidence).

e. Neuropyschological outcome

Scores of cognitive scales assessing recall (Rey Auditory Verbal Learning Test, Rey Complex Figure Test) were generally lower in the active stimulation compared to the sham group (P > 0.05; one study, six participants; very low-quality evidence).

f. Quality of life

The overall QOLIE-89 score at seven months was worse by 13 points with sham stimulation compared to an improvement of three points with active stimulation (P > 0.05; one study, six participants; very low-quality evidence). Positive changes correspond to a better quality of life, improvements of 5 to 11.7 points have been defined in the literature (Borghs 2012; Cramer 2004; Wiebe 2002) as being clinically meaningful.
Subjective memory scores using QOLIE-89 memory scales decreased by 34 points with sham stimulation and increased by 10 points with active stimulation (P > 0.05). The QOLIE-89 attention/concentration scores decreased by four points with sham and increased by 20 points with active stimulation (borderline statistically significant difference, P < 0.06)

5. Nucleus accumbens stimulation

a. Seizure freedom

None of the four patients in Kowski 2015 was seizure-free during either nucleus accumbens or sham stimulation (OR 1.00; 95% CI 0.07 to 13.64; one cross-over trial, eight treatment periods; low-quality evidence) (Analysis 1.1).

b. Responder rate

Three out of four patients experienced a ≥50% seizure reduction during nucleus accumbens stimulation, whereas there were no responders during sham stimulation (OR 10.00; 95% CI 0.53 to 189.15; one cross-over trial, eight treatment periods; low-quality evidence) (Analysis 1.2). The same figures are obtained when excluding simple partial seizures (these only occurred in the non-responding patient) and only taking into account the 'disabling' seizures (sum of complex partial and generalized tonic-clonic seizures).

c. Seizure frequency reduction

Nucleus accumbens stimulation was associated with a statistically non-significant -33.8% lower frequency compared to sham stimulation (95% CI -117.4 to 49.8; one cross-over trial, eight treatment periods; low-quality evidence) (Analysis 1.3). Exclusion of the simple partial seizures of the non-responding patient yielded a -22.9% lower frequency of disabling seizures during nucleus accumbens compared to sham stimulation (95% CI -139.8 to 94.0).

d. Adverse events

Three out of four patients reported adverse events during the BEP (one cross-over trial, eight treatment periods; low-quality evidence). However, except for one patient feeling sad for two weeks during the active stimulation period after a close relative had died, there were no adverse events that were exclusively linked to the active stimulation period. Reported adverse events included: an increased frequency of disabling seizures (n = 1, both during sham and active stimulation), loss of interests (n = 1, both during sham and active stimulation), sleep disturbance (n = 2, one both during sham and active stimulation, one only during sham stimulation), a first-time generalized tonic-clonic seizure (n = 1, sham stimulation), depressive mood (n = 1, sham stimulation) and listlessness (n = 1, sham stimulation). Device- or procedure-related adverse events occurred in one patient who developed a local subcutaneous infection with colonization of the pulse generator and the leads two weeks post-surgery urging antibiotic therapy and hardware removal. This patient consented to participate again nine months later.

e. Neuropsychological outcome

Neurocognitive test scores were similar and not statistically significantly different during sham and active stimulation in this small trial (one cross-over trial, eight treatment periods; low-quality evidence). There were no categorical changes in Beck-Depression-Inventory scores during the BEP. However, the Mini International Neuropsychiatric Interview revealed a new-onset major depression under nucleus accumbens stimulation in one patient and an ongoing low suicidal risk following one suicide attempt 10 years before the trial in another patient.

f. Quality of life

Compared to baseline, mean QOLIE-31-P total score was -2.1 lower during active stimulation and -4.9 lower during sham stimulation (treatment effect +2.8; 95% CI -7.4 to 13.0; one cross-over trial, eight treatment periods; low-quality evidence) (Analysis 1.4). The QOLIE-31-P is a (slightly) modified version of the QOLIE-31 questionnaire for which changes of 5 to 11.7 have been defined in the literature (Borghs 2012; Cramer 2004; Wiebe 2002) as being clinically meaningful; positive scores indicate improvement.

6. Closed-loop ictal onset zone stimulation

a. Seizure freedom

There were no statistically significant differences in seizures freedom during the three-month BEP of Morrell 2011, with 2/97 and 0/94 patients being seizure-free in the treatment and control group, respectively (OR 4.95; 95% CI 0.23 to 104.44; one study, 191 participants; moderate-quality evidence) (Analysis 1.1).

b. Responder rate

With 28.9% of participants experiencing ≥ 50% reductions in seizure frequency in the treatment group compared to 26.6% in the group receiving sham stimulation, stimulation status did not significantly influence responder rates (OR 1.12; 95% CI 0.59 to 2.11; one study, 191 participants; moderate-quality evidence) (Analysis 1.2).

c. Seizure frequency reduction

Closed-loop stimulation of the ictal onset zone significantly reduced seizure frequency, the treatment effect being -24.9% (95% CI -40.1% to -6.0%; one study, 191 participants; high-quality evidence) (Analysis 1.3). A trend for increasing efficacy over time could be observed during the three-month BEP, with statistically significant reductions in seizure frequency from the second month of stimulation on (treatment versus control group: month one: -34.2% versus -25.2% (P = 0.28), month two: -38.1% versus -17.2% (P = 0.016) and month three: -41.5% versus -9.4% (P = 0.008)).

d. Adverse events

There were no significant differences between the treatment and sham groups in the percentages of patients with mild or serious adverse events (overall or for any type) (one study, 191 participants; moderate-quality evidence). In fact, with the exception of increased complex partial seizures (treatment versus sham: n = 2 versus n = 2), headache (n = 3 versus n = 1) and incision site infection (n = 2 versus n = 0), each individual type of device-related

(definite or uncertain) adverse event occurred in no more than one participant in the treatment group. Two participants had device-related serious adverse events: one patient in the treatment group and another in the control group had one and three events related to a change in seizures, respectively.

Postoperative intracranial haemorrhage considered as serious adverse events occurred in 1.6% of patients but none of the patients had permanent neurologic sequelae. After five years, serious intracranial haemorrhages had occurred in 4.7% of patients (additional cases mainly due to seizure-related trauma). Postoperative implant or incision site soft tissue infections occurred in 2.0% of patients, urging explantation in 0.5%. After five years, 9.4% of patients had experienced soft tissue infection (additional cases mainly upon battery replacement, explantation in the majority of cases). There were no parenchymal brain infections. The most frequently reported adverse events during the first year of the trial were related to the cranial implantation of the pulse generator and included implant site pain (15.7%), headache (10.5%), procedural headache (9.4%) and dysaesthesia (6.3%). Although the SUDEP rate reported in the first manuscript (four SUDEPs over 340 patient-years = 11.8 per 1000 patient-years) was slightly higher than that usually reported in refractory epilepsy patients (2.2 to 10 per 1000 patient-years) (Tellez-Zenteno 2005; Tomson 2008), longer follow-up during the open-label period has now reported reassuring figures: SUDEP rates of 3.5 per 1000 patient implant years (95% CI 1.5 to 8.5) and of 2.6 per 1000 patient stimulation years (95% CI 1.0 to 7.0).

e. Neuropsychological outcome

Neuropsychological assessment at the end of the BEP could not reveal any significant differences between the treatment and sham groups in any measure (one study, 160 to 177 participants; high-quality evidence). In addition, there were no adverse changes in mood inventories at the end of the blinded phase of the trial. The neuropsychological and mood assessment batteries can be found in Characteristics of included studies. Self-reported depression occurred in one patient in each group and subjective memory impairment was reported by one participant belonging to the treatment group.

f. Quality of life

Changes from baseline in overall QOLIE-89 scores were comparable for the treatment (+2.04) and control (+2.18) groups. The MD in change score (-0.14) was neither statistically (95% CI -2.88 to 2.60; one study, 180 participants; high-quality evidence) nor clinically significant (positive was better, improvements of 5 to 11.7 have been defined in the literature (Borghs 2012; Cramer 2004; Wiebe 2002) as being clinically meaningful) (Analysis 1.4). These conclusions applied to the overall as well as any subscale QOLIE-89 score.

Sensitivity analyses

Expressing treatment effects of dichotomous outcomes as risk ratios (RR) instead of odds ratios (OR) did not change our conclusions (Analysis 2.1; Analysis 2.2). For seizure freedom (Analysis 2.1), effect estimators were nearly identical however with slightly smaller CIs. With regards to the responder rate (Analysis 2.2), effect estimators were (discretely) lower and CIs smaller when using RR.

Empty cells hindered calculation of ORs or RRs. In these situations, it is customary to add +0.5 to each cell (Deeks 2011). Given the small number of included patients in most trials, we examined if adding +0.25 instead of +0.5 would change our conclusions (Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 2.6). In general, this was not the case. Concerning seizure freedom (Analysis 2.3; Analysis 2.5), however, CIs were larger (for all targeted structures, for OR as well as RR) and the treatment effect seemed more pronounced (but with higher uncertainty) for closed-loop stimulation of the ictal onset zone. With regards to the responder rate (,Analysis 2.4; Analysis 2.6) treatment effect estimators and CIs were generally comparable although effect estimators were higher, but with a greater degree of uncertainty for nucleus accumbens stimulation and hippocampal DBS (four to six months of stimulation) besides a larger 95% CI for cerebellar stimulation.

Including only trials with a low risk of bias due to an outlasting effect after prior stimulation (and thus excluding three cross-over trials without washout periods) did not change our conclusions. For cerebellar stimulation only one trial remained (Velasco 2005); and for hippocampal stimulation (one to three months of stimulation), the following pooled effect estimates were calculated: seizure freedom OR 1.06 (95% CI 0.12 to 9.62), responder rate OR 1.75 (95% CI 0.22 to 14.13) and seizure frequency reduction -28.5% (95% CI -34.6 to -22.4). Risks of other types of bias which could have directly influenced our conclusions were mainly present in the three cross-over trials.

As the two participants in McLachlan 2010 experienced very similar treatment effects, the standard error associated with the MD in seizure frequency in this study was the lowest (3.13) among all trials on hippocampal stimulation. In this way, this very small cross-over study (n = 2) substantially influenced the pooled mean treatment effect. As its weight in the standard analysis appeared disproportionally high (94%), we checked the robustness of the conclusions to the other extreme situation in which the standard error of this trial would be (equal to) the highest of all trials on hippocampal DBS. The sensitivity analysis using 29.01 (the standard error of Velasco 2007) instead of 3.13 as the standard error for McLachlan 2010 yielded a similar -28.2% treatment effect, however with a higher degree of uncertainty (95% CI -50.7 to -5.8). Excluding Tellez-Zenteno 2006 (a cross-over trial without washout period) in this latter analysis resulted in a -45.7% treatment effect for hippocampal stimulation (95% CI -85.9 to -5.5). To avoid treatment effects > 100%, we directly compared 'on' and 'off' stimulation periods for Van Buren 1978 (see Appendix

1). However, taking baseline seizure frequency as the reference also for Van Buren 1978 (responder rate OR 2.40; 95% CI 0.21 to 26.82; seizure frequency reduction -123.5%; 95% CI -280.3 to 33.3) did not change our conclusion regarding the efficacy of cerebellar stimulation (responder rate OR 2.85; 95% CI 0.64 to 12.68; seizure frequency reduction -15.9%; 95% CI -40.3 to 8.5). An unpaired analysis of Fisher 1992, including the patient who seemed to benefit from stimulation but whose absence of stimulation 'off' data (see Characteristics of included studies) prevented inclusion in a paired analysis, could not demonstrate a significant responder rate increase (OR 2.00; 95% CI 0.13 to 29.81) or reduction in seizure frequency (-6.6%; 95% CI -93.7 to 80.5), even after exclusion of a patient with only complex partial seizures (OR 2.00; 95% CI 0.13 to 31.98; -20.7% 95% CI -101.6 to 60.2). Also other sensitivity analyses using data imputation to allow paired analyses did not change the conclusions on centromedian thalamic DBS, irrespective whether data imputation was done with a 'best-case scenario' (responder rate 1.75 with 95% CI 0.38 to 8.06; mean seizure frequency -20.2% with 95% CI -100 to +65.6%), a 'worst-case scenario' (responder rate 1.00 with 95% CI 0.36 to 2.66; mean seizure frequency +6.9% with 95% CI -47.0 to 60.8%) or a 'last observation carried forward scenario' (responder rate 1.00 with 95% CI 0.36 to 2.66; mean seizure frequency +6.1 with 95% CI -47.9 to 60.0%).

As there is some evidence for increasing efficacy of intracranial neurostimulation treatments over time, we decided to pool results per three-month stimulation epochs only. As we could only identify one small trial with a BEP with active stimulation longer than three months (Wiebe 2013), this was in practice only relevant for the estimated pooled treatment effect of hippocampal stimulation. Combining all trials on hippocampal stimulation irrespective of the duration of active stimulation period did not change the conclusions of this review but did result into slightly more favourable pooled treatment effects for seizure freedom (OR 1.11; 95% CI 0.25 to 4.98) and the 50% responder rate (OR 1.46; 95% 0.47 to 4.58) (sensitivity analysis not possible for other outcomes due to lack of details on statistical dispersion).

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Centromedian thalamic nucleus stimulation for refractory epilepsy

Patient or population: patients with refractory (multi)focal or generalized epilepsy
Settings: epilepsy centres in the USA and in Mexico
Intervention: centromedian thalamic nucleus stimulation
Comparison: sham stimulation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Sham stimulation	Centromedian thalamic nucleus stimulation				
Seizure freedom (3-month blinded evaluation period)	**Observed in** Fisher 1992		**OR 1.00** (0.11 to 9.39)	6 (1)[2]	⊕◯◯◯ **very low**[3,4]	
	0 per 6	**0 per 6** (not estimable)				
	Low risk population[1]					
	1 per 1000	**1 per 1000** (0 to 9)				
	High risk population[1]					
	15 per 1000	**15 per 1000** (2 to 125)				
Responder rate (3-month blinded evaluation period)	**Low risk population**[1]		**OR 1.00** (0.27 to 3.69)	6 (1)[2]	⊕◯◯◯ **very low**[3,4,5]	

	10 per 100	**10 per 1000** (3 to 29)				
	Medium-high risk population[1]					
	25 per 100	**25 per 1000** (8 to 55)				
Seizure frequency reduction (3-month blinded evaluation period)	The mean seizure frequency reduction in the control group was **4%**	The mean seizure frequency in the intervention groups was **-0.** **+7.1% higher** (-44.1% lower to +58.2% higher)		6 (1)[2]	⊕○○○ **very low**[3,4,5]	Also another trial (Velasco 2000a) (n = 13) could not demonstrate significant differences between stimulation ON and OFF periods. However, its cross-over design without any washout period could mask a possible treatment effect
Adverse events	See comment	See comment		19 (2)[2] 21 (2)[2]	⊕⊕○○ **low**[4,6]	Stimulation-related adverse events did not occur. Postoperative CT revealed an asymptomatic and minimal haemorrhage in one patient, 1 patient required repair of the connection to the pulse generator and skin erosion urged device explantation in 3 other patients (including 2 young children)

Neuropsychological outcome (3 months)	See comment	See comment	6 (1)[2]	⊕◯◯◯ **very low**[3,4]	There were no significant differences in any of the neuropsychological tests between baseline, stimulation ON and OFF periods
Quality of life	See comment	See comment	0 (0)	See comment	Impact of centromedian thalamic nucleus stimulation on quality of life has not been studied yet

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The assumed risks (low, medium and high) are based on the range of the number of events observed in the sham stimulation control groups of all RCTs evaluating deep brain and cortical stimulation in refractory epilepsy patients
[2] Cross-over trial(s).
[3] No more than one small RCT was identified, resulting into wide 95% confidence intervals (GRADE score -2). This is of particular concern for neuropsychological outcome, as no exact figures were reported or could be provided, so evaluation of certain statistically non-significant trends is not possible.
[4] Only 2 hours of intermittent stimulation per day in Fisher 1992 (GRADE score -1).
[5] Incomplete outcome data may introduce bias (GRADE score -1).
[6] Number of participants too low to identify less frequent adverse events (GRADE score -1)

Cerebellar stimulation for refractory epilepsy

Patient or population: patients with refractory (multi)focal or generalized epilepsy
Settings: epilepsy centres in the USA and in Mexico
Intervention: stimulation of the superomedial surface of the cerebellum
Comparison: sham stimulation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Sham stimulation	Cerebellar stimulation				
Seizure freedom (1- to 3-month blinded evaluation period)	**Observed**		**OR 0.96** (0.22 to 4.12)	22 (3)[2]	⊕⊕⊕○ **moderate**[3]	
	0 per 19	**0 per 20** (not estimable)				
	Low risk population[1]					
	1 per 1000	**1 per 1000** (0 to 4)				
	High risk population[1]					
	15 per 1000	**14 per 1000** (3 to 59)				
Responder rate (1- to 3-month blinded evaluation period)	**Low risk population**[1]		**OR 2.43** (0.46 to 12.84)	19 (3)[2]	⊕⊕○○ **low**[3,4]	
	10 per 100	**21 per 100** (5 to 59)				
	Medium-high risk population[1]					

	25 per 100	**45 per 100** (13 to 81)			
Seizure frequency reduction (1- to 3-month blinded evaluation period)	The mean seizure frequency reduction ranged across control groups from **0 to -18.8%**	The mean seizure frequency in the intervention groups was **-12.4% lower** (-35.3% lower to +10.6% higher)	19 (3)[2]	⊕⊕○○ **low**[3,4]	
Adverse events	See comment	See comment	22 (3)[2]	⊕⊕○○ **low**[3,5]	Stimulation-related adverse events were not reported in any of the trials In contrast, about half of the patients in every trial required repeated surgery due to electrode migration (n = 6), leakage of cerebrospinal fluid (n = 3), wound infection (n = 1), skin erosion (n = 2), lead problems (n = 1), subcutaneous seroma drainage (n = 1) and defective hardware (n = 1). Wound infections were solved with antibiotics only in 2 additional patients. In particular, electrode migration remains of specific concern, even in the most recent trial (Velasco 2005) (occurring in 3/5 patients).

Neuropsychological outcome (1 to 2 months)	See comment	See comment	16 (2)[2]	⊕◯◯◯ **very low**[3,4,6]	'Psychometry' did not reveal any major change in any patient in any phase of the Wright 1984 trial. Comparing ON to OFF stimulation full scale intelligence and memory scores in Van Buren 1978 showed very similar results in two participants, a moderate increase in one patient and a moderate decrease in another
Quality of life (2 months)	See comment	See comment	12 (1)[7]	⊕◯◯◯ **very low**[3,4,8]	Eleven out of 12 patients in Wright 1984 felt better for cerebellar stimulation, but only 5 chose one phase as being different from the others, being either the continuous (n = 2), contingent (n = 1) or no-stimulation (n = 2) phase

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The assumed risks (low, medium and high) are based on the range of the number of events observed in the sham stimulation control groups of all RCTs evaluating deep brain and cortical stimulation in refractory epilepsy patients

[2] Including 2 cross-over trials: Van Buren 1978 (n = 4-5) and Wright 1984 (n = 9-12)

[3] The small number of patients leave a considerable amount of uncertainty with regards to stimulation effects (GRADE -1).

[4] Wright 1984 and Van Buren 1978 are cross-over trials without any washout period which could mask or reduce potential benefits of cerebellar stimulation (and explain some heterogeneity) (GRADE -1).

[5] Unclear if, how and to what extent stimulation-related side effects were evaluated in Van Buren 1978 and Wright 1984 (GRADE -1).

[6] Unclear what neuropsychological tests were performed in Wright 1984 ('psychometry'). Moreover, as testing scores were not published and could not be provided, evaluation of certain statistically non-significant trends is not possible. Unclear if neuropsychological testing in Van Buren 1978 was done in blinded or unblinded evaluation periods (GRADE-1).

[7] Cross-over trial: Wright 1984 (n = 12).

[8] No formal scoring of quality of life but evaluation of patients' impressions on cerebellar stimulation (GRADE -1).

Hippocampal stimulation for refractory epilepsy

Patient or population: patients with refractory medial temporal lobe epilepsy
Settings: epilepsy centres in Canada and in Mexico
Intervention: hippocampal deep brain stimulation
Comparison: sham stimulation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Sham stimulation	Hippocampal stimulation				
Seizure freedom (1- to 3-month blinded evaluation periods)	**Observed**		**OR 1.03** (0.21 to 5.15)	15 (3)[2]	⊕⊕⊕◯ **moderate**[3]	Also in Wiebe 2013[4] no single patient achieved seizure freedom after six months of hippocampal active or sham stimulation
	0 per 11	**0 per 10** (not estimable)				
	Low risk population[1]					
	1 per 1000	**1 per 1000** (0 to 5)				
	High risk population[1]					
	15 per 1000	**15 per 1000** (3 to 73)				
Responder rate (1- to 3-month blinded evaluation periods)	**Low risk population**[1]		**OR 1.20** (0.36 to 4.01)	15 (3)[2]	⊕⊕◯◯ **low**[3,5]	In Wiebe 2013[4] there was one responder in the stimulation group (n = 2) compared to none in the sham group (n = 4) after six months of follow-up

	10 per 100	**12 per 100** (4 to 31)				
	Medium-high risk population[1]					
	25 per 100	**29 per 100** (11 to 57)				
Seizure frequency (1- to 3-month blinded evaluation periods)	The mean change in seizure frequency ranged across control groups from **-4.7% to +33.7%**	The mean seizure frequency in the intervention groups was **-28.1% lower** (-34.1 to -22.2% lower)	15 (3)[2]	⊕⊕⊕○ **moderate**[3]	One trial (Tellez-Zenteno 2006) has a cross-over design without any washout period which could result into an underestimation of the true treatment effect In Wiebe 2013[4] the sham stimulation group reported a median seizure frequency increase of 60% compared to a 45% decrease in the stimulation group after 6 months of follow-up	
Adverse events	See comment	See comment	15 (3)[2]	⊕⊕○○ **low**[6]	There were neither stimulation-related adverse events, nor early surgical complications. Skin erosion and local infection required explantation after >2 years in 3/9 patients in Velasco 2007. Wiebe 2013[4] also did	

						not report any adverse event after 6 months of follow-up
Neuropsychological outcome (1- to 3-month periods)	See comment	See comment		6 (2)[2]	⊕◯◯◯ **very low**[5,6]	Neuropsychological test results were the same or very similar during stimulation ON and OFF periods in Tellez-Zenteno 2006 (n = 4) and in one patient in McLachlan 2010. The other patient in McLachlan 2010 showed worse verbal and visuospatial memory scores when stimulated, notwithstanding that he reported subjective memory improvement during the same period At seven months in Wiebe 2013[4], scores of cognitive scales assessing recall (Rey Auditory Verbal Learning Test, Rey Complex Figure Test) were generally lower in the active stimulation compared to the sham group (p>0.05)
Quality of life (QOLIE-89) (1- to 3-month periods)	The mean QOLIE-89 score in the control group was **60**	The mean QOLIE-89 in the intervention group was **-5 lower** (-53 lower to +43 higher).		3 (1)[7]	⊕◯◯◯ **very low**[5,6]	Positive changes in QOLIE-89 (quality of life in epilepsy 89) scores indicate improvement.

			Changes of 5-11.7 have been defined in literature as being clinically meaningful (Borghs 2012; Cramer 2004; Wiebe 2002). The overall QOLIE-89 score at seven months in Wiebe 2013 [4] worsened by 13 points with sham stimulation compared to an improvement of 3 points with active stimulation (p>0.05), and there was a trend for increased QOLIE-89 subjective memory and attention/concentration scores

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The assumed risks (low, medium and high) are based on the range of the number of events observed in the sham stimulation control groups of all RCTs evaluating deep brain and cortical stimulation in refractory epilepsy patients
[2] Including two cross-over trials: McLachlan 2010 (n = 2) and Tellez-Zenteno 2006 (n = 4)
[3] The small number of patients preclude more definitive judgements on effects of hippocampal stimulation (GRADE -1).
[4] Wiebe 2013 is a small parallel-group RCT (n = 6) with a 6-month blinded evaluation period. As there were no more than 2 participants in the active stimulation group and details needed for full methodological assessment are missing, the quality of the evidence is very low and we decided not to create separate 6-month outcomes or a separate summary of findings table

but only to describe the results. As the results of the first 3-month epoch were not reported, the data of this trial could not be combined with the other trials evaluating one to three months of hippocampal stimulation. However, the reported six-month results are generally compatible and in line with the estimated three-month results. For more details and a sensitivity analysis combining all trials on hippocampal stimulation irrespective of the BEP duration, see text.

[5] One trial (Tellez-Zenteno 2006) had a cross-over design without any washout period and allowed important changes in antiepileptic drugs, both of which could reduce or mask more important treatment effects. See also 'Sensitivity analyses' (GRADE -1).

[6] Number of patients is too low to identify less frequent adverse events or changes in neuropsychological outcome or quality of life (GRADE-score -2).

[7] One cross-over trial: Tellez-Zenteno 2006 (n = 3)

Nucleus accumbens stimulation for refractory epilepsy

Patient or population: adults with IQ >70 with refractory focal epilepsy
Settings: epilepsy centre in Germany
Intervention: nucleus accumbens stimulation
Comparison: sham stimulation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Sham stimulation	Nucleus accumbens stimulation				
Seizure freedom (3-month blinded evaluation period)	**Observed in Kowski 2015**		**OR 1.00** (0.07 to 13.64)	4 (1)[2]	⊕⊕◯◯ **low**[3]	
	0 per 4	**0 per 4** (not estimable)				
	Low risk population[1]					
	1 per 1000	**1 per 1000** (0 to 13)				
	High risk population[1]					
	15 per 1000	**15 per 1000** (0 to 172)				
Responder rate (3-month blinded evaluation period)	**Low risk population**[1]		**OR 10.0** (0.53 to 189.15)	4 (1)[2]	⊕⊕◯◯ **low**[3]	
	10 per 100	**53 per 100** (6 to 95)				

	Medium risk population[1]					
	25 per 100	77 per 100 (15 to 98)				
Seizure frequency reduction (3-month blinded evaluation period)	The mean change in seizure frequency in the control group was **-13.8%**	The mean seizure frequency in the intervention group was **-33.8% lower** (-100% lower to +49.8% higher)		4 (1)[2]	⊕⊕○○ **low**[3]	When focusing on 'disabling seizures' only and excluding simple partial seizures (occurring in one patient), the mean change in seizure frequency in the control group was +8.2% with a -22.9% lower seizure frequency in the intervention group (-100 lower to +94.0 higher)
Adverse events	See comment	See comment		4 (1)[2]	⊕⊕○○ **low**[3]	Except for one patient feeling sad for two weeks during the active stimulation period after a close relative had died, there were no adverse events that were exclusively linked to the active stimulation period (although various adverse events were reported in the sham and the active stimulation group, see text) One patient developed a local subcutaneous infection with colonization of the pulse gen-

					erator and the leads 2 weeks post-surgery urging antibiotic therapy and temporary hardware removal
Neuropsychological outcome (3 months)	See comment	See comment	4 (1)[2]	⊕⊕○○ **low**[3]	Neurocognitive test scores were similar and not statistically significantly different during sham and active stimulation in this small trial. There were no categorical changes in Beck-Depression-Inventory scores during the BEP. However, the Mini International Neuropsychiatric Interview revealed a new-onset major depression under nucleus accumbens stimulation in one patient, besides an ongoing low suicidal risk following one suicide attempt 10 years before the trial in another patient
Quality of Life (QOLIE-31-P) (3 months)	The mean change in the QOLIE-31-P score in the control group was **-4.9**	The mean change in the QOLIE-31-P score in the intervention group was **+2.8 higher** (-7.4 lower to +13.0 higher)	4 (1)[2]	⊕⊕○○ **low**[3]	The QOLIE-31-P is a (slightly) modified version of the QOLIE-31 questionnaire for which changes of 5 to 11.7 have been defined in the literature (Cramer

				2004; Wiebe 2002; Borghs 2012) as being clinically meaningful; positive scores indicate improvement

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds Ratio; **BEP:** blinded evaluation period

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The assumed risks (low, medium and high) are based on the range of the number of events observed in the sham stimulation control groups of all RCTs evaluating deep brain and cortical stimulation in refractory epilepsy patients
[2] Cross-over trial
[3]No more than one small RCT was identified which leaves a considerable amount of uncertainty with regards to stimulation effects (GRADE score -2).

Closed-loop stimulation of the ictal onset zone for refractory epilepsy

Patient or population: adults with refractory focal epilepsy (1 or 2 epileptogenic regions)
Settings: epilepsy centres in the USA
Intervention: responsive stimulation of the ictal onset zone(s)
Comparison: sham stimulation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Sham stimulation	Responsive ictal onset zone stimulation				
Seizure freedom (3-month blinded evaluation period)	**Observed in** Morrell 2011		**OR 4.95** (0.23 to 104.44)	191 (1)	⊕⊕⊕◯ **moderate**[2]	
	0 per 94	**2 per 97** (not estimable)				
	Low risk population[1]					
	1 per 1000	**5 per 1000** (0 to 95)				
	High risk population[1]					
	15 per 1000	**70 per 1000** (3 to 614)				
Responder rate (3-month blinded evaluation period)	**27 per 100**	**29 per 100** (18 to 43)	**OR 1.12** (0.59 to 2.11)	191 (1)	⊕⊕⊕◯ **moderate**[2]	

Seizure frequency reduction (3-month blinded evaluation period)	The mean estimated seizure frequency reduction in the control group was **-17.3%**	The mean seizure frequency in the intervention group was **-24.9% lower** (-40.1 to -6.0% lower)	191 (1)	⊕⊕⊕⊕ **high**[3]	A trend for increasing efficacy over time was observed during the blinded evaluation period and could result into an underestimation of the treatment effect (treatment effect of month 3: -32%)
Adverse events	See comment	See comment	191 (1) 256 (2)	⊕⊕⊕◯ **moderate**[2]	Adverse events during the blinded evaluation period were rare and there were no significant differences between the treatment and control group Asymptomatic intracranial haemorrhages considered as serious adverse event were found postoperatively in 1.6% of participants. Postoperative implant or incision site infection occurred in 2.0% of participants, increasing to 9.4% of participants after 5 years of follow-up (additional cases mainly upon battery replacement; urge for (temporary) explantation in the majority of cases) . Cranial implantation

						of the neurostimulator was the probable cause of most adverse events, which include: implant site pain (16% during the first year of the trial), headache (11%) , procedural headache (9%) and dysaesthesia (6%). Although the SUDEP rate (4 SUDEPs over 340 patient-years = 11.8 per 1000 patient-years) reported in the initial manuscript was slightly higher than those usually reported in refractory epilepsy patients (2.2 to 10 per 1000 p-y) (Tellez-Zenteno 2005; Tomson 2008), long-term open-label follow-up has now reported reassuring figures (SUDEP rates of 3.5 per 1000 implant p-y or 2.6 per 1000 stimulation p-y)
Neuropsychological outcome (3 months)	See comment	See comment	160-177 (1)	⊕⊕⊕⊕ **high**		Changes in neuropsychological testing results were very similar in both groups and 95% confidence intervals did not include clinically meaningful differences

Quality of life (QOLIE-89) (3 months)	The mean improvement of the QOLIE-31 score in the control group was **+2.18 higher**	The mean improvement in QOLIE-31 score in the intervention group was **-0.14 lower** (-2.88 lower to +2.60 higher)		180 (1)	⊕⊕⊕⊕ **high**	Positive changes in QOLIE-89 (quality of life in epilepsy 89) scores indicate improvement. Changes of 5-11.7 have been defined in literature as being clinically meaningful (Borghs 2012; Cramer 2004; Wiebe 2002).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **SUDEP:** sudden unexpected death in epilepsy patients; **p-y:** patient-years

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The assumed risks (low and high) are based on the range of the number of events observed in the sham stimulation control groups of all RCTs evaluating deep brain and cortical stimulation in refractory epilepsy patients
[2] More trials and patients are needed to allow more precise estimation of stimulation effects (GRADE -1).
[3] The confidence interval includes clinically non-significant changes (GRADE -1), however, the observed trend for increasing efficacy over time probably underestimates the treatment effect (GRADE +1).

DISCUSSION

More than 30% of all epilepsy patients have pharmacologically refractory epilepsy (Kwan 2000). Epilepsy surgery is the first treatment of choice for these patients. However, most patients are not suitable surgical candidates, some are reluctant to undergo brain surgery, and many do not achieve long-term seizure freedom (de Tisi 2011; Engel 2003). Other treatment options include vagus nerve stimulation, the ketogenic diet or inclusion in trials with newly developed drugs. However, these options yield seizure freedom in only a small minority of patients. Invasive brain stimulation, including deep brain and cortical stimulation, may be an alternative treatment for these patients. Uncontrolled open-label trials have often shown promising but at the same time mixed results, and in addition are at high risk of bias. To increase our understanding of the efficacy and safety of invasive brain stimulation we performed a systematic review of the literature selecting only randomized controlled trials (RCTs).

Summary of main results

For a more detailed summary, see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6.

We identified 10 RCTs which met our eligibility criteria and could be fully included in the meta-analysis, including one trial on anterior thalamic nucleus deep brain stimulation (DBS) for (multi)focal epilepsy (n = 109), one trial on centromedian thalamic DBS for (multi)focal or generalized epilepsy (n = 7; 14 treatment periods due to cross-over design), three trials on cerebellar stimulation for (multi)focal or generalized epilepsy (n = 22; 39 treatment periods), three RCTs on hippocampal DBS for medial temporal lobe epilepsy (n = 15; 21 treatment periods), one trial on nucleus accumbens stimulation (n = 4; eight treatment periods) and one trial on responsive stimulation of the ictal onset zone (one or two epileptogenic regions) (n = 191). In addition, the results of two RCTs were mainly qualitatively described as the unavailability of at least some exact figures prevented full inclusion in the meta-analysis: one trial investigated centromedian thalamic DBS for (multi)focal or generalized epilepsy (n = 13; 26 treatment periods), and another compared six months of hippocampal stimulation to sham stimulation (n = 6). All trials compared active versus sham stimulation. For reasons of clinical heterogeneity, we did not combine results across different stimulated targets but pooled data per individual target. As an increasing efficacy over time has been reported in various trials (see also below) results were pooled per three-month stimulation epochs.

Statistically significant effects on seizure freedom during the blinded evaluation periods (BEPs) (one to three months except for Wiebe 2013) could not be demonstrated for any target. However, the small number of trials and patients cannot exclude the possibility of clinically meaningful improvements for any target. Nevertheless, it should be noticed that across all different trials only three patients were seizure-free for the duration of the BEP. Two of these belonged to the treatment group of the RCT evaluating closed-loop stimulation of the ictal onset zone (OR 4.95; 95% CI 0.23 to 104.44) and another to the sham group of the trial on anterior thalamic nucleus DBS (OR 0.33; 95% CI 0.01 to 8.36). Besides seizure freedom, the 50% responder rate was our other primary outcome measure. Statistically significant effects on responder rates after one to three months of stimulation could not be observed for any target, but again the wide CIs cannot exclude clinically meaningful changes for either the stimulation or the control group. The fact that ORs were $\geq$ 1.00 in every single trial and > 1.00 for every target (except for centromedian thalamic DBS: OR 1.00; 95% CI 0.27 to 3.69) do not suggest equivalence. However, apart from cerebellar (OR 2.43; 95% CI 0.46 to 12.84), nucleus accumbens (OR 10.0; 95% CI 0.53 to 189.15) and six months of hippocampal stimulation (OR 9.00; 95% CI 0.22 to 362.46), the pooled effect estimates seem of little clinical importance for anterior thalamic nucleus DBS (OR 1.20; 95% CI 0.52 to 2.80), one to three months of hippocampal DBS (OR 1.20; 95% CI 0.36 to 4.01) and responsive ictal onset zone stimulation (OR 1.12; 95% CI 0.59 to 2.11).

Statistically significant seizure frequency reductions due to one to three months of active stimulation were demonstrated for anterior thalamic DBS (-17.4%; 95% CI -31.2 to -1.0) hippocampal DBS (-28.1%; 95% CI -34.1 to -22.2) and responsive ictal onset zone stimulation (-24.9%; 95% CI -40.1 to -6.0). When interpreting these results, one should keep in mind that these effect estimates may be rather conservative due to observed trends for increasing efficacy over time for anterior thalamic DBS (month one: -10%, month three: -29%) and responsive ictal onset zone stimulation (month one: -9%, month three: -32%) and a possible outlasting effect in the stimulation 'off' period in Tellez-Zenteno 2006, a cross-over trial on hippocampal DBS without any washout period. Significant reductions could not be demonstrated for cerebellar (-12.4%; 95% CI -35.3 to 10.6%), centromedian thalamic (+7.1%; 95% -44.1% to 58.2%; no effect in another cross-over trial (Velasco 2000a), P = 0.23), nucleus accumbens (-33.4%; 95% CI -100% to +49.8%) or six months of hippocampal (active -45% versus sham +60%, P > 0.05) stimulation, although the small number of patients and possible carryover effects in stimulation 'off' periods in Velasco 2000a (centromedian thalamic DBS), Van Buren 1978 and Wright 1984 (cerebellar stimulation) preclude more definitive judgements.

Only for anterior thalamic DBS were there statistically significant differences in stimulation-related adverse events. These included (treatment versus control group) depression (14.8% versus 1.8%; P = 0.02), subjective memory impairment (13.8% versus 1.8%; P = 0.03) and epilepsy-related injuries (7.4% versus 25.5%; P = 0.01). In addition, confusional state and anxiety were more frequent, and standard stimulation parameters could be inappropriate and increase seizure frequency in a small minority of patients.

For the other targets, stimulation-related adverse events did not occur (centromedian thalamic DBS, cerebellar and hippocampal stimulation), or were not more prevalent in the treatment group (responsive ictal onset zone and nucleus accumbens stimulation). In general, however, the size of the included studies (in particular those on centromedian thalamic DBS, cerebellar, hippocampal and nucleus accumbens stimulation) is too limited to make more conclusive statements, although responsive ictal onset zone stimulation seems to be well-tolerated. After initial concerns about the slightly elevated sudden unexpected death in epilepsy patients (SUDEP) rate mentioned in the first paper on responsive ictal onset zone stimulation, long-term open-label follow-up has now been reassuring both for anterior thalamic DBS and responsive ictal onset zone stimulation.

The invasive nature of direct brain stimulation treatments resulted in various surgery- or device-related adverse events. In the two largest trials, asymptomatic intracranial haemorrhages were detected postoperatively in 1.6% to 3.7% of participants and postoperative implant or incision site infection occurred in 2.0% to 4.5% of participants, increasing to 9.4% to 12.7% after five years of follow-up urging (temporary) hardware removal in the majority of cases (Fisher 2010; Morrell 2011). Inadequate stereotactic placement of electrodes needed repeated surgery in 8.2% of patients in Fisher 2010. Electrode migration seems of particular concern for cerebellar stimulation electrodes (n = 6/22). Other adverse events included skin erosions, defective hardware, leakage of cerebrospinal fluid, a lead causing pain and a subcutaneous seroma. Cranial implantation of the neurostimulator in Morrell 2011 was associated with implant site pain (16% in year one), headache (11%), procedural headache (9%) and dysaesthesia (6%).

Statistically significant differences in formal neuropsychological testing results could not be demonstrated on the group level for any target. However, only for responsive ictal onset zone stimulation is there reasonable evidence for the absence of adverse neuropsychological sequelae. In contrast, the higher prevalence of depression and subjective memory impairment with anterior thalamic DBS (see above) and the low number of (neuropsychologically tested) participants in studies on centromedian thalamic, cerebellar, nucleus accumbens and hippocampal stimulation urge further research. In this respect, it should be mentioned that one (n = 1/6) patient receiving one to three months of hippocampal stimulation showed objective worsening of memory scores (although he reported a subjective memory improvement) and cognitive scales assessing recall were generally lower after six months of active compared to sham hippocampal stimulation (again, in contrast to increased subjective QOLIE-89 memory and attention/concentration scales). In addition, results were often incompletely published and the content of the neuropsychological test battery was not clear for Wright 1984 (cerebellar stimulation) and Wiebe 2013 (six months of hippocampal stimulation).

Anterior thalamic nucleus DBS and responsive ictal onset zone stimulation do not significantly improve or worsen quality of life after three months of stimulation. With regards to the other targets, only two trials on hippocampal stimulation (n = 9) (Tellez-Zenteno 2006; Wiebe 2013) and one trial on nucleus accumbens stimulation (n = 4) (Kowski 2015) have formally evaluated quality of life, while in Wright 1984, the patients' impressions on cerebellar stimulation were described. Even for those targets, however, data are too sparse to make any sensible conclusion.

Overall completeness and applicability of evidence

Currently available evidence is far from complete. The completeness and applicability of the evidence are highly dependent on its quality. All factors limiting the quality of the evidence at the same time limit, to a greater or lesser extent, the completeness and applicability of the evidence. In this review this is especially the case for the small number of trials and patients in which deep brain and cortical stimulation have been studied. Furthermore, only a subset of trials have evaluated the impact of stimulation on the neuropsychological outcome (nine out of 12 trials, with varying degree of extensiveness of testing) and on quality of life (only five to six out of 10 trials). More large and well-designed RCTs are definitely needed to demonstrate or exclude benefits and side effects of invasive brain stimulation therapies. This applies to every single target although there are important differences between the different targeted structures. Taken together, evidence is most complete for responsive ictal onset zone stimulation, followed by anterior thalamic DBS, hippocampal DBS, cerebellar cortical stimulation, nucleus accumbens DBS and finally centromedian thalamic DBS. In addition, several other targets have yielded promising results in uncontrolled open-label trials but have not been studied in blinded and randomized conditions (or the results have not been published yet), for example the subthalamic nucleus (Chabardes 2002; Wille 2011), the caudate nucleus (Chkhenkeli 2004) and the motor cortex (Elisevich 2006).

Trials on cerebellar and centromedian thalamic DBS included both patients with (multi)focal epilepsy and patients suffering from generalized epilepsy. In contrast, trials on anterior thalamic DBS, hippocampal DBS, nucleus accumbens DBS and responsive ictal onset zone stimulation recruited only (multi)focal, temporal lobe, focal and focal (one or two epileptogenic regions) epilepsy patients, respectively. Although this makes sense for hippocampal DBS and responsive ictal onset zone stimulation, further studies are needed to determine if anterior thalamic or nucleus accumbens DBS could also be useful for generalized epilepsy patients.

Only Velasco 2000a (centromedian thalamic DBS) recruited a substantial number of minors; 5/13 or 7/15 patients were between four and 15 years old. Authors reported that skin erosion may be of particular concern in children under eight years of age as a result of the relatively large size of the pulse generator and the leads, originally designed for an adult population. Of the other trials, Fisher 1992 (centromedian thalamic DBS), Velasco 2005 (cere-

bellar stimulation) and Velasco 2007 (hippocampal stimulation), each included one 14 to 16 year old adolescent, whereas in all other trials all patients were adult. Therefore, current evidence is basically limited to adult refractory epilepsy patients. Fisher 2010 (anterior thalamic DBS) and Wiebe 2013 (hippocampal DBS, six months) only allowed adults with normal mental capacities (intelligence quotient (IQ) > 70). These are important restrictions which should be taken into consideration when evaluating the overall completeness and applicability of current evidence. Furthermore, evidence is limited to stimulation parameters or parameter strategies used in the respective trials and to the RNS® System (NeuroPace, Mountain View, CA) for responsive ictal onset zone stimulation.

Besides the low number of trials and patients, the limited duration of the BEPs (one to three-month stimulation 'on' periods in all but one small trial on hippocampal stimulation) represents a second major gap in the available evidence. This seems of particular concern for invasive brain stimulation therapies as increasing efficacy over time has been reported during BEPs in some RCTs (Fisher 2010; Morrell 2011), during open-label follow-up after completion of RCTs (Fisher 2010; Morrell 2011; Velasco 2007), and in some small open-label trials (Franzini 2008; Khan 2009). Various RCTs have followed their patients for many months or years after the randomized and blinded phase had been finished and it may be relevant for the reader to cite the results they reported to illustrate the shortcomings of today's evidence. Fisher 2010 (anterior thalamic DBS) reported seizure freedom in 0% at the end of the BEP (n = 54), in 2.0% at the end of the ensuing nine month open-label period (stimulation parameters adjusted on an individual basis, antiepileptic drug (AEDs) unchanged) (n = 99) and 11 of 83 (13.3%; 10% of all implanted participants) participants that were still in the trial after five years of follow-up were seizure-free for at least six months at the five-year assessment (changes in the AED regimen were allowed). Responder rates were 30%, 43% (n = 99 participants with at least 70 diary days) and 68% (n = 59) respectively, with mean seizure frequency reductions of -40%, -41% and -69%. Fisher 1992 (centromedian thalamic DBS) observed a 50% seizure reduction in 3/7 patients (2/7 during the BEP) after an additional three to 13 months of open-label follow-up (24 hours of stimulation per day), the mean reduction in seizure frequency being -30% (-7% during the BEP). With regards to the same target, Velasco 2000a reported seizure freedom in 1/13 patients (7.7%), a 85% responder rate and a mean 72% seizure frequency reduction at maximum follow-up (12 to 94 months). Velasco 2005 (cerebellar stimulation) showed a 50% improvement in 2/3 patients during the BEP (mean seizure frequency reduction of 56%) and in 4/5 patients after 12 to 24 months follow-up (68% reduction). The most spectacular improvement was found in Velasco 2007 (hippocampal stimulation) who reported seizure freedom in 4/9 patients after 18 months follow-up (0/4 during the BEP), a 50% reduction in all nine patients (1/4 during the BEP) and a mean seizure frequency reduction of -85% (-30% during the BEP). Finally, three-month seizure freedom, the 50% responder rate and the median reduction in seizure frequency after two years of open-label follow-up (n = 174) in Morrell 2011 (responsive ictal onset zone stimulation) were 7.1%, 55% and 53% compared to 2.1%, 29% and 37.9%, respectively during the BEP. Notwithstanding that these open-label data often show very favourable results, we would like to emphasize that at the same time these are at high risk of bias, including but not limited to placebo effects and improvements due to changes in AED or spontaneous evolution of the disease (see also below). Only one small RCT with longer than three months of active stimulation has been published to date and data are too sparse to make any sensible conclusion. More RCTs with a more extensive BEP are needed to unequivocally determine whether and to what extent the efficacy of invasive brain stimulation treatments increases over time. Meanwhile, we pooled results per three-month stimulation epochs and reported for each individual study if and to what extent such an increasing efficacy over time was observed during the BEP.

Finally, although three RCTs are currently recruiting patients to compare deep brain stimulation (DBSI with resective surgery, 'usual' treatment and vagus nerve stimulation, respectively, all trials published so far have compared active to sham stimulation only.

Quality of the evidence

For a more detailed assessment of the quality of the evidence see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6.

Several factors affect the quality of currently available evidence. Of major importance is the limited number of trials, which in addition mostly have very small sample sizes. Although this holds true for every target, this is of particular concern for centromedian thalamic DBS, cerebellar, hippocampal and nucleus accumbens stimulation. Moreover, neuropsychological testing and assessment of quality of life were only performed in a subset of trials. These limitations make it harder to demonstrate the statistical significance of clinically meaningful differences or to exclude the possibility of such improvements when clinically non-meaningful differences are found.

In five cross-over RCTs on cerebellar (n = 2/3), centromedian thalamic (n = 1/2), hippocampal (n = 1/4) and nucleus accumbens (n = 1/1) DBS, there was no or a possibly too short washout period before outcome measures were evaluated during stimulation 'off' periods (Kowski 2015; Tellez-Zenteno 2006; Van Buren 1978; Velasco 2000a; Wright 1984). As some or all patients had previously been stimulated and findings consistent with a carryover effect of invasive neurostimulation have been reported in the literature (Andrade 2006; Lim 2007; McLachlan 2010; Velasco 2007; Vonck 2013), this may mask or reduce possible beneficial or adverse effects of stimulation. In addition, changes in the antiepileptic drug (AED) regimen in 3/4 patients during the trial may further

have influenced the results of Tellez-Zenteno 2006 (hippocampal stimulation, one to three months stimulation). A sensitivity analysis excluding those four trials did not change our main conclusions, although this did result in more pronounced estimates of stimulation effects for cerebellar (responder rate OR 8.33; 95% CI 0.22 to 320.4; seizure frequency reduction -36.7%; 95% CI -95.5 to 21.1) and hippocampal stimulation (one to three months of stimulation) (responder rate OR 1.75; 95% CI 0.22 to 14.1; if also larger standard error for McLachlan 2010 for seizure frequency reduction of -45.7%; 95% CI -85.9 to -5.5). Obviously, in the case of a clear absence of any effect (for example, on seizure freedom), the possibility of an outlasting effect in these trials does not complicate interpretation of the results.

The quality of the evidence on centromedian thalamic DBS is very low. Two RCTs were identified in the literature. However, one trial (Velasco 2000a) (n = 13) evaluated stimulation 'off' periods after six to nine months of stimulation without any washout period. The trial only studied two outcome measures (seizure frequency reduction and adverse events), compared blinded stimulation 'off' to the three months preceding it (instead of consistently comparing outcomes to blinded stimulation 'on' periods), and the non-reporting of exact figures prevented inclusion in the meta-analysis. In the second trial (Fisher 1992), seven patients received only two hours of stimulation per day and incomplete outcome data could have biased the results.

Risk of bias was present or unclear in various other trials. It was unclear if the neuropsychological outcome in Van Buren 1978 (cerebellar stimulation) was assessed during blinded or unblinded evaluation periods; methods for random sequence generation and allocation concealment were not well-described in Tellez-Zenteno 2006 (hippocampal stimulation, one to three months) and Wright 1984 (cerebellar cortical stimulation), and evidence of selective reporting was present in two other trials (Fisher 2010 for anterior thalamic DBS; McLachlan 2010 for hippocampal DBS, one to three months), although we think the latter has not greatly affected the results of this review. Some trials also reported their results incompletely (mainly neuropsychological testing results) and without evidence for selective reporting (Fisher 1992 for centromedian thalamic DBS; Tellez-Zenteno 2006 for hippocampal DBS; Wright 1984 for cerebellar cortical stimulation). Wiebe 2013 (hippocampal stimulation, six months) was only published as an abstract with many details missing for a more in depth methodological assessment or for full incorporation in the quantitative synthesis.

As no more than three trials could be identified for each individual target (per three-month epoch in case of hippocampal stimulation), we were not able to assess the risk of publication bias.

For more detailed assessments of the quality of the evidence per outcome parameter and per stimulation target we refer to the 'Summary of findings' tables. In general, the quality of the evidence was rated as moderate to high for responsive ictal-onset zone stimulation and anterior thalamic DBS. The two trials evaluating these targets were well-designed and each included more than 100 participants. Nevertheless, more trials are needed to obtain high-quality evidence on all outcome parameters. The quality of the evidence on hippocampal DBS (one to three months of stimulation) and cerebellar stimulation is limited by some potential biases in the individual trials (see above) and the overall low number of participants, ranging from very low to moderate depending on the outcome parameter taken into consideration. Nucleus accumbens and hippocampal (four to six months) DBS were each studied in only one very small trial. For nucleus accumbens DBS, this trial was methodologically well-designed resulting into low-quality evidence overall. As details needed for full methodological assessment of the trial on hippocampal DBS (four to six months) are missing, the quality of the evidence was rated as very low. For reasons outlined above, the quality of the evidence on centromedian thalamic DBS is only very low.

Potential biases in the review process

When performing meta-analyses, the results of various trials are pooled yielding pooled treatment effects of which the precision and accuracy depend on the quality of the individual trials. Therefore, pooling results of various trials including some trials with a risk of bias adds some risk of bias to the review process. For this specific review, besides of course other types of bias, this remark particularly holds true for the inclusion of four cross-over trials without any washout period as outlasting effects after neurostimulation treatments have been described (although still being controversial). We therefore performed a sensitivity analysis excluding these trials. Although this resulted in a slightly more favourable effect estimate, it did not change the review's main conclusions.

As empty cells hinder calculation of odds ratios (seizure freedom, responder rate), it is customary to add +0.5 to each cell if applicable (Deeks 2011). However, given the small number of patients included in most trials, this approach may have biased our results. A sensitivity analysis adding +0.25 instead of +0.5 did not change our main conclusions, but did increase the degree of uncertainty around the effect estimates for seizure freedom.

For cerebellar and hippocampal stimulation, results of BEPs with different durations of active stimulation BEP (one to three months) were pooled. As some reports have suggested increasing efficacy over time, this may have lead to an overestimation compared to the one-month treatment effect and an underestimation compared to the three-month treatment effect. We therefore refer to the observed treatment effects as occurring after 'one to three months' of stimulation. In addition, we described in the text if and to what extent increasing efficacy over time was observed during the BEP of each individual trial. As outlined in the previous version of this review, results of RCTs with longer BEPs are pooled per three-month epochs. So far, only one very small RCT on hippocampal DBS (Wiebe 2013) had a BEP with longer than six months of active stimulation. A sensitivity analysis combining all

trials on hippocampal DBS irrespective of the BEP duration did not change the conclusions of this review.

Agreements and disagreements with other studies or reviews

Although various non-systematic reviews have been published the past years, to our knowledge this is the first systematic review on RCTs studying deep brain and cortical stimulation. The non-systematic reviews also discussed uncontrolled, often unblinded trials. These uncontrolled and unblinded trials have often yielded remarkably more favourable results than the RCTs. Besides the placebo effect, several other factors may account for this discrepancy. First of all, RCTs compare real stimulation to sham stimulation, whereas in uncontrolled trials baseline seizure frequency is taken for the reference data. Accordingly, seizure frequency reductions due to (temporary) implantation effects (Fisher 2010; Hodaie 2002;Lim 2007; Morrell 2011) and microlesions resulting from electrode insertion (Boëx 2011; Katariwala 2001; Schulze-Bonhage 2010) contribute to the observed treatment effects in uncontrolled trials, whereas they do not in RCTs. Second, uncontrolled trials have longer follow-up periods and increasing efficacy over time has been suggested (see above). However, one should realize that medication-induced and spontaneous improvements can be quite impressive on a group level (Neligan 2012; Selwa 2003) and therefore are likely to contribute to the more favourable results obtained in uncontrolled trials. Third, the cross-over design used in four RCTs without any washout period may undervalue the efficacy of neurostimulation treatments, as discussed above. Finally, further improvements due to optimization of stimulation parameter settings have been reported (Boëx 2011; Vonck 2013; Wille 2011) and uncontrolled trials often use variable parameter settings, whereas RCTs have a fixed stimulation protocol. In conclusion, it is likely that several factors overestimate the efficacy of invasive neurostimulation in uncontrolled trials, whereas some others may contribute to an underestimation of its full potential in RCTs.

Vagus nerve stimulation is another type of invasive neurostimulation which nowadays has become routinely available in many epilepsy centres worldwide. Although the treatment effects reported in two large RCTs (-12.7% and -18.4%) (Handforth 1998; VNS Study Group 1995) were similar or slightly inferior to those of anterior thalamic DBS (-17.4%), hippocampal DBS (-28.1%) and closed-loop ictal onset zone stimulation (-24.9%), a Cochrane Review on vagus nerve stimulation did demonstrate a significantly higher responder rate with vagus nerve stimulation using a high stimulation paradigm ('standard stimulation') compared to a low stimulation paradigm ('sham stimulation') (RR 1.73; 95% CI 1.13 to 2.64) (Panebianco 2015). As outlined above, we did not find such a significant improvement for any intracranial target.

AUTHORS' CONCLUSIONS

Implications for practice

Making general recommendations about the practical usefulness of intracranial neurostimulation treatments implies making trade-offs between potential benefits and harms, costs, healthcare resources and alternative treatments such as newly developed drugs, the ketogenic diet, vagus nerve stimulation and epilepsy surgery. We believe such a trade-off should be made on an individual patient basis, differing from country to country, and therefore goes beyond the scope of this review. In this section we will consequently only focus on available evidence on the benefits and harms of intracranial neurostimulation treatments.

Of all potential intracranial targets, only six have been studied in randomized and double-blind conditions so far. The main limitation is the number of trials, which in addition mostly have very small sample sizes and are of short duration. Nevertheless, high-quality evidence is available that three months of anterior thalamic nucleus deep brain stimulation (DBS) and responsive ictal onset zone stimulation can reduce seizure frequency in refractory (multi)focal epilepsy patients, whereas moderate-quality evidence shows the same for one to three months of hippocampal DBS in refractory temporal lobe epilepsy patients. However, compared to sham stimulation, the observed improvements were moderate (ranging between 17% and 28%) and there is no evidence for either a clinically or statistically significant impact on seizure freedom, responder rate or quality of life (although anterior thalamic DBS did reduce epilepsy-associated injuries). Given these rather moderate improvements, possible harms should be carefully considered. Anterior thalamic DBS and responsive ictal onset zone stimulation were in general safe and well-tolerated, however, anterior thalamic DBS was associated with statistically significant higher incidences of self-reported depression (no group-level changes in objective measures) and subjective memory impairment (no group-level changes in objective measures) besides statistically non-significant increases in anxiety, confusional state and seizure frequency in some patients. Hippocampal DBS seemed safe and relatively well-tolerated but these findings should be confirmed in more and larger trials, with particular concern for memory impairment. Besides stimulation-related side effects, the invasive nature of these treatments resulted in soft tissue infections and asymptomatic intracranial haemorrhages, but no permanent symptomatic sequelae resulting from electrode implantation were reported. Finally, when balancing benefits and risks of the aforementioned treatments, one should keep in mind that many of the patients included in the trials on intracranial neurostimulation had previously turned out to be refractory to various other treatments (including antiepileptic drugs (AEDs), resective surgery and vagal nerve stimulation) and had no other evident or ideal treatment options.

Besides the three targets mentioned in the previous paragraph,

centromedian thalamic nucleus DBS, cerebellar cortical stimulation and nucleus accumbens DBS have been studied in randomized controlled trials (RCTs) but no statistically significant effects were found in these small trials, which in addition often suffered from various other limitations. In conclusion, there is insufficient evidence to accept or refute their efficacy or tolerability. No trials comparing intracranial stimulation to 'best medical practice', surgery or vagus nerve stimulation have been published yet.

Implications for research

Given the limited number of RCTs identified in the literature, more double-blind randomized controlled clinical trials are required to provide evidence on the efficacy and safety of intracranial neurostimulation treatments for refractory epilepsy. These trials should preferably consider the following points.

- Include large numbers of patients. However, given the limited number of patients included in RCTs so far, even smaller trials would increase the available evidence and are therefore worthwhile to be undertaken. For the same reason, results of preliminary terminated trials (e.g. due to insufficient patient enrolment) should be published. Given the difficulties in patient recruitment, multicentre participation may be recommended.

- Make interpretation easier by avoiding possible outlasting effects of stimulation. The most straightforward way to do so is using a parallel study design. When a cross-over design is used, due to difficulties in patient recruitment, a washout period should be introduced (e.g. three months without stimulation after three months of stimulation).

- Make interpretation easier by avoiding possible implantation effects (as in Fisher 2010 and Morrell 2011) by using a sufficient time window (e.g. four months) between electrode implantation and the start of the blinded evaluation period.

- Assess and report all significant outcome variables, including seizure freedom, responder rate, seizure frequency reduction, adverse events, neuropsychological outcome and quality of life.

Additionally, there is a need for RCTs comparing intracranial neurostimulation treatments to 'best medical practice' (including vagal nerve stimulation); reported trends for increasing efficacy over time should be verified in randomized and if possible double-blind conditions (comparison to 'best medical treatment' could overcome ethical issues); and, finally, more efforts should be made to identify optimal stimulation parameter paradigms, which could be patient-specific.

ACKNOWLEDGEMENTS

We thank A Beamond and G Chan for their assistance in the literature search and Dr M Miatton (Ghent University Hospital) for her valuable assistance in the interpretation of the neuropsychological data. Dr M Sprengers is supported by an "FWO-aspirant" grant (Research Foundation Flanders). Prof Dr K Vonck is supported by a BOF-ZAP grant from Ghent University Hospital. Prof Dr P Boon is supported by grants from FWO-Flanders, grants from BOF, and by the Clinical Epilepsy Grant from Ghent University Hospital.

REFERENCES

References to studies included in this review

Fisher 1992 ***{published and unpublished data}***

Fisher RS. Personal communication 2012.

Fisher RS, Uematsu S, Krauss GL, Cycyk BJ, Lesser RP, Rise M. A controlled pilot study of centromedian thalamic stimulation for epilepsy. *Epilepsia* 1991;**32 Suppl 3**:86. CENTRAL: CN–00745383]

* Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, et al. Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. *Epilepsia* 1992;**33**(5):841–51.

Fisher 2010 ***{published and unpublished data}***

Fisher RS. Personal communication 2012.

* Fisher RS, Salanova V, Witt T, Worth R, Henry T, Gross R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 2010;**51**(5):899–908.

Gross RE, Worth R, Witt T, Mapstone T, Kaplitt M, Sharan A. Stimulation of the anterior nucleus of the thalamus for epilepsy (sante) trial: Results related to region of onset and prior surgical treatments. Stereotactic and functional neurosurgery (16th Quadrennial Meeting of the World Society for Stereotactic and Functional Neurosurgery Tokyo Japan). 2013; Vol. 91:16. CENTRAL: CN–01027089; EMBASE: 71073454]

Medtronic. Medtronic DBS therapy for epilepsy: sponsor information. http://www.fda.gov. February 2010.

MedtronicNeuro. SANTE - Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy. https://www.clinicaltrials.gov/ct2/show/NCT00101933?term=NCT00101933 January 2005, last update December 2014. Clinicaltrials.gov: NCT00101933]

Salanova V, Fisher R. Long term efficacy of the SANTE trial (Stimulation of the Anterior Nucleus of Thalamus

for Epilepsy) [abstract no: 2.269]. Epilepsy currents (64th Annual Meeting of the American Epilepsy Society, AES and 3rd Biennial North American Regional Epilepsy Congress San Antonio, TX United States). 2011; Vol. 11, issue 1 Suppl 1. CENTRAL: CN–00775388; CENTRAL: CN–01004916; EMBASE: 70830787]
Salanova V, Fisher R, Sante G. Long term efficacy of the sante trial (stimulation of the anterior nucleus of thalamus for epilepsy). Epilepsy Currents (2012 Annual Meeting of the American Epilepsy Society, AES 2012 San Diego, CA United States). 2013; Vol. 13:123–4. CENTRAL: CN–01006584; EMBASE: 71196472]
Salanova V, Witt T, Worth R, Henry TR, Gross RE, Nazzaro JM, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology* 2015;**84**(10):1017–25. CENTRAL: CN–01089472; DOI: 10.1212/WNL.0000000000001334; PUBMED: 25663221

Kowski 2015 ***{published data only}***
Kowski A. Deep brain stimulation in patients with refractory epilepsy. http://www.drks.de/DRKS00003148 July 2011. German Clinical Trials Register: DRKS00003148]
* Kowski AB, Voges J, Heinze H-J, Oltmanns F, Holtkamp M, Schmitt FC. Nucleus accumbens stimulation in partial epilepsy - a randomized controlled case series. *Epilepsia* 2015;**56**(6):e78–e82. CENTRAL: CN–01084158; DOI: 10.1111/epi.12999; EMBASE: 2015053810; PUBMED: 25940212

McLachlan 2010 ***{published and unpublished data}***
Mc Lachlan RS. Personal communication 2012.
* McLachlan RS, Pigott S, Tellez-Zenteno JF, Wiebe S, Parrent A. Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: impact on seizures and memory. *Epilepsia* 2010;**51**(2):304–7.

Morrell 2011 ***{published and unpublished data}***
Bergey GK, Morrell MJ, Mizrahi EM, Goldman A, King-Stephens D, Nair D, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology* 2015;**84**(8):810–7. CENTRAL: CN–01077409; DOI: 10.1212/WNL.0000000000001280; EMBASE: 2015788347; PUBMED: 25616485
Duncan JS, Hamani C. Stimulating the brain for epilepsy (editorial). Neurology 2015; Vol. 84, issue 8:768–9. DOI: 10.1212/WNL.0000000000001297; PUBMED: 25616484
Heck CN, King-Stephens D, Massey AD, Nair DR, Jobst BC, Barkley GL, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. *Epilepsia* 2014;**55**(3):432–41. CENTRAL: CN–00985374; DOI: 10.1111/epi.12534; EMBASE: 2014190630; PUBMED: 24621228
Loring DW, Kapur R, Meador KJ, Morrell MJ. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. *Epilepsia* 2015; **56**(11):1836–44. DOI: 10.1111/epi.13191; PUBMED: 26385758
Loring DW, Kapur R, Meador KJ, Morrell MJ. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. *Epilepsia* 2015; **56**(11):1836–44. PUBMED: 26385758]
Meador KJ, Kapur R, Loring DW, Kanner AM, Morrell MJ, RNS® System Pivotal Trial Investigators. Quality of life and mood in patients with medically intractable epilepsy treated with targeted responsive neurostimulation. *Epilepsy Behavior* 2015;**45**:242–7. DOI: 10.1016/j.yebeh.2015.01.012; PUBMED: 25819949
Morrell MJ. Personal communication 2012.
Morrell MJ. In response: The RNS System multicenter randomized double-blinded controlled trial of responsive cortical stimulation for adjunctive treatment of intractable partial epilepsy: knowledge and insights gained. Epilepsia 2014; Vol. 55, issue 9:1470–1. CENTRAL: CN–01050599; DOI: 10.1111/epi.12736; EMBASE: 2014837377; PUBMED: 25223509
* Morrell MJ, Group RNSSiES. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* 2011;**77**(13):1295–304.
Neuoropace. RNS® System Pivotal Study. https://clinicaltrials.gov/ct2/show/NCT00264810 December 2005, last update August 2013. Clinicaltrials.gov: NCT00264810]
Osorio I. The NeuroPace trial: missing knowledge and insights. Epilepsia 2014; Vol. 55, issue 9:1469–70. DOI: 10.1111/epi.12701; PUBMED: 25223508
Smith B. Improvements in quality of life and mood with treatment of medically intractable partial epilepsy with a responsive neurostimulator. Neurology (64th American Academy of Neurology Annual Meeting New Orleans, LA United States). 2012; Vol. 78:1 Meeting Abstract. CENTRAL: CN–01033715; EMBASE: 70725867]

Tellez-Zenteno 2006 ***{published data only (unpublished sought but not used)}***
Parrent A, Wiebe S, Matijevic S, Janzen L, Piggot S, Kubu C, et al. Randomized controlled studies of long-term hippocampal stimulation in single patients with temporal lobe epilepsy. *Epilepsia* 2003;**44 Suppl 9**:326–7. CENTRAL: CN–00745104]
* Tellez-Zenteno JF, McLachlan RS, Parrent A, Kubu CS, Wiebe S. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. *Neurology* 2006;**66**(10):1490–4.

Van Buren 1978 ***{published data only (unpublished sought but not used)}***
Van Buren JM, Wood JH, Oakley J, Hambrecht F. Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. *Journal of Neurosurgery* 1978;**48**(3):407–16.

Velasco 2000a ***{published and unpublished data}***
Velasco F. Personnal communication 2012.
* Velasco F, Velasco M, Jimenez F, Velasco AL, Brito F, Rise M, et al. Predictors in the treatment of difficult-to-control seizures by electrical stimulation of the centromedian

thalamic nucleus. *Neurosurgery* 2000;**47**(2):295-304; discussion -5.

Velasco 2005 *{published and unpublished data}*
Kellinghaus C, Loddenkemper T. Double-blind, randomized controlled study of bilateral cerebellar stimulation. *Epilepsia* 2006;**47**(7):1247; author reply 8-9.
Velasco F. Personal communication 2012.
* Velasco F, Carrillo-Ruiz JD, Brito F, Velasco M, Velasco AL, Marquez I, et al. Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. *Epilepsia* 2005;**46**(7):1071–81.

Velasco 2007 *{published and unpublished data}*
Velasco AL. Personal communication 2012.
Velasco AL, Velasco F, Velasco M, Jimenez F, Carrillo-Ruiz JD, Castro G. The role of neuromodulation of the hippocampus in the treatment of intractable complex partial seizures of the temporal lobe. *Acta Neurochirurgica Supplement* 2007;**97**(Pt 2):329–32.
* Velasco AL, Velasco F, Velasco M, Trejo D, Castro G, Carrillo-Ruiz JD. Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. *Epilepsia* 2007;**48**(10):1895–903.

Wiebe 2013 *{published data only (unpublished sought but not used)}*
Wiebe S. Medical versus Electrical Therapy for Temporal Lobe Epilepsy (METTLE). www.clinicaltrials.gov/ct/show/NCT00717431. Vol. July 2008, last update: March 2012. CENTRAL: CN–00643489; CTG: NCT00717431]
* Wiebe S, Kiss Z, Ahmed N, Andrade D, Brownstone R, Del Campo M, et al. Medical vs electrical therapy for mesial temporal lobe epilepsy: A multicenter randomized trial. Epilepsy Currents (2012 Annual Meeting of the American Epilepsy Society, AES 2012 San Diego, CA United States). 2013; Vol. 13:289. CENTRAL: CN–01006580; EMBASE: 71196839]

Wright 1984 *{published data only (unpublished sought but not used)}*
Wright GD, McLellan DL, Brice JG. A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry* 1984;**47**(8):769–74.

References to studies excluded from this review

Alaraj 2001 *{published data only}*
Alaraj A, Commair Y, Mikati M, Wakim J, Louak E, Atweh S. Subthalamic nucleus deep brain stimulation: a novel method for the treatment of non-focal intractable epilepsy. Neuromodulation: defining the future, poster presentation at Cleveland Ohio. 2001.

Anderson 2008 *{published data only}*
Anderson WS, Kossoff EH, Bergey GK, Jallo GI. Implantation of a responsive neurostimulator device in patients with refractory epilepsy. *Neurosurgical Focus* 2008; **25**(3):E12.

Andrade 2006 *{published data only}*
Andrade DM, Zumsteg D, Hamani C, Hodaie M, Sarkissian S, Lozano AM, et al. Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy. *Neurology* 2006;**66**(10):1571–3.

Bidzin ski 1981 *{published data only}*
Bidzin ski J, Bacia T, Ostrowski K, Czarkwiani L. Effect of cerebellar cortical electrostimulation on the frequency of epileptic seizures in severe forms of epilepsy. *Neurologia i Neurochirurgia Polska* 1981;**15**(5-6):605–9. PUBMED: 6979000]

Boëx 2011 *{published data only}*
Boëx C, Seeck M, Vulliemoz S, Rossetti AO, Staedler C, Spinelli L, et al. Chronic deep brain stimulation in mesial temporal lobe epilepsy. *Seizure* 2011;**20**(6):485–90. PUBMED: 21489828]

Boon 2007a *{published data only}*
Boon P, Vonck K, De Herdt V, Van Dycke A, Goethals M, Goossens L, et al. Deep brain stimulation in patients with refractory temporal lobe epilepsy. *Epilepsia* 2007;**48**(8): 1551–60.

Brown 2006 *{published data only}*
Brown JA, Lutsep HL, Weinand M, Cramer SC. Motor cortex stimulation for the enhancement of recovery from stroke: a prospective, multicenter safety study. *Neurosurgery* 2006;**58**(3):464–73. PUBMED: 16528186]

Chabardes 2002 *{published data only}*
Chabardes S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid AL. Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. *Epileptic Disorders* 2002;**4 Suppl 3**:S83–93. PUBMED: 12495878]

Child 2014 *{published data only}*
Child ND, Stead M, Wirrell EC, Nickels KC, Wetjen NM, Lee KH, et al. Chronic subthreshold subdural cortical stimulation for the treatment of focal epilepsy originating from eloquent cortex. *Epilepsia* 2014;**55**(3):e18–21. PUBMED: 24571166]

Chkhenkeli 2004 *{published data only}*
Chkhenkeli SA, Sramka M, Lortkipanidze GS, Rakviashvili TN, Bregvadze E, Magalashvili GE, et al. Electrophysiological effects and clinical results of direct brain stimulation for intractable epilepsy. *Clinical Neurology and Neurosurgery* 2004;**106**(4):318–29. PUBMED: 15297008]

Cooper 1976 *{published data only}*
Cooper IS, Amin I, Riklan M, Waltz JM, Poon TP. Chronic cerebellar stimulation in epilepsy. Clinical and anatomical studies.. *Archives of Neurology* 1976;**33**(8): 559–70. PUBMED: 821458]

Cordella 2013 *{published data only}*
Cordella R, Acerbi F, Marras CE, Carozzi C, Vailati D, Saini M, et al. Risk of seizures during intraoperative electrocortical stimulation of brain motor areas: a retrospective study on 50 patients. *Neurological Sciences* 2013;**34**(1):63–70. PUBMED: 22350148]

Cukiert 2009 *{published data only}*
Cukiert A, Burattini JA, Cukiert CM, Argentoni-Baldochi M, Baise-Zung C, Forster CR, et al. Centro-median

stimulation yields additional seizure frequency and attention improvement in patients previously submitted to callosotomy. *Seizure* 2009;**18**(8):588–92. PUBMED: 19577937]

Cukiert 2014 ***{published data only}***
Cukiert A, Cukiert CM, Burattini JA, Lima AM. Seizure outcome after hippocampal deep brain stimulation in a prospective cohort of patients with refractory temporal lobe epilepsy. *Seizure* 2014;**23**(1):6–9. PUBMED: 23992890]

Davis 1992 ***{published data only}***
Davis R, Emmonds SE. Cerebellar stimulation for seizure control: 17-year study. *Stereotactic and Functional Neurosurgery* 1992;**58**(1-4):200–8. PUBMED: 1439341]

Davis 2000 ***{published data only}***
Davis R. Cerebellar stimulation for cerebral palsy spasticity, function, and seizures. *Archives of Medical Research* 2000;**31**(3):290–9. PUBMED: 11036180]

Ding 2016 ***{published data only}***
Ding P, Zhang S, Zhang J, Hu X, Yu X, Liang S, et al. Contralateral hippocampal stimulation for failed unilateral anterior temporal lobectomy in patients with bilateral temporal lobe epilepsy. *Stereotactic and Functional Neurosurgery* 2016;**94**(5):327–35. PUBMED: 27723659]

Dinner 2002 ***{published data only}***
Dinner DS, Neme S, Nair D, Montgomery EB Jr, Baker KB, Rezai A, et al. EEG and evoked potential recording from the subthalamic nucleus for deep brain stimulation of intractable epilepsy. *Clinical Neurophysiology* 2002;**113**(9):1391–402. PUBMED: 12169320]

Elisevich 2006 ***{published data only}***
Elisevich K, Jenrow K, Schuh L, Smith B. Long-term electrical stimulation-induced inhibition of partial epilepsy - Case report. *Journal of Neurosurgery* 2006;**105**(6):894–7. PUBMED: WOS:000242431300015]

Esteller 2004 ***{published data only}***
Esteller R, Echauz J, Tcheng T. Comparison of line length feature before and after brain electrical stimulation in epileptic patients. *Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society* 2004;**7**:4710–3. PUBMED: 17271360]

Feinstein 1989 ***{published data only}***
Feinstein B, Gleason CA, Libet B. Stimulation of locus coeruleus in man. Preliminary trials for spasticity and epilepsy. *Stereotactic and Functional Neurosurgery* 1989;**52**(1):26–41. PUBMED: 2784007]

Fell 2013 ***{published data only}***
Fell J, Staresina BP, Do Lam AT, Widman G, Helmstaedter C, Elger CE, et al. Memory modulation by weak synchronous deep brain stimulation: a pilot study. *Brain Stimulation 2013* 2013;**6**(3):270–3.

Fountas 2005 ***{published data only}***
Fountas KN, Smith JR, Murro AM, Politsky J, Park YD, Jenkins PD. Implantation of a closed-loop stimulation in the management of medically refractory focal epilepsy: a technical note. *Stereotactic and Functional Neurosurgery* 2005;**83**(4):153–8. PUBMED: 16205108]

Fountas 2007 ***{published data only}***
Fountas KN, Smith JR. A novel closed-loop stimulation system in the control of focal, medically refractory epilepsy. *Acta Neurochirurgica Supplement* 2007;**97**(Pt2):357–62. PUBMED: 17691324]

Franzini 2008 ***{published data only}***
Franzini A, Messina G, Marras C, Villani F, Cordella R, Broggi G. Deep brain stimulation of two unconventional targets in refractory non-resectable epilepsy. *Stereotactic and Functional Neurosurgery* 2008;**86**(6):373–81. PUBMED: 19033706]

Fregni 2005 ***{published data only}***
Fregni F, Thome-Souza S, Nitsche M, Freedman S, Valente KD, Pascual-Leone A. A controlled clinical trial of direct current stimulation in patients with refractory epilepsy. *Epilepsia* 2005;**46**(Suppl 8):329–30. CENTRAL: CN–00745158]

Fregni 2006 ***{published data only}***
Fregni F, Thome-Souza S, Nitsche MA, Freedman SD, Valente KD, Pascual-Leone A. A controlled clinical trial of cathodal DC polarization in patients with refractory epilepsy. *Epilepsia* 2006;**47**(2):335–42. PUBMED: 16499758]

Galvez-Jimenez 1998 ***{published data only}***
Gálvez-Jiménez N, Lozano A, Tasker R, Duff J, Hutchison W, Lang AE. Pallidal stimulation in Parkinson's disease patients with a prior unilateral pallidotomy. *Canadian Journal of Neurological Sciences* 1998;**25**(4):300–5. PUBMED: 9827231]

Handforth 2006 ***{published data only}***
Handforth A, DeSalles AA, Krahl SE. Deep brain stimulation of the subthalamic nucleus as adjunct treatment for refractory epilepsy. *Epilepsia* 2006;**47**(7):1239–41. PUBMED: 16886990]

Hodaie 2002 ***{published data only}***
Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM. Chronic anterior thalamus stimulation for intractable epilepsy. *Epilepsia* 2002;**43**(6):603–8.

Huang 2008 ***{published data only}***
Huang M, Harvey RL, Stoykov ME, Ruland S, Weinand M, Lowry D, et al. Cortical stimulation for upper limb recovery following ischemic stroke: a small phase II pilot study of a fullyimplanted stimulator. *Topics in Stroke Rehabilitation* 2008;**15**(2):160–72. PUBMED: 18430685]

Kerrigan 2004 ***{published data only}***
Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, et al. Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. *Epilepsia* 2004;**45**(4):346–54. PUBMED: 15030497]

Khan 2009 ***{published data only}***
Khan S, Wright I, Javed S, Sharples P, Jardine P, Carter M, et al. High frequency stimulation of the mamillothalamic

tract for the treatment of resistant seizures associated withhypothalamic hamartoma. *Epilepsia* 2009;**50**(6): 1608–11. PUBMED: 19243422]

Kossoff 2004 ***{published data only}***
Kossoff EH, Ritzl EK, Politsky JM, Murro AM, Smith JR, Duckrow RB, et al. Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. *Epilepsia* 2004;**45** (12):1560–7. PUBMED: 15571514]

Koubeissi 2013 ***{published data only}***
Koubeissi MZ, Kahriman E, Syed TU, Miller J, Durand DM. Low-frequency electrical stimulation of a fiber tract in temporal lobe epilepsy. *Annals of Neurology* 2013;**74**(2): 223–31. PUBMED: 23613463]

Larkin 2016 ***{published data only}***
Larkin M, Meyer RM, Szuflita NS, Severson MA, Levine ZT. Post-traumatic, drug-resistant epilepsy and review of seizure control outcomes from blinded, randomized controlled trials of brain stimulation treatments for drug-resistant epilepsy. *Cureus* 2016;**8**(8):e744. PUBMED: 27672534]

Lee 2006 ***{published data only}***
Lee KJ, Jang KS, Shon YM. Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy. *Acta Neurochirurgica Supplement* 2006;**99**:87–91. PUBMED: 17370771]

Lee 2012 ***{published data only}***
Lee KJ, Shon YM, Cho CB. Long-term outcome of anterior thalamic nucleus stimulation for intractable epilepsy. *Stereotactic and Functional Neurosurgery* 2012;**90**(6): 379–85. PUBMED: 22922474]

Levy 2008 ***{published data only}***
Levy R, Ruland S, Weinand M, Lowry D, Dafer R, Bakay R. Cortical stimulation for the rehabilitation of patients with hemiparetic stroke: a multicenter feasibility study ofsafety and efficacy. *Journal of Neurosurgery* 2008;**108**(4): 707–14. PUBMED: 18377250]

Lim 2007 ***{published data only}***
* Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, Chen JL, et al. Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. *Epilepsia* 2007;**48**(2):342–7.
Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, Chen JL, et al. Long-term anterior thalamus stimulation for intractable epilepsy. *Chang Gung Medical Journal* 2008;**31**(3):287–96.

Loddenkemper 2001 ***{published data only}***
Loddenkemper T, Pan A, Neme S, Baker KB, Rezai AR, Dinner DS, et al. Deep brain stimulation in epilepsy. *Journal of Clinical Neurophysiology* 2001;**18**(6):514–32. PUBMED: 11779965]

Marras 2011 ***{published data only}***
Marras CE, Rizzi M, Villani F, Messina G, Deleo F, Cordella R, et al. Deep brain stimulation for the treatment of drug-refractory epilepsy in a patient with a hypothalamichamartoma. Case report. *Neurosurgical Focus* 2011;**30**(2):E4. PUBMED: 21284450]

Miatton 2011 ***{published data only}***
Miatton M, Van Roost D, Thiery E, Carrette E, Van Dycke A, Vonck K, et al. The cognitive effects of amygdalohippocampal deep brain stimulation in patients with temporal lobe epilepsy. *Epilepsy and Behaviour* 2011; **22**(4):759–64. PUBMED: 22030536]

Miller 2015 ***{published data only}***
Miller JP, Sweet JA, Bailey CM, Munyon CN, Luders HO, Fastenau PS. Visual-spatial memory may be enhanced with theta burst deep brain stimulation of the fornix: a preliminary investigation with four cases. *Brain* 2015;**137** (Pt7):1833–42. PUBMED: 26106097]

Nguyen 1999 ***{published data only}***
Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, et al. Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. *Pain* 1999;**82**(3):245–51. PUBMED: 10488675]

Osorio 2001 ***{published data only}***
Osorio I, Frei MG, Manly BF, Sunderam S, Bhavaraju NC, Wilkinson SB. An introduction to contingent (closed-loop) brain electrical stimulation for seizure blockage, to ultra-short-term clinical trials, and to multidimensional statistical analysis of therapeutic efficacy. *Journal of Clinical Neurophysiology* 2001;**18**(6):533–44. PUBMED: 11779966]

Osorio 2005 ***{published data only}***
Osorio I, Frei MG, Sunderam S, Giftakis J, Bhavaraju NC, Schaffner SF, et al. Automated seizure abatement in humans using electrical stimulation. *Annals of Neurology* 2005;**57** (2):258–68. PUBMED: 15668970]

Osorio 2007 ***{published data only}***
Osorio I, Overman J, Giftakis J, Wilkinson SB. High frequency thalamic stimulation for inoperable mesial temporal epilepsy. *Epilepsia* 2007;**48**(8):1561–71. PUBMED: 17386053]

Pahwa 1999 ***{published data only}***
Pahwa R, Lyons KL, Wilkinson SB, Carpenter MA, Tröster AI, Searl JP. Bilateral thalamic stimulation for the treatment of essential tremor. *Neurology* 1999;**53**(7):1447–50. PUBMED: 10534249]

Riklan 1976 ***{published data only}***
Riklan M, Cullinan T, Shulman M, Cooper IS. A psychometric study of chronic cerebellar stimulation in man. *Biological Psychiatry* 1976;**11**(5):543–74. PUBMED: 786383]

Rocha 2007 ***{published data only}***
Rocha L, Cuellar-Herrera M, Velasco M, Velasco F, Velasco AL, Jiménez F, et al. Opioid receptor binding in parahippocampus of patients with temporal lobe epilepsy: its association with theantiepileptic effects of subacute electrical stimulation. *Seizure* 2007;**16**(7):645–52. PUBMED: 17560811]

Savard 2003 ***{published data only}***
Savard G, Bhanji NH, Dubeau F, Andermann F, Sadikot A. Psychiatric aspects of patients with hypothalamic

hamartoma and epilepsy. *Epileptic Disorders* 2003;**5**(4): 229–34. PUBMED: 14975791]

Schmitt 2014 ***{published data only}***
Schmitt FC, Voges J, Heinze HJ, Zaehle T, Holtkamp M, Kowski AB. Safety and feasibility of nucleus accumbens stimulation in five patients with epilepsy. *Journal of Neurology* 2014;**261**(8):1477–84. PUBMED: 24801491]

Schulze-Bonhage 2016 ***{published data only}***
Schulze-Bonhage A, Hamer HM, Hirsch M, Hagge M. Invasive stimulation procedures and EEG diagnostics in epilepsy. *Nervenarzt* 2016;**87**(8):829–37. CENTRAL: CN–01195580]

Spencer 2011 ***{published data only}***
Spencer D, Gwinn R, Salinsky M, O'Malley JP. Laterality and temporal distribution of seizures in patients with bitemporal independent seizures during a trial of responsive neurostimulation. *Epilepsy Research* 2011;**93**(2-3):221–5. PUBMED: 21256715]

Sussman 1988 ***{published data only}***
Sussman NM, Goldman HW, Jackel RA, Kaplan L, Callanan M, Bergen J, et al. Anterior thalamus stimulation in medically intractable epilepsy, part II: preliminary clinical results. *Epilepsia* 1988;**29**:677.

Tanriverdi 2009 ***{published data only}***
Tanriverdi T, Al-Jehani H, Poulin N, Olivier A. Functional results of electrical cortical stimulation of the lower sensory strip. *Journal of Clinical Neuroscience* 2009;**16**(9):1188–94. PUBMED: 19497753]

Torres 2013 ***{published data only}***
Torres CV, Sola RG, Pastor J, Pedrosa M, Navas M, García-Navarrete E, et al. Long-term results of posteromedial hypothalamic deep brain stimulation for patients with resistant aggressiveness. *Journal of Neurosurgery* 2013;**119** (2):277–87. PUBMED: 23746102]

Tyrand 2012 ***{published data only}***
Tyrand R, Seeck M, Spinelli L, Pralong E, Vulliémoz S, Foletti G, et al. Effects of amygdala-hippocampal stimulation on interictal epileptic discharges. *Epilepsy Research* 2012;**99**(1-2):87–93. PUBMED: 22079883]

Upton 1985 ***{published data only}***
Upton AR, Cooper IS, Springman M, Amin I. Suppression of seizures and psychosis of limbic system origin by chronic stimulation of anterior nucleus of the thalamus. *International Journal of Neurology* 1985;**19-20**:223–30. PUBMED: 2980675]

Valentin 2013 ***{published data only}***
Valentin A, Chelvarajah R, Selway R, Vico L, García De Sola R, Garcia Navarrete E, et al. Centromedian thalamic deep brain stimulation for the treatment of refractory generalised and frontal epilepsy: a blinded controlled study. *Epilepsia* 2012;**53 Suppl. 5**:32, Abstract no: p104. CENTRAL: CN–00833257; DOI: 10.1111/j.1528-1167.2012.03677.x
* Valentín A, García Navarrete E, Chelvarajah R, Torres C, Navas M, Vico L, et al. Deep brain stimulation of the centromedian thalamic nucleus for the treatment of generalized and frontal epilepsies. *Epilepsia* 2013;**54**(10): 1823–33. DOI: 10.1111/epi.12352; PUBMED: 24032641

Velasco 1987 ***{published data only}***
Velasco F, Velasco M, Ogarrio C, Fanghanel G. Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. *Epilepsia* 1987;**28**(4):421–30. PUBMED: 3497802]

Velasco 1993 ***{published data only}***
Velasco F, Velasco M, Velasco AL, Jiménez F. Effect of chronic electrical stimulation of the centromedian thalamic nuclei on various intractable seizure patterns: I. Clinical seizures and paroxysmal EEG activity. *Epilepsia* 1993;**34**(6): 1052–64. PUBMED: 8243357]

Velasco 1995 ***{published data only}***
Velasco F, Velasco M, Velasco AL, Jimenez F, Marquez I, Rise M. Electrical stimulation of the centromedian thalamic nucleus in control of seizures: long-term studies. *Epilepsia* 1995;**36**(1):63–71. PUBMED: 8001511]

Velasco 2000b ***{published data only}***
Velasco M, Velasco F, Velasco AL, Jiménez F, Brito F, Márquez I. Acute and chronic electrical stimulation of the centromedian thalamic nucleus: modulation of reticulo-cortical systems and predictor factors for generalized seizure control. *Archives of Medical Research* 2000;**31**(3):304–15. PUBMED: 11036182]

Velasco 2001 ***{published data only}***
Velasco M, Velasco F, Velasco AL. Centromedian-thalamic and hippocampal electrical stimulation for the control of intractable epileptic seizures. *Journa of Clinical Neurophysiology* 2001;**18**(6):495–513. PUBMED: 11779964]

Velasco 2006 ***{published data only}***
Velasco AL, Velasco F, Jiménez F, Velasco M, Castro G, Carrillo-Ruiz JD, et al. Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox-Gastaut syndrome. *Epilepsia* 2006;**47**(7):1203–12. PUBMED: 16886984]

Velasco 2009 ***{published data only}***
Velasco AL, Velasco F, Velasco M, María Núñez J, Trejo D, García I. Neuromodulation of epileptic foci in patients with non-lesional refractory motor epilepsy. *International Journal of Neural Systems* 2009;**19**(3):139–47. PUBMED: 19575504]

Vonck 2002 ***{published data only}***
Vonck K, Boon P, Achten E, De Reuck J, Caemaert J. Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. *Annals of Neurology* 2002;**52**(5): 556–65. PUBMED: 12402252]

Vonck 2013 ***{published data only}***
Vonck K, Sprengers M, Carrette E, Dauwe I, Miatton M, Meurs A, et al. A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. *International Journal of Neural Systems* 2013; **23**(1):1250034. PUBMED: 23273130]

Wakerley 2011 *{published data only}*
Wakerley B, Schweder P, Green A, Aziz T. Possible seizure suppression via deep brain stimulation of the thalamic ventralis oralis posterior nucleus. *Journal of Clinical Neuroscience* 2011;**18**(7):972–3.

Wei 2016 *{published data only}*
Wei Z, Gordon CR, Bergey GK, Sacks JM, Anderson WS. Implant site infection and bone flap osteomyelitis associated with the neuropace responsive neurostimulation system. *World Neurosurgery* 2016;**88**:687.e1–6. PUBMED: 26743382]

Wille 2011 *{published data only}*
Wille C, Steinhoff BJ, Altenmuller DM, Staack AM, Bilic S, Nikkhah G, et al. Chronic high-frequency deep-brain stimulation in progressive myoclonic epilepsy in adulthood--report of five cases. *Epilepsia* 2011;**52**(3): 489–96. PUBMED: 21219312]

Yamamoto 2006 *{published data only}*
Yamamoto J, Ikeda A, Kinoshita M, Matsumoto R, Satow T, Takeshita K, et al. Low-frequency electric cortical stimulation decreases interictal and ictal activity in human epilepsy. *Seizure* 2006;**15**(7):520–7. PUBMED: 16908203]

References to studies awaiting assessment

Chabardes 2005 *{published data only (unpublished sought but not used)}*
Chabardes S. Assessment of subthalamic nucleus stimulation in drug resistant epilepsy associated with dopaminergic metabolism deficit. a randomized, double blind, controlled trial. www.clinicaltrials.gov/ct/show/NCT00228371. September 2005, last update May 2015. CENTRAL: CN–00643474; CTG: NCT00228371]

van Rijckevorsel 2004 *{published data only (unpublished sought but not used)}*
Raftopoulos C, van Rijckevorsel K, Abu Serieh B, de Tourtchaninoff M, Ivanoiu A, Mary G, et al. Epileptic discharges in a mammillary body of a patient with refractory epilepsy. *Neuromodulation* 2005;**8**(4):236–40.
Raftopoulos C, van Rijckevorsel K, Abu Serieh B, de Tourtchaninoff M, Ivanoiu A, Mary G, et l. Chronic electrical stimulation of the mammillary bodies and the mammillothalamic tracts in chronic refractory epilepsy. *Neuromodulation* 2004;**7**(2):148.
* van Rijckevorsel K, Abu Serieh B, de Tourtchaninoff M, Ivanoiu A, Mary G, Gradin C, et al. Safety and tolerability of deep brain stimulation of mammillary bodies and mammillothalamic area in patients with chronic refractory epilepsy. *Epilepsia* 2004;**45 Suppl 7**:164.
van Rijckevorsel K, Abu Serieh B, de Tourtchaninoff M, Raftopoulos C. Deep EEG recordings of the mammillary body in epilepsy patients. *Epilepsia* 2005;**46**(5):781–5.

References to ongoing studies

Boon 2007b *{published data only}*
* Boon P. Prospective randomized controlled study of neurostimulation in the medial temporal lobe for patients with medically refractory medial temporal lobe epilepsy; Controlled Randomized Stimulation Versus Resection (CoRaStiR). http://www.clinicaltrials.gov/ct2/show/NCT00431457 February 2007, last update: December 2014. CTG: NCT00431457]
Schulze-Bonhage A. Hippocampus stimulation instead of amygdalohippocampectomy. Prospective, randomized study for treatment of mesiotemporal epilepsy [Hippocampusstimulation statt Amygdalohippokampektomie. Prospektive, randomisierte Behandlungsstudie bei mesiotemporaler Epilepsie]. *Zeitschrift fur Epileptologie* 2009;**22**(2):89–92. CENTRAL: CN–00754119; EMBASE: EMBASE 2009227430]

Chabardes 2014 *{published data only}*
Chabardes S. Deep brain stimulation of the anterior nucleus of the thalamus in epilepsy (FRANCE). https://www.clinicaltrials.gov/ct2/show/NCT02076698 February 2014, last update December 2015. CTG: NCT02076698]

Koubeissi 2015 *{published data only}*
Koubeissi MZ. Low frequency electrical stimulation of the fornix in intractable Mesial Temporal Lobe Epilepsy (MTLE) (MTLE-DBS). https://www.clinicaltrials.gov/ct2/show/NCT02383407 February 2015, last update March 2015. CTG: NCT02383407]

Zhang 2015 *{published data only}*
Zhang K, Zhang C. Prospective randomized trial comparing vagus nerve stimulation and deep brain stimulation of the anterior nucleus of the thalamus in patient with pharmacoresistant epilepsy. http://www.chictr.org.cn/showproj.aspx?proj=10139 December 2014, last update May 2015. ChiCTR: IPR–14005721]

Additional references

Becker 1993
Becker MP, Balagtas CC. Marginal modeling of binary cross-over data. *Biometrics* 1993;**49**(4):997–1009. [PUBMED: 8117910]

Beyenburg 2009
Beyenburg S, Stavem K, Schmidt D. Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: Systematic review and meta-analysis. *Epilepsia* 2010;**51**(1):7–26.

Borghs 2012
Borghs S, de la Loge C, Cramer JA. Defining minimally important change in QOLIE-31 scores: Estimates from three placebo-controlled lacosamide trials in patients with partial-onset seizures. *Epilepsy & Behavior* 2012;**23**(3): 230–4. [PUBMED: WOS:000301657900009]

Cramer 1998
Cramer JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann B. Development and cross-cultural translations of a 31-item quality of life in epilepsy

inventory. *Epilepsia* 1998;**39**(1):81–8. [PUBMED: WOS: 000071467600012]

Cramer 2004

Cramer JA, Hammer AE, Kustra RP. Quality of life improvement with conversion to lamotrigine monotherapy. *Epilepsy & Behavior* 2004;**5**(2):224–30. [PUBMED: WOS: 000220531700014]

Curtin 2002

Curtin F, Elbourne D, Altman DG. Meta-analysis combining parallel and cross-over clinical trials II: Binary outcomes. *Statistics in Medicine* 2002;**21**(15):2145–59. [PUBMED: 12210630]

de Tisi 2011

de Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WF, Sander JW, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *Lancet* 2011;**378**(9800):1388–95. [PUBMED: 22000136]

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011)*. The Cochrane Collaboration, 2011.

Devinsky 1995

Devinsky O, Vickrey BG, Cramer J, Perrine K, Hermann B, Meador K, et al. Development of the Quality-of-Life in Epilepsy Inventory. *Epilepsia* 1995;**36**(11):1089–104. [PUBMED: WOS:A1995TC20300005]

Elbourne 2002

Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9. [PUBMED: 11914310]

Engel 2003

Engel J Jr, Wiebe S, French J, Sperling M, Williamson P, Spencer D, et al. Practice parameter: temporal lobe and localized neocortical resection for epilepsy. *Epilepsia* 2003; **44**(6):741–51.

Forsgren 2005

Forsgren L, Beghi E, Oun A, Sillanpaa M. The epidemiology of epilepsy in Europe - a systematic review. *European Journal of Neurology* 2005;**12**(4):245–53.

Guyatt 2008

Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924–6. DOI: 10.1136/bmj.39489.470347.AD; PUBMED: 18436948

Handforth 1998

Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology* 1998;**51**(1):48–55. [PUBMED: 9674777]

Higgins 2011

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011)*. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

ILAE classification

Commission of Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1989;**30**:389–99.

Jehi 2008

Jehi L. Mesial temporal lobectomy: post-surgical seizure frequency. *Textbook of Epilepsy Surgery*. Luders HO, 2008: 1223–5.

Katariwala 2001

Katariwala NM, Bakay RA, Pennell PB, Olson LD, Henry TR, Epstein CM. Remission of intractable partial epilepsy following implantation of intracranial electrodes. *Neurology* 2001;**57**(8):1505–7. [PUBMED: 11673602]

Kwan 2000

Kwan P, Brodie MJ. Early identification of refractory epilepsy. *New England Journal of Medicine* 2000;**342**(5): 314–9.

Kwan 2009

Kwan P, Brodie MJ. Definition of refractory epilepsy: defining the indefinable?. *Lancet Neurology* 2010;**9**(1):27–9.

Kwan 2010

Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser AW, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;**51** (6):1069–77.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011)*. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Neligan 2012

Neligan A, Bell GS, Elsayed M, Sander JW, Shorvon SD. Treatment changes in a cohort of people with apparently drug-resistant epilepsy: an extended follow-up. *Journal of Neurology, Neurosurgery, and Psychiatry* 2012;**83**(8):810–3. [PUBMED: 22733083]

Panebianco 2015

Panebianco M, Rigby A, Weston J, Marson AG. Vagus nerve stimulation for partial seizures. *Cochrane Database Systematic Reviews* 2015;**4**:CD002896. DOI: 10.1002/ 14651858.CD002896.pub2; PUBMED: 25835947

Schulze-Bonhage 2010

Schulze-Bonhage A, Dennig D, Wagner K, .Cordeiro J, Carius A, Fauser S, Trippel M. Seizure control resulting from intrahippocampal depth electrode insertion. *Journal of*

Neurology, Neurosurgery, and Psychiatry 2010;**81**(3):352–3. [PUBMED: 20185477]

Selwa 2003
Selwa LM, Schmidt SL, Malow BA, Beydoun A. Long-term outcome of nonsurgical candidates with medically refractory localization-related epilepsy. *Epilepsia* 2003;**44**(12):1568–72. [PUBMED: 14636329]

Stedman 2011
Stedman MR, Curtin F, Elbourne DR, Kesselheim AS, Brookhart MA. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2011;**40**(6):1732–4. [PUBMED: 20026595]

Tellez-Zenteno 2005
Tellez-Zenteno JF, Ronquillo LH, Wiebe S. Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors. *Epilepsy Research* 2005;**65**(1-2):101–15. [PUBMED: 16005188]

Tomson 2008
Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurology* 2008;**7**(11):1021–31. [PUBMED: 18805738]

VNS Study Group 1995
The Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. *Neurology* 1995;**45**(2):224–30. [PUBMED: 7854516]

West 2015
West J, Nolan SJ, Cotton J, Gandhi S, Weston J, Sudan A, et al. Surgery for epilepsy. *Cochrane Database of Systematic Reviews* 2015, Issue 7. DOI: 10.1002/14651858.CD010541.pub2

Wiebe 2002
Wiebe S, Matijevic S, Eliasziwa M, Derry PA. Clinically important change in quality of life in epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry* 2002;**73**(2):116–20. [PUBMED: WOS:000177059900007]

Zou 2007
Zou GY. One relative risk versus two odds ratios: implications for meta-analyses involving paired and unpaired binary data. *Clinical Trials* 2007;**4**(1):25–31. [PUBMED: 17327243]

References to other published versions of this review

Boon 2003
Boon P, Van Dycke A, Carrette E, Marson AG, Vonck K. Deep brain and cortical stimulation for epilepsy. *Cochrane Database of Systematic Reviews* 2003, Issue 3. DOI: 10.1002/14651858.CD008497

Sprenger 2014
Sprengers M, Vonck K, Carrette E, Marson AG, Boon P. Deep brain and cortical stimulation for epilepsy. *Cochrane Database of Systematic Reviews* 2014, Issue 6. DOI: 10.1002/14651858.CD008497.pub2

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Fisher 1992

Methods	Double-blind balanced cross-over randomized controlled trial • prospective baseline seizure frequency recording for several months • electrode implantation • stimulators OFF until randomization 1 to 2 months postoperatively • cross-over design of 3-month treatment blocks (receiving each treatment once) with a 3-month washout phase • long-term open-label follow-up with stimulation ON in all patients
Participants	n = 7, 42.9% male, mean age 28.0 years (range 16-41 y), duration of epilepsy ranged from 14 to 29 years 2 patients with focal epilepsy (one with and one without secondary generalization), 5 patients with generalized epilepsy (2/5 had Lennox-Gestaut syndrome); poor candidates for resective surgery mean baseline seizure frequency of 23.4 (SD 15.9) seizures per month
Interventions	Active: bilateral stimulation of the centromedian thalamic nucleus • output voltage was set to half the sensory threshold and ranged from 0.5 to 10 V • stimulation frequency of 65 Hz • pulse width 90 µsec • 1 minute of bipolar stimulation each 5 minutes for 2 hours per day Control: sham stimulation (output voltage set at zero)
Outcomes	(1) Proportion of participants who were seizure-free (2) Proportion of participants with a ≥ 50% seizure frequency reduction (responder rate) (3) Seizure frequency reduction (4) Adverse events (spontaneous reporting, postoperative CT scan) (5) Neuropsychological outcome [tests of general intelligence (WAIS-R), speech and language functions (the Boston Naming Test, the Controlled Oral Word Association Test, a written description of the Cookie Theft Picture from the BDAE), visual and verbal memory functions (the Weschler Memory Scale, the Rey Auditory Verbal Learning Test with delayed recall and the Warrington Recongnition Memory Test (words and faces)), parietal lobe-type functions (the Rey Osterreith Complex Figure Test with delayed recall), frontal lobe-type functions (the Wisconsin Card Sorting Test) and psychomotor functions (the Trial Making Test (A and B) and the Perdue Grooved Pegboard)]
Notes	The study was supported by Medtronic Inc. (Minneapolis, MN) who also donated hardware for the protocol

Risk of bias

Bias	Authors' judgement	Support for judgement

Fisher 1992 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "patients were randomized to either stimulation ON for A and OFF for B or to stimulation OFF for A and ON for B" Personal communication: "envelopes were chosen at random picking from a pile for each patient"
Allocation concealment (selection bias)	Low risk	Quote: "randomization order was provided in a sealed envelope" Personal communication: sealed and sequentially numbered envelopes, unclear if they were specific opaque envelopes (study was conducted more than 20 years ago); however, randomization was performed by a third person, not involved in selecting, treating or evaluating patients
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "neither patient, families, treating medical team nor data analysts knew whether the stimulator was ON or OFF during phases A and B"; "patients could not detect when stimulation was ON or OFF"; "stimulation was set to half the sensory threshold"; "a single unblinded individual was aware of treatment parameters and tested stimulator function at each monthly visit" Personal communication: the single unblinded individual was not involved in treating or evaluating patients
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: see above; seizure frequency was recorded in a seizure calendar
Incomplete outcome data (attrition bias) All outcomes	High risk	One of the two patients who improved markedly with centromedian thalamic stimulation experienced several episodes of multiple daily seizures in the washout period and therefore was dropped from the blinded protocol and stimulation was reinstalled. As there were only seven patients, with only two responders, this one patient represents a significant proportion
Selective reporting (reporting bias)	High risk	- The results of a statistical analysis including all patients, to evaluate the efficacy of the intervention on seizure frequency, are not reported. Instead, only the results of

Fisher 1992 (*Continued*)

		an analysis including all patients with (primarily or secondarily) generalized seizures are presented (thus excluding one patient with only complex partial seizures). This was not prespecified in the Methods section. However, as all raw data are present in the article, all information necessary for this review is available - Concerning the neuropsychological outcome: "multivariate analysis with repeated measures showed no significant differences in any measure between baseline, placebo (OFF) and treatment (ON) conditions" Personal communication: exact figures no longer available Comment: no exact figures were reported, probably because there was too much data for a journal article (rather incomplete than selective reporting)
Outlasting effect due to prior stimulation	Low risk	Comment: cross-over design, but with a 3-month washout period
Anti-epileptic drug policy	Low risk	Quote: "AED dosages were kept constant throughout the study"
Other bias	Low risk	Comment: there is no clear evidence for a risk of 'other bias'

Fisher 2010

Methods	Multicentre, double-blind, parallel-design, randomized controlled trial: • 3-month baseline period • electrode implantation • 1 month of recovery • 3-month blinded randomized phase during which half of participants received stimulation and half did not; stimulation parameters and AEDs were kept constant • 9-month open-label unblinded stimulation in all patients; AEDs were kept constant but limited stimulation parameter changes were allowed • long-term follow-up unblinded stimulation in which AEDs and stimulation parameters could vary freely
Participants	n = 109, 50.0% male, mean age 36.1 years (inclusion criterion:18-65 y), mean duration of epilepsy was 22.3 (SD 13.3) years; all patients suffered from partial-onset epilepsy (partial seizures and/or secondarily generalized seizures), IQ > 70 in all patients, 24.5% and 44.5% had prior resection and vagus nerve stimulation, respectively; median baseline seizure frequency of 19.5 seizures per month (inclusion criterion: ≥6 seizures)

Fisher 2010 (*Continued*)

Interventions	Active (n = 55): bilateral anterior thalamic nucleus stimulation • stimulation intensity was set at 5 V • stimulation frequency of 145 Hz • pulse width of 90 μsec • intermittent (1 min ON, 5 min OFF) monopolar cathodal stimulation Control (n = 54): sham stimulation
Outcomes	(1) Proportion of participants who were seizure-free (2) Proportion of participants with a ≥ 50% seizure frequency reduction (responder rate) (3) Seizure frequency reduction (4) Adverse events (based on spontaneous reporting by patients, postoperative MRI) (5) Neuropsychological outcome (attention, executive function, verbal memory, visual memory, intelligence, expressive language, depression, tension / anxiety, total mood disturbance, confusion, subjective cognitive function) (6) Quality of life (QOLIE-31)
Notes	The study was supported by Medtronic Inc. (Minneapolis, MN)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization was done by a central statistical site, using random numbers tables, a one-to-one allocation to active stimulation versus control, balanced at each study site and with no weighting for any subject characteristics"
Allocation concealment (selection bias)	Low risk	Quote: "randomization was done by a central statistical site"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "no care or assessment personnel knew the voltage settings" and "participants were unaware of their treatment group"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "no care or assessment personnel knew the voltage settings"
Incomplete outcome data (attrition bias) All outcomes	Low risk	108 out of 109 randomized patients completed the blinded phase. One patient (control group) developed an infection requiring explant, but was included in all analyses as randomized

Fisher 2010 (*Continued*)

Selective reporting (reporting bias)	High risk	Quote: "Changes in additional outcome measures did not show significant (...) differences during the double-blind phase, including 50% responder rates, Liverpool Seizure Severity Scale and Qulatiy of Life in Epilepsy scores" Comment 1: not all available (as can be deducted from the protocol on clinicaltrials.gov or the online "Medtronic DBS therapy for epilepsy sponsor information", www.fda.gov) outcome measures (including seizure-free days and seizure-free intervals) were mentioned or reported in the paper in Epilepsia Comment 2: different analyses were performed; one patient of the treatment group who experienced a marked seizure frequency increase was excluded (not prespecified) and another patient with only 66 of 70 protocol-required diary days was included (ITT analysis) in the analysis used to estimate the treatment effect for the entire BEP (and not per month). As there were good reasons to do so and the results of the other prespecified analysis were also reported, we do not consider this as a major source of selective reporting
Outlasting effect due to prior stimulation	Low risk	Comment: parallel-group design, no stimulation prior to the randomized phase
Anti-epileptic drug policy	Low risk	Quote: "medication were kept constant during the 3-month blinded phase and the 9-month unblinded phase"
Other bias	Low risk	Comment: there is no clear evidence for a risk of 'other bias'

Kowski 2015

Methods	Double-blind cross-over randomized controlled trial • 3-month baseline period • bilateral implantation of electrodes in the nucleus accumbens and in the anterior thalamic nucleus (4 electrodes in total) • stimulation OFF during the first postoperative month (note: testing for side effects of stimulation day 3 and day 7 of electrode implantation) • 3-month nucleus accumbens stimulation ON / OFF (randomized) • 1-month washout period • 3-month nucleus accumbens stimulation OFF / ON (randomized) • 1-month washout period • 3-month open-label period with bilateral anterior thalamic DBS in all patients, and additional bilateral nucleus accumbens DBS if the patient had experienced a ≥ 50% reduction in seizure frequency during the randomized double-blind phase of the trial
Participants	n = 4, 25% male, mean age 36.7 years (range 28-44 y), mean duration of epilepsy was 12.5 years (range 9-15 years); all patients suffered from pharmaco-resistant partial-onset epilepsy, resection or further invasive assessment had been dismissed or surgery had been unsuccessful, patients preferred participation in the study above VNS or standard anterior thalamic DBS treatment, region of seizure onset was bilateral frontal in 2 patients and bilateral temporal in the 2 other patients mean baseline seizure frequency of 7.3, 4.3, 10.5 and 20.3 'disabling' seizures (complex partial or generalized tonic-clonic seizure) per month (inclusion criterion: at least 3 'disabling' seizures every 4 weeks during the 12-week baseline period), 1 of the patients also experienced 99.2 simple partial seizures per month
Interventions	Active: bilateral nucleus accumbens stimulation • stimulation intensity was set at 5 V • stimulation frequency of 125 Hz • pulse width of 90 µsec • intermittent (1 min ON, 5 min OFF) bipolar stimulation with the most centrally located contacts selected as cathode aiming for stimulation of the medial, central and lateral part of the nucleus accumbens Control: sham stimulation Note: all patients had quadripolar electrodes implanted in both the nucleus accumbens and the anterior nucleus of the thalamus
Outcomes	(1) Proportion of participants who were seizure-free (2) Proportion of participants with a ≥ 50% seizure frequency reduction (responder rate) (3) Seizure frequency reduction (4) Adverse events (5) Neuropsychological outcome (Test of Attentional Performance, Trail Making Test, Performance Evaluation System subtest 7 (Leistungspruefungssystem (LPS), subtest 7) , d2-Attention Stress Test, 'Regensburger' Word Fluency Test, Hamasch 5-Point Test, Verbal Learning and Memory Test, Wechsler Memory Scale-Revised, and the Boston Naming Test; during the visits (V1-V8) different tests were done; Beck-Depression-Inventory Version IA; Mini International Neuropsychiatric Interview) (6) Quality of life (QOLIE-31-P)

Notes	Institutional budget, no external funding for this trial; several authors had previously received reimbursement for travelling expenses and/or speaker honoraria from Medtronic Inc. (Minneapolis, MN) and 1 author also served as consultant for Medtronic Inc. (Minneapolis, MN) and Sapiens Inc. (California, CA)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the sequence was randomized using an internet-randomizing tool (www.random.org)"
Allocation concealment (selection bias)	Low risk	Quote: "individuals not involved in the study performed allocation process"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "individuals not involved in the study performed allocation process and change of stimulation parameters. Patients and assessing epileptologists remained blinded until start of the open-label phase"; "none of the patients reported to notice nucleus accumbens, anterior thalamic nucleus or combined nucleus accumbens / anterior thalamic nucleus stimulation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "individuals not involved in the study performed allocation process and change of stimulation parameters. Patients and assessing epileptologists remained blinded until start of the open-label phase"; "none of the patients reported to notice nucleus accumbens, anterior thalamic nucleus or combined nucleus accumbens / anterior thalamic nucleus stimulation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 4 patients underwent electrode implantation for DBS and all outcomes are reported for all patients
Selective reporting (reporting bias)	Low risk	Comment: selective reporting very unlikely. The study was registered in the German Trial Registry (http://www.drks.de/DRKS00003148). All outcomes mentioned in this protocol are reported on in the published paper (including online sup-

Kowski 2015 (*Continued*)

		porting information) in a very detailed and extensive way. The only shortcoming is the fact that specific details on the measurements that were planned to be used to assess the outcomes mentioned were not provided in the protocol. However, the published report includes all expected outcomes
Outlasting effect due to prior stimulation	Unclear risk	Comment: cross-over study with a 1-month washout period after 3 months of stimulation which might be too short although we recognize that clear judgements on this issue are difficult to make and arbitrary
Anti-epileptic drug policy	Low risk	Quote: "antiepileptic drug dosages remained unchanged in all patients. Furthermore, serum concentrations of antiepileptic drugs (except retigabine/ezogabine) were determined at each visit and showed no clinically relevant variability"
Other bias	Low risk	Comment: there is no clear evidence for a risk of 'other bias'

McLachlan 2010

Methods	Double-blind balanced cross-over randomized controlled trial Total duration 15 months: • implantation of the electrodes • 3-month baseline period without stimulation • 3 months ON / OFF (randomized) • 3-month washout period (if ON) • 3 months OFF / ON (opposite of month 4-6) • 3-month washout period (if ON)
Participants	n = 2, 50% male, 45 and 54 years old, duration of epilepsy was 15 and 29 years; medically intractable focal epilepsy, poor candidates for resective surgery on the basis of independent bitemporal originating seizures, normal MRI in patient 1 and bilateral hippocampal sclerosis in patient 2; baseline seizure frequency of 32 and 16 seizures per month
Interventions	Active: bilateral hippocampal stimulation • output voltage was determined by starting at 0.5V and increasing until symptoms occurred, the voltage was then decreased until it was subthreshold for conscious appreciation • stimulation frequency of 185 Hz • pulse width 90 µsec • continuous monopolar bilateral stimulation

	Control: sham stimulation
Outcomes	(1) Proportion of participants who were seizure-free (2) Proportion of participants with a ≥ 50% seizure frequency reduction (responder rate) (3) Seizure frequency reduction (4) Adverse events (standard questionnaire) (5) Neuropsychological outcome (objective memory: Hopkins Verbal Learning Test-Revised and the Brief visuospatial Memory Test-Revised; subjective memory: Memory Assessment Clinic Self-Rating Scale)
Notes	No external funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization of the first treatment" Personal communication: computer-generated randomized sequences
Allocation concealment (selection bias)	Low risk	Quote: "randomization of the first treatment was determined independently by the research unit and placed in a sealed envelope" Personal communication: sealed, double-opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both the treating neurologist and patient were blind to the stimulator status"; "the voltage was decreased until it was subthreshold for conscious appreciation so that patients were unaware of the status of the stimulator"; "neither patient was able to accurately assess when the stimulator was ON or OFF"; "the envelope with the stimulation sequence was given to a neurosurgeon not involved in outcome assessment who turned the device ON or OFF at each 3-month visit"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: see above, only one neurosurgeon, not involved in outcome assessment, knew the stimulator status
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: for the ON- and OFF-period all data were available; only the objective memory data of one patient in the washout

		period were not available
Selective reporting (reporting bias)	High risk	Quote: in the Methods section: "differences in mean monthly seizure frequency were assessed using repeated measures ANOVA" ; in the Results section: "ANOVA revealed a significant difference in the median monthly seizure frequency between the four epochs (p<0.01)" Comment: unclear why (only) the median monthly seizure frequency was used in this analysis instead of all available data, i.e. total number of seizures (or mean monthly seizure frequency, as announced in the methods section and as was indeed reported as a descriptive variable to quantify the treatment effect); however, as all available individual patient data were provided to us by the author, this had no influence on this review
Outlasting effect due to prior stimulation	Low risk	Comment: cross-over study, but with a 3-month washout phase
Anti-epileptic drug policy	Low risk	Quote: "(...) antiseizure drugs, which remained unchanged during the study"
Other bias	Low risk	Comment: there is no clear evidence for a risk of 'other bias'

Morrell 2011

Methods	Multicentre, double-blind, parallel-design, randomized controlled trial: • 12-week baseline period • implantation of the electrodes: 1 or 2 recording and stimulating depth or subdural cortical strip leads were surgically placed in the brain according to the seizure focus • 4-week postoperative stabilization period: the neurostimulator was programmed to sense and record the electrocorticogram, but not to deliver stimulation • randomization • 4-week stimulation optimization period: neurostimulators only of patients in the treatment group were programmed to deliver stimulation (not in the sham group) • 12-week blinded evaluation period (BEP): treatment versus sham group • open-label evaluation period: all patients were able to receive responsive stimulation
Participants	n = 191, 52% male, mean age 34.9 years (range 18-66 y), duration of epilepsy ranged from 2 to 57 years all patients suffered from medically intractable partial onset seizures, 45% had only one seizure focus and 55% had two seizure foci, 32 and 34% had prior therapeutic surgery

	and vagus nerve stimulation, respectively mean baseline seizure frequency of 1.2 (SD 2.2) seizures per day (inclusion criterion ≥3 seizures per month)
Interventions	Active (n = 97): stimulation directly to the seizure focus in response to epileptiform electrographic events (device: RNS® System, NeuroPace, Mountain View, CA) • stimulation parameters were determined individually during the 4-week stimulation optimization period • amplitude (range used): 0.5 - 12 mA • frequency (range used): 2-333 Hz • pulse width (range used): 40-520 µsec • responsive stimulation, burst duration (range used): 10-1000 msec Control (n = 94): sham stimulation
Outcomes	(1) Proportion of participants who were seizure-free (2) Proportion of participants with a ≥ 50% seizure frequency reduction (responder rate) (3) Seizure frequency reduction (4) Adverse events (as assessed by clinicians, additionally vital signs were collected and a neurological examination was conducted at every office appointment) (5) Neuropsychological outcome [visual motor speed (trailmaking part A and B), motor speed / dexterity (grooved pegboard, dominant and nondominant), auditory attention (Wechsler Adult Intelligence Scale (WAIS)-III digit span), general verbal ability (WAIS-III information), general visuospatial ability (WAIS-III block design), verbal memory (Rey Auditory Verbal Learning Test (RAVLT) I-V, VII (delayed recall) and memory recognition), visuospatial memory (Brief Visuospatial Memory Test-Revised (BVMT-R) total recall, delayed recall and recognition discrimination index), language (Boston Naming Test (60 items) spontaneous with semantic clue; Delis-Kaplan Executive Function System (D-KEFS) verbal fluency test, condition 1: letter fluency), design fluency (D-KEFS design fluency, total composite); mood inventories included the Beck Depression Inventory II (BDI-II) and the Center for Epidemiologic Studies Depression Scale (CES-D)] (6) Quality of life (QOLIE-89)
Notes	The study was sponsored by NeuroPace Inc., Mountain View, California (USA)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "subjects were assigned 1:1 to treatment or sham groups using an adaptive randomization algorithm controlling for investigational site, location and number of seizure onsets and prior epilepsy surgery" Personal communication: "computer based random sequence generation", "an adaptive randomization process was used to minimize the imbalance within the covariates

		listed above: imbalance was calculated for each covariate and each potential therapy allocation, the less-imbalancing therapy allocation was selected with a 75% probability, and the more-imbalancing therapy allocation was selected with a 25% probability"
Allocation concealment (selection bias)	Low risk	Personal communication: central allocation, "An adaptive randomization was performed to minimize imbalance (...). So that therapy allocation could not be guessed or determined for a given subject (even with knowledge of the therapy allocation of all other subjects), the final therapy allocation for a subject was selected with a 75% probability towards the less imbalancing allocation and 25% probability towards the more imbalancing allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "a blinded physician gathered all outcome data and a nonblinded physician managed the neurostimulator"; "to maintain the subject blind, all subjects underwent actual or sham programming of the neurostimulator to ensure that time with the physician was similar"; "the blind was successfully maintained. At the end of the BEP 24% said that they did not know to which group they had been randomized, 33% guessed incorrectly and 43% guessed correctly"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: see above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Active stimulation group: 95/97 participants completed the trial: one patient did not complete the stimulation optimization period (participant preference), one did not complete the BEP (emergent explant) Sham stimulation group: 92/94 participants completed the trial: one patient did not complete the stimulation optimization period (death), one did not complete the BEP (emergent explant)

Morrell 2011 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: - no evidence of selective reporting; study was registered on www.clinicaltrials.gov but outcome measures were not mentioned; - concerning the neuropsychological outcome, quality of life and adverse events, no or not all exact figures per group (sham versus treatment group) were reported, they only mentioned that there were no significant differences. Probably this was due to the fact that there was too much data for publication (rather incomplete than selective reporting). Authors provided us these data upon our request
Outlasting effect due to prior stimulation	Low risk	Comment: parallel-group design, no stimulation prior to the randomized phase
Anti-epileptic drug policy	Low risk	Quote: "anti-epileptic drugs were to be held constant through the BEP, and then could be adjusted as needed; benzodiazepines for seizure clusters or prolonged seizures were permitted"
Other bias	Low risk	Comment: there is no clear evidence for a risk of 'other bias'

Tellez-Zenteno 2006

Methods	Double-blind, multiple cross-over, constrained (paired) randomized controlled design • 3-month baseline period (unclear if this was before or after electrode implantation) • three 2-month treatment pairs during which the stimulator was randomly allocated to be ON for 1 month and OFF for 1 month
Participants	n = 4, 25% male, mean age 31.8 years (range 24-37 y), duration of epilepsy ranged from 16 to 24 years the patients suffered from refractory left unilateral medial temporal lobe epilepsy whose risk to memory contraindicated temporal lobe resection, all patients showed mesial temporal sclerosis on MRI mean baseline seizure frequency of 4, 2.3, 25 and 4 seizures per month
Interventions	Active: left hippocampal stimulation • intensity was determined individually so that it was subthreshold for conscious appreciation (range 1.8 to 4.5V) • stimulation frequency of 190 Hz • pulse width 90 µsec

	• continuous monopolar stimulation Control: sham stimulation
Outcomes	(1) Proportion of participants who were seizure-free (2) Proportion of participants with a ≥ 50% seizure frequency reduction (responder rate) (3) Seizure frequency reduction (4) Adverse events (open questions) (5) Neuropsychological outcome (this included alternate forms of the Boston Naming Test; alternate forms of the Digit Span Test; Hopkins Verbal Learning Test; the Brief Visual Memory Test; Memory Assessment Clinic Self-Rating Scale; due to concerns with potential floor effects associated with standard neuropsychological memory tests, one patient underwent some alternative tests; the Center for Epidemiologic Studies Depression (CES-D) scale was used to assess mood) (6) Quality of Life (QOLIE-89)
Notes	The authors reported no conflicts of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"
Allocation concealment (selection bias)	Low risk	Quote: "randomization to one of the eight possible sequences was done independently by the research unit, each month's sequence was placed in sealed, double-opaque, sequentially numbered envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "patients, treating clinicians and outcome assessors were blinded"; "stimulation was set subthreshold for conscious appreciation"; "the patients' ability to guess ON or OFF status was no better than chance"; "a neurosurgeon not involved in outcome assessment or medical therapy received one envelope each month and turned the stimulator ON or OFF"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: see above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: one patient did not complete quality of life related assessments; however, this was the case both during active and sham stimulation, so no real risk of attrition

Tellez-Zenteno 2006 (*Continued*)

		bias; all other outcome data were complete
Selective reporting (reporting bias)	Low risk	- Quote: "neuropsychological testing revealed no differences between ON, OFF or baseline periods in any of the patients on any of the formal measures, or in the subjective memory scale" Comment: exact figures were not reported for the subjective memory scores (the Memory Assessment Clinic Self-Rating Scale) and for none of the test results measures of variance were provided. However, this seems more a case of incomplete rather than selective reporting. - No evidence of selective reporting for other outcomes, but no protocol available
Outlasting effect due to prior stimulation	Unclear risk	Comment: multiple cross-over design without washout period
Anti-epileptic drug policy	High risk	Comment: anti-epileptic drugs remained unchanged in only one patient
Other bias	Low risk	Comment: there is no clear evidence for a risk of 'other bias'

Van Buren 1978

Methods	Double-blind, multiple cross-over, randomized controlled trial • preoperative seizure rates were observed in the hospital before implantation (baseline seizure frequency) • implantation • stimulation ON as soon as preoperative seizure frequency had resumed after surgery • seizure frequency was evaluated in hospital during 3 or 4 admissions over the ensuing 15-21 months, each lasting 4 to 6 weeks; this time was made up of 1 or more weeks of ON-and-OFF stimulation without double-blind conditions and a roughly similar period of ON-and-OFF stimulation in the double-blind mode; for this review, only double-blind data were considered (in total 26 days ON and 26 days OFF)
Participants	n = 5, mean age 27.2 years (range 18-34 y), duration of epilepsy ranged from 8 to 23 years the patients suffered from medically intractable seizures; seizures were not classified but described; presumably, four suffered from focal epilepsy with partial seizures (and secondarily generalized seizures in two patients) and one from generalized epilepsy (with myoclonic seizures and unresponsive episodes with prolonged bilateral jerking) mean baseline seizure frequency of 0.6 to 21.2 seizures per day (mean 5.1)

Interventions	Active: bilateral stimulation of the superior surface of the cerebellum parallel to and about 1 cm from either side of the midline • stimulation was carried out at levels just below that producing sensation referable to meningeal irritation, usually at 10 to 14 V • stimulation frequency of 10 Hz (200 Hz in case of myoclonic seizures) • pulse width not reported • 8-minute periods of stimulation alternating from one side of the cerebellum to the other Control: same procedure, but with inserting an adhesive pad that had a layer of aluminium foil within it, which blocked radiofrequency transmission and in this way prevented true stimulation (versus active group: adhesive pad which consisted solely of adhesive plaster)
Outcomes	(1) Proportion of participants who were seizure-free (2) Proportion of participants with a ≥ 50% seizure frequency reduction (responder rate) (3) Seizure frequency reduction (4) Adverse events (5) Neuropsychological outcome (full scale intelligence quotients and memory quotients)
Notes	No statement concerning external support

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the pairs of pads (with or without an aluminium foil within it) were selected at random" Comment: probably completely random selection (picking one out of two)
Allocation concealment (selection bias)	Low risk	Quote: "the pairs of pads were marked with identifying letters"; "the pair containing the foil was identified in a sealed note, which was opened only after the patient's observation period" Comment: although it was not mentioned explicitly, one could expect that the pads (note: the pads were selected randomly, not the notes) had an identical appearance (foil was within it) and the identifying letters were non-disclosing (as efforts were made to conceal their meaning)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind"; "the pairs of pads were marked with identifying letters"; "the pair containing the foil was identified in a

		sealed note, which was opened only after the patient's observation period" Comment 1: although it was not mentioned explicitly, one could expect that the pads had an identical appearance (foil was within it) and the identifying letters were non-disclosing (as efforts were made to conceal their meaning); unclear if the sealed notes were double-opaque and by whom they were handled Comment 2: not mentioned if neuropsychological testing was performed during the double-blind or the unblinded evaluation period
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: see above
Incomplete outcome data (attrition bias) All outcomes	Low risk	- Although in two patients only three inpatient evaluations were performed (instead of the four planned), enough data are available to evaluate the effects of the intervention - Neuropsychological testing was not performed in one patient (not testable due to myoclonus), but low risk of attrition bias as this was the case both during effective and sham stimulation; incomplete preoperative neuropsychological testing in two additional patients, however postoperative evaluations (most important ones) were complete
Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective reporting, but no protocol available
Outlasting effect due to prior stimulation	Unclear risk	Comment: multiple cross-over study without washout period; inpatient evaluations after 1 to 21 months of stimulation
Anti-epileptic drug policy	Low risk	Quote: "serum levels of phenytoin, primidone and phenobarbital were verified several times during each admission"; "additional (to the above mentioned drugs) diazepam was given in two patients and ethosuximide in one patient, but the serum levels were not monitored" Comment: probably a policy to keep anti-

Van Buren 1978 (*Continued*)

		epileptic drugs / their serum levels unchanged
Other bias	Low risk	Comment: there is no clear evidence for a risk of 'other bias'

Velasco 2000a

Methods	Double-blind, cross-over randomized controlled trial • a 3-month baseline period • electrode implantation • 6-9 months of stimulation in all patients • a 6-month randomized double-blind cross-over (2 x 3 months) phase (ON/OFF or OFF/ON) • stimulation again ON in all patients
Participants	n = 13, 62% male, mean age 19.2 years (range 4-31 y), duration of epilepsy ranged from 4 to 33 years there were 8 patients with Lennox-Gastaut syndrome (suffering mainly from atypical absences and generalized tonic-clonic seizures), and 5 with refractory localization-related epilepsy (suffering mainly from complex partial and secondarily generalized seizures) mean baseline seizure frequency of 1051 (SD 1434) seizures per month (median 119, interquartile range 56, 2576)
Interventions	Active: stimulation of the centromedian thalamic nucleus • stimulation amplitude of 4-6 V (400-600 µA) • stimulation frequency of 60 Hz • pulse width 450 µsec • one minute of bipolar stimulation, alternating between the left and the right side with a 4-minute interval Control: sham stimulation
Outcomes	(1) Seizure frequency reduction (2) Adverse events (open questions (not systematically) and physical examination - spontaneous reporting; postoperative MRI)
Notes	Medtronic Inc. (Minneapolis, MN) donated the neurostimulators for the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients entered into a double-blind protocol" Personal communication: random selection of a folded paper (with a number on it) out of a box by the patient, who did not know the meaning of the number

Allocation concealment (selection bias)	Low risk	Personal communication: the folded paper was randomly selected by the patient, who did not know the meaning of number (i.e. if it corresponded to switching stimulation OFF between months 6 and 9 or between months 9 and 12)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "patients entered into a double-blind protocol"; "because neither the patient nor the examiner could determine when the stimulator was OFF, the double-blind protocol was considered valid" Personal communication: only an EEG technician who was not involved in treating or evaluating the patients knew the stimulation status Comment: although the blinding procedure seems adequate, performance bias may exist as the double-blind stimulation OFF periods were compared to the 3-month periods preceding them (stimulation ON in all patients, but double-blind in only half of patients!) instead of consistently comparing to the double-blind stimulation ON periods
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: see above, as outcome was assessed by the patient and the treating physician
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: despite good initial seizure control, neurostimulators were explanted in 2/15 patients originally included in the study due to skin erosions along the internalized stimulation system; however, this occurred before the patients entered the randomized phase
Selective reporting (reporting bias)	Low risk	Comment 1: no evidence of selective reporting, but no protocol available Comment 2: although there is no evidence of selective reporting, authors reported their findings incompletely: exact figures of seizure frequency (reduction) were not reported and are no longer readily available (personal communication), which prevents inclusion into the meta-analysis (the results were only presented in graphs in the original article)

Velasco 2000a (*Continued*)

Outlasting effect due to prior stimulation	Unclear risk	Comment: cross-over protocol with 6 to 9 months of stimulation before the randomized phase and without washout period
Anti-epileptic drug policy	Low risk	Quote: "anticonvulsive medication remained unchanged and anticonvulsive blood levels were repeated every 3 to 6 months throughout the study"
Other bias	Low risk	Comment: there is no clear evidence for a risk of 'other bias'

Velasco 2005

Methods	Double-blind, parallel-group randomized controlled trial • a 3-month baseline period • implantation of the electrodes • sham (= OFF) stimulation during the first postoperative month • a 3-month randomized double-blind phase during which three patients received cerebellar stimulation and two did not • stimulation ON (unblinded) in all patients after the fourth month after implantation (21 months)
Participants	n = 5, 80% male, mean age 26.0 years (range 16-35 y), duration of epilepsy ranged from 11 to 27 years three patients had generalized epilepsy and two patients (multi)focal epilepsy of frontal origin; all patients suffered from generalized tonic-clonic seizures, 4/5 patients also had tonic seizures, 2/5 had drop attacks and 1/5 had myoclonic seizures / atypical absences mean baseline seizure frequency of 14.1 (SD 6.2) seizures per month (generalized tonic-clonic seizures 6.3 (SD 3.1))
Interventions	Active (n = 3): bilateral stimulation of the superomedial surface of the cerebellum • stimulation intensity of 3.8 mA, which was equivalent to a charge density of 2.0 μC/cm²/phase (the voltage needed for this was calculated at each visit by measuring the electrodes' impedance) • stimulation frequency of 10 Hz • pulse width of 450 μsec • monopolar stimulation turned ON for 4 min alternating with 4 min OFF Control (n = 2): sham stimulation
Outcomes	(1) Proportion of participants who were seizure-free (2) Proportion of participants with a ≥ 50% seizure frequency reduction (responder rate) (3) Seizure frequency reduction (4) Adverse events (standard open questions, postoperative CT scan or MRI)
Notes	Medtronic Inc. (Minneapolis, MN) supported the study by providing the cerebellar stimulation systems

Velasco 2005 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the procedure used for randomisation was to assign patients a lottery number" Personal communication: random selection of a folded paper (with a number on it) out of a box by the patient, who did not know the meaning of the number
Allocation concealment (selection bias)	Low risk	Personal communication: the folded paper was randomly selected by the patient, who did not know the meaning of number (i.e. if it corresponded to ON or OFF)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both patients and the evaluator were blinded with regard to whether the stimulator was ON or OFF, a different investigator manipulated the stimulation code"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: see above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all patients completed the double-blind randomized phase and all data were available
Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective reporting, but no protocol available
Outlasting effect due to prior stimulation	Low risk	Comment: parallel-group design, no stimulation prior to the randomized double-blind phase
Anti-epileptic drug policy	Low risk	Quote: "All patients but one continued baseline AEDs throughout the study. Phenytoin was reduced from 300 to 200 mg per day in case 5 because of drug intolerance. Seizure decreases were not likely to be due to AEDs, because they were not modified." Personal communication: phenytoin dose reduction in case 5 was at the seventh month of the study

Velasco 2005 (*Continued*)

		Comment: AEDs were not changed during the randomized double-blind phase of the trial
Other bias	Low risk	Comment: there is no clear evidence for a risk of 'other bias'

Velasco 2007

Methods	Double-blind, parallel-group, randomized controlled trial • 3-month baseline period • electrode implantation • 1-month double blind randomized phase (stimulator ON or OFF) • long-term follow-up (range 18-84 months) with stimulation ON in all patients
Participants	n = 9, 66% male, mean age 29.1 years (range 14-43 y), duration of epilepsy ranged from 3 to 37 years intractable temporal lobe epilepsy patients, poor surgery candidates (bilateral independent foci (n = 4), unilateral focus (n = 3), lateralization not completely clear (n = 2)); neuroimaging: normal MRI (n = 5), left (n = 3) or bilateral (n = 1) hippocampal sclerosis; 6 patients had mild memory impairment in neuropsychological tests, three had severe abnormalities mean baseline seizure frequency of 37.9 (SD 16.8) seizures per month
Interventions	Active (n = 4): uni- or bilateral hippocampal stimulation (according to seizure focus) • stimulation amplitude of 300 µA (= 50% of the amplitude needed to obtain electrocortical responses) • stimulation frequency of 130 Hz • pulse width of 450 µsec • cyclic bipolar stimulation with 1-min trains with a 4 min interstimulus interval; in case of bilateral stimulation: alternating 1-min stimulation on one side with a 4-min interval between right and left sides Control (n = 5): sham stimulation
Outcomes	(1) Proportion of participants who were seizure-free (2) Proportion of participants with a ≥ 50% seizure frequency reduction (responder rate) (3) Seizure frequency reduction (4) Adverse events (open questions (not systematically) - spontaneous reporting; post-operative MRI)
Notes	No statement concerning external support

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Quote: "an aleatory (randomized by lottery number) double-blind maneuver" Personal communication: a non see-through box with small folded pieces of paper (with a code on it) within it, out of which one was randomly taken by the patient who did not know the meaning of the code
Allocation concealment (selection bias)	Low risk	Personal communication: "folded papers in a non see-through box" and the aleatory manoeuvre was performed by the patient who did not know the meaning of the code
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"; "because the stimulation at the therapeutic stimulation parameters induced no subjective or objective sensation, the double-blind maneuver was considered valid" Personal communication: the only person who knew if the stimulation was ON or OFF was an EEG technician who was not involved in other parts of the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: see above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no data missing or patients excluded from analyses
Selective reporting (reporting bias)	Low risk	Comment: - exact figures of seizure frequency with stimulation ON during the blinded period were not reported (only graphs of individual patient data, from which one could estimate these exact figures). We consider this more as incomplete rather than selective reporting. The authors provided us these data upon our request - no evidence of selective reporting, but no protocol available
Outlasting effect due to prior stimulation	Low risk	Parallel-group design, no stimulation prior to the randomized phase
Anti-epileptic drug policy	Low risk	Quote: anti-epileptic drug therapy was maintained with no modifications during follow-up

Other bias	Low risk	Comment: there is no clear evidence for a risk of 'other bias'

Wiebe 2013

Methods	Five-centre parallel-group, double-blind (participant, caregiver, investigator and outcome assessor) randomized controlled trial: • baseline period (?) (? months) • electrode implantation • 1 month for 'adjustments of interventions' • 6-month randomized double-blind phase with stimulation ON or OFF
Participants	n = 6 (sham stimulation: n = 4; active stimulation: n = 2), age 30-46 years, IQ ≥70 adults with refractory uni- (n = 4) or bilateral (n = 2) mesial temporal lobe epilepsy (failure of ≥ 2 AEDs), preference for non-resective surgery, or not a candidate for mesial temporal resection median baseline monthly seizure frequency of 10 (all seizures; CPS + GTCS = 1) in the sham group and 12 (CPS + GTCS = 2) in the stimulation group
Interventions	Active (n = 2): uni- or bilateral hippocampal stimulation for 6 months • stimulation intensity unknown • stimulation frequency of 135 Hz • pulse width unknown • continuous cathodal stimulation of all electrodes involved in seizure generation Control (n = 4): sham stimulation for 6 months
Outcomes	(1) Seizure freedom (2) Responder rate (3) Seizure frequency reduction (4) Adverse events (5) Neuropsychological outcome (6) Quality of life
Notes	The study has been preliminary terminated in March 2012 after recruitment of only 6 participants (target sample = 57) due to difficulties in patient recruitment despite the multicentre participation; the results collected in those 6 patients were published as an abstract. However, many details on the methodology, participants, interventions and outcomes are missing for a complete judgement of the methodology used or for full incorporation into this review. We tried to contact the authors but could not obtain additional information or data yet. Another attempt will be made by the next update of this review The trial was sponsored by the University of Calgary, no evidence for external funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Wiebe 2013 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: 'randomized' Comment: additional information on the methods used for random sequence generation could not be obtained
Allocation concealment (selection bias)	Unclear risk	Quote: 'randomized' Comment: additional information on the methods used for concealment of treatment allocation could not be obtained
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: 'double-blind (subject, caregiver, investigator and outcome assessor)' Comment: additional information on the methods used for blinding could not be obtained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: 'double-blind (subject, caregiver, investigator and outcome assessor)' Comment: additional information on the methods used for blinding could not be obtained
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no evidence for incomplete outcome data leading to attrition bias but insufficient details available for full appreciation
Selective reporting (reporting bias)	Low risk	Comment 1: no clear evidence for selective reporting, all outcome measures mentioned in the protocol were briefly discussed in the abstract although many details are missing for full appreciation (see comment 2); Comment 2: although there was no evidence for selective reporting, the authors reported their results incompletely as these were only published as an abstract and many details on the collected outcomes are missing for full incorporation of this trial into the review (e.g. results after 3 months, detailed neuropsychological outcomes, variance between participants...)
Outlasting effect due to prior stimulation	Low risk	Quote: parallel-group randomized controlled trial
Anti-epileptic drug policy	Unclear risk	Comment: AED policy not specified

Wiebe 2013 (*Continued*)

Other bias	Low risk	Comment: there is no clear evidence for a risk of 'other bias'

Wright 1984

Methods	Double-blind, cross-over randomized controlled study • electrode implantation • the first phase of the trial was begun several months after implantation when the individual had returned to his or her preoperative seizure frequency • a 6-month double-blind randomized phase, consisting of three 2-month periods (continuous, contingent and sham stimulation)
Participants	n = 12, 83% male, mean age 30 years (range 20-38 y), duration of epilepsy ranged from 10 to 32 years type of epilepsy not reported, 5/12 patients had only generalized seizures, 1/12 only partial seizures, 4/12 partial and generalized seizures, 2/12 dd complex partial seizures versus complex absences; in addition it was reported that the EEG in each case contained quantifiable generalized paroxysmal activity, but six patients showed additional focal activity in the frontal or temporal regions, all patients had an IQ of ≥ 80 mean seizure frequency during sham stimulation: 61.7 (SD 53.3) seizures per month
Interventions	Electrode pads were placed on the upper surface of the cerebellum, positioned parasagittally approximately 2 cm from the midline on each side; stimulation parameters were: • stimulation amplitude: 7 mA in 8/12 patients (default), 5 mA in 3/12 patients (in 2/3 because 7 mA could be detected by the patients), 7 mA (one side) and 1 mA (other side) due to technical reasons in 1/12 patients • stimulation frequency 10 Hz (default); 200 Hz (5 mA) in one patient because he showed reduction in the amplitude of somatosensory evoked potentials during one recording session after bursts of stimulation with these parameters • pulse width not reported • bipolar stimulation Treatment 1: continuous stimulation • continuous stimulation alternating from one cerebellar hemisphere to the other every minute Treatment 2: contingent (responsive) stimulation • intermittent contingent stimulation of both cerebellar hemispheres occurred whilst the "seizure button" on the transmitter was depressed (during an aura or seizure) and for two minutes after it was released Control: sham stimulation
Outcomes	(1) Proportion of participants who were seizure-free (2) Proportion of participants with a ≥ 50% seizure frequency reduction (responder rate) (3) Seizure frequency reduction (4) Adverse events (5) Neuropsychological outcome ('psychometry') (6) 'Proxy' of quality of life (patients' impressions on cerebellar stimulation)

Wright 1984 (*Continued*)

Notes	Baseline seizure frequency was not reported, changes in seizure frequency are therefore expressed relative to the sham stimulation phase; no statement concerning external support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the sequence of the phases was randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Quote: "the sequence of the phases was randomly allocated"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"; "the sequence of the phases was randomly allocated and the code was not broken until the trial had been completed"; "stimulation was set at stimulation parameters that couldn't be detected by the patients"; "before surgery and at the end of each phase of the trial, each patient was assessed clinically by two independent consultant neurologists who were not involved in the trial or the patient's routine management"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: see above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: seizure frequency during the three phases was not fully quantifiable in 3/12 patients (reasons: 1) one patient became uncooperative; 2) one patient mislaid some of his records; 3) one patient suffered prolonged periods of confusion associated with absence attacks and myoclonic jerks which were difficult to quantify); however, this was the case for each phase of the study; moreover, the evolution of the seizure frequency during the three phases of the trial was qualitatively described
Selective reporting (reporting bias)	Low risk	Quote: "psychometry did not reveal any major changes in any patients in any of the phases of the trial" Comment: no exact figures were provided, probably because there was too much data

Wright 1984 (*Continued*)

		for publication in the journal article (rather incomplete than selective reporting) Comment: no evidence of selective reporting concerning the other outcomes, but no protocol available
Outlasting effect due to prior stimulation	Unclear risk	Comment: cross-over design without a washout period between the different treatment phases
Anti-epileptic drug policy	Low risk	Quote: "at the time of admission to the trial they were considered to be on the best combination of anticonvulsants at optimum dosage and this dosage had not been changed during the previous six months" Comment: although it was not stated explicitly, it seems unlikely that the antiepileptic drug regimen was changed during the trial
Other bias	Low risk	Comment: there is no clear evidence for a risk of 'other bias'

AED: antiepileptic drug
BEP: blinded evaluation period
CT: computed tomography
DBS: deep brain stimulation
ITT: intention-to-treat
MRI: magnetic resonance imaging
SD: standard deviation
VNS: Vagus Nerve Stimulation
WAIS: Wechsler Adult Intelligence Scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alaraj 2001	not a randomized controlled trial
Anderson 2008	4/7 patients not in a randomized controlled trial; 3/7 patients participated in a randomized trial but no information about outcomes relevant to this study; additionally patients were also included in a large randomized controlled trial already included in this review (Morrell 2011)
Andrade 2006	not a randomized controlled trial

(*Continued*)

Bidzi n ski 1981	not a randomized controlled trial
Boon 2007a	not a randomized controlled trial
Boëx 2011	not a randomized controlled trial
Brown 2006	intracranial stimulation for other purposes / not to treat refractory epilepsy patients
Chabardes 2002	not a randomized controlled trial
Child 2014	not a randomized controlled trial
Chkhenkeli 2004	not a randomized controlled trial
Cooper 1976	not a randomized controlled trial
Cordella 2013	not a randomized controlled trial
Cukiert 2009	not a randomized controlled trial
Cukiert 2014	not a randomized controlled trial
Davis 1992	not a randomized controlled trial
Davis 2000	not a randomized controlled trial
Ding 2016	not a randomized controlled trial
Dinner 2002	not a randomized controlled trial
Elisevich 2006	not a randomized controlled trial
Esteller 2004	intracranial stimulation for other purposes / not to treat refractory epilepsy patients
Feinstein 1989	not a randomized controlled trial
Fell 2013	intracranial stimulation for other purposes / not to treat refractory epilepsy patients
Fountas 2005	not a randomized controlled trial
Fountas 2007	not a randomized controlled trial
Franzini 2008	not a randomized controlled trial
Fregni 2005	not intracranial stimulation
Fregni 2006	not intracranial stimulation
Galvez-Jimenez 1998	intracranial stimulation for other purposes / not to treat refractory epilepsy patients

(*Continued*)

Handforth 2006	not a randomized controlled trial
Hodaie 2002	not a randomized controlled trial
Huang 2008	intracranial stimulation for other purposes / not to treat refractory epilepsy patients
Kerrigan 2004	not a randomized controlled trial
Khan 2009	not a randomized controlled trial
Kossoff 2004	not a randomized controlled trial
Koubeissi 2013	not a randomized controlled trial
Larkin 2016	not a randomized controlled trial / no new randomized controlled trials included
Lee 2006	not a randomized controlled trial
Lee 2012	not a randomized controlled trial
Levy 2008	intracranial stimulation for other purposes / not to treat refractory epilepsy patients
Lim 2007	not a randomized controlled trial
Loddenkemper 2001	not a randomized controlled trial
Marras 2011	not a randomized controlled trial
Miatton 2011	not a randomized controlled trial
Miller 2015	intracranial stimulation for other purposes / not to treat refractory epilepsy patients
Nguyen 1999	intracranial stimulation for other purposes / not to treat refractory epilepsy patients
Osorio 2001	not a randomized controlled trial
Osorio 2005	not a randomized controlled trial
Osorio 2007	not a randomized controlled trial
Pahwa 1999	intracranial stimulation for other purposes / not to treat refractory epilepsy patients
Riklan 1976	not a randomized controlled trial
Rocha 2007	not a randomized controlled trial
Savard 2003	not a randomized controlled trial
Schmitt 2014	not a randomized controlled trial

(*Continued*)

Schulze-Bonhage 2016	not a randomized controlled trial
Spencer 2011	not a randomized controlled trial
Sussman 1988	not a randomized controlled trial
Tanriverdi 2009	intracranial stimulation for other purposes / not to treat refractory epilepsy patients
Torres 2013	intracranial stimulation for other purposes / not to treat refractory epilepsy patients
Tyrand 2012	not a randomized controlled trial
Upton 1985	not a randomized controlled trial
Valentin 2013	not a randomized controlled trial
Velasco 1987	not a randomized controlled trial
Velasco 1993	not a randomized controlled trial
Velasco 1995	not a randomized controlled trial
Velasco 2000b	not a randomized controlled trial
Velasco 2001	not a randomized controlled trial
Velasco 2006	not a randomized controlled trial
Velasco 2009	not a randomized controlled trial
Vonck 2002	not a randomized controlled trial
Vonck 2013	not a randomized controlled trial
Wakerley 2011	not a randomized controlled trial
Wei 2016	not a randomized controlled trial
Wille 2011	not a randomized controlled trial
Yamamoto 2006	not a randomized controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Chabardes 2005

Methods	Double-blind (participant, investigator, outcome assessor), randomized controlled clinical trial with two cross-over groups
Participants	Epilepsy resistant to AEDs and dopaminergic D2-agonist Curative resective surgery not possible Metabolism deficiency of DOPA above 1 DS, evaluated by Positron Emission Tomography (PET) using fluorodopa Age ranging from 18 to 50
Interventions	Group 1: 3 months high-frequency stimulation of the subthalamic nucleus followed by 3 months SHAM stimulation Group 2: 3 months SHAM stimulation followed by 3 months high-frequency stimulation of the subthalamic nucleus
Outcomes	(1) Proportion of participants with a $\geq$ 50% seizure frequency reduction (responder rate) (2) Seizure frequency reduction (3) Adverse events (4) Neuropsychological outcome (WAIS, GROBER and Busckhe, Wisconsin Card Sorting Test, TRAIL test, LURIA test, Beck Depression Inventory, verbal flow test, empathy test) (5) Quality of life (SEALS, QOLIE-31 and NHP scales)
Notes	The study has been preliminary terminated in March 2010 due to insufficient patient recruitment. Four participants were recruited. Results have not been published yet. We tried to contact the authors but could not obtain any results yet. Further efforts will be made

van Rijckevorsel 2004

Methods	
Participants	
Interventions	
Outcomes	
Notes	A randomized controlled trial evaluating the efficacy and safety of DBS of the mammillary bodies and mammillothalamic tracts was announced but results have not been published yet; authors were contacted but results could not be provided yet. Further efforts will be made

AED: antiepileptic drug
DBS: deep brain stimulation

Characteristics of ongoing studies *[ordered by study ID]*

Boon 2007b

Trial name or title	Prospective randomized controlled study of neurostimulation in the medial temporal lobe for patients with medically refractory medial temporal lobe epilepsy;: Controlled Randomized Stimulation Versus Resection (CoRaStiR)
Methods	Prospective, multicentre, parallel-group, single-blind (participant) randomized controlled trial
Participants	Presurgical candidates with pharmacoresistant partial seizures despite optimal medical treatment and history of temporal lobe epilepsy Video-EEG characteristics showing temporal lobe seizure onset (left-sided or right-sided seizure onset) in at least one recorded habitual seizure Presence of a structural abnormality in the medial temporal lobe, suggestive of hippocampal sclerosis as evidenced by optimum MRI Age ≥ 18 years Total IQ > 80
Interventions	Group 1: electrode implantation in the medial temporal lobe and immediate unilateral hippocampal neurostimulation (12 months) Group 2: electrode implantation in the medial temporal lobe but unilateral hippocampal neurostimulation (6 months) is delayed for 6 months Group 3: amygdalohippocampectomy
Outcomes	(1) Proportion of participants with a ≥ 50% seizure frequency reduction (responder rate) (2) Seizure frequency reduction (3) Adverse events (4) Neuropsychological outcome (5) Quality of life (QOLIE 89)
Starting date	June 2007
Contact information	Kristl Vonck, MD, PhD - Ghent University, Belgium - kristl.vonck@UGent.be
Notes	Currently still recruiting participants (December 2014) Sponsored by Medtronics

Chabardes 2014

Trial name or title	Clinical and medico-economical assessment of deep brain stimulation of the anterior nucleus of the thalamus for the treatment of pharmacoresistant partial epilepsy
Methods	Open-label parallel-group randomized controlled trial
Participants	Pharmacoresistant (≥ 2 AEDS) focal or multifocal epilepsy patients Epilepsy inoperable at the time of inclusion Failure of vagus nerve stimulation Age 16-60 years IQ > 55

Chabardes 2014 (*Continued*)

Interventions	Group 1: anterior thalamic nucleus deep brain stimulation Group 2: maintaining 'usual' treatment, including vagus nerve stimulation
Outcomes	(1) Seizure severity (2) Adverse events (special focus on depression) (3) Neuropyschological outcome (4) Quality of life
Starting date	March 2014
Contact information	Sandra David-Tchouda, MD - University Hospital of Grenoble Michallon, France - SDavidTchouda@chu-grenoble.fr Sandrine Massicot, CRA - University Hospital of Grenoble Michallon, France - SMassicot@chu.grenoble.fr
Notes	Currently still recruiting patients (December 2015) Sponsored by Grenoble University Hospital

Koubeissi 2015

Trial name or title	Low frequency electrical stimulation of the fornix in intractable Mesial Temporal Lobe Epilepsy (MTLE)
Methods	Parallel-group single-blind (participant) randomized controlled trial
Participants	Patients with intractable (failure of $\geq$ 2 AEDs) uni- or bilateral medial temporal lobe epilepsy (based on non-invasive video-EEG monitoring; lesional or non-lesional hippocampus) Demonstration that the hippocampus ipsilateral to seizure onset is contributing to memory function Not candidates for resective surgery for reasons that include an increased risk of memory decline Age 18-65 years IQ $\geq$ 70
Interventions	Group 1: 1 Hz low-frequency electrical stimulation of the fornix using a Medtronic deep brain stimulation device Group 2: 5 Hz low-frequency electrical stimulation of the fornix using a Medtronic deep brain stimulation device
Outcomes	(1) Seizure frequency (2) Adverse events, especially safety and tolerability with regards to memory function - Psychiatriac Health (3) Quality of life (QOLIE-31 and SF-36)
Starting date	December 2013
Contact information	Mohamad Z Koubeissi, MD - George Washington University, Washington DC, USA - mkoubeissi@mfa.gwu.edu
Notes	Currently still recruiting participants (March 2015) Sponsored by George Washington University

Zhang 2015

Trial name or title	Prospective randomized trial comparing vagus nerve stimulation and deep brain stimulation of the anterior nucleus of the thalamus in patient with pharmacoresistant epilepsy
Methods	Parallel-group randomized controlled clinical trial
Participants	Patients with diagnosis of pharmacoresistant partial-onset seizures (persistent seizures despite at least 3 AEDs) Prior electroencephalography and magnetic resonance imaging studies are consistent with the diagnosis Age 12-60 years
Interventions	Group 1: vagus nerve stimulation Group 2: anterior thalamic nucleus deep brain stimulation
Outcomes	(1) Seizure frequency reduction (2) Adverse events including depression and anxiety (3) Quality of life
Starting date	January 2015
Contact information	Zhang K - Beijing Neurosurgical Institute, China - zhangkai62035@sina.com
Notes	Currently still recruiting participants (May 2015) Sponsored by Beijing Tiantan Hospital, Capital Medical University

AED: antiepileptic drug
MRI: magnetic resonance imaging

DATA AND ANALYSES

Comparison 1. Stimulation versus sham stimulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seizure freedom	11		Odds Ratio (Fixed, 95% CI)	Subtotals only
1.1 Anterior thalamic nucleus	1	109	Odds Ratio (Fixed, 95% CI)	0.33 [0.01, 8.36]
1.2 Centromedian thalamic stimulation	1	12	Odds Ratio (Fixed, 95% CI)	1.0 [0.11, 9.39]
1.3 Cerebellar stimulation	3	39	Odds Ratio (Fixed, 95% CI)	0.96 [0.22, 4.12]
1.4 Hippocampal stimulation (1 to 3 months)	3	21	Odds Ratio (Fixed, 95% CI)	1.03 [0.21, 5.15]
1.5 Hippocampal stimulation (4 to 6 months)	1	6	Odds Ratio (Fixed, 95% CI)	1.80 [0.03, 121.68]
1.6 Nucleus accumbens stimulation	1	8	Odds Ratio (Fixed, 95% CI)	1.0 [0.07, 13.64]
1.7 Closed-loop ictal onset zone stimulation	1	191	Odds Ratio (Fixed, 95% CI)	4.95 [0.23, 104.44]
2 Responder rate	11		Odds Ratio (Fixed, 95% CI)	Subtotals only
2.1 Anterior thalamic nucleus	1	108	Odds Ratio (Fixed, 95% CI)	1.20 [0.52, 2.80]
2.2 Centromedian thalamic stimulation	1	12	Odds Ratio (Fixed, 95% CI)	1.0 [0.27, 3.69]
2.3 Cerebellar stimulation	3	33	Odds Ratio (Fixed, 95% CI)	2.43 [0.46, 12.84]
2.4 Hippocampal stimulation (1 to 3 months)	3	21	Odds Ratio (Fixed, 95% CI)	1.20 [0.36, 4.01]
2.5 Hippocampal stimulation (4 to 6 months)	1	6	Odds Ratio (Fixed, 95% CI)	9.00 [0.22, 362.46]
2.6 Nucleus accumbens stimulation	1	8	Odds Ratio (Fixed, 95% CI)	10.00 [0.53, 189.15]
2.7 Closed-loop ictal onset zone stimulation	1	191	Odds Ratio (Fixed, 95% CI)	1.12 [0.59, 2.11]
3 Seizure frequency reduction	10		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 Anterior thalamic nucleus stimulation	1	108	Mean Difference (Fixed, 95% CI)	-17.44 [-32.53, -2.35]
3.2 Centromedian thalamic stimulation	1	12	Mean Difference (Fixed, 95% CI)	7.05 [-44.05, 58.15]
3.3 Cerebellar stimulation	3	33	Mean Difference (Fixed, 95% CI)	-12.37 [-35.30, 10.55]
3.4 Hippocampal stimulation (1 to 3 months)	3	21	Mean Difference (Fixed, 95% CI)	-28.14 [-34.09, -22.19]
3.5 Nucleus accumbens stimulation	1	8	Mean Difference (Fixed, 95% CI)	-33.8 [-117.37, 49.77]
3.6 Closed-loop ictal onset zone stimulation	1	191	Mean Difference (Fixed, 95% CI)	-24.95 [-42.00, -7.90]
4 Quality of Life	4		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 Anterior thalamic nucleus stimulation	1	105	Mean Difference (Fixed, 95% CI)	-0.3 [-3.50, 2.90]

4.2 Hippocampal stimulation (1 to 3 months)	1	6	Mean Difference (Fixed, 95% CI)	-5.0 [-53.25, 43.25]
4.3 Nucleus accumbens stimulation	1	8	Mean Difference (Fixed, 95% CI)	2.78 [-7.41, 12.97]
4.4 Closed-loop ictal onset zone stimulation	1	180	Mean Difference (Fixed, 95% CI)	-0.14 [-2.88, 2.60]

Comparison 2. Stimulation versus sham stimulation - sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seizure freedom RR	11		Risk Ratio (Fixed, 95% CI)	Subtotals only
1.1 Anterior thalamic nucleus	1	109	Risk Ratio (Fixed, 95% CI)	0.34 [0.01, 8.15]
1.2 Centromedian thalamic stimulation	1	12	Risk Ratio (Fixed, 95% CI)	1.0 [0.14, 7.10]
1.3 Cerebellar stimulation	3	33	Risk Ratio (Fixed, 95% CI)	0.96 [0.26, 3.52]
1.4 Hippocampal stimulation (1 to 3 months)	3	21	Risk Ratio (Fixed, 95% CI)	1.03 [0.25, 4.19]
1.5 Hippocampal stimulation (4 to 6 months)	1	6	Risk Ratio (Fixed, 95% CI)	1.67 [0.04, 64.08]
1.6 Nucleus accumbens stimulation	1	8	Risk Ratio (Fixed, 95% CI)	1.0 [0.14, 7.10]
1.7 Closed-loop ictal onset zone stimulation	1	191	Risk Ratio (Fixed, 95% CI)	4.85 [0.24, 99.64]
2 Responder rate RR	11		Risk Ratio (Fixed, 95% CI)	Subtotals only
2.1 Anterior thalamic nucleus	1	108	Risk Ratio (Fixed, 95% CI)	1.14 [0.62, 2.10]
2.2 Centromedian thalamic stimulation	1	12	Risk Ratio (Fixed, 95% CI)	1.0 [0.38, 2.66]
2.3 Cerebellar stimulation	3	33	Risk Ratio (Fixed, 95% CI)	2.00 [0.51, 7.86]
2.4 Hippocampal stimulation (1 to 3 months)	3	21	Risk Ratio (Fixed, 95% CI)	1.12 [0.47, 2.66]
2.5 Hippocampal stimulation (4 to 6 months)	1	6	Risk Ratio (Fixed, 95% CI)	5.00 [0.29, 87.54]
2.6 Nucleus accumbens stimulation	1	8	Risk Ratio (Fixed, 95% CI)	4.00 [0.56, 28.40]
2.7 Closed-loop ictal onset zone stimulation	1	191	Risk Ratio (Fixed, 95% CI)	1.09 [0.69, 1.72]
3 Seizure freedom OR 0.25	11		Odds Ratio (Fixed, 95% CI)	Subtotals only
3.1 Anterior thalamic nucleus	1	109	Odds Ratio (Fixed, 95% CI)	0.20 [0.00, 15.17]
3.2 Centromedian thalamic stimulation	1	12	Odds Ratio (Fixed, 95% CI)	1.0 [0.05, 19.79]
3.3 Cerebellar stimulation	3	33	Odds Ratio (Fixed, 95% CI)	0.96 [0.13, 6.83]
3.4 Hippocampal stimulation (1 to 3 months)	3	21	Odds Ratio (Fixed, 95% CI)	1.03 [0.13, 8.41]
3.5 Hippocampal stimulation (4 to 6 months)	1	6	Odds Ratio (Fixed, 95% CI)	1.89 [0.01, 608.05]
3.6 Nucleus accumbens stimulation	1	8	Odds Ratio (Fixed, 95% CI)	1.0 [0.04, 27.83]

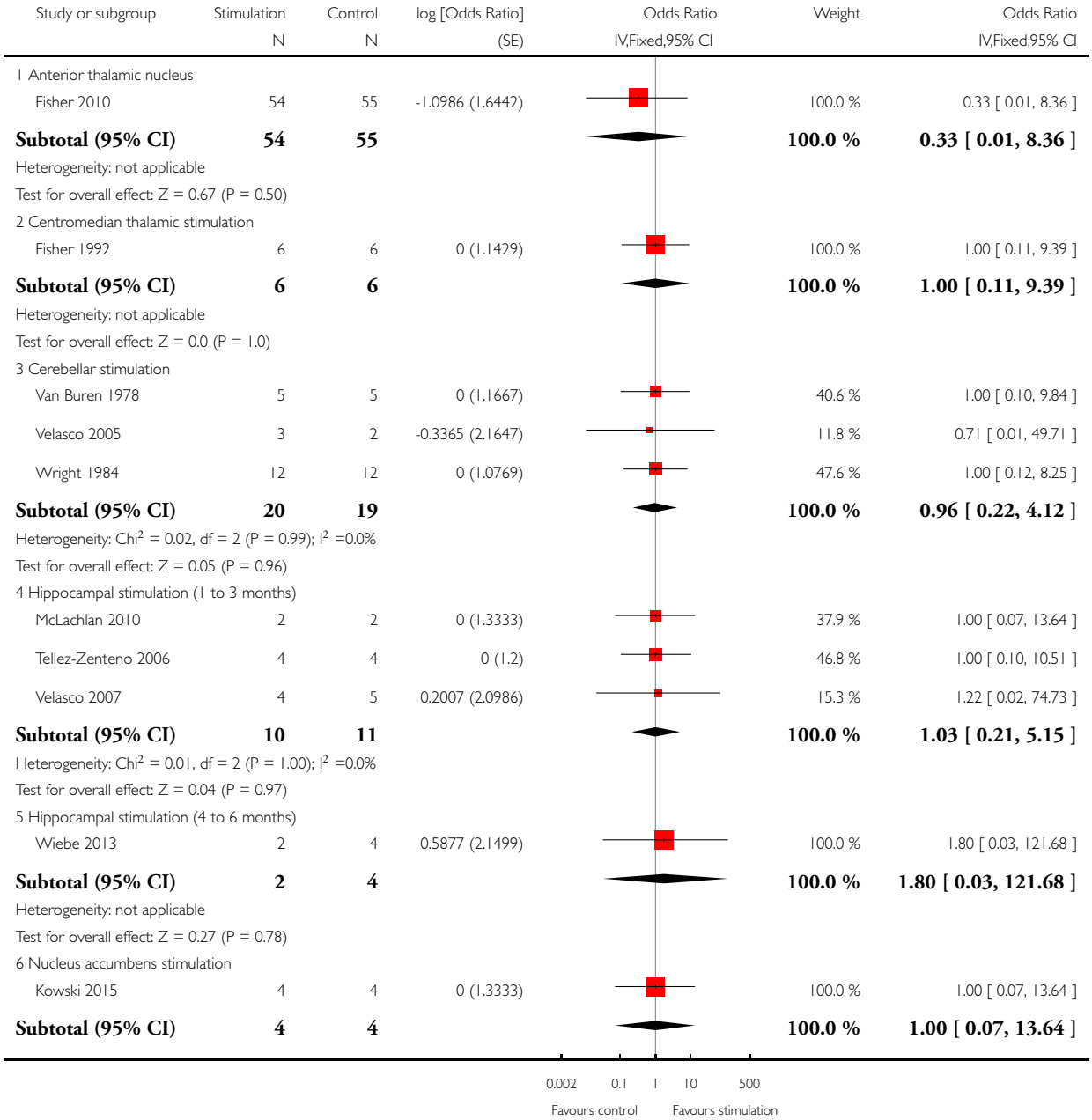
3.7 Closed-loop ictal onset zone stimulation	1	191	Odds Ratio (Fixed, 95% CI)	8.91 [0.14, 560.31]
4 Responder rate OR 0.25	11		Odds Ratio (Fixed, 95% CI)	Subtotals only
4.1 Anterior thalamic nucleus	1	108	Odds Ratio (Fixed, 95% CI)	1.20 [0.52, 2.80]
4.2 Centromedian thalamic stimulation	1	12	Odds Ratio (Fixed, 95% CI)	1.0 [0.31, 3.24]
4.3 Cerebellar stimulation	3	33	Odds Ratio (Fixed, 95% CI)	2.98 [0.39, 22.77]
4.4 Hippocampal stimulation (1 to 3 months)	3	21	Odds Ratio (Fixed, 95% CI)	1.15 [0.35, 3.77]
4.5 Hippocampal stimulation (4 to 6 months)	1	6	Odds Ratio (Fixed, 95% CI)	17.00 [0.15, 1934.66]
4.6 Nucleus accumbens stimulation	1	8	Odds Ratio (Fixed, 95% CI)	21.00 [0.51, 864.51]
4.7 Closed-loop ictal onset zone stimulation	1	191	Odds Ratio (Fixed, 95% CI)	1.12 [0.59, 2.11]
5 Seizure freedom RR 0.25	11		Risk Ratio (Fixed, 95% CI)	Subtotals only
5.1 Anterior thalamic nucleus	1	109	Risk Ratio (Fixed, 95% CI)	0.21 [0.00, 14.95]
5.2 Centromedian thalamic stimulation	1	12	Risk Ratio (Fixed, 95% CI)	1.0 [0.06, 15.99]
5.3 Cerebellar stimulation	3	33	Risk Ratio (Fixed, 95% CI)	0.96 [0.15, 6.04]
5.4 Hippocampal stimulation (1 to 3 months)	3	21	Risk Ratio (Fixed, 95% CI)	1.02 [0.16, 6.46]
5.5 Hippocampal stimulation (4 to 6 months)	1	6	Risk Ratio (Fixed, 95% CI)	1.80 [0.01, 369.24]
5.6 Nucleus accumbens stimulation	1	8	Risk Ratio (Fixed, 95% CI)	1.0 [0.06, 15.99]
5.7 Closed-loop ictal onset zone stimulation	1	191	Risk Ratio (Fixed, 95% CI)	8.72 [0.14, 538.18]
6 Responder rate RR 0.25	11		Risk Ratio (Fixed, 95% CI)	Subtotals only
6.1 Anterior thalamic nucleus	1	108	Risk Ratio (Fixed, 95% CI)	1.14 [0.62, 2.10]
6.2 Centromedian thalamic stimulation	1	12	Risk Ratio (Fixed, 95% CI)	1.0 [0.40, 2.52]
6.3 Cerebellar stimulation	3	33	Risk Ratio (Fixed, 95% CI)	2.28 [0.40, 13.02]
6.4 Hippocampal stimulation (1 to 3 months)	3	21	Risk Ratio (Fixed, 95% CI)	1.08 [0.46, 2.55]
6.5 Hippocampal stimulation (4 to 6 months)	1	6	Risk Ratio (Fixed, 95% CI)	9.00 [0.16, 494.41]
6.6 Nucleus accumbens stimulation	1	8	Risk Ratio (Fixed, 95% CI)	7.00 [0.44, 111.91]
6.7 Closed-loop ictal onset zone stimulation	1	191	Risk Ratio (Fixed, 95% CI)	1.09 [0.69, 1.72]

Analysis 1.1. Comparison 1 Stimulation versus sham stimulation, Outcome 1 Seizure freedom.

Review: Deep brain and cortical stimulation for epilepsy

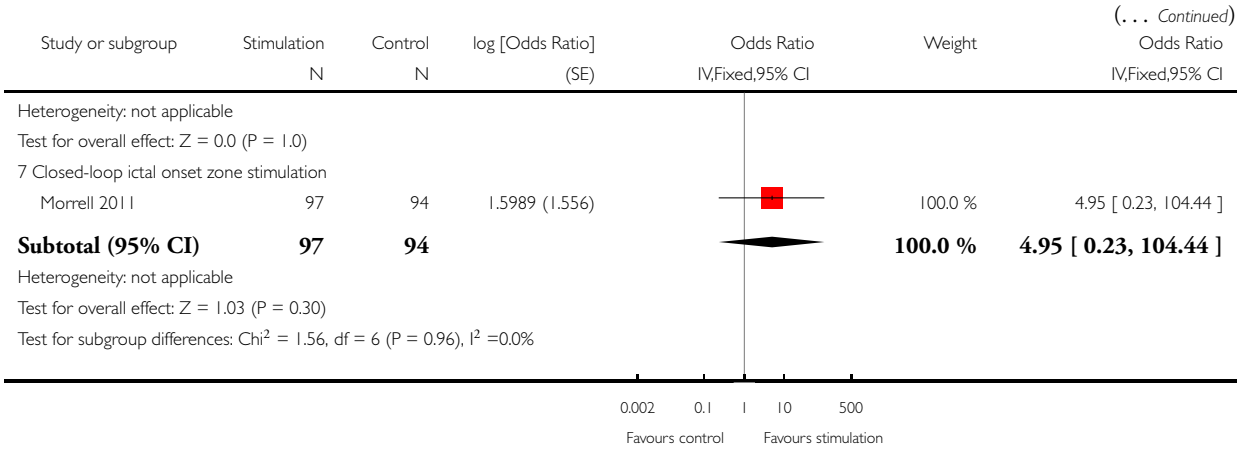
Comparison: 1 Stimulation versus sham stimulation

Outcome: 1 Seizure freedom



(*Continued . . .*)

(. . . *Continued*)

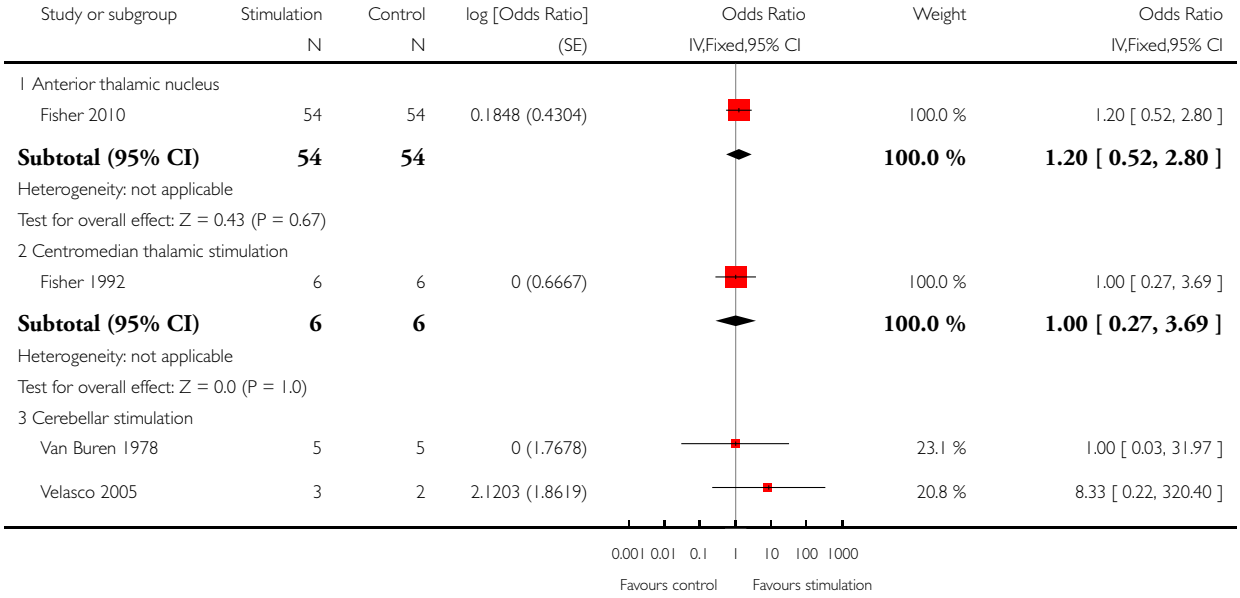


Analysis 1.2. Comparison 1 Stimulation versus sham stimulation, Outcome 2 Responder rate.

Review: Deep brain and cortical stimulation for epilepsy

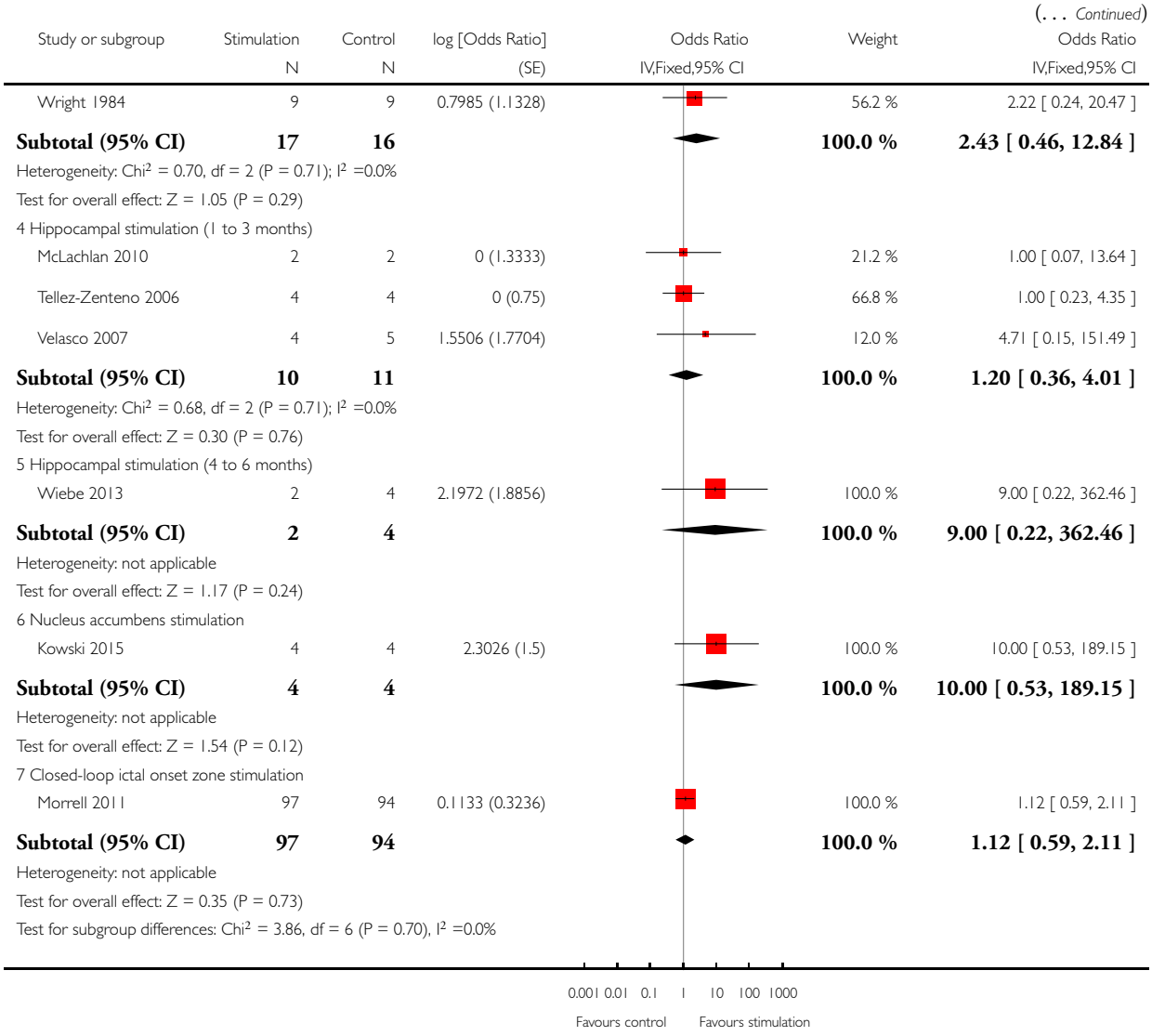
Comparison: 1 Stimulation versus sham stimulation

Outcome: 2 Responder rate



(*Continued* . . .)

(. . . *Continued*)

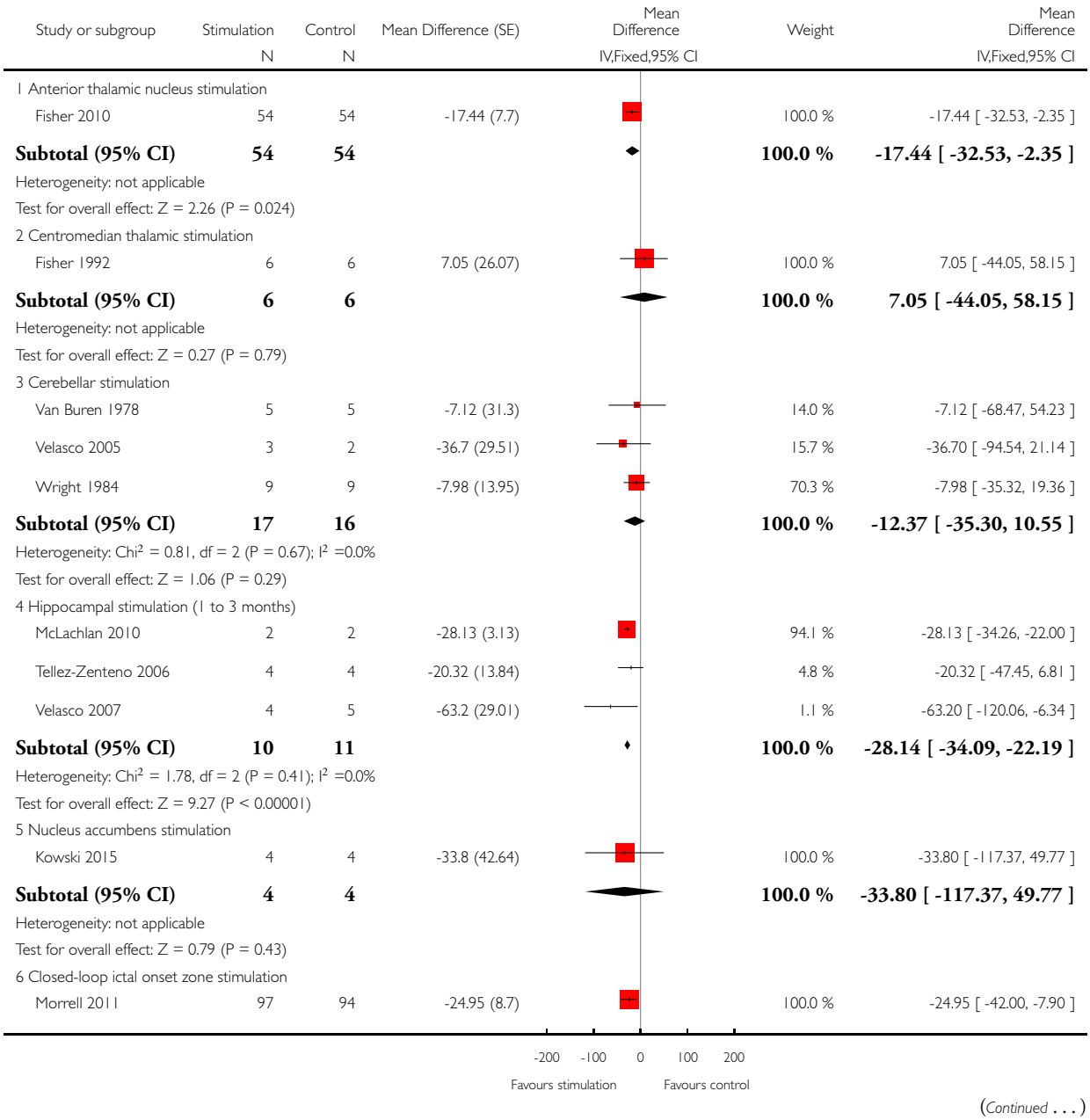


Analysis 1.3. Comparison 1 Stimulation versus sham stimulation, Outcome 3 Seizure frequency reduction.

Review: Deep brain and cortical stimulation for epilepsy

Comparison: 1 Stimulation versus sham stimulation

Outcome: 3 Seizure frequency reduction



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Stimulation N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Subtotal (95% CI)	**97**	**94**			**100.0 %**	**-24.95 [-42.00, -7.90]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.87 (P = 0.0041)						
Test for subgroup differences: Chi^2 = 4.71, df = 5 (P = 0.45), I^2 =0.0%						

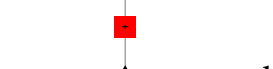
Analysis 1.4. Comparison 1 Stimulation versus sham stimulation, Outcome 4 Quality of Life.

Review: Deep brain and cortical stimulation for epilepsy

Comparison: 1 Stimulation versus sham stimulation

Outcome: 4 Quality of Life

Study or subgroup	Favours control N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Anterior thalamic nucleus stimulation						
Fisher 2010	52	53	-0.3 (1.6319)		100.0 %	-0.30 [-3.50, 2.90]
Subtotal (95% CI)	**52**	**53**			**100.0 %**	**-0.30 [-3.50, 2.90]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.18 (P = 0.85)						
2 Hippocampal stimulation (1 to 3 months)						
Tellez-Zenteno 2006	3	3	-5 (24.617)		100.0 %	-5.00 [-53.25, 43.25]
Subtotal (95% CI)	**3**	**3**			**100.0 %**	**-5.00 [-53.25, 43.25]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.20 (P = 0.84)						
3 Nucleus accumbens stimulation						
Kowski 2015	4	4	2.78 (5.2)		100.0 %	2.78 [-7.41, 12.97]
Subtotal (95% CI)	**4**	**4**			**100.0 %**	**2.78 [-7.41, 12.97]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.53 (P = 0.59)						
4 Closed-loop ictal onset zone stimulation						



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Favours control N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Morrell 2011	93	87	-0.14 (1.4003)		100.0 %	-0.14 [-2.88, 2.60]
Subtotal (95% CI)	**93**	**87**			**100.0 %**	**-0.14 [-2.88, 2.60]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.10 (P = 0.92)

Test for subgroup differences: Chi^2 = 0.36, df = 3 (P = 0.95), I^2 =0.0%

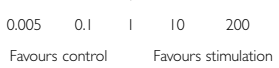
Analysis 2.1. Comparison 2 Stimulation versus sham stimulation - sensitivity analyses, Outcome 1 Seizure freedom RR.

Review: Deep brain and cortical stimulation for epilepsy

Comparison: 2 Stimulation versus sham stimulation - sensitivity analyses

Outcome: 1 Seizure freedom RR

Study or subgroup	Experimental N	Control N	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Anterior thalamic nucleus						
Fisher 2010	54	55	-1.0806 (1.6219)		100.0 %	0.34 [0.01, 8.15]
Subtotal (95% CI)	**54**	**55**			**100.0 %**	**0.34 [0.01, 8.15]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.67 (P = 0.51)						
2 Centromedian thalamic stimulation						
Fisher 1992	6	6	0 (1)		100.0 %	1.00 [0.14, 7.10]
Subtotal (95% CI)	**6**	**6**			**100.0 %**	**1.00 [0.14, 7.10]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P = 1.0)						
3 Cerebellar stimulation						
Van Buren 1978	5	5	0 (1)		43.6 %	1.00 [0.14, 7.10]
Velasco 2005	3	2	-0.288 (1.8484)		12.8 %	0.75 [0.02, 28.07]
Wright 1984	9	9	0 (1)		43.6 %	1.00 [0.14, 7.10]



(*Continued* . . .)

(. . . *Continued*)

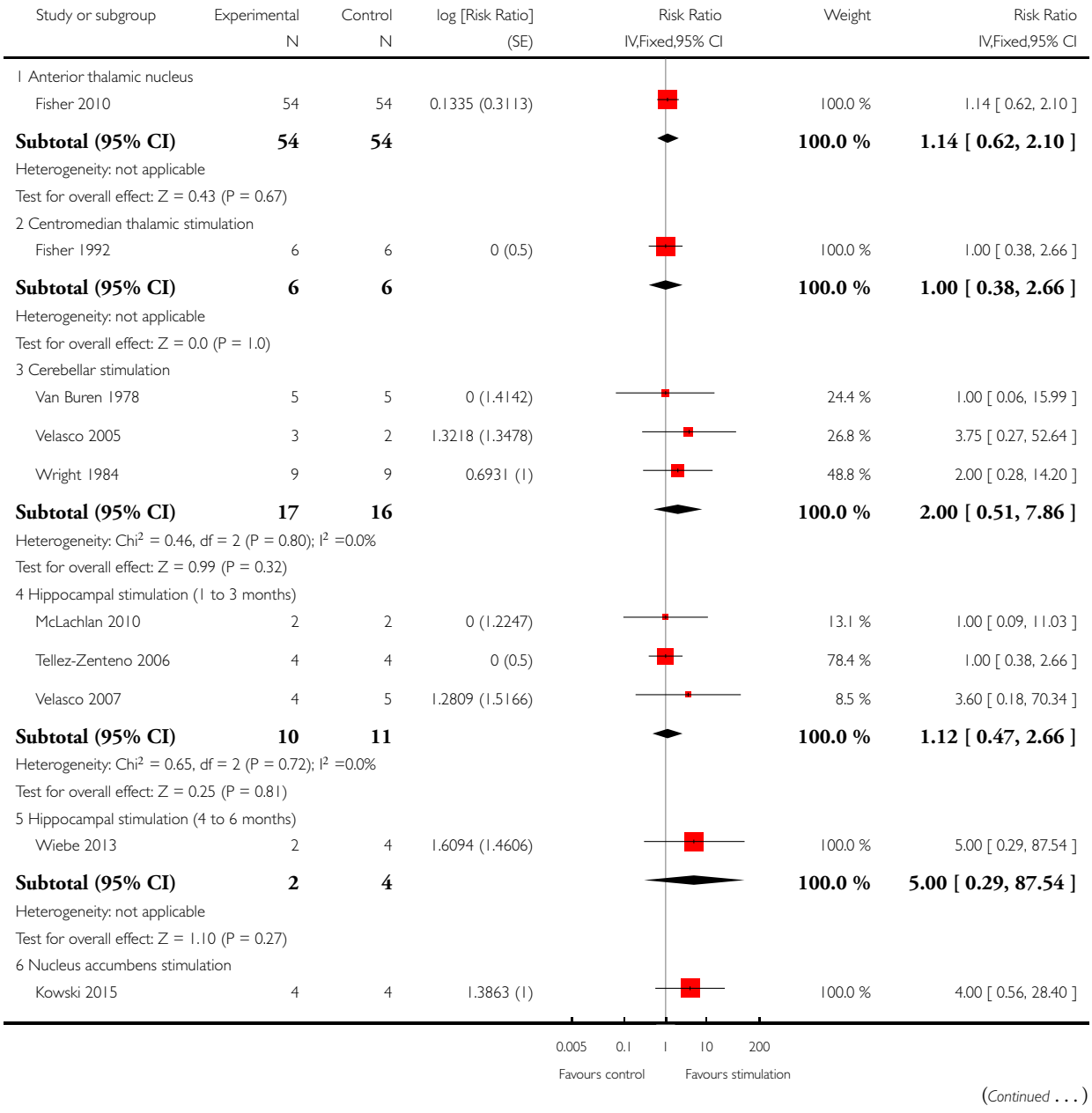
Study or subgroup	Experimental N	Control N	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Subtotal (95% CI)	**17**	**16**			**100.0 %**	**0.96 [0.26, 3.52]**
Heterogeneity: Chi² = 0.02, df = 2 (P = 0.99); I² =0.0%						
Test for overall effect: Z = 0.06 (P = 0.96)						
4 Hippocampal stimulation (1 to 3 months)						
McLachlan 2010	2	2	0 (1.2247)		34.3 %	1.00 [0.09, 11.03]
Tellez-Zenteno 2006	4	4	0 (1)		51.5 %	1.00 [0.14, 7.10]
Velasco 2007	4	5	0.1823 (1.9061)		14.2 %	1.20 [0.03, 50.31]
Subtotal (95% CI)	**10**	**11**			**100.0 %**	**1.03 [0.25, 4.19]**
Heterogeneity: Chi² = 0.01, df = 2 (P = 1.00); I² =0.0%						
Test for overall effect: Z = 0.04 (P = 0.97)						
5 Hippocampal stimulation (4 to 6 months)						
Wiebe 2013	2	4	0.5108 (1.8619)		100.0 %	1.67 [0.04, 64.08]
Subtotal (95% CI)	**2**	**4**			**100.0 %**	**1.67 [0.04, 64.08]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.27 (P = 0.78)						
6 Nucleus accumbens stimulation						
Kowski 2015	4	4	0 (1)		100.0 %	1.00 [0.14, 7.10]
Subtotal (95% CI)	**4**	**4**			**100.0 %**	**1.00 [0.14, 7.10]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P = 1.0)						
7 Closed-loop ictal onset zone stimulation						
Morrell 2011	97	94	1.5783 (1.5425)		100.0 %	4.85 [0.24, 99.64]
Subtotal (95% CI)	**97**	**94**			**100.0 %**	**4.85 [0.24, 99.64]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
Test for subgroup differences: Chi² = 1.55, df = 6 (P = 0.96), I² =0.0%						

Analysis 2.2. Comparison 2 Stimulation versus sham stimulation - sensitivity analyses, Outcome 2 Responder rate RR.

Review: Deep brain and cortical stimulation for epilepsy

Comparison: 2 Stimulation versus sham stimulation - sensitivity analyses

Outcome: 2 Responder rate RR



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Experimental N	Control N	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Subtotal (95% CI)	**4**	**4**			**100.0 %**	**4.00 [0.56, 28.40]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.39 (P = 0.17)						
7 Closed-loop ictal onset zone stimulation						
Morrell 2011	97	94	0.0819 (0.234)		100.0 %	1.09 [0.69, 1.72]
Subtotal (95% CI)	**97**	**94**			**100.0 %**	**1.09 [0.69, 1.72]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.35 (P = 0.73)						
Test for subgroup differences: Chi^2 = 3.30, df = 6 (P = 0.77), I^2 =0.0%						

Analysis 2.3. Comparison 2 Stimulation versus sham stimulation - sensitivity analyses, Outcome 3 Seizure freedom OR 0.25.

Review: Deep brain and cortical stimulation for epilepsy

Comparison: 2 Stimulation versus sham stimulation - sensitivity analyses

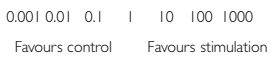
Outcome: 3 Seizure freedom OR 0.25

Study or subgroup	Experimental N	Control N	log [Odds Ratio] (SE)	Odds Ratio IV,Fixed,95% CI	Weight	Odds Ratio IV,Fixed,95% CI
1 Anterior thalamic nucleus						
Fisher 2010	54	55	-1.5912 (2.1992)		100.0 %	0.20 [0.00, 15.17]
Subtotal (95% CI)	**54**	**55**			**100.0 %**	**0.20 [0.00, 15.17]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
2 Centromedian thalamic stimulation						
Fisher 1992	6	6	0 (1.523)		100.0 %	1.00 [0.05, 19.79]
Subtotal (95% CI)	**6**	**6**			**100.0 %**	**1.00 [0.05, 19.79]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P = 1.0)						
3 Cerebellar stimulation						
Van Buren 1978	5	5	0 (1.5428)		42.2 %	1.00 [0.05, 20.57]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Experimental N	Control N	log [Odds Ratio] (SE)	Odds Ratio IV,Fixed,95% CI	Weight	Odds Ratio IV,Fixed,95% CI
Velasco 2005	3	2	-0.3677 (2.9584)		11.5 %	0.69 [0.00, 228.30]
Wright 1984	9	9	0 (1.4708)		46.4 %	1.00 [0.06, 17.86]
Subtotal (95% CI)	**17**	**16**			**100.0 %**	**0.96 [0.13, 6.83]**
Heterogeneity: Chi² = 0.01, df = 2 (P = 0.99); I² =0.0%						
Test for overall effect: Z = 0.04 (P = 0.97)						
4 Hippocampal stimulation (1 to 3 months)						
McLachlan 2010	2	2	0 (1.6971)		39.9 %	1.00 [0.04, 27.83]
Tellez-Zenteno 2006	4	4	0 (1.5713)		46.5 %	1.00 [0.05, 21.75]
Velasco 2007	4	5	0.2113 (2.9027)		13.6 %	1.24 [0.00, 365.22]
Subtotal (95% CI)	**10**	**11**			**100.0 %**	**1.03 [0.13, 8.41]**
Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² =0.0%						
Test for overall effect: Z = 0.03 (P = 0.98)						
5 Hippocampal stimulation (4 to 6 months)						
Wiebe 2013	2	4	0.636 (2.9461)		100.0 %	1.89 [0.01, 608.05]
Subtotal (95% CI)	**2**	**4**			**100.0 %**	**1.89 [0.01, 608.05]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.22 (P = 0.83)						
6 Nucleus accumbens stimulation						
Kowski 2015	4	4	0 (1.6971)		100.0 %	1.00 [0.04, 27.83]
Subtotal (95% CI)	**4**	**4**			**100.0 %**	**1.00 [0.04, 27.83]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P = 1.0)						
7 Closed-loop ictal onset zone stimulation						
Morrell 2011	97	94	2.1867 (2.1132)		100.0 %	8.91 [0.14, 560.31]
Subtotal (95% CI)	**97**	**94**			**100.0 %**	**8.91 [0.14, 560.31]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
Test for subgroup differences: Chi² = 1.63, df = 6 (P = 0.95), I² =0.0%						

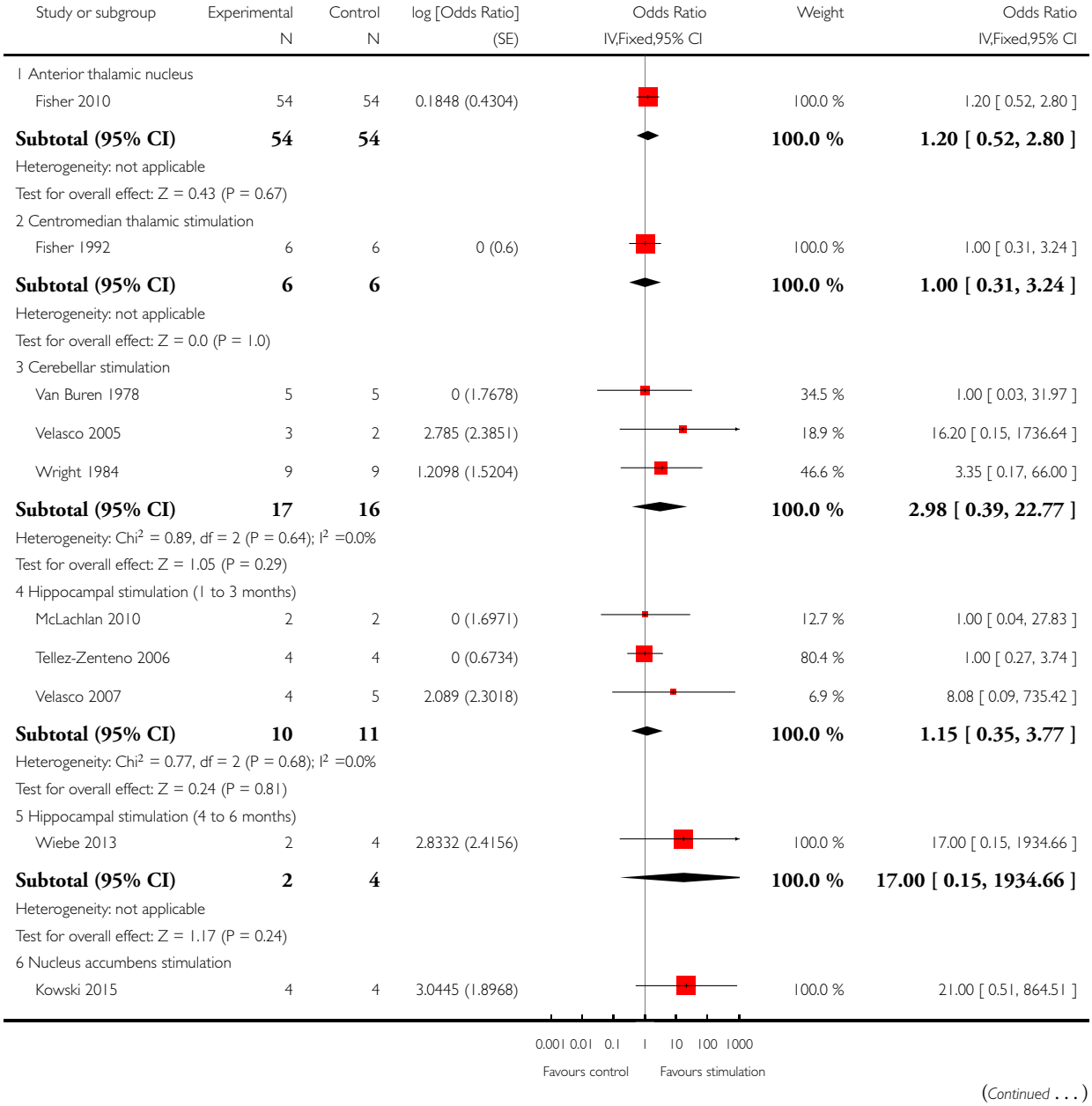


Analysis 2.4. Comparison 2 Stimulation versus sham stimulation - sensitivity analyses, Outcome 4 Responder rate OR 0.25.

Review: Deep brain and cortical stimulation for epilepsy

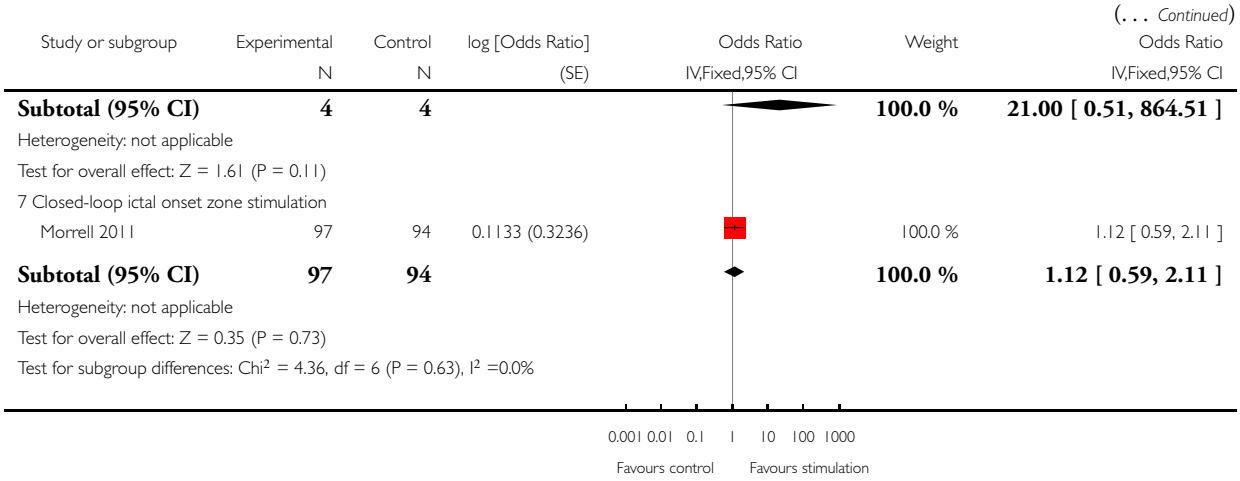
Comparison: 2 Stimulation versus sham stimulation - sensitivity analyses

Outcome: 4 Responder rate OR 0.25



(*Continued . . .*)

(. . . *Continued*)

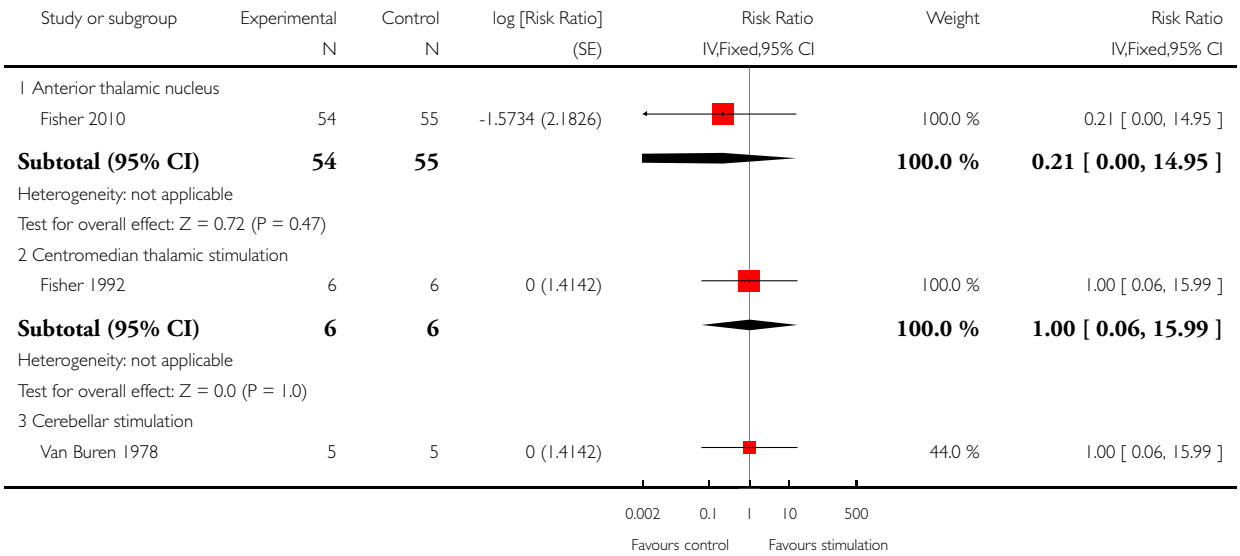


Analysis 2.5. Comparison 2 Stimulation versus sham stimulation - sensitivity analyses, Outcome 5 Seizure freedom RR 0.25.

Review: Deep brain and cortical stimulation for epilepsy

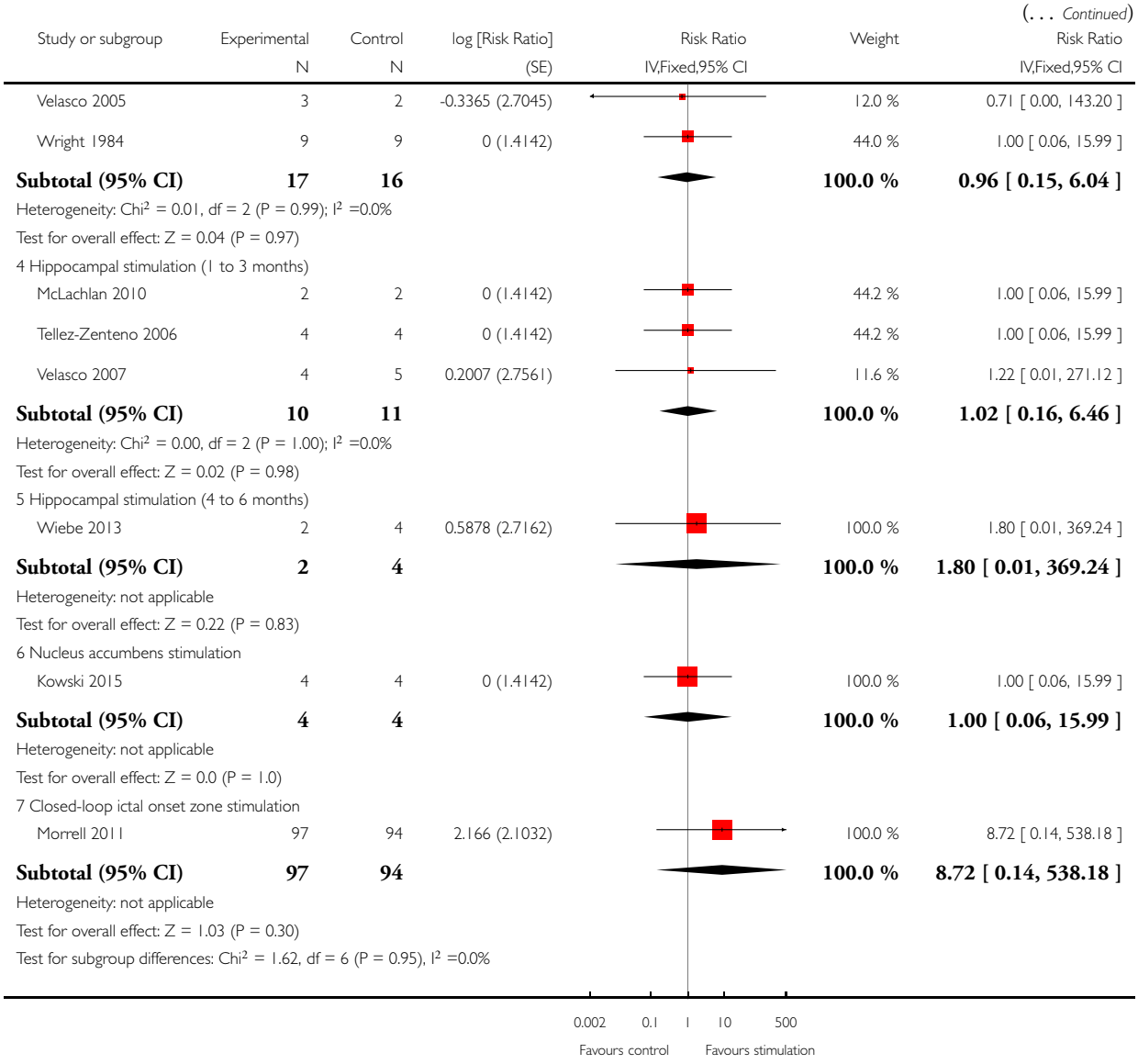
Comparison: 2 Stimulation versus sham stimulation - sensitivity analyses

Outcome: 5 Seizure freedom RR 0.25



(*Continued* . . .)

(. . . *Continued*)

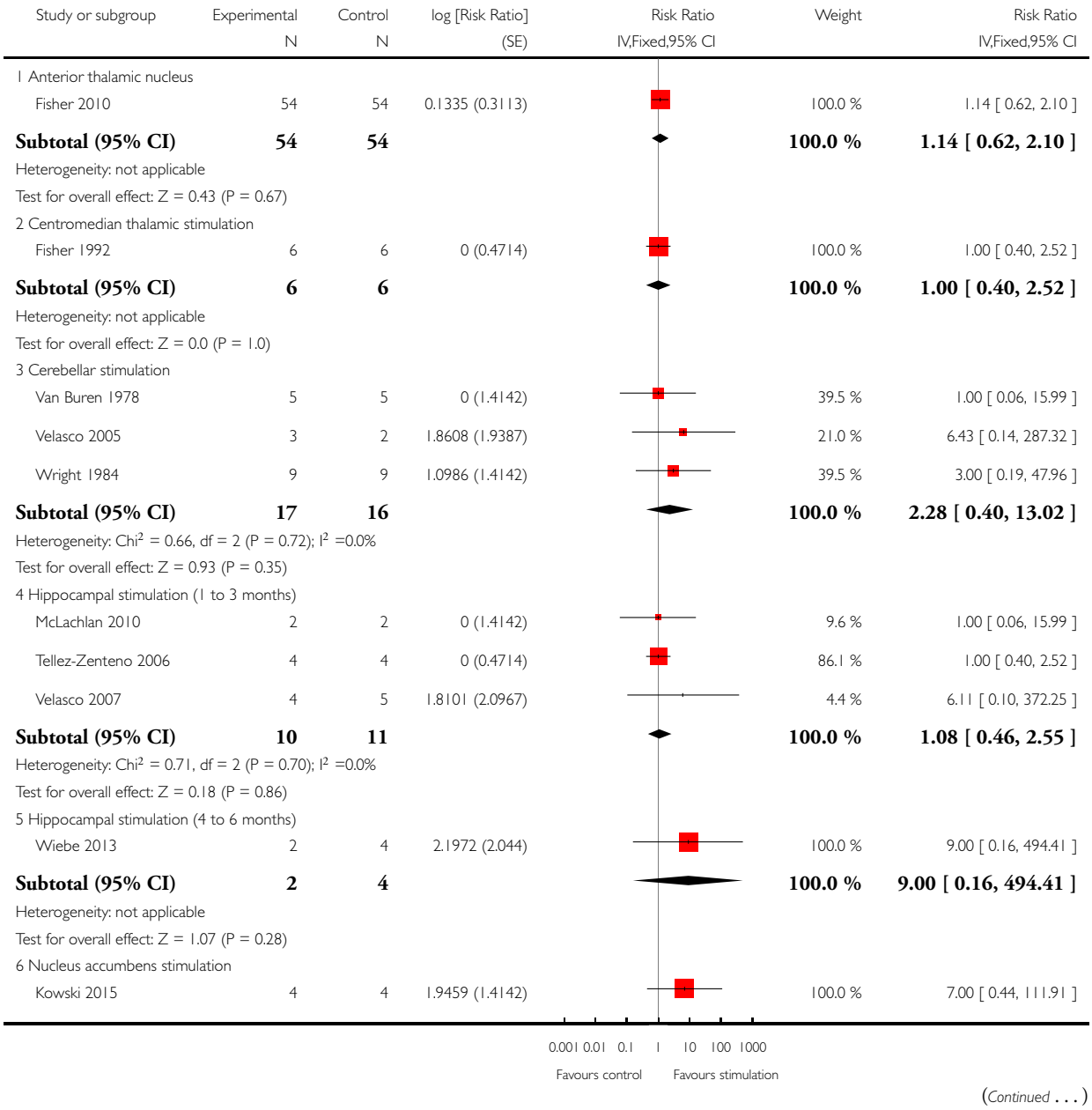


Analysis 2.6. Comparison 2 Stimulation versus sham stimulation - sensitivity analyses, Outcome 6 Responder rate RR 0.25.

Review: Deep brain and cortical stimulation for epilepsy

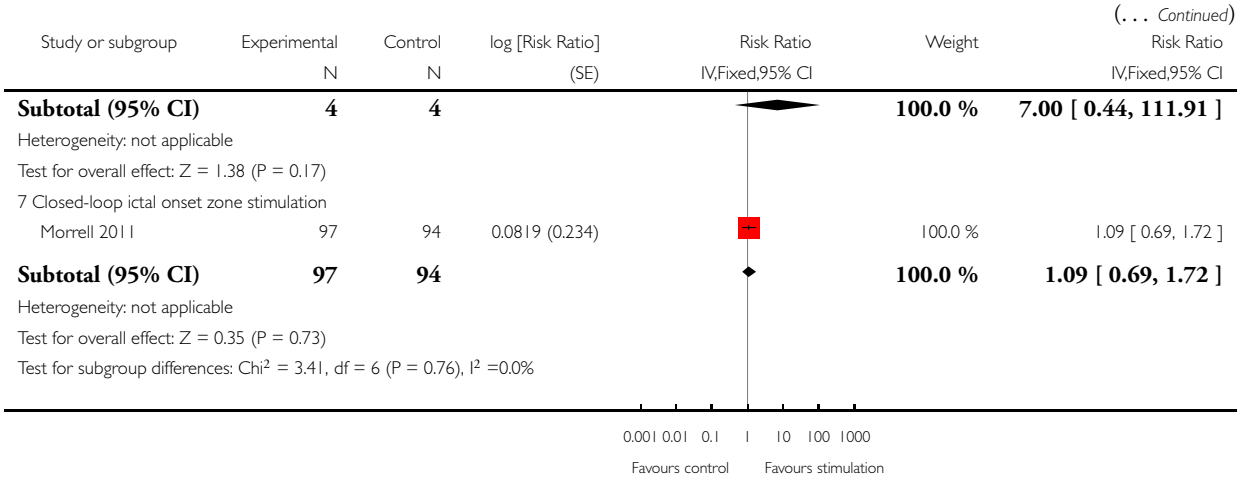
Comparison: 2 Stimulation versus sham stimulation - sensitivity analyses

Outcome: 6 Responder rate RR 0.25



(*Continued . . .*)

(. . . *Continued*)



APPENDICES

Appendix 1. Calculation of treatment effects in Van Buren 1978

We illustrate the way we calculated treatment effects for Van Buren 1978 taking patient two of their trial as an example. Van Buren 1978 reported 183% seizure frequency increase during the early double-blind stimulation ON period, a 125% increase during the late double-blind stimulation ON period, a 812% increase during the early double-blind stimulation OFF period and finally a 156% increase during the late double-blind stimulation OFF period. This can be formulated as 283%, 225%, 912% and 256% of baseline seizure frequency, respectively. Comparing stimulation ON to stimulation OFF periods with regard to baseline seizure frequency would result in a 330% seizure reduction with stimulation ON [(283-912+225-256)% x ½]. As four out of five patients' seizure frequency increased during the trial (more accurate seizure detection? spontaneous evolution of their disease?), we decided to directly compare stimulation ON to stimulation OFF periods to avoid treatment effects > 100%. For patient two, this results into 69% (1-[283/912]) and 12% (1-[225/256]) seizure frequency reductions during early and late double-blind evaluations respectively, or a mean 41% ([69+12)% x ½) reduction in seizure frequency across both periods. Responders during stimulation ON periods were defined as participants experiencing a ≥ 50% seizure frequency reduction with regard to stimulation OFF periods (direct comparison), whereas the inverse definition was used to define responders during stimulation OFF periods.

Appendix 2. Search strategies

1. Cochrane Epilepsy Group Specialized Register search strategy

#1 MeSH DESCRIPTOR Deep Brain Stimulation Explode All
#2 (cort* OR brain OR thalam* OR hippocamp* OR cerebel* OR cerebr*) NEAR4 stimul*
#3 MeSH DESCRIPTOR Vagus Nerve Stimulation Explode All
#4 MeSH DESCRIPTOR Transcranial Magnetic Stimulation Explode All
#5 ("transcranial magnetic stimulation" OR rTMS OR "vagus nerve stimulation" OR "vagal nerve stimulation"):TI
#6 #3 OR #4 OR #5
#7 #2 NOT #6
#8 #1 OR #7

2. CENTRAL search strategy

#1 MeSH descriptor Epilepsy explode all trees
#2 MeSH descriptor Seizures explode all trees
#3 epilep* OR seizure* OR convulsion*
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Deep Brain Stimulation explode all trees
#6 stimul*
#7 (#5 OR #6)
#8 (#4 AND #7)

3. PubMed search strategy

Our search strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE (sensitivity-maximizing version, 2008 revision; Pubmed format) (Lefebvre 2011).
#1 randomized controlled trial [pt]
#2 controlled clinical trial [pt]
#3 random* [tiab]
#4 placebo [tiab]
#5 sham [tiab]
#6 trial [tiab]
#7 groups [tiab]
#8 blind* [tiab]
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 animals [mh] NOT humans [mh]
#11 (#9 NOT #10)
#12 epilepsy [MeSH]
#13 seizures [MeSH]
#14 epileps* OR epilept*
#15 seizure*
#16 convulsion*
#17 (#12 OR #13 OR #14 OR #15 OR #16)
#18 deep brain stimulation [MeSH]
#19 stimulat* OR stimuli* OR stimulu*
#20 (#18 OR #19)
#21 (#11 AND #17 AND #20)

4. ClinicalTrials.gov

Epilepsy in the Condition
AND Stimulation in the Intervention

5. WHO International Clinical Trials Registry Platform ICTRP

Epilepsy in the Condition
AND Stimulation in the Intervention
Recruitment status is ALL

Appendix 3. Quality of life in Tellez-Zenteno 2006

Tellez-Zenteno 2006 reported mean QOLIE-89 scores of 57 (standard deviation (SD) 47), 55 (SD 33) and 27 (SD 60) during baseline, stimulation ON and stimulated OFF periods. These scores are based on repeated testing (once per month) in three patients, resulting in 9 QOLIE-89 scores in total. Tellez-Zenteno 2006 also reported median QOLIE-89 scores (with corresponding interquartile ranges), being 57 (24 to 90), 64 (30 to 78) and 61 (39 to 80) respectively. Taking into account the total number of QOLIE-89 scores (only nine), the different effect estimators and their corresponding measures of variability, we assume that the authors switched figures for the QOLIE-89 score during the stimulation OFF period, the mean being 60 and 27 representing the standard deviation. Indeed, it is impossible to calculate a mean score of 27 when the median is 61 and the interquartile range (39 to 80), with only nine measurements in total.

WHAT'S NEW

Last assessed as up-to-date: 5 November 2016.

Date	Event	Description
16 November 2016	New citation required but conclusions have not changed	Conclusions are unchanged.
5 November 2016	New search has been performed	Searched updated 5 November 2016; two new studies have been included and three studies have been added as ongoing studies

CONTRIBUTIONS OF AUTHORS

Mathieu Sprengers, Paul Boon, Evelien Carrette and Kristl Vonck co-operated in the literature search, data extraction, data analysis and in writing the review. Anthony Marson contributed in the case of disagreements.

DECLARATIONS OF INTEREST

Medtronic Inc has provided support in terms of free devices for a pilot study and an international multicentre randomized trial of hippocampal deep brain stimulation in epilepsy co-ordinated by Ghent University Hospital.

AGM: A consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool. Professor Tony Marson is Theme Leader for Managing Complex Needs at NIHR CLAHRC NWC.

SOURCES OF SUPPORT

Internal sources

- Dr. M. Miatton, Belgium.

Assistance in the interpretation of the neuropsychological data.

External sources

- National Institute for Health Research, UK.

This review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Epilepsy Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title of the review was changed from '*Deep brain and cerebellar stimulation for epilepsy*' to '*Deep brain and cortical stimulation for epilepsy*' as we thought neocortical stimulation also fits the scope of this review (which may be particularly relevant for future updates of the review).

The percentage seizure frequency reduction was added as an additional outcome measure. This was done in a prespecified way after one author involved in the writing of the protocol (Annelies Van Dycke) was replaced by another author (MS). The reason to do so was to allow a more precise estimation of the efficacy of the different invasive intracranial neurostimulation treatments.

We planned to express the treatment effect for dichotomous outcome measures by risk ratio (RR). However, for reasons outlined in the Methods section, we used odds ratios (OR) and performed a sensitivity analysis with RRs to evaluate any possible influence of this change.

As we judged that (future) trials comparing deep brain or cortical stimulation versus other neurostimulation treatments (e.g. vagus nerve stimulation, other intracranial target,...) might also be relevant to the reader and fit the scope of this review, this type of control group was added to the selection criteria.

We performed various sensitivity analyses and not all of these were mentioned in the initial protocol, including several post-hoc sensitivity analyses. See Methods section on Sensitivity analysis for more details.

INDEX TERMS

Medical Subject Headings (MeSH)

Anterior Thalamic Nuclei; Cerebral Cortex; Deep Brain Stimulation [instrumentation; *methods]; Electrodes, Implanted [adverse effects]; Epilepsy [*therapy]; Hippocampus; Mediodorsal Thalamic Nucleus; Nucleus Accumbens; Outcome Assessment (Health Care); Randomized Controlled Trials as Topic

MeSH check words

Humans

CHAPTER 7

Mechanism of action of DBS: acute experiments

Deep brain stimulation reduces evoked potentials with a dual time course in freely moving rats: potential neurophysiological basis for intermittent as an alternative to continuous stimulation

Sprengers M[1], Raedt R[1], Larsen LE[1], Delbeke J[1], Wadman WJ[2], Boon P[1], Vonck K[1].

[1] 4Brain, Department of Neurology, Ghent University Hospital, Ghent, Belgium

[2] Swammerdam Institute of Life Sciences, University of Amsterdam, The Netherlands

Epilepsia 2020, Apr 16. doi: 10.1111/epi.16498 (online ahead of print).

ABSTRACT

Objective: Deep brain stimulation (DBS) is an increasingly applied treatment for various neuropsychiatric disorders including drug-resistant epilepsy and may be optimized by rationalizing the stimulation protocol based on increased knowledge of its mechanism of action. We evaluated the effects of minutes to hours of hippocampal DBS on hippocampal evoked potentials (EPs) and local field potentials (LFPs) in freely moving male rats to further investigate some of the previously proposed mechanisms of action.

Methods: Hippocampal high-frequency (130 Hz) DBS was administered for 0, 1 or 6 min every 10 min for 160 min. Stimulation parameter settings were similar to those that had previously been shown to reduce seizures in epileptic rats. EPs and LFPs were recorded in the stimulation-free intervals. We investigated both the immediate temporary effects of 1 or 6 min of DBS and the effects of 160 min intermittent DBS. Input-specificity was investigated by using two different stimulation electrodes.

Results: Relatively low DBS intensities corresponding to only 1.8% of the intensity evoking a maximum EP were required to prevent unintended seizure occurrence in healthy rats. Both 1 and 6 min of DBS caused input-specific short-lasting (<60s) reductions (5-7%) of the field excitatory postsynaptic potential (fEPSP) slope (p=0.005). We observed longer-lasting, input-specific EP reductions during the 160 min intermittent DBS, with statistically significant reductions (3-4%) of the fEPSP slope (p=0.009 to 0.018). The LFP spectrogram remained unaltered.

Significance: DBS induced both acute temporary effects compatible with axonal block and/or synaptic depression, and longer-lasting potentially cumulative EP reductions suggesting the involvement of homeostatic plasticity or long-term depression. This dual time course may parallel the different temporal patterns of improvement observed in clinical trials. The longer-lasting reductions provide a potential neurophysiological basis for the use of intermittent DBS – as typically used in epilepsy patients – as an alternative to continuous DBS.

INTRODUCTION

Deep brain stimulation (DBS) is used as a treatment for various neuropsychiatric disorders, including drug-resistant epilepsy. Despite extensive research its mechanism of action remains incompletely understood which limits the development of more rational and efficacious stimulation protocols. Various hypotheses on its mode of action have been proposed, including depolarization block, synaptic depression, synaptic and recurrent inhibition, axonal conduction block, overriding pathological activity by imposing new (stimulus-locked) activity, desynchronization and suppression of pathological oscillations, neuroplasticity, neurogenesis and neuroprotective effects [1-11].

The specific contribution of each of these mechanisms in patients treated with DBS remains unclear and could be both disease- and target-specific. Prior studies support the simultaneous involvement of different mechanisms.[6, 7] In contrast, other studies reported seemingly conflicting results highlighting the importance of the experimental setup. In this context, it should be noted that most of the previous studies on the mechanism of action of DBS focused on the basal ganglia network and Parkinson's disease, requiring caution when generalizing the findings to other targets and diseases.

An interesting technique to further investigate the mechanism of action of DBS is the measurement of monosynaptically evoked field potentials (EPs) of a neuronal population following administration of an electrical stimulus to its afferent axons. It allows to measure changes in postsynaptic input (field excitatory postsynaptic potential, fEPSP), output (population spike, PS) as well as intrinsic excitability (PS-fEPSP relationship). EPs are thus appropriate to study several of the proposed modes of action including synaptic depression, synaptic inhibition, axonal block, neuroplasticity and depolarization block.

The majority of previous EP studies on the mechanism of action of DBS showed short-lasting, strong EP reductions.[7, 9, 12-18] In some other studies, however, longer-lasting but heterogeneous neuroplasticity changes were observed including short- and long-term potentiation, as well as long-term depression (LTD).[19-22] All these studies, however, only evaluated the effects of seconds to minutes of DBS. Furthermore, they were all performed in *in vitro* preparations or urethane-anesthetized rats which could impact the obtained effects, especially those relevant for disorders such as epilepsy.[23, 24]

The aim of our study was to evaluate the effects of high-frequency DBS on EPs in the hippocampus of freely moving rats. We decided to target the hippocampus as 1) hippocampal DBS previously reduced seizures both in humans and rats and 2) the hippocampus has an orderly laminated neuronal arrangement allowing the recording of high-quality EPs.[25-28] We hypothesized that DBS would lead to strong EP reductions as demonstrated in the aforementioned studies.[7, 9, 12-15, 17, 18] Similar to these studies we investigated the acute temporary effects of short-term DBS in the order of minutes. In addition, we also investigated whether longer-lasting and/or cumulative effects occurred with several hours of DBS as effects in clinical trials have increased or varied with longer stimulation durations.[1, 2, 25, 28-30] We recorded hippocampal local field potentials (LFPs) to investigate the occurrence of desynchronization or other changes in the spectrogram.

METHODS

Twenty-one male Sprague-Dawley rats (Harlan Laboratories, IN, USA) were treated according to the European Ethics Committee guidelines (2010/63/EU). Animals were housed under environmentally controlled conditions. The study protocol was approved by the Animal Experimental Ethical Committee of Ghent University Hospital (ECD 13/63).

Surgery

Rats (350-400g) were anesthetized using an isoflurane/oxygen mixture. Besides two custom-made epidural electrodes serving as ground/reference electrode, three custom-made depth electrodes were implanted (all coordinates in mm): a quadripolar recording electrode in the CA1 region (anteroposterior (AP) -5.0, mediolateral (ML) +3.0, approximate depth -3.2), a quadripolar stimulation electrode at the Schaffer collaterals (EP stimulation electrode, EpSE) (AP -3.0, ML 1.5, approximate depth -3.6) and an additional bipolar stimulation electrode (AddSE) implanted in close proximity to the recording electrode (AP -4.55, ML +2.8, approximate depth -3.6).[31] The recording electrode consisted of four twisted polyimide-coated stainless steel wires (diameter of 70 µm, intercontact distance 225 µm). The EpSE and AddSE were made of four (intercontact distance 300 µm) and two (tip separation 850 µm to span most of the hippocampus in the coronal plane) twisted PFA-coated platinum-iridium wires (diameter 140 µm, A-M Systems), respectively. The depth of the EpSE and recording electrode were adjusted under electrophysiological guidance to evoke a maximal PS. The upper contact of the AddSE was stereotactically implanted in the Schaffer collaterals at the stratum radiatum and its depth was adapted individually for each rat based on the dorsoventral coordinates of the recording electrode. To characterize the relationship between both stimulation electrodes a paired-pulse protocol was performed with the first pulse administered via the AddSE and the second via the EpSE. This protocol did not yield paired-pulse facilitation of low-intensity EPs, indicating that different axons were stimulated. Electrode leads were collected in a custom-made connector block that was fixed to the skull with anchor screws and dental acrylic cement. Buprenorphine (0.03 mg/kg) and meloxicam (1 mg/kg) were used for postoperative analgesia.

Recording and stimulation setup

After a three-week postoperative recovery period, animals were connected to the setup through a commutator allowing free movement. LFPs were acquired with an epidural electrode as reference. Analog signals were high-pass filtered at 0.1 Hz, amplified 248 times and digitized by a USB-6259 NI-DAQ card (National Instruments, TX, USA). EPs were sampled at 20 kHz and LFPs at 5 kHz. Electrode impedances were verified with a < 30 nA test pulse and remained stable throughout the experiment. They never exceeded 65 kΩ allowing the constant-current stimulators (40V maximum output) to generate up to at least 615 µA currents in all animals.

Stimulation parameter settings

Bipolar biphasic charge-balanced square-wave pulses with a pulse width of 200 µs were used for EP evocation, unless mentioned otherwise. The two electrode contacts of the quadripolar EpSE that evoked EPs with the best quality at the lowest intensity were chosen as cathode-anode pair. EP intensities were scaled in percentage values between the threshold to evoke an fEPSP (= 0%) and the

intensity giving rise to the maximum PS amplitude (= 100%) as determined from input-output curves (0-600 µA). Paired pulses had a 20 ms interpulse interval.

DBS (frequency 130 Hz, pulse width 50 µs) was delivered either through the EpSE (same cathode-anode pair as for the EPs) or through the AddSE (upper electrode contact as cathode) which allowed to study the input-specificity of the DBS-induced EP changes.

Stimulation intensity was determined individually for each rat and set just above the threshold for evoking a clear summated fEPSP. This threshold was determined by slowly (2 µA increments) increasing the stimulation intensity above the single stimulus EP threshold until 130 Hz stimuli evoked a clear and consistent summated fEPSP. In previous trials we used 60% of the afterdischarge (= electroencephalographic seizure) threshold. Using the summated fEPSP threshold in this study – typically observed around this 60% afterdischarge threshold in a pilot study – avoided the need for repeated seizure provocation and guaranteed that the hippocampal network was indeed recruited. To compare the intensities in the present to previous studies, the summated fEPSP and afterdischarge threshold were determined once on the same day in the beginning of the experiment.[26, 27] The latter was determined by 10-second DBS trains with gradually increasing stimulus intensities (10 µA increments) until seizure activity occurred, with a 1-minute interval between successive trains.

Experimental protocol

The experimental protocol consisted of repetitions of the same basic block (figure 1a). Four baseline blocks without DBS were followed by 16 blocks with 0 (sham), 1 or 6 min of DBS. An entire block lasted 10 min and started with 0 (baseline blocks and sham DBS), 1 or 6 min of DBS. During the subsequent DBS OFF-time EPs and 18-seconds long LFP sweeps were alternatingly recorded. The first EP was measured 2 (if DBS was administered via the AddSE) or 100 ms (DBS via the EpSE, longer interval due to hardware limitations) after the final DBS pulse and EPs were then repeatedly evoked every 20 seconds. In total 12 EPs with four different and alternating intensities (10, 25, 50 and 80%; 3 repetitions) were obtained. In this series of 12 EPs the position of each stimulus intensity trial alternated over successive blocks so that every intensity was equally used for every position within the block.

The design of the experiment allowed to average EPs with the same intensity in two different ways. EPs belonging to different blocks but with the same position within their block could be averaged (4 repetitions per intensity per position) to study the acute temporary effects 2-100 ms to 220 s after 1 or 6 min of DBS. In addition, the design also allowed to investigate longer-lasting and potentially cumulative effects of 160 min of 1/9 and 6/4 min ON/OFF intermittent DBS by averaging EPs with identical intensities belonging to the same block (3 repetitions per intensity per block) and comparing averages over 16 successive blocks.

Five different DBS regimens were delivered: sham DBS and 1 or 6 min DBS via either the EpSE or the AddSE. Each regimen was repeated twice on separate days and results of both days were averaged per rat prior to group level averaging to minimize variability. The EP threshold and maximum and the DBS intensity were repeatedly determined prior to every experiment. To minimize the influence of the behavioral state of the animal, the timing of all recordings was the same every day (10 am-4.30 pm). Animals were asleep most of the time.

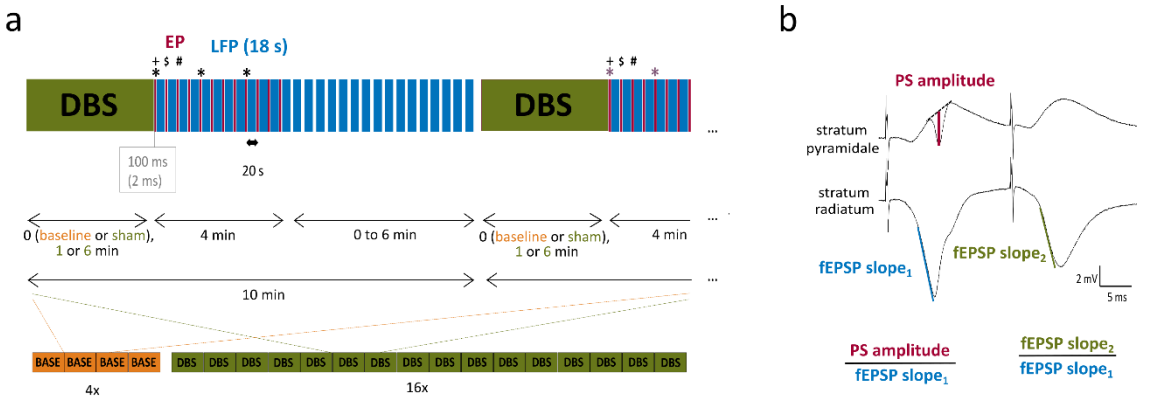


Figure 1. A schematic illustration of the experimental design and overview of the different EP outcome parameters. **(a)** The experiment consisted of repetitions of the same basic blocks, each lasting 10 minutes. Four baseline blocks (no DBS) were followed by 16 DBS blocks with 0 (sham), 1 or 6 min DBS. Twelve EPs with four different intensities (10, 25, 50 and 80% EPs) were recorded every 20 seconds in the stimulation-free interval, starting 2 or 100 ms after the final DBS pulse. Eightteen seconds of LFP were recorded in between the EPs. EPs with the same stimulus intensity could be averaged based on their position within each block (e.g. '+' versus '$' versus '#') to evaluate the immediate temporary DBS effects. Alternatively, EPs with the same stimulus intensity could be averaged per block and compared over successive DBS blocks (e.g. '*' (black) versus '*' (purple)) to evaluate longer-lasting and potential cumulative DBS effects. Note that, although not the case in the figure because of illustrative reasons, the position of each stimulus intensity trial in the series of 12 EPs alternated over successive blocks so that every intensity was equally used for every position within the block. **(b)** The EP outcome parameters evaluated in the experiments include the field excitatory post-synaptic potential (fEPSP) slope (i.e. fEPSP slope$_1$), the population spike (PS) amplitude, the fEPSP slope paired-pulse ratio (i.e. fEPSP slope$_2$ / fEPSP slope$_1$) and the PS amplitude / fEPSP slope ratio.

EP analysis

All data were processed using Matlab (MathWorks, Natick, USA). The fEPSP slope was measured in the stratum radiatum by fitting a slope to the falling phase of the fEPSP waveform using the least squares method. The PS amplitude was measured in the pyramidal cell layer and defined as the vertical distance between the negative peak of the PS and the tangent connecting the positive peaks before and after the PS (figure 1b). We further calculated the PS amplitude/fEPSP slope ratio and paired-pulse (fEPSP slope$_2$/fEPSP slope$_1$) relationship.

Spectral analysis

To isolate local activity in the stratum radiatum, the difference between the signals in the stratum radiatum and the upper hippocampal electrode contact recording a PS was calculated. A sensitivity analysis using the original signals (referenced to the scalp electrode) yielded the same results. LFP sweeps excessively affected by artifacts were rejected automatically when the total power reached more than 3 standard deviations from the mean. The signals were filtered offline between 2-100 Hz with a first order Butterworth filter. Each 18-seconds LFP sweep was split into 1-second windows overlapping by 0.5 s. Using the Fast Fourier algorithm for each 1-second window yielded 19 power spectra that were averaged to provide one power spectrum per LFP sweep.

Statistical analysis

Prior to any statistical analysis all EP outcome measures were normalized to their mean baseline values for each individual rat. Power spectra were normalized to the baseline mean total power. Statistical analyses were performed using SPSS Statistics 25 (IBM Corporation) and Sigmaplot 11.0 (Systat Software Inc).

A repeated measures two-way ANOVA was used to evaluate the effects of DBS. The repeated-measures factors were Time and Stimulation Condition (0, 1 or 6 min DBS). A Greenhouse-Geisser correction was used in cases where the assumption of sphericity was violated as indicated by the Mauchly's Test of Sphericity ($p<0.05$). Statistical significance was defined as $p<0.05$. A Holm-Sidak correction was used for post-hoc testing. Values are expressed as mean +/- standard error, unless otherwise stated.

RESULTS

1. DBS intensity

DBS intensity was set just above the summated fEPSP threshold. An example of a summated fEPSP is shown in figure 2. After the initial summation and despite ongoing stimulation, the summated fEPSP decreased in amplitude and faded within 100-200 ms after DBS onset. Mean DBS intensity was 79.0 µA (standard deviation (SD) 24.8) for the EpSE and 84.1 µA (SD 23.9) for the AddSE. In most rats, application of isolated single pulses with the summated fEPSP threshold intensity only evoked a barely perceptible deflection that could only be distinguished after averaging multiple EPs. DBS intensity was on average 12.5 µA (SD 9.3) above the single EP threshold (evoked with 50-µs pulses) roughly corresponding to 1.8% of the maximum EP intensity. With an electrode impedance of up to 65 kΩ and a maximum stimulator output of 40V, 200-µs pulses were required to determine the maximum EP intensity after which a 200-to-50 µs pulse width conversion factor of 2.71 was applied (for more details, see figure 3).

The summated fEPSP threshold corresponded to 66.2% (SD 12.1) of the afterdischarge threshold. Nonetheless, seizures were unintentionally provoked at stimulation onset in 4.4% of all DBS sessions. Rats with seizures were excluded from statistical analysis.

2. DBS and EPs via the same electrode (EpSE)

A. Immediate temporary effects of 1 or 6 min of continuous DBS

In freely moving rats (n=16) administering 1 or 6 min of DBS was associated with a small but statistically significant short-lasting reduction of the 10% fEPSP slope compared to sham stimulation (Condition x Time: $F(22,330)=2.015$, $p=0.005$). The effect size was similar for both DBS durations but the effect lasted longer after 6 compared to 1 min of DBS. Hundred milliseconds after 1 min of DBS, the 10% fEPSP slope was 6.8 +/- 2.6% lower compared to sham stimulation ($p=0.002$). This effect disappeared within 20 seconds ($p=0.13$) (see figure 4a). In contrast, the 4.4 +/- 3.0 to 5.9 +/- 2.5% reduction observed after 6 min of DBS ($p=0.006$ to 0.045) only disappeared after 60 seconds ($p=0.34$) (see figure 4b), with a statistically significant 6.1 +/- 2.2% difference between the 10% fEPSP slopes 40 seconds after 1 versus after 6 min of DBS ($p=0.005$).

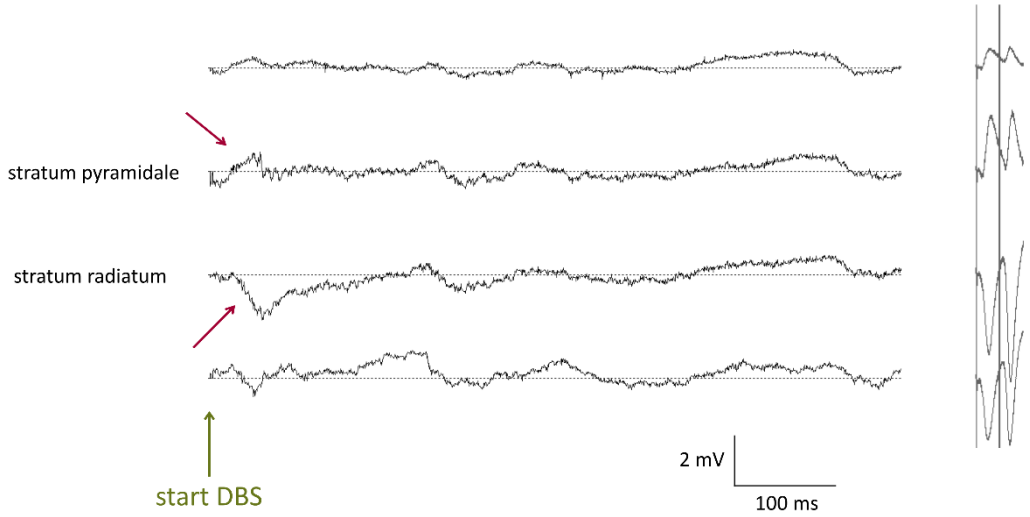


Figure 2. Representative example of a summated field excitatory postsynaptic potential (fEPSP) (red arrows) at the onset of DBS (green arrow). The four LFP traces shown correspond to the four contacts of the recording electrode, with the second and third contact being located in the stratum pyramidale and stratum radiatum, respectively. Stimulation artifacts were removed to allow a better appreciation of the summated fEPSP. Similar to the 10% fEPSP (right), the summated fEPSP is positive in the stratum pyramidale and negative in the stratum radiatum. Note the difference in amplitude between the summated fEPSP and the 10% fEPSP.

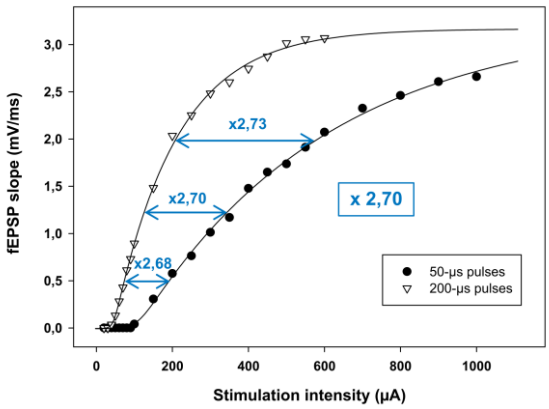


Figure 3. Conversion of 50- to 200-µs pulses. The 2.71 'conversion factor' used to compare 50- to 200-µs pulses was inferred from input-output curves with 50- and 200-µs pulses in 8 rats. Three-parameter sigmoidal curves (f=a/(1+exp(-(x-x0)/b)) were fitted to the input-output curves. The stimulation intensities required to reach three different fEPSP slope values in the exponential phase of the curve (0.50, 1.25 and 2.00 mV/ms in this example) were compared in input-output curves obtained with 50- and 200-µs pulses. The corresponding ratios (2.68, 2.70 and 2.73 in this example) were then averaged (2.70 in this example). This was done for 8 eight rats, yielding a mean 2.71 conversion factor (standard deviation 0.22).

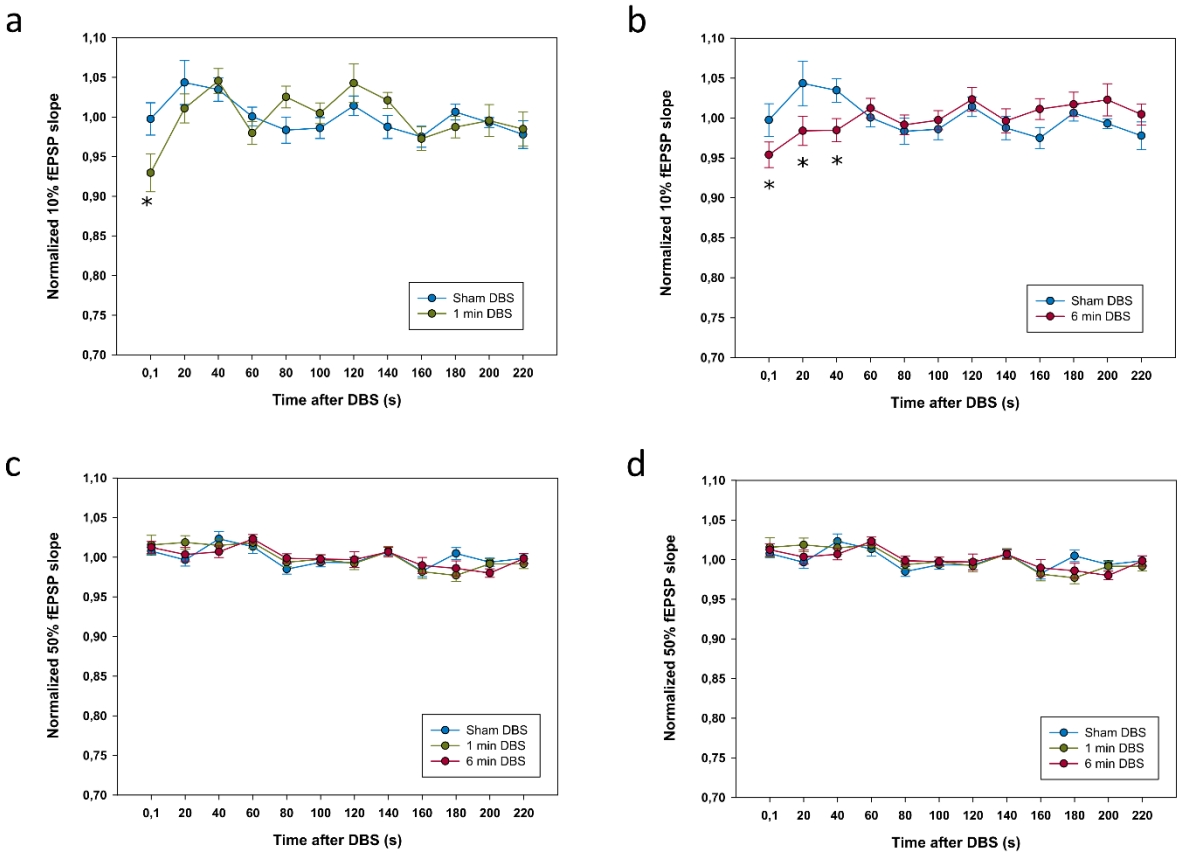


Figure 4. Immediate temporary effects of 1 or 6 minutes of DBS compared to sham DBS on the evoked potentials evoked via the same electrode. Statistically significant reductions were found for the 10% fEPSP slope after 1 **(a)** and 6 **(b)** minutes of DBS, but not for the other EP outcome parameters including the 50% fEPSP slope **(c)** and the 80% PS amplitude (**d)**. Mean normalized values +/- standard error of the mean are plotted over time (0.1 to 220 s after DBS). Significant differences are marked with an asterisk.

No significant effects could be demonstrated after either 1 or 6 min of DBS for all the other EP outcome parameters. These include the higher intensity (25, 50 and 80%) fEPSP slopes, the PS amplitude, the fEPSP slope/PS amplitude ratio and the fEPSP slope paired-pulse relationship (see figure 4c-d for the 50% fEPSP slope and the 80% PS amplitude).

There were no immediate temporary effects on the hippocampal LFP 2-100 Hz spectrogram after 1 or 6 min of DBS, as shown in figure 5.

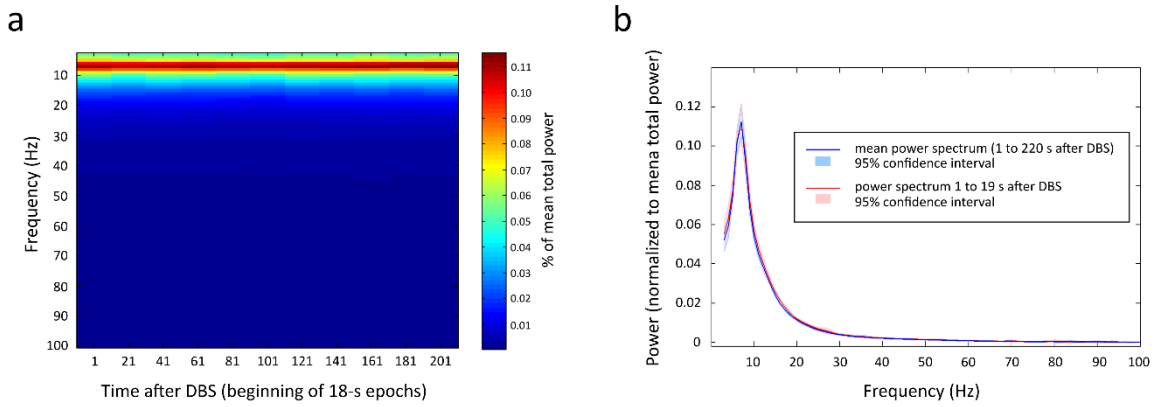


Figure 5. There were no acute temporary changes in the hippocampal LFP power spectrum (2-100 Hz) after 6 min of DBS. The graph in **(a)** illustrates the evolution of the normalized power spectrum from 1 to 219 s after DBS in 18-s epochs. Panel **(b)** shows more detailed normalized power spectra of the first 18-s epoch after DBS and the mean power spectrum from 1 sec to 219 s after DBS (shaded areas indicate the respective 95% confidence intervals). Statistical analysis could not demonstrate significant differences between sham and 6 min of DBS in total (2-100 Hz), theta (4-12 Hz) , beta (13-30 Hz) or gamma (31-100 Hz) band power.

B. Longer-lasting / cumulative effects during 160 min of intermittent DBS

Compared to sham stimulation fEPSP slopes and PS amplitudes for all delivered intensities were lower during both 1/9 and 6/4 min ON/OFF intermittent DBS (figure 6). Statistical significance was demonstrated for the 50% ($F(2,450)=4.459$, $p=0.020$) and 80% ($F(2,450)=4.267$, $p=0.023$) fEPSP slopes, the 2 outcome parameters displaying the lowest degree of variance. Compared to sham stimulation 1/9 min intermittent DBS resulted in a 3.3 +/- 0.5% ($p=0.018$) lower 50% fEPSP slope and 6/4 min intermittent DBS in a 3.6 +/- 0.5% ($p=0.012$) lower 50% and a 2.5 +/- 0.3% ($p=0.009$) lower 80% fEPSP slopes (figure 6b), respectively.

The 80% fEPSP slope reduction was accompanied by a significant reduction in paired-pulse depression ($F(2,450)=5.502$, $p=0.009$). There were no statistically significant changes in the lower intensity paired-pulse ratios nor in the 50 and 80% PS amplitude/fEPSP slope relationships.

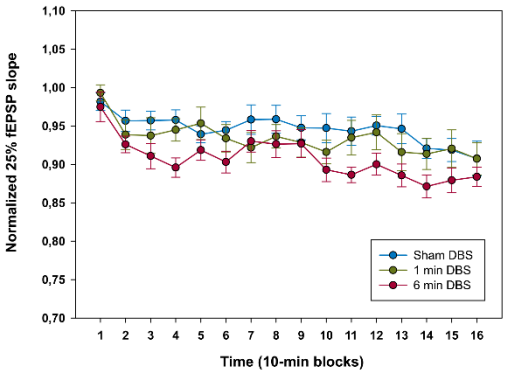
Visual inspection of the time course of the observed effects could suggest that the longer-lasting effects mainly arose after two to three stimulation cycles (figure 6a-b). However, when not incorporating the four baseline measurements formal statistical testing could not reveal statistically significant Time x Condition interactions.

No longer-lasting or cumulative effects could be demonstrated in the hippocampal LFP spectrogram.

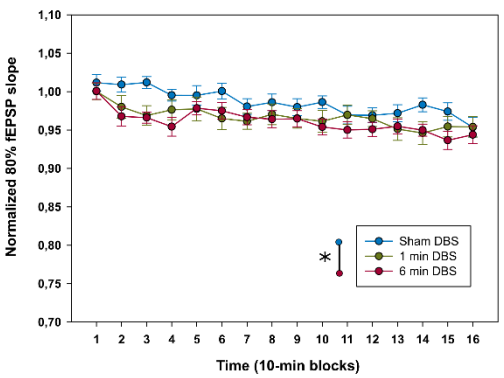
3. DBS (AddSE) and EPs (EpSE) through different electrodes

To investigate the input-specificity of the changes encountered, separate experiments were performed with two different electrodes for DBS administration (AddSE) and EP evocation (EpSE).

a



b



c

	10%	25%	50%	80%
fEPSP slope	F=1.362, p=0.27	F=2.533, p=0.10	**F=4.459, p=0.02**	**F=4.267, p=0.02**
1 min DBS vs sham	-2.9 ± 0.8%	-1.2 ± 0.6%	**-3.3 ± 0.5%**	-1.9 ± 0.4%
6 min DBS vs sham	-4.9 ± 1.1%	-3.9 ± 0.6%	**-3.6 ± 0.4%**	**-2.5 ± 0.3%**
6 vs 1 min DBS	-2.0 ± 1.2%	-2.7 ± 0.7%	-0.2 ± 0.5%	-0.6 ± 0.4%
Paired-pulse fEPSP slope ratio	F=0.351, p=0.71	F=1.165, p=0.33	F=1.947, p=0.16	**F=5.502, p=0.009**
1 min DBS vs sham	-1.5 ± 0.8%	+1.9 ± 0.5%	+5.0 ± 1.0%	**+4.0 ± 0.5%**
6 min DBS vs sham	-1.2 ± 0.8%	+2.6 ± 0.5%	+5.5 ± 1.1%	**+3.3± 0.5%**
6 vs 1 min DBS	+0.2 ± 0.8%	+0.7 ± 0.7%	+0.5 ± 0.9%	-0.6± 0.5%
PS amplitude	-	-	F=1.572, p=0.22	F=0.609, p=0.55
1 min DBS vs sham			-5.9 ± 3.0%	+0.6 ± 1.1%
6 min DBS vs sham			-15.3 ± 2.5%	-2.9 ± 0.9%
6 vs 1 min DBS			-9.4 ± 2.3%	-3.3 ± 1.1%
PS amplitude / fEPSP slope ratio	-	-	F=1.189, p=0.32	F=0.520, p=0.60
1 min DBS vs sham			-2.8 ± 3.0%	+2.7 ± 1.0%
6 min DBS vs sham			-12.5 ± 2.4%	-0.4 ± 0.9%
6 vs 1 min DBS			-9.7 ± 2.2%	-3.1 ± 1.0%

Figure 6. Effects of 160 min of intermittent DBS with a 1/9 and 6/4 min ON/OFF duty cycle on the evoked potentials, compared to sham stimulation. In **(a)** and **(b)** mean 25% **(a)** and 50% **(b)** fEPSP slope values +/- standard errors are plotted over time. Statistical significance is indicated by an asterisk. The table in **(c)** provides an overview of the effects on all EP outcome parameters evaluated. The F(2,450)-values of the repeated measures two-way ANOVA and the corresponding p-values are listed for each outcome parameter. Mean differences ± standard error are given for the different pairwise comparisons. Statistically significant effects are marked in **bold** for the main F-value and the post-hoc tests using a Holm-Sidak correction.

Compared to sham stimulation, EPs evoked via the EpSE did not change after administering 1 or 6 min of AddSE DBS (n=15). Even when the first EP stimulus was given 2 ms after the last DBS pulse (thus mimicking measuring EPs during DBS given the 7.7 ms interpulse interval), no effects were found (n=13).

Similarly, 160 minutes of 1/9 min or 6/4 min ON/OFF intermittent DBS (n=15) did not change any of the studied outcome parameters.

DISCUSSION

We demonstrated that high-frequency hippocampal DBS modifies hippocampal EPs in freely moving rats. We observed a temporary, input-specific and short-lasting (<20-60 s) reduction of the 10% fEPSP slope after 1 to 6 min of DBS. Longer-lasting effects not subsiding between successive stimulation blocks were observed with 160 min of intermittent DBS. These fEPSP slope reductions indicate a decreased postsynaptic input and could contribute to the therapeutic effects of DBS, for example the seizure-suppressive effects in epilepsy as fEPSP slope increases have been demonstrated in the epileptic hippocampus.[32, 33] However, more research is needed to determine the clinical correlations of the observed fEPSP reductions, including potential side effects such as memory impairment.[34]

Previous studies have shown short-lasting temporary reductions of the (f)EPSP, the excitatory postsynaptic current and the PS amplitude after short-term DBS in *in vitro* preparations[9, 12, 14, 15, 17, 18] and anesthetized rats.[7, 13] In analogy to our findings, the EP reductions were also typically preceded by a short-lasting temporally summated fEPSP at stimulation onset.[9, 12, 14, 17, 18] This summated fEPSP probably results from repeated paired-pulse facilitations due to the successive administration of closely spaced stimulation pulses causing (amongst others) presynaptic calcium accumulation leading to increased neurotransmitter release.[35]

In previous studies, DBS was administered for 1 second to a couple of minutes and the EP reductions outlasted DBS for 2 seconds to several minutes. This is in the same range as in our study. However, in contrast to the relatively small 5-7% reduction of the 10% fEPSP slope we observed, the EP decreases in these studies were much larger ranging from 48 to >85%. Two factors may explain the difference in effect size. First, DBS was administered with much higher stimulation intensities in the previous studies (e.g. intensities evoking a PS with 75% of the maximal PS amplitude in Feng et al.[7, 13]). In our study the DBS intensity corresponded to only 1.8% of the maximum EP intensity. Although this may seem quite low, higher intensities seem to be poorly tolerated in the in vivo unanesthetized rat as evidenced by the unintended seizure provocation in 4.4% of all DBS sessions and even higher seizure incidences in a pilot trial with higher stimulation intensities. Furthermore, our DBS intensities corresponded to 66% of the afterdischarge threshold which is even slightly higher than the 60% afterdischarge threshold intensity applied in our previous hippocampal stimulation studies and that was shown to significantly reduce seizures in epileptic rats.[26, 27] Secondly, our first EP was evoked 100 ms after the final DBS pulse. In this 100-ms time window, partial recovery may have occurred.[13] For example, the antidromic PS reduction diminished from 80 to 40% within 100 ms after 1 min of 100 Hz DBS indicating partial recovery of the axonal conduction block.

Various mechanisms that can provoke a temporary reduction in postsynaptic input have been described in earlier DBS literature. From these, neurotransmitter depletion and/or axonal conduction block fit best with the temporal dynamics and the input-specificity observed in our study.[7, 9, 12, 13, 15, 17, 18, 35, 36] These mechanisms probably also prevent a runaway amplification of the summated fEPSP at the onset of stimulation. Synaptic inhibition due to activation of GABAergic presynaptic axon terminals is another proposed mechanism of action.[5, 37, 38] Although activation of local inhibitory interneurons could contribute to the fEPSP reductions observed in our study, the 40-second outlasting effect, the input-specificity and the unchanged paired-pulse inhibition are arguments against this mechanism. A fourth previously suggested mechanism of action that could cause EP reductions is

depolarization block, induced either synaptically or nonsynaptically.[3, 16, 39] The PS amplitude was not influenced in our study and we did not find a sustained depolarization as shown in these previous studies.[3, 16] However, compared to Garcia et al[39] and taking into account differences in the distance between the recording and stimulation electrode, our stimulation intensities might have been too low to directly, nonsynaptically influence the voltage-gated currents of the neurons surrounding the recording electrode in a significant manner[40], not excluding this possibility for a smaller proportion of neurons closer to the stimulation electrode.

Besides the acute temporary fEPSP slope reductions we also observed longer-lasting reductions during 160 min of intermittent DBS. It is possible that these reductions are due to cumulative DBS effects, only becoming apparent over two to three successive stimulation blocks as suggested in figure 6 but not confirmed by statistical analysis. As no trend for recovery after the immediate temporary slope reductions was observed during the stimulation-free intervals, these reductions are characterized by longer outlasting effects. This is in line with previous clinical studies reporting different symptoms to be affected by DBS with different time courses. For example, in Parkinson's disease, DBS induces nearly instantaneous tremor suppression, whereas other extrapyramidal symptoms might take minutes, hours or even weeks to achieve maximal improvement after DBS onset and fully return after DBS cessation.[1, 2, 29] These longer outlasting effects also provide a potential neurophysiological explanation for the efficacy of intermittent DBS – typically used in epilepsy and preliminary explored in Tourette's syndrome – as an alternative to continuous DBS.[25, 28, 30, 41] From a mechanistic point of view they indicate the occurrence of neuroplasticity. We hypothesize that the observed EP reductions following increased neuronal activity provoked by DBS could be due to the recruitment of homeostatic plasticity mechanisms aiming to keep overall activity within a certain range by changing synaptic strength and/or intrinsic excitability.[42] The associated increase in the paired-pulse ratio suggests a presynaptic origin of the EP reductions.[35, 43] Presynaptic homeostatic plasticity by modulation of presynaptic calcium metabolism and/or the readily releasable pool of synaptic vesicles has been demonstrated previously.[44] Another possibility is that the longer-lasting changes result from LTD. This type of plasticity is typically induced by low-frequency stimulation and mediated by postsynaptic changes.[45] However, LTD following high-frequency stimulation as well as primarily presynaptically expressed types of LTD have been shown.[19-22, 45] Future studies will be designed to investigate these neuroplasticity changes in more detail.

The stimulation protocol used in the present study is based on previous experiments demonstrating significant seizure reductions in epileptic rats.[26, 27] To what extent the results are generalizable to other stimulation parameters and targets needs further research. In this context, it should be noted that a trend for decreased EPs was also seen in the sham group after 160 min. Whether this results from the repeated 0.05 Hz EP stimuli or represents a daytime effect cannot be discriminated by our study design. Although some studies suggest superior efficacy of high-frequency hippocampal DBS, antiepileptic effects of low-frequency (albeit typically ≥1 Hz) DBS have been demonstrated.[46-48]

In contrast to the reductions in evoked activity, we found no changes in the spontaneous LFPs. It is possible that the reductions in evoked activity were too small to be reflected or noticeable in the spectrogram, or they could be compensated by increased input from non-stimulated pathways. We could thus not support previous reports suggesting desynchronization to be involved in the mechanism of action of DBS.[6, 10, 49] Although various studies have demonstrated suppression of pathologically elevated beta-oscillations with DBS in Parkinson's disease[1, 4], our results are in line with the findings

of Dejean et al[50] who also did not find any modification of the LFP spectrogram by DBS in healthy rats. Changes in the spectrogram during DBS cannot be excluded based on the results of our study.

In conclusion, we showed that hippocampal DBS in freely moving rats results into fEPSP slope reductions with two different time courses. First, we found short-lasting reductions after 1 to 6 min of DBS. These were smaller compared to previously reported changes probably because stimulation intensity in freely moving rats needs to be remarkably low to prevent seizure occurrence. Secondly, we observed longer-lasting and possibly cumulative effects with 160 min of intermittent DBS. The observed dual effects may parallel the different temporal patterns of clinical improvement observed with DBS, although this needs further study. The longer-lasting reductions provide a potential neurophysiological basis for the use of intermittent DBS as an alternative to continuous DBS. This could pave the way for the development of disease-tailored stimulation protocols based on the presumed dominant mechanism of action. A limitation of our study is that we were not able to analyze DBS-induced changes during DBS, such as stimulus-locked evoked activity. More research is also required to investigate whether similar effects can be demonstrated in other brain regions, pathological brain tissue including epileptic networks and human subjects.

Acknowledgements

Mathieu Sprengers is supported by an aspirant grant provided by the Flemish Research Fund (FWO), Kristl Vonck and Robrecht Raedt by the Ghent University Special Research Funds (BOF) and Paul Boon by research grants from FWO, BOF and Ghent University Hospital.

Conflict of interests

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

[1] Herrington TM, Cheng JJ, Eskandar EN. Mechanisms of deep brain stimulation. J Neurophysiol 2016;115(1):19-38.
[2] Udupa K, Chen R. The mechanisms of action of deep brain stimulation and ideas for the future development. Prog Neurobiol 2015;133:27-49.
[3] Beurrier C, Bioulac B, Audin J, Hammond C. High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. J Neurophysiol 2001;85(4):1351-6.
[4] Bronte-Stewart H, Barberini C, Koop MM, Hill BC, Henderson JM, Wingeier B. The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation. Exp Neurol 2009;215(1):20-8.
[5] Dostrovsky JO, Levy R, Wu JP, Hutchison WD, Tasker RR, Lozano AM. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J Neurophysiol 2000;84(1):570-4.
[6] Feng Z, Wang Z, Guo Z, Zhou W, Cai Z, Durand DM. High frequency stimulation of afferent fibers generates asynchronous firing in the downstream neurons in hippocampus through partial block of axonal conduction. Brain Res 2017;1661:67-78.
[7] Feng Z, Zheng X, Yu Y, Durand DM. Functional disconnection of axonal fibers generated by high frequency stimulation in the hippocampal CA1 region in-vivo. Brain Res 2013;1509:32-42.
[8] Grill WM, Snyder AN, Miocinovic S. Deep brain stimulation creates an informational lesion of the stimulated nucleus. Neuroreport 2004;15(7):1137-40.
[9] Iremonger KJ, Anderson TR, Hu B, Kiss ZH. Cellular mechanisms preventing sustained activation of cortex during subcortical high-frequency stimulation. J Neurophysiol 2006;96(2):613-21.
[10] McCairn KW, Turner RS. Deep brain stimulation of the globus pallidus internus in the parkinsonian primate: local entrainment and suppression of low-frequency oscillations. J Neurophysiol 2009;101(4):1941-60.
[11] Alarcon G, Martinez J, Kerai SV, Lacruz ME, Quiroga RQ, Selway RP, et al. In vivo neuronal firing patterns during human epileptiform discharges replicated by electrical stimulation. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2012;123(9):1736-44.
[12] Anderson TR, Hu B, Iremonger K, Kiss ZH. Selective attenuation of afferent synaptic transmission as a mechanism of thalamic deep brain stimulation-induced tremor arrest. J Neurosc 2006;26(3):841-50.
[13] Feng Z, Yu Y, Guo Z, Cao J, Durand DM. High frequency stimulation extends the refractory period and generates axonal block in the rat hippocampus. Brain Stimul 2014;7(5):680-9.
[14] Kim E, Owen B, Holmes WR, Grover LM. Decreased afferent excitability contributes to synaptic depression during high-frequency stimulation in hippocampal area CA1. J Neurophysiol 2012;108(7):1965-76.
[15] Li B, Piriz J, Mirrione M, Chung C, Proulx CD, Schulz D, et al. Synaptic potentiation onto habenula neurons in the learned helplessness model of depression. Nature 2011;470(7335):535-9.
[16] Magarinos-Ascone C, Pazo JH, Macadar O, Buno W. High-frequency stimulation of the subthalamic nucleus silences subthalamic neurons: a possible cellular mechanism in Parkinson's disease. Neuroscience 2002;115(4):1109-17.
[17] Schiller Y, Bankirer Y. Cellular mechanisms underlying antiepileptic effects of low- and high-frequency electrical stimulation in acute epilepsy in neocortical brain slices in vitro. J Neurophysiol 2007;97(3):1887-902.
[18] Shen KZ, Johnson SW. Complex EPSCs evoked in substantia nigra reticulata neurons are disrupted by repetitive stimulation of the subthalamic nucleus. Synapse 2008;62(4):237-42.
[19] Braz BY, Belforte JE, Murer MG, Galinanes GL. Properties of the corticostriatal long term depression induced by medial prefrontal cortex high frequency stimulation in vivo. Neuropharmacology 2017;121:278-86.
[20] Calabresi P, Maj R, Pisani A, Mercuri NB, Bernardi G. Long-term synaptic depression in the striatum: physiological and pharmacological characterization. J Neurosc 1992;12(11):4224-33.

[21] Shen KZ, Zhu ZT, Munhall A, Johnson SW. Synaptic plasticity in rat subthalamic nucleus induced by high-frequency stimulation. Synapse 2003;50(4):314-9.
[22] Yamawaki N, Magill PJ, Woodhall GL, Hall SD, Stanford IM. Frequency selectivity and dopamine-dependence of plasticity at glutamatergic synapses in the subthalamic nucleus. Neuroscience 2012;203:1-11.
[23] Riedel G, Seidenbecher T, Reymann KG. LTP in hippocampal CA1 of urethane-narcotized rats requires stronger tetanization parameters. Physiol Behav 1994;55(6):1141-6.
[24] Shirasaka Y, Wasterlain CG. The effect of urethane anesthesia on evoked potentials in dentate gyrus. Eur J Pharmacol 1995;282(1-3):11-7.
[25] Sprengers M, Vonck K, Carrette E, Marson AG, Boon P. Deep brain and cortical stimulation for epilepsy. Cochrane Database Syst Rev 2017;7:CD008497.
[26] Van Nieuwenhuyse B, Raedt R, Delbeke J, Wadman WJ, Boon P, Vonck K. In search of optimal DBS paradigms to treat epilepsy: bilateral versus unilateral hippocampal stimulation in a rat model for temporal lobe epilepsy. Brain Stimul 2015;8(2):192-9.
[27] Van Nieuwenhuyse B, Vonck K, Raedt R, Meurs A, Wytse W, Boon PAJM. Deep Brain Stimulation Early during Epileptogenesis Modifies Disease Progression in the Hippocampus. Epilepsia 2012;53:26-7.
[28] Vonck K, Sprengers M, Carrette E, Dauwe I, Miatton M, Meurs A, et al. A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. Int J Neural Syst 2013;23(1):1250034.
[29] Temperli P, Ghika J, Villemure JG, Burkhard PR, Bogousslavsky J, Vingerhoets FJ. How do parkinsonian signs return after discontinuation of subthalamic DBS? Neurology 2003;60(1):78-81.
[30] Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51(5):899-908.
[31] Paxinos G, Watson C. The Rat Brain in Stereotaxic Coordinates, 6th Edition. Elsevier/Academic Press, Amsterdam, The Netherlands; 2009.
[32] Kamphuis W, Lopes da Silva FH, Wadman WJ. Changes in local evoked potentials in the rat hippocampus (CA1) during kindling epileptogenesis. Brain Res 1988;440(2):205-15.
[33] Lancaster B, Wheal HV. Chronic failure of inhibition of the CA1 area of the hippocampus following kainic acid lesions of the CA3/4 area. Brain Res 1984;295(2):317-24.
[34] Morris RG, Moser EI, Riedel G, Martin SJ, Sandin J, Day M, et al. Elements of a neurobiological theory of the hippocampus: the role of activity-dependent synaptic plasticity in memory. Philosophical transactions of the Royal Society of London Series B, Biological sciences 2003;358(1432):773-86.
[35] Fioravante D, Regehr WG. Short-term forms of presynaptic plasticity. Curr Opin Neurobiol 2011;21(2):269-74.
[36] Urbano F, Leznik E, Llinás R. Cortical activation patterns evoked by afferent axons stimuli at different frequencies: an in vitro voltage-sensitive dye imaging study. Thalamus Relat Syst 2002;1(4):371-8.
[37] Anderson ME, Postupna N, Ruffo M. Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. J Neurophysiol 2003;89(2):1150-60.
[38] Filali M, Hutchison WD, Palter VN, Lozano AM, Dostrovsky JO. Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus. Exp Brain Res 2004;156(3):274-81.
[39] Garcia L, Audin J, D'Alessandro G, Bioulac B, Hammond C. Dual effect of high-frequency stimulation on subthalamic neuron activity. J Neurosc 2003;23(25):8743-51.
[40] Ranck JB, Jr. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res 1975;98(3):417-40.
[41] Rossi PJ, Opri E, Shute JB, Molina R, Bowers D, Ward H, et al. Scheduled, intermittent stimulation of the thalamus reduces tics in Tourette syndrome. Parkinsonism Relat Disord 2016;29:35-41.

[42] Turrigiano G. Too many cooks? Intrinsic and synaptic homeostatic mechanisms in cortical circuit refinement. Annu Rev Neurosci 2011;34:89-103.
[43] Manabe T, Wyllie DJ, Perkel DJ, Nicoll RA. Modulation of synaptic transmission and long-term potentiation: effects on paired pulse facilitation and EPSC variance in the CA1 region of the hippocampus. J Neurophysiol 1993;70(4):1451-9.
[44] Davis GW, Muller M. Homeostatic control of presynaptic neurotransmitter release. Annu Rev Physiol 2015;77:251-70.
[45] Citri A, Malenka RC. Synaptic plasticity: multiple forms, functions, and mechanisms. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 2008;33(1):18-41.
[46] Boex C, Vulliemoz S, Spinelli L, Pollo C, Seeck M. High and low frequency electrical stimulation in non-lesional temporal lobe epilepsy. Seizure 2007;16(8):664-9.
[47] Wyckhuys T, Raedt R, Vonck K, Wadman W, Boon P. Comparison of hippocampal Deep Brain Stimulation with high (130Hz) and low frequency (5Hz) on afterdischarges in kindled rats. Epilepsy Res 2010;88(2-3):239-46.
[48] Wyckhuys T, Geerts PJ, Raedt R, Vonck K, Wadman W, Boon P. Deep brain stimulation for epilepsy: knowledge gained from experimental animal models. Acta Neurol Belg 2009;109(2):63-80.
[49] Medeiros Dde C, Moraes MF. Focus on desynchronization rather than excitability: a new strategy for intraencephalic electrical stimulation. Epilepsy & behavior : E&B 2014;38:32-6.
[50] Dejean C, Gross CE, Bioulac B, Boraud T. Dynamic changes in the cortex-basal ganglia network after dopamine depletion in the rat. J Neurophysiol 2008;100(1):385-96.

CHAPTER 8

Mechanism of action of DBS: chronic experiments

Long-lasting decreased excitability induced by high-frequency hippocampal deep brain stimulation in freely moving rats

Sprengers M[1], Raedt R[1], Larsen LE[1], Delbeke J[1], Wadman WJ[2], Boon P[1], Vonck K[1].

[1] 4Brain, Department of Neurology, Ghent University Hospital, Ghent, Belgium

[2] Swammerdam Institute of Life Sciences, University of Amsterdam, The Netherlands

In preparation for submission to Progress in Neurobiology.

ABSTRACT

Background: Nearly all experimental attempts to elucidate the mechanism of action of deep brain stimulation (DBS) have only evaluated the effects of up to a couple of minutes of DBS. However, many clinical changes take much longer to become fully apparent. The present study investigates the impact of more prolonged durations of DBS on evoked potentials (EPs) and local field potentials (LFPs) in freely moving rats.

Methods: Hippocampal EPs and LFPs were recorded 3 times daily 2 days before (baseline), during and after (washout) 2 days of 130 Hz continuous hippocampal DBS. DBS and EP stimuli were administered via the same or via different electrodes to investigate input-specificity. Continuous DBS was compared to intermittent DBS applied with 2 different duty cycles.

Results: Compared to sham stimulation, 2 days of continuous DBS caused input-specific and increasing reductions of the field excitatory postsynaptic potential (fEPSP) slope and of the population spike (PS) amplitude. These changes outlasted the stimulation period by 5-7 days. The fEPSP slope/PS amplitude and fEPSP slope/fEPSP slope paired-pulse ratio relationships remained unaffected. Compared to continuous DBS the effects of intermittent DBS were less pronounced at identical time points, but when normalized to the cumulative number of DBS pulses administered similar effects were observed. The LFP spectrogram remained unaltered.

Conclusion: Longer DBS durations were associated with progressively increasing EP reductions with long stimulation outlasting effects. These reductions could be caused by presynaptic homeostatic plasticity and provide a potential neurophysiological basis for the clinically reported increasing efficacy over time and long-lasting aftereffects of DBS.

INTRODUCTION

Deep brain stimlulation (DBS) is used or under investigation as a treatment for various neuropsychiatric disorders, including Parkinson's disease, dystonia, epilepsy and obsessive-compulsive disorder. A better understanding of the mechanism of action of DBS could lead to the development of more rational and efficacious stimulation protocols. Various mechanisms of action have been proposed to underlie the effects of DBS including depolarization block, synaptic depression, synaptic inhibition, axonal conduction block, jamming of pathological activity by imposing new (stimulus-locked) activity, desynchronization and suppression of pathological oscillations, neuroplasticity, neurogenesis and neuroprotective effects [1-12].

In previous experiments we used Schaffer collateral stimulation evoked potentials (EP) in the hippocampal CA1 region to investigate the mechanism of action of hippocampal DBS in freely moving rats [13]. We demonstrated immediate and short-lasting (less than 60 s) reductions of the field postsynaptic excitatory potential (fEPSP) after 1 to 6 min of DBS, fitting the hypothesis of neurotransmitter depletion and/or axonal conduction block as the underlying mechanism of action. In addition, we also observed longer-lasting and possibly cumulative fEPSP reductions with 160 min of intermittent DBS applied with 1/9 and 6/4 min ON/OFF duty cycles.

While in patients the full clinical potential of DBS for various indications becomes apparent only after several hours to many years of treatment, mechanistic research has primarily focused on the investigation of the immediate brain effects of seconds to minutes of DBS only. Homeostatic plasticity refers to changes in synaptic strength and/or intrinsic excitability occurring after prolonged perturbations of neuronal or network activity aiming to stabilize the activity within a certain physiological range [14-16]. We hypothesize that homeostatic plasticity is a potential mechanism underlying the long-term effects of DBS. The administered electrical fields may induce prolonged increases in neuronal activity leading to reduced synaptic strength and/or intrinsic excitability. Such a mechanism would also fit the fEPSP reductions observed during 160 min of intermittent DBS in our previous experiments [13]. Although homeostatic plasticity has previously been suggested as a potential mechanism of action of DBS [17], it was never the objective of a dedicated experimental set-up.

The aim of the present study was to characterize in more detail whether and how more prolonged durations of both continuous and intermittent high-frequency hippocampal DBS affect the hippocampal network by means of EP and LFP recordings in freely moving rats.

METHODS

Thirty male Sprague-Dawley rats (Harlan Laboratories, Indianapolis, IN, USA) were treated according to the European Ethics Committee guidelines (2010/63/EU). Animals were housed under controlled conditions with a 12h/12h light-dark cycle, temperature between 21-23°C and ad libitum access to water and food. The study protocol was approved by the Animal Experimental Ethical Committee of Ghent University Hospital (ECD 13/63). The surgical procedure, recording and stimulation setup as well as the methods used for EP and LFP analysis have been described previously [13].

Surgical procedure

Rats (350-400 g) were anesthetized using a mixture of isoflurane and medical oxygen. Two custom-made epidural electrodes serving as ground/reference electrode and three custom-made depth electrodes were implanted. The latter included a quadripolar recording electrode (four twisted polyimide-coated stainless steel wires, diameter 70 µm, intercontact distance 225 µm) in the CA1 region (anteroposterior (AP) -5.0, mediolateral (ML) +3.0, approximate depth -3.2), a quadripolar stimulation electrode at the Schaffer collaterals (EP stimulation electrode, EpSE) (AP -3.0, ML +1.5, approximate depth -3.6) and an bipolar additional stimulation electrode (AddSE) implanted in close proximity to the recording electrode (AP -4.55, ML +2.8, approximate depth -3.6), all coordinates in mm [18]. The stimulation electrodes consisted of respectively four (intercontact distance 300 µm) and two (tip separation 850 µm to span most of the hippocampus in the coronal plane) twisted PFA-coated platinum-iridium wires (diameter 140 µm, A-M Systems, WA, USA). The depth of the EpSE and recording electrode were adjusted under electrophysiological guidance to evoke a maximal population spike, the upper contact op the AddSE was stereotactically implanted in the stratum radiatum based on the dorsoventral coordinates of the nearby recording electrode. Electrophysiological data confirmed the AddSE cathode localization in the stratum radiatum in 81% (13/16) of rats. In the remaining 3 rats (19%) the cathode was located slightly deeper in the dentate gyrus molecular layer stimulating perforant path fibers (see figure S1). Subgroup analyses excluding these 3 rats yielded similar results. To further characterize the relationship between both stimulation electrodes a paired-pulse protocol was performed with the first pulse being administered via the AddSE and the second via the EpSE. This protocol did not yield paired-pulse facilitation of the low-intensity EPs, indicating that indeed different axons were stimulated. All electrode leads were collected in a custom-made connector block that was fixed to the skull with anchor screws and dental acrylic cement. Buprenorphine (0.03 mg/kg sc, 1 day) and meloxicam (1 mg/kg sc, 2 days) were used for postoperative analgesia.

Recording and stimulation setup

After a three-week postoperative recovery period, rats were connected to the setup through a swivel allowing free movement. Local field potentials were acquired with an epidural electrode as reference. Analog signals were high-pass filtered at 0.1 Hz and amplified 248 times after which they were digitized by a USB-6259 NI-DAQ card (National Instruments, TX, USA). EPs were sampled at 20 kHz and LFPs at 5 kHz. Electrode impedances were checked with a less then 30nA test pulse and found to remain stable throughout the experiment. They never exceeded 65 kΩ allowing the constant-current stimulators (40V maximum output) to generate up to at least 615 µA currents in all animals.

Stimulation parameter settings

Electrical currents consisted of bipolar biphasic charge-balanced square-wave pulses. For the EPs, the two electrode contacts of the EpSE that evoked EPs with the best quality at the lowest intensity were chosen as cathode-anode pair. EPs were administered as paired pulses (pulse width 200 µs) with a 20 ms interpulse-interval. EP intensities were scaled in percentage values between the fEPSP threshold (0%) and the intensity evoking a maximal PS amplitude (100%).

DBS parameters were: 130 Hz, 50 µs pulse width; stimulation intensity was set just above the threshold to evoke a clear summated fEPSP as has been described in more detail previously [13]. DBS could be

delivered either through the EpSE (same cathode-anode pair as for the EPs) or through the AddSE (upper contact as cathode).

Experimental protocol

During the experiments input-output curves (0-10-25-40-50-60-80-100[-135]%; 4 repetitions) were performed daily on three fixed time points (11 am, 2.30 pm and 6 pm) to minimize the influence of the behavioral state of the animal. Rats were asleep most of the time. During each 10-second inter-EP interval, 8 seconds of LFPs were recorded. DBS was only interrupted for the EP measurements (3x 7 min per day).

DBS was started in the evening of the second of two baseline recording days. For the first experiment, DBS was administered continuously for 2 days followed by a washout period of 2 days or until measurements had returned to baseline values. In subsequent separate experiments we investigated the effect of intermittent DBS with 2 different duty cycles: 6 days of 1/5 min and 10 days of 1/29 min ON/OFF intermittent DBS.

To investigate the input-specificity and spatial extent of the changes that were encountered, separate experiments were performed where DBS administration (via the AddSE) and EP evocation (via the EpSE) occurred via different electrodes.

EP analysis

All data were processed using Matlab (The MathWorks Inc., Natick, US). The fEPSP slope was measured in the stratum radiatum by fitting a slope to the falling phase of the fEPSP waveform using the least squares method. The PS amplitude was measured in the pyramidal cell layer and defined as the vertical distance between the negative peak of the PS and the tangent connecting the positive peaks before and after the PS (figure 1). We further investigated the PS amplitude/fEPSP slope and fEPSP $slope_2$/fEPSP $slope_1$ (paired-pulse ratio) relationship.

Spectral analysis

To isolate local activity in the stratum radiatum, the difference between the signals in the stratum radiatum and the upper hippocampal electrode contact recording a PS was calculated. A sensitivity analysis using the original signals referenced to the scalp electrode was also performed and yielded the same results. LFP sweeps excessively affected by artifacts were rejected when the total power reached more than 3 standard deviations from the mean. The signals were filtered offline between 2 and 100 Hz with a first order Butterworth filter. Each 8-seconds LFP sweep was split into 1-second windows overlapping by 0.5 s. Using the Fast Fourier algorithm for each 1-second window yielded 9 power spectra that were averaged to provide one power spectrum per LFP sweep.

Statistical analysis

Prior to any statistical analysis all EP outcome measures were normalized to their respective mean baseline values. Power spectra were normalized to the mean total power during baseline. A repeated measures two-way ANOVA (‘mixed ANOVA’) with one within-subjects (Time) and one between-subjects factor (Stimulation Condition: sham DBS versus DBS – continuous, intermittent 1/5 or 1/29) was used for statistical analysis. A Greenhouse-Geisser correction was used in cases where the

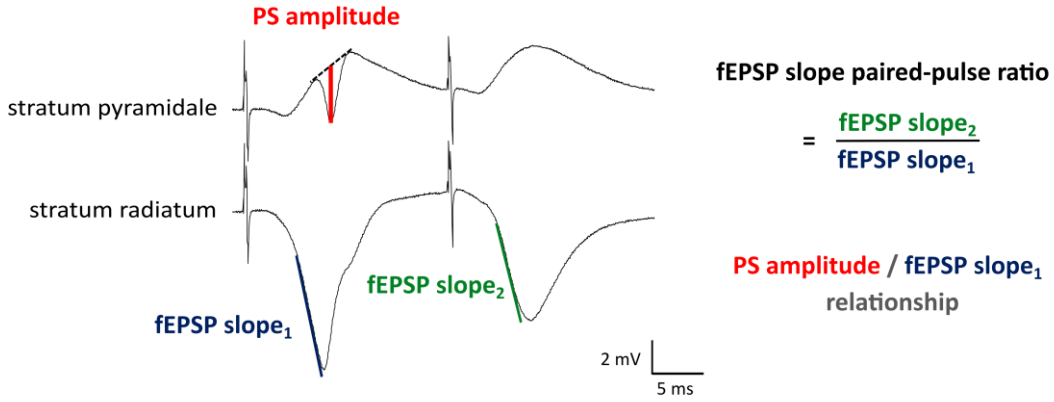


Figure 1. EPs were evoked by stimulation of the Schaffer collaterals and recorded in the CA1 region of the hippocampus. The EP outcome parameters included the field excitatory postsynaptic potential (fEPSP) slope (i.e. fEPSP slope$_1$), the population spike (PS) amplitude, the PS amplitude / fEPSPS slope relationship and the fEPSP slope$_2$/fEPSP slope$_1$ relationship (paired-pulse ratio). The fEPSP slope was measured in the stratum radiatum by fitting a slope to the falling phase of the fEPSP waveform using the least squares method. The PS amplitude was measured in the pyramidal cell layer and defined as the vertical distance between the negative peak of the PS and the tangent connecting the positive peaks before and after the PS.

assumption of sphericity was violated as indicated by the Mauchly's Test of Sphericity ($p<0.05$). Statistical significance was defined as $p<0.05$. A Holm-Sidak correction was applied for post-hoc testing. To evaluate the fESPS slope/PS amplitude, the fEPSP slope$_2$/fEPSP slope$_1$ and the stimulation intensity/fEPSP slope relationships, 3-parameter (f=a/(1+exp(-(x-x0)/b)) or 4-parameter (f= y0+a/(1+exp(-(x-x0)/b)) sigmoid curves were fitted to the data. Sigmoid curves were fitted both on the individual rat data (group averaging after curve fitting) and the mean group data (curve fitting after group averaging). As the range of the independent variable (the fEPSP slope) varied at different time points during the experiment, curve fitting was restricted to the range of the fEPSP slope that was available throughout the entire experiment. To compare the fEPSP slopes of the AddSE-evoked EPs before and after 2 days of DBS, a paired t-test was used. Values are expressed as mean +/- standard error, unless otherwise stated.

RESULTS

Mean DBS stimulation intensity was 81.0 (standard deviation (SD) 22.7) µA for the EpSE and 84.1 (SD 22.8) µA for the AddSE. This corresponded to 2.1% of the maximum EP intensity. These intensities are very similar to those in our previous trial where they corresponded to 66% of the seizure threshold [13]. Nevertheless seizures were unintentionally provoked in 3 rats (5.1% of all DBS sessions). Rats with seizures were excluded from statistical analysis.

1. Effects of DBS administered through the EP stimulation electrode

Two days of continuous DBS in 16 rats (input-output curves 0-100% in the first 4 rats, 0-135% in 12 rats) caused pronounced fEPSP slope and PS amplitude reductions (see figure 2 and 3). Compared to sham stimulation, statistically significant fEPSP slope reductions were demonstrated for all EP intensities tested except for the 9.4 +/- 1.7% reduction of the 135% fEPSP slope that did not reach

statistical significance (F(4.130,99.114)=2.020, p=0.10). Lower EP stimulus intensities yielded larger relative fEPSP reductions. For example, the 10, 25, 50 and 80% fEPSP slope were reduced by 69.9 +/- 3.7% (F(2.281,63.875)=14.232, p<0.001), 47.5 +/- 3.2% (F(3.580,100.229)=14.583, p<0.001), 34.3 +/- 3.1% (F(4.383,122.732)=16.305, p<0.001) and 20.6 +/- 2.6% (F(4.709,131.849)=9.507, p<0.001), respectively (figure 3a). When studying the absolute effects by normalizing for each individual rat the various fEPSP slope values to the baseline 100% EP fEPSP slope value, a more equal effect among the different EP intensities could be appreciated (figure 3b).

Except for the 135% PS all EP intensities tested also showed statistically significant lower PS amplitudes after 2 days of DBS. For example, the 50% PS was nearly completely abolished with a decrease of 85.8 +/- 4.9% (F(2.178,60.970)=5.869, p=0.004) and the 80% PS amplitude was cut down by 51.1 +/- 6.4% (F(3.878,108.587)=7.071, p<0.001) (see figure 3c).

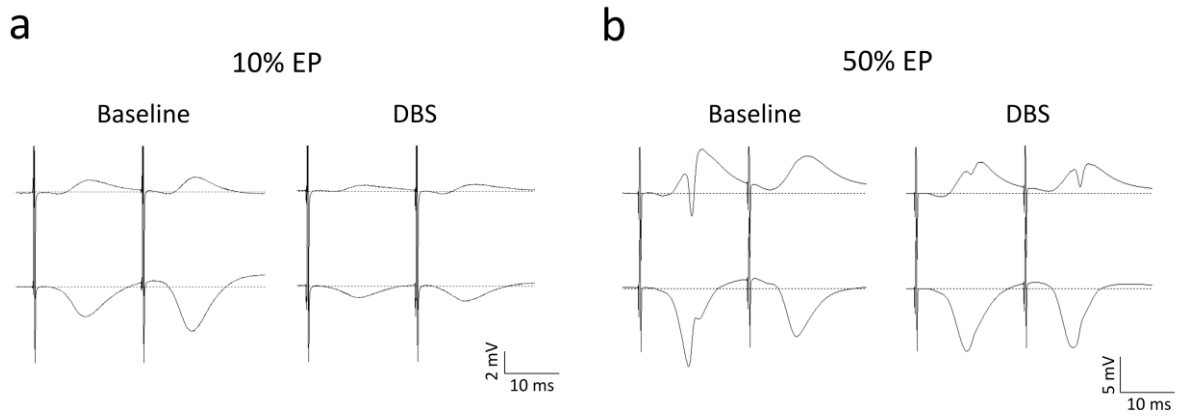


Figure 2. Representative examples illustrating the EP reductions caused by 2 days of continuous DBS. On average, the 10% fEPSP slope was reduced by 69.9 +/- 3.7% (p<0.001) **(a)**, the 50% fEPSP slope by 34.3 +/- 3.1% (p<0.001) and the 50% PS amplitude by 85.8 +/- 4.9% (p=0.004) **(b)**.

Comparing the effects of various EP stimulation intensities on the fEPSP slope and on the PS amplitude reveals a more pronounced effect on the latter (figure 3c). This might suggest a decrease in intrinsic excitability, i.e. a lower PS amplitude for a given fEPSP slope. However, PS amplitudes and fEPSP slopes are not characterized by a linear but by a sigmoid relationship. Therefore we fitted 3-parameter sigmoidal curves to the data. This was done either before (i.e. on the fEPSP slope and PS amplitude values of each individual rat) or after (i.e. on the mean fEPSP slope and PS amplitude values) averaging group data. Both analyses yielded similar results and showed that the intrinsic excitability was largely unaffected by DBS (see figure 4). Although slightly lower PS amplitudes were seen after DBS, a similar reduction was also seen after 2 days of sham DBS. Slow electrode shifting away from the pyramidal cell layer is probably responsible for these slightly smaller PS amplitudes, as was evident by PS moving to deeper electrode contacts over longer (2-3 months) time periods. In contrast, fEPSP have an unchanged morphology over a longer distance and therefore are less susceptible to minor electrode movements.

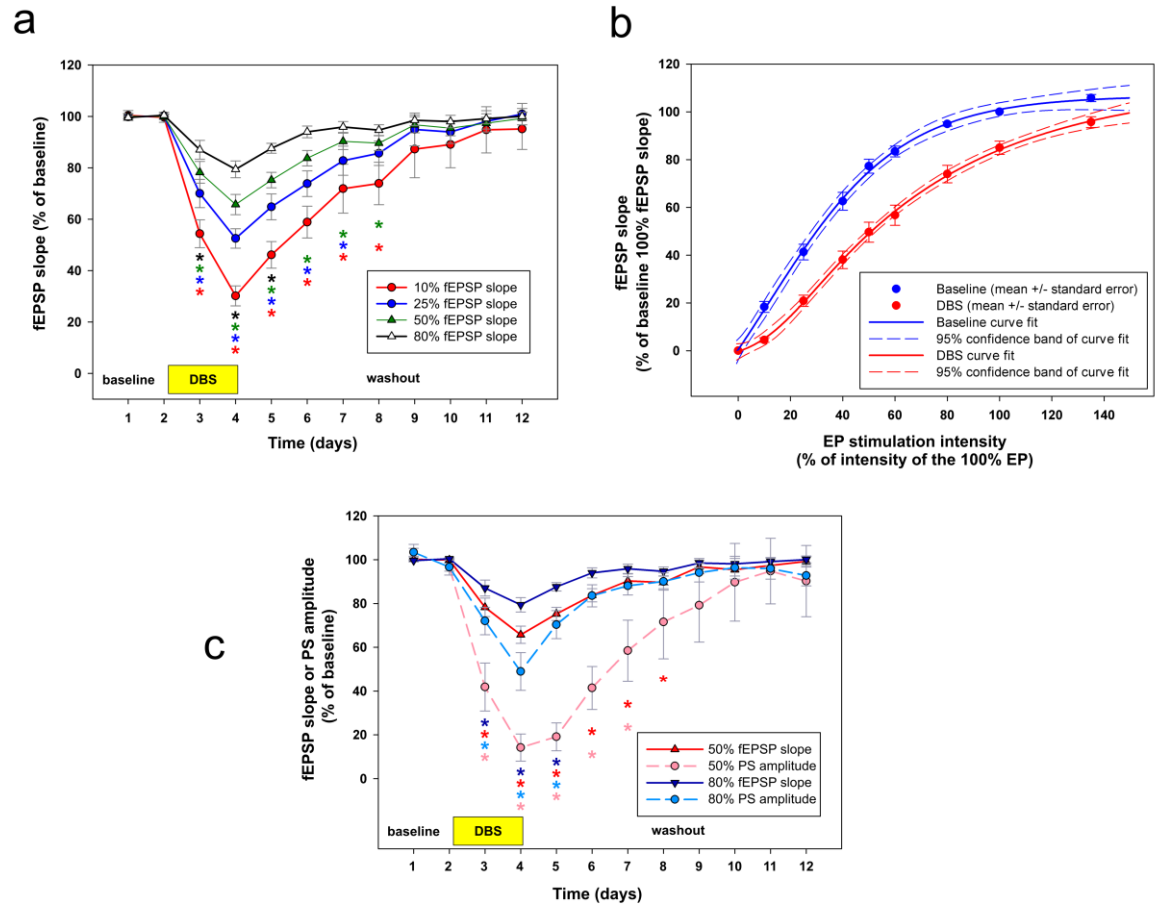


Figure 3. After 2 days of DBS, the fEPSP slopes **(a,b,c)** and PS amplitudes **(c)** were strongly reduced. Both for the fEPSP slope and the PS amplitude progressively increasing reductions were found, with larger reductions after 2 days compared to after 1 day of DBS. An outlasting effect of at least five days was observed before the effects disappeared. Lower EP stimulus intensities yielded larger relative fEPSP reductions (a) but normalizing the fEPSP slope values to the baseline 100% fEPSP slope values showed more equal absolute fEPSP slope reductions among the different EP intensities (b). In (**a**) and (**c**) mean values +/- standard errors are plotted over time for each day. Asterisks indicate statistically significant differences compared to sham stimulation (not shown for visual readability, no statistically significant changes over 12 days). Three-parameter sigmoid curves (f=a/(1+exp(-(x-x0)/b)) were fitted to the fEPSP slope values in **(b)**.

The paired-pulse fEPSP slope ratio was significantly increased for all intensities but the 10% and 135% EPs. For example, after two days of continuous DBS the 25% paired-pulse ratio increased by 13.0 +/- 3.4% ($F(3.725,104.308)=5.441$, $p=0.001$), the 50% paired-pulse ratio by 63.3 +/- 11.7% ($F(2.003,56.094)=15.086$, $p<0.001$) and the 80% paired-pulse ratio by 28.8 +/- 9.7% ($F(1.585,44.389)=6.495$, $p=0.006$). Similarly to the PS amplitude, however, the paired-pulse interaction is strongly dependent on the fEPSP slope. Therefore the effect of DBS on the paired-pulse interaction was also investigated by fitting 4-parameter sigmoidal curves to the fEPSP slope / fEPSP slope ratio data. When normalized for the fEPSP slope, DBS affected neither the paired-pulse facilitation nor the paired-pulse inhibition (see figure 5).

Both for the fEPSP slope and the PS amplitude the effect of DBS increased with longer stimulation duration showing more pronounced reductions after two compared to one day of DBS. For example,

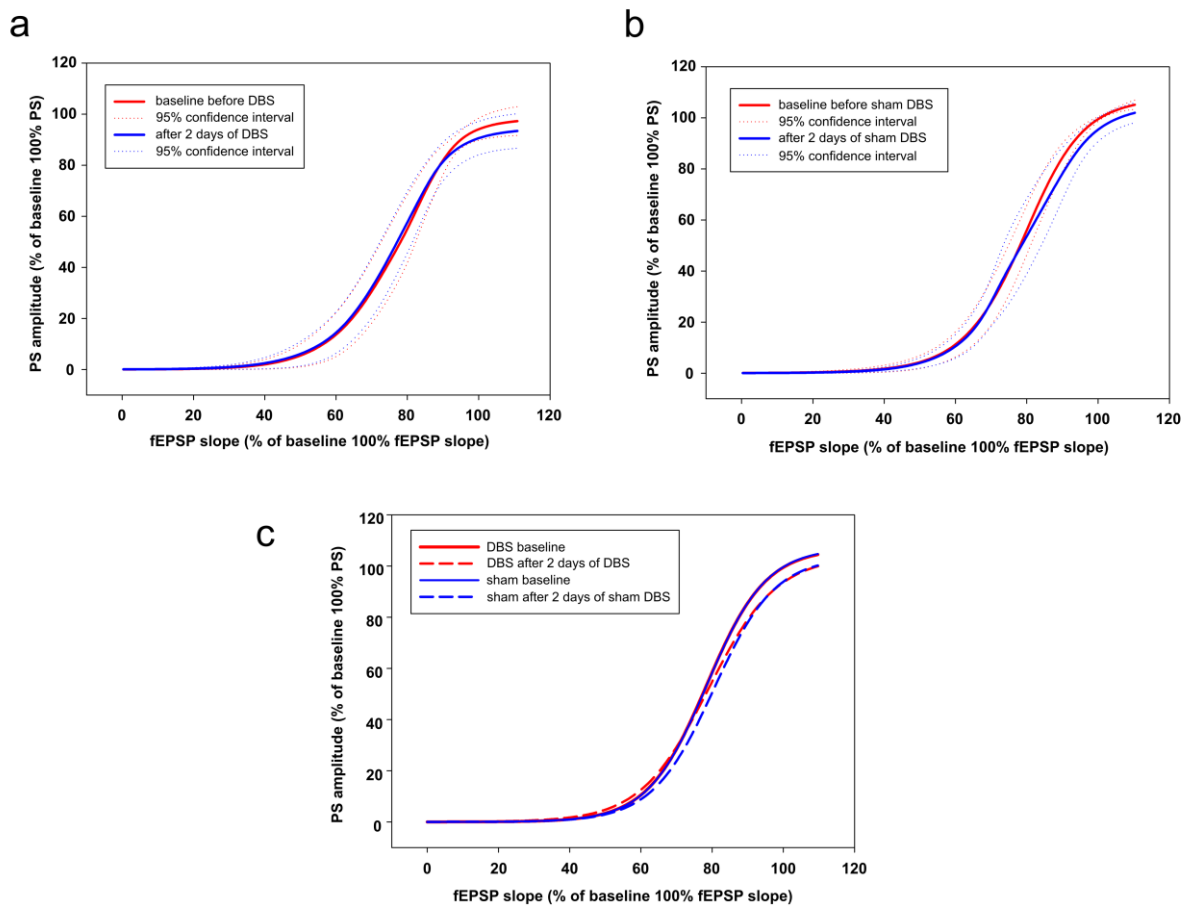


Figure 4. Compared to sham stimulation, two days of continuous DBS did not change the fEPSP slope / PS amplitude relationship (postsynaptic intrinsic excitability). Graphs in **(a)** and **(b)** show the average +/- 95% confidence interval of 16 three-parameter sigmoid curves (f=a/(1+exp(-(x-x0)/b)) fitted to the individual data of each rat during baseline (red) and after 2 days of DBS **(a)** or sham DBS **(b)** (blue) (curve fitting before group averaging). The graph in **(c)** shows 3-parameter sigmoid curves fitted to the mean values of the fEPSP slope and PS amplitude during baseline (continuous line) and after 2 days of DBS (red) or sham DBS (blue) (dashed lines) (curve fitting after group averaging). The 95% confidence intervals of the curve fits are not shown for visual readability. Although population spike amplitudes for identical fEPSP slope values were slightly lower after 2 days of DBS, similar reductions were also seen after sham DBS (see text).

the 10% and 50% fEPSP slopes and the 50% PS amplitude decreased further by 24.2 +/- 6.2% ($p<0.001$), 12.5 +/- 3.1% ($p<0.001$) and 27.6 +/- 8.6% ($p=0.016$, ns), respectively. Interestingly, a long outlasting effect was seen after termination of DBS and it took 5-7 days before the fEPSP slopes and PS amplitudes had returned to their baseline values.

In contrast to the EPs, the 2-100 Hz hippocampal LFP spectrogram was not changed by DBS as is shown in figure 6.

2. Intermittent versus continuous DBS

In addition to the 2 days continuous DBS experiments, we also investigated the effects of 6 days 1/5 (n=13) and 10 days 1/29 (n=10) min ON/OFF intermittent DBS. Compared to sham DBS (n=14), both

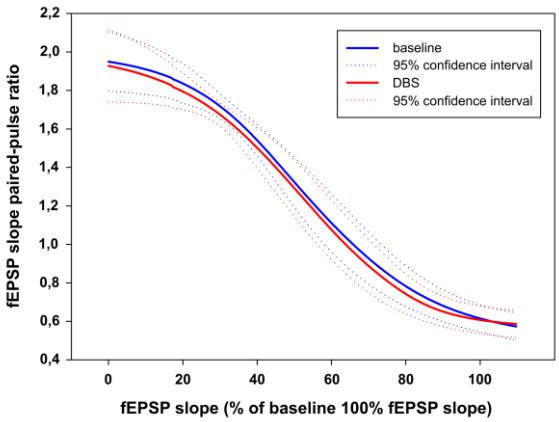


Figure 5. The fEPSP slope paired-pulse relationship was not affected by 2 days of continuous DBS. The graph shows the group average (+/- 95% confidence interval) of 16 four-parameter sigmoid curves fitted to the data of each individual rat.

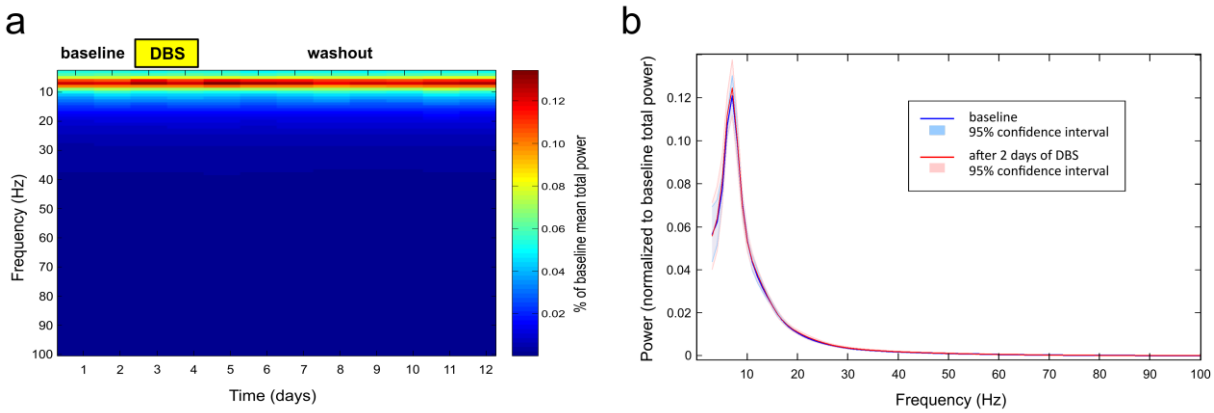


Figure 6. Two days of hippocampal DBS did not change the hippocampal LFP spectrogram that was recorded during three 7-min intervals per day during which DBS was shortly interrupted. Panel **(a)** shows the evolution of the normalized power spectra (3-100 Hz) per day before, during and after 2 days of continuous DBS. Panel **(b)** shows more detailed normalized power spectra during baseline and after 2 days of DBS. Shaded areas indicate the 95% confidence intervals. Statistical analysis could not demonstrate significant differences between DBS and sham DBS in total (3-100 Hz), theta (4-12 Hz) , beta (13-30 Hz) or gamma (31-100 Hz) band power.

1/5 and 1/29 intermittent DBS caused a progressive reduction of the fEPSP slope and the PS amplitude. At identical time points after initiation of the stimulation, however, the decrease in the fEPSP slope was larger for continuous than for 1/5 intermittent DBS, which was itself more efficacious than 1/29 intermittent DBS (see figure 7a-b). Statistically significant differences could be demonstrated for all pair wise comparisons between different stimulation conditions from the second stimulation day onwards. On the other hand, at time points reaching similar cumulative number of administered stimuli, similar effect sizes were observed for all three conditions with even slight but statistically non-significant larger fEPSP slope reductions for the less dense stimulation paradigms (see figure 7c-d).

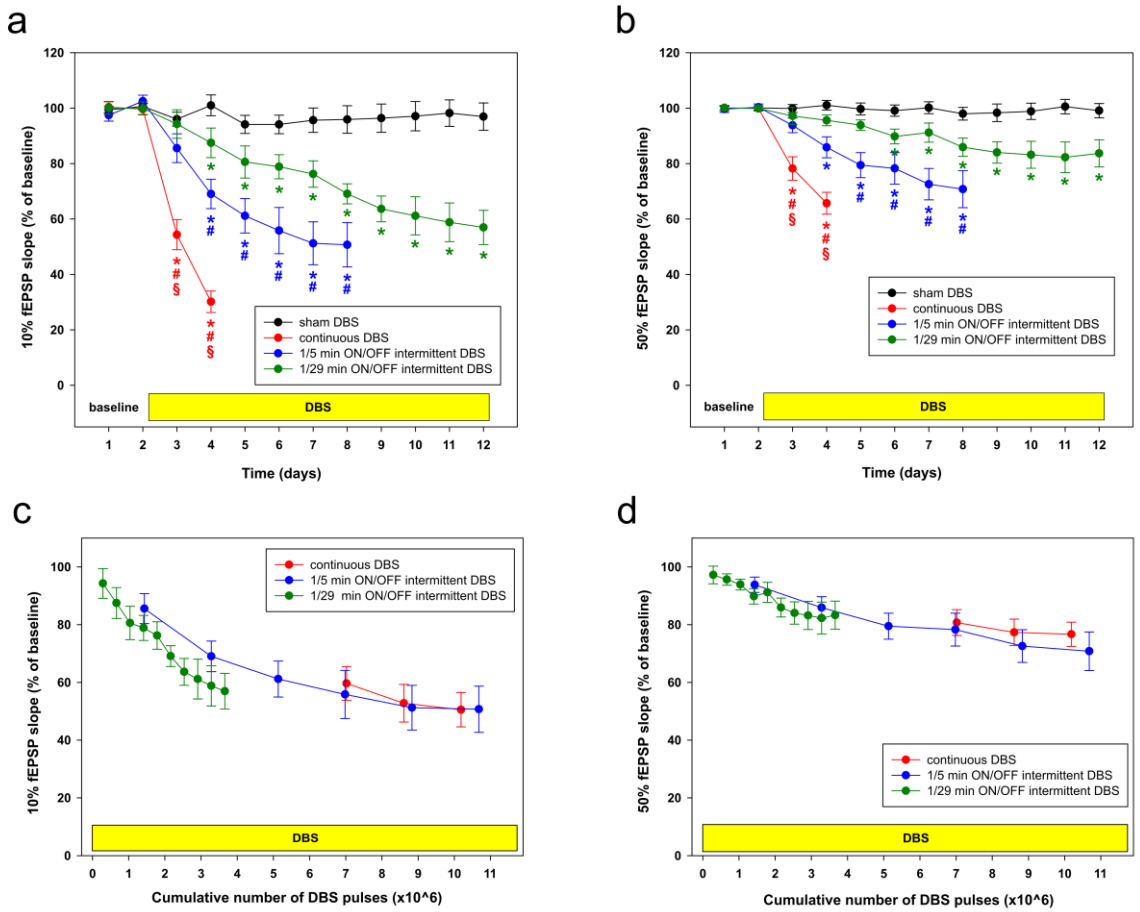


Figure 7. Effects of intermittent DBS with a 1/5 and 1/29 min ON/OFF duty cycle on the 10 **(a,c)** and 50% **(b,d)** fEPSP slopes, compared to sham and continuous DBS. In **(a)** and **(b)** mean fEPSP slope values +/- standard errors are plotted over time per day of stimulation. In **(c)** and **(d)**, they are plotted against the cumulative number of administered stimuli. Compared to sham stimulation, both 1/5 and 1/29 intermittent DBS reduced the fEPSP slopes and effects increased over time. For identical time points after the onset of DBS, however, continuous DBS showed more pronounced effects, and 1/5 was more efficacious than 1/29 intermittent DBS. Statistically significant differences are indicated with '*****', '**#**' or '**§**' where one group of the post-hoc pairwise comparison is represented by the nature of the symbol ('*****' stands for sham, '**#**' for 1/5 intermittent DBS and '**§**' for 1/29 intermittent DBS) and the other by its color. However, after identical number of cumulatively administered DBS pulses **(c,d)** similar effects sizes were found and statistical testing did not show any significant difference. This indicates a dose-response relationship where the fEPSP slope reduction is primarily dependent on the cumulative number of administered DBS pulses..

3. DBS and EPs administered through separate stimulation electrodes

In contrast to the marked reductions described above, 2 days of continuous AddSE DBS did not influence EpSE-evoked EPs in any way (n=16). This is illustrated for the 10% and 50% fEPSP slope and the 50% PS amplitude in figure 8 but it holds true for every outcome parameter that was investigated.

To exclude the possibility that the effects seen in the EpSE DBS experiment were specific to the location of the EpSE implanted under electrophysiological guidance, we also evaluated the effect of 2 days of continuous AddSE DBS on the AddSE-evoked low-intensity EPs. This experiment showed a similar 58.4 +/- 7.3% reduction of the fEPSP slope of the AddSE low-intensity EP ($t=-7.991$, $p<0.001$).

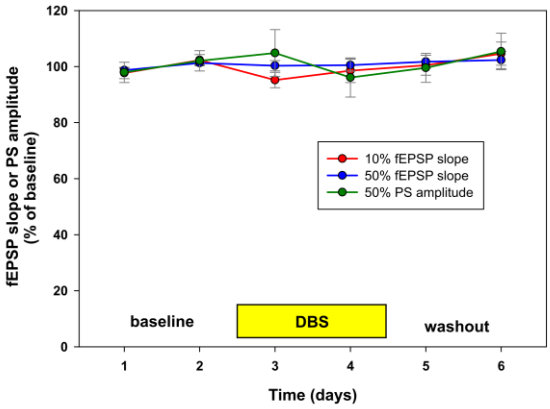


Figure 8. When DBS was administered and EPs were evoked through different stimulation electrodes ('additional stimulation electrode' and 'EP stimulation electrode', respectively), EPs were not affected by DBS. Mean values +/- standard error of the 10% fEPSP slope, 50% fEPSP slope and 50% PS amplitude are plotted over time per day.

DISCUSSION

We evaluated the effect of prolonged high-frequency hippocampal DBS on hippocampal EPs and LFPs. We demonstrated profound but input-specific fEPSP slope reductions after 2 days of continuous DBS, increasing over time and displaying a long stimulation outlasting effect. The slope reductions resulted in secondary strong PS amplitude reductions but there were no changes in postsynaptic intrinsic excitability. Similar but slower effects were observed with intermittent DBS, suggesting a dose-response relationship primarily dependent on the cumulative number of pulses administered. We found no changes in the LFP spectrogram.

Compared to the small fEPSP slope reductions observed in our previous study evaluating the effect of up to 6 min of continuous DBS and 160 min of intermittent DBS [13], the effects were much more pronounced after the longer DBS durations of the present experiment. Prior studies on the mechanism of action of DBS have almost exclusively focused on the effects of seconds to minutes of DBS. Besides technical and practical issues, this may be related to the fact that the visually eye-catching tremor suppression in Parkinson's disease occurs within seconds after turning the stimulation on. However, for other parkinsonian symptoms such as postural imbalance as well as for many other diseases treated with DBS (epilepsy, dystonia, obsessive-compulsive disorder, depression, Tourette's syndrome, cluster headache,…) it often takes hours, days, weeks or even months to achieve maximum symptom relief [8, 12, 19-27]. Besides neurogenesis and neuroprotective effects, neuroplasticity might account for these delayed improvements. Neuronal plasticity induced by DBS has been investigated in a few experiments, demonstrating the occurrence of short-term potentiation [28], long-term depression [28-31] and long-term potentiation [28, 32] in the basal ganglia after one second to one minute of high-frequency stimulation in *in vitro* preparations [28, 30-32] or anesthetized animals [29, 32]. None of these trials, however, investigated the effects of DBS durations longer than one minute.

In the present study, DBS was administered continuously for 2 days resulting in marked and increasing fEPSP slope reductions. We suggest that homeostatic plasticity might be responsible for these reductions [15, 16]. Unlike the induction of long-term potentiation or depression, homeostatic plasticity typically requires hours to days of increased or decreased activity. The continuous neuronal activation brought about by DBS is likely to exceed the homeostatic set point and thus recruit homeostatic plasticity machinery to downscale neuronal responses.

Homeostatic plasticity is a diverse phenomenon that can involve changes in synaptic strength and/or membrane excitability at different levels (network-wide, cell-autonomous or synapse-specific), loci (pre- or postsynaptic) and types of synapses (excitatory or inhibitory) [14-16, 33-36]. In this context, the pathway-specificity of the effects observed in our experiments is an important finding. This was true even if 1) recordings were obtained from the same electrode and hence probably at least in part from the same neuronal population, and 2) the cathodes of both stimulation electrodes were in the same molecular layer for the vast majority of rats though each electrode presumably did activate different axons given the absence of paired-pulse facilitation between the two electrodes.

One effect of DBS in the frame of homeostatic plasticity could be a reduction of postsynaptic membrane (intrinsic) excitability. However, this can hardly be reconciled with the fact that the fEPSP slope / PS amplitude relationship remained unaltered. Other possibilities include 1) a reduction of the presynaptic membrane (axonal) excitability, 2) downscaling synaptic strength at the level of the neurotransmitter release mechanism or 3) the postsynaptic membrane depolarization induced by receptor activation, or 4) a potentiation of postsynaptic inhibitory GABAergic synapses. The completely unaffected paired-pulse inhibition renders this last option less likely. Furthermore, the paired-pulse ratio increased in parallel to the fEPSP slope reductions, accurately following the paired-pulse relationship observed during baseline. This pattern **is** in agreement with a reduction in probability of neurotransmitter release and hence a presynaptic origin of the fEPSP slope reduction [35, 37, 38].

Homeostatic control of presynaptic neurotransmitter release has been demonstrated at the neuromuscular junction as well as in the mammalian central nervous system, including hippocampal synapses [16, 34, 39, 40]. It depends on the modulation of presynaptic calcium influx and the readily releasable pool of synaptic vesicles (e.g. by influencing voltage-gated calcium channels). Presynaptic intrinsic excitability, on the other hand, can be regulated by changes of the intrinsic electrical properties of neurons, mainly the inward and outward voltage-dependent currents [15, 33, 41]. It has been suggested that in hippocampal networks, intrinsic excitability homeostasis may be recruited first and precede synaptic mechanisms [15, 36]. Another interesting study on stimulation-induced changes in neuronal excitability was performed in the context of the development of an auditory prosthesis [42]. High-frequency stimulation (250-500 Hz but not 100 Hz) by micro-electrodes implanted in the feline cochlear nucleus induced a reduction of the compound action potential measured in the inferior colliculus. Although contrary to our data this reduction did not become more severe from day to day, it also displayed a similarly long stimulation outlasting effect.

Likewise the delayed or increasing efficacy after DBS onset, outlasting effects after cessation of DBS have been described in various disorders, including epilepsy, dystonia, Tourette's syndrome and for axial symptoms in Parkinson's disease [17, 20, 26, 43-48]. A positive correlation has been shown between the time necessary for symptom relief upon DBS initiation and symptom recurrence upon DBS cessation, suggesting a common underlying mechanism [20, 48]. The 5 to 7 days outlasting effect in our study provides a potential neurophysiological correlate for these clinically reported outlasting effects.

Desynchronization of neuronal activity is another mechanism of action proposed for DBS [4, 11, 49]. However, we did not find any change in the LFP spectrogram and thus no evidence for any reduced local neuronal network synchrony. This is in contrast with previous studies in patients with Parkinson's disease where DBS of the subthalamic nucleus or the internal globus pallidus has been shown to

suppress beta-oscillations in the subthalamic nucleus, the interal globus pallidus and the motor cortex [2, 8, 10, 11, 50, 51]. Characteristically, oscillations in this frequency band are pathologically increased in Parkinsonian patients [52, 53]. As beta activity suppression was observed both during and tens of seconds to several minutes after DBS, the fact that we only analyzed hippocampal LFP signals immediately after DBS cannot explain this discrepancy [2, 10]. However, similar reductions in beta power were also shown to be induced by dopaminergic drugs. Therefore, they probably represent a secondary consequence of DBS-induced changes rather than its primary mechanism of action [52, 54, 55]. This is further supported by the finding that DBS of the same target induces different changes in the LFP spectrogram in different diseases, typically normalizing pathological oscillations [50, 53, 56-58]. Finally, our results are in line with those of Dejean et al. who also found no effect of subthalamic nucleus DBS on the EEG spectrogram in healthy rats, whereas it reduced the pathologically increased beta activity in a rat model of Parkinson's disease [59].

DBS is typically administered continuously. This seems evident for diseases and symptoms for which DBS has no significant outlasting effects. However, in conditions for which the neuroplasticity effects of DBS become more important, continuous stimulation may be less indispensable. Continuous and intermittent DBS have been used interchangeably in epilepsy patients without substantiate grounds to prefer one strategy and intermittent DBS has shown promising results in Tourette's syndrome and depression [60-63]. We have now compared – to the best of our knowledge for the first time – the electrophysiological effects of continuous and intermittent DBS. We showed that both continuous and intermittent DBS induce strong EP reductions. For identical time points after initiation of DBS, however, the fEPSP slope reductions were more pronounced with continuous than intermittent DBS, and the 1/5 duty cycle was more efficacious than the 1/29 duty cycle. When plotted against the cumulative number of administered stimuli, however, similar fEPSP slope reductions were found with the three stimulation regimens. To what extent this dose-response relationship continues and if identical final plateau levels are reached could not be determined by our study given the unexpectedly long ongoing slope reductions observed with 1/29 min intermittent DBS. Only 2 trials have previously compared the clinical efficacy of continuous to intermittent DBS [26, 64]. They reported maintained seizure control in epilepsy patients following initiation of intermittent DBS after many months to years of continuous DBS. These studies, however, do not exclude the possibility that intermittent DBS is only capable of maintaining the beneficial effects induced by continuous DBS or obtains its effects with a slower rate. In line with our data weekly increasing effect sizes with intermittent DBS and slightly smaller or similar final effects after two weeks of intermittent and continuous DBS have been shown in preclinical models of depression [60, 61, 65].

In conclusion, we found that longer DBS durations are associated with marked and increasing fEPSP slope reductions which might reflect the recruitment of presynaptic homeostatic plasticity mechanisms. Our recordings were performed in freely moving rats with stimulation parameter settings similar to a protocol previously shown to be efficacious in epileptic rats, which adds strength to our findings [66, 67]. However, a definite relationship between the observed EP reductions and the therapeutic effect of DBS remains to be proven. A limitation of our study is that for now we only evaluated the effects in the hippocampus of healthy rats. More research is required to evaluate whether similar EP reductions are also present in other brain regions such as the basal ganglia network and in pathological brain tissue, with the possibility of disease-specific effects. Finally, our findings need validation in human subjects treated with commercially available DBS hardware systems before to impact on clinical therapy.

Acknowledgements

Mathieu Sprengers is supported by an aspirant grant provided by the Flemish Research Fund (FWO), Kristl Vonck and Robrecht Raedt by the Ghent University Special Research Funds (BOF) and Paul Boon by research grants from FWO, BOF and Ghent University Hospital.

Conflict of interests

None of the authors has any conflict of interest to disclose.

REFERENCES

[1] Beurrier C, Bioulac B, Audin J, Hammond C. High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. J Neurophysiol 2001;85(4):1351-6.

[2] Bronte-Stewart H, Barberini C, Koop MM, Hill BC, Henderson JM, Wingeier B. The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation. Exp Neurol 2009;215(1):20-8.

[3] Dostrovsky JO, Levy R, Wu JP, Hutchison WD, Tasker RR, Lozano AM. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J Neurophysiol 2000;84(1):570-4.

[4] Feng Z, Wang Z, Guo Z, Zhou W, Cai Z, Durand DM. High frequency stimulation of afferent fibers generates asynchronous firing in the downstream neurons in hippocampus through partial block of axonal conduction. Brain Res 2017;1661:67-78.

[5] Feng Z, Zheng X, Yu Y, Durand DM. Functional disconnection of axonal fibers generated by high frequency stimulation in the hippocampal CA1 region in-vivo. Brain Res 2013;1509:32-42.

[6] Grill WM, Snyder AN, Miocinovic S. Deep brain stimulation creates an informational lesion of the stimulated nucleus. Neuroreport 2004;15(7):1137-40.

[7] Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. J Neurosc 2003;23(5):1916-23.

[8] Herrington TM, Cheng JJ, Eskandar EN. Mechanisms of deep brain stimulation. J Neurophysiol 2016;115(1):19-38.

[9] Iremonger KJ, Anderson TR, Hu B, Kiss ZH. Cellular mechanisms preventing sustained activation of cortex during subcortical high-frequency stimulation. J Neurophysiol 2006;96(2):613-21.

[10] Kuhn AA, Kempf F, Brucke C, Gaynor Doyle L, Martinez-Torres I, Pogosyan A, et al. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. J Neurosc 2008;28(24):6165-73.

[11] McCairn KW, Turner RS. Deep brain stimulation of the globus pallidus internus in the parkinsonian primate: local entrainment and suppression of low-frequency oscillations. J Neurophysiol 2009;101(4):1941-60.

[12] Udupa K, Chen R. The mechanisms of action of deep brain stimulation and ideas for the future development. Prog Neurobiol 2015;133:27-49.

[13] Sprengers M, Raedt R, Larsen LE, Delbeke J, Wadman WJ, Boon P, et al. Deep brain stimulation reduces evoked potentials with a dual time course in freely moving rats: Potential neurophysiological basis for intermittent as an alternative to continuous stimulation. Epilepsia 2020.

[14] Lee KF, Soares C, Beique JC. Tuning into diversity of homeostatic synaptic plasticity. Neuropharmacology 2014;78:31-7.

[15] Turrigiano G. Too many cooks? Intrinsic and synaptic homeostatic mechanisms in cortical circuit refinement. Annu Rev Neurosci 2011;34:89-103.

[16] Turrigiano G. Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. Cold Spring Harb Perspect Biol 2012;4(1):a005736.

[17] Wyckhuys T, Raedt R, Vonck K, Wadman W, Boon P. Comparison of hippocampal Deep Brain Stimulation with high (130Hz) and low frequency (5Hz) on afterdischarges in kindled rats. Epilepsy Res 2010;88(2-3):239-46.

[18] Paxinos G, Watson C. The Rat Brain in Stereotaxic Coordinates, 6th Edition. Elsevier/Academic Press, Amsterdam, The Netherlands; 2009.

[19] Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, et al. Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 2006;31(11):2384-93.

[20] Johnson MD, Miocinovic S, McIntyre CC, Vitek JL. Mechanisms and targets of deep brain stimulation in movement disorders. Neurotherapeutics 2008;5(2):294-308.

[21] Krauss JK, Yianni J, Loher TJ, Aziz TZ. Deep brain stimulation for dystonia. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society 2004;21(1):18-30.
[22] Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biol Psychiatry 2008;64(6):461-7.
[23] Pedersen JL, Barloese M, Jensen RH. Neurostimulation in cluster headache: a review of current progress. Cephalalgia : an international journal of headache 2013;33(14):1179-93.
[24] Sachdev PS, Mohan A, Cannon E, Crawford JD, Silberstein P, Cook R, et al. Deep brain stimulation of the antero-medial globus pallidus interna for Tourette syndrome. PLoS One 2014;9(8):e104926.
[25] Servello D, Porta M, Sassi M, Brambilla A, Robertson MM. Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation. Journal of neurology, neurosurgery, and psychiatry 2008;79(2):136-42.
[26] Vonck K, Sprengers M, Carrette E, Dauwe I, Miatton M, Meurs A, et al. A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. Int J Neural Syst 2013;23(1):1250034.
[27] Yianni J, Bain PG, Gregory RP, Nandi D, Joint C, Scott RB, et al. Post-operative progress of dystonia patients following globus pallidus internus deep brain stimulation. Eur J Neurol 2003;10(3):239-47.
[28] Shen KZ, Zhu ZT, Munhall A, Johnson SW. Synaptic plasticity in rat subthalamic nucleus induced by high-frequency stimulation. Synapse 2003;50(4):314-9.
[29] Braz BY, Belforte JE, Murer MG, Galinanes GL. Properties of the corticostriatal long term depression induced by medial prefrontal cortex high frequency stimulation in vivo. Neuropharmacology 2017;121:278-86.
[30] Calabresi P, Maj R, Pisani A, Mercuri NB, Bernardi G. Long-term synaptic depression in the striatum: physiological and pharmacological characterization. J Neurosc 1992;12(11):4224-33.
[31] Yamawaki N, Magill PJ, Woodhall GL, Hall SD, Stanford IM. Frequency selectivity and dopamine-dependence of plasticity at glutamatergic synapses in the subthalamic nucleus. Neuroscience 2012;203:1-11.
[32] McCracken CB, Grace AA. High-frequency deep brain stimulation of the nucleus accumbens region suppresses neuronal activity and selectively modulates afferent drive in rat orbitofrontal cortex in vivo. J Neurosc 2007;27(46):12601-10.
[33] Echegoyen J, Neu A, Graber KD, Soltesz I. Homeostatic plasticity studied using in vivo hippocampal activity-blockade: synaptic scaling, intrinsic plasticity and age-dependence. PLoS One 2007;2(8):e700.
[34] Fernandes D, Carvalho AL. Mechanisms of homeostatic plasticity in the excitatory synapse. J Neurochem 2016;139(6):973-96.
[35] Goold CP, Nicoll RA. Single-cell optogenetic excitation drives homeostatic synaptic depression. Neuron 2010;68(3):512-28.
[36] Karmarkar UR, Buonomano DV. Different forms of homeostatic plasticity are engaged with distinct temporal profiles. Eur J Neurosci 2006;23(6):1575-84.
[37] Fioravante D, Regehr WG. Short-term forms of presynaptic plasticity. Curr Opin Neurobiol 2011;21(2):269-74.
[38] Manabe T, Wyllie DJ, Perkel DJ, Nicoll RA. Modulation of synaptic transmission and long-term potentiation: effects on paired pulse facilitation and EPSC variance in the CA1 region of the hippocampus. J Neurophysiol 1993;70(4):1451-9.
[39] Davis GW, Muller M. Homeostatic control of presynaptic neurotransmitter release. Annu Rev Physiol 2015;77:251-70.
[40] Jeans AF, van Heusden FC, Al-Mubarak B, Padamsey Z, Emptage NJ. Homeostatic Presynaptic Plasticity Is Specifically Regulated by P/Q-type Ca(2+) Channels at Mammalian Hippocampal Synapses. Cell Rep 2017;21(2):341-50.

[41] Desai NS. Homeostatic plasticity in the CNS: synaptic and intrinsic forms. J Physiol Paris 2003;97(4-6):391-402.
[42] McCreery DB, Yuen TG, Agnew WF, Bullara LA. A characterization of the effects on neuronal excitability due to prolonged microstimulation with chronically implanted microelectrodes. IEEE transactions on bio-medical engineering 1997;44(10):931-9.
[43] Hebb MO, Chiasson P, Lang AE, Brownstone RM, Mendez I. Sustained relief of dystonia following cessation of deep brain stimulation. Mov Disord 2007;22(13):1958-62.
[44] Houeto JL, Karachi C, Mallet L, Pillon B, Yelnik J, Mesnage V, et al. Tourette's syndrome and deep brain stimulation. Journal of neurology, neurosurgery, and psychiatry 2005;76(7):992-5.
[45] Motlagh MG, Smith ME, Landeros-Weisenberger A, Kobets AJ, King RA, Miravite J, et al. Lessons Learned from Open-label Deep Brain Stimulation for Tourette Syndrome: Eight Cases over 7 Years. Tremor Other Hyperkinet Mov (N Y) 2013;3.
[46] Ruge D, Cif L, Limousin P, Gonzalez V, Vasques X, Coubes P, et al. Longterm deep brain stimulation withdrawal: clinical stability despite electrophysiological instability. J Neurol Sci 2014;342(1-2):197-9.
[47] Sprengers M, Vonck K, Carrette E, Marson AG, Boon P. Deep brain and cortical stimulation for epilepsy. Cochrane Database Syst Rev 2017;7:CD008497.
[48] Temperli P, Ghika J, Villemure JG, Burkhard PR, Bogousslavsky J, Vingerhoets FJ. How do parkinsonian signs return after discontinuation of subthalamic DBS? Neurology 2003;60(1):78-81.
[49] Medeiros Dde C, Moraes MF. Focus on desynchronization rather than excitability: a new strategy for intraencephalic electrical stimulation. Epilepsy & behavior : E&B 2014;38:32-6.
[50] Brown P, Mazzone P, Oliviero A, Altibrandi MG, Pilato F, Tonali PA, et al. Effects of stimulation of the subthalamic area on oscillatory pallidal activity in Parkinson's disease. Exp Neurol 2004;188(2):480-90.
[51] Whitmer D, de Solages C, Hill B, Yu H, Henderson JM, Bronte-Stewart H. High frequency deep brain stimulation attenuates subthalamic and cortical rhythms in Parkinson's disease. Front Hum Neurosci 2012;6:155.
[52] Kuhn AA, Tsui A, Aziz T, Ray N, Brucke C, Kupsch A, et al. Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. Exp Neurol 2009;215(2):380-7.
[53] Stein E, Bar-Gad I. beta oscillations in the cortico-basal ganglia loop during parkinsonism. Exp Neurol 2013;245:52-9.
[54] Levy R, Ashby P, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO. Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. Brain 2002;125(Pt 6):1196-209.
[55] Marceglia S, Foffani G, Bianchi AM, Baselli G, Tamma F, Egidi M, et al. Dopamine-dependent non-linear correlation between subthalamic rhythms in Parkinson's disease. J Physiol 2006;571(Pt 3):579-91.
[56] Air EL, Ryapolova-Webb E, de Hemptinne C, Ostrem JL, Galifianakis NB, Larson PS, et al. Acute effects of thalamic deep brain stimulation and thalamotomy on sensorimotor cortex local field potentials in essential tremor. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2012;123(11):2232-8.
[57] Barow E, Neumann WJ, Brucke C, Huebl J, Horn A, Brown P, et al. Deep brain stimulation suppresses pallidal low frequency activity in patients with phasic dystonic movements. Brain 2014;137(Pt 11):3012-24.
[58] Maling N, Hashemiyoon R, Foote KD, Okun MS, Sanchez JC. Increased thalamic gamma band activity correlates with symptom relief following deep brain stimulation in humans with Tourette's syndrome. PLoS One 2012;7(9):e44215.
[59] Dejean C, Gross CE, Bioulac B, Boraud T. Dynamic changes in the cortex-basal ganglia network after dopamine depletion in the rat. J Neurophysiol 2008;100(1):385-96.

[60] Falowski SM, Sharan A, Reyes BA, Sikkema C, Szot P, Van Bockstaele EJ. An evaluation of neuroplasticity and behavior after deep brain stimulation of the nucleus accumbens in an animal model of depression. Neurosurgery 2011;69(6):1281-90.
[61] Meng H, Wang Y, Huang M, Lin W, Wang S, Zhang B. Chronic deep brain stimulation of the lateral habenula nucleus in a rat model of depression. Brain Res 2011;1422:32-8.
[62] Okun MS, Foote KD, Wu SS, Ward HE, Bowers D, Rodriguez RL, et al. A trial of scheduled deep brain stimulation for Tourette syndrome: moving away from continuous deep brain stimulation paradigms. JAMA neurology 2013;70(1):85-94.
[63] Rossi PJ, Opri E, Shute JB, Molina R, Bowers D, Ward H, et al. Scheduled, intermittent stimulation of the thalamus reduces tics in Tourette syndrome. Parkinsonism Relat Disord 2016;29:35-41.
[64] Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, Chen JL, et al. Long-term anterior thalamus stimulation for intractable epilepsy. Chang Gung Med J 2008;31(3):287-96.
[65] Rummel J, Voget M, Hadar R, Ewing S, Sohr R, Klein J, et al. Testing different paradigms to optimize antidepressant deep brain stimulation in different rat models of depression. J Psychiatr Res 2016;81:36-45.
[66] Van Nieuwenhuyse B, Raedt R, Delbeke J, Wadman WJ, Boon P, Vonck K. In search of optimal DBS paradigms to treat epilepsy: bilateral versus unilateral hippocampal stimulation in a rat model for temporal lobe epilepsy. Brain Stimul 2015;8(2):192-9.
[67] Van Nieuwenhuyse B, Vonck K, Raedt R, Meurs A, Wytse W, Boon PAJM. Deep Brain Stimulation Early during Epileptogenesis Modifies Disease Progression in the Hippocampus. Epilepsia 2012;53:26-7.

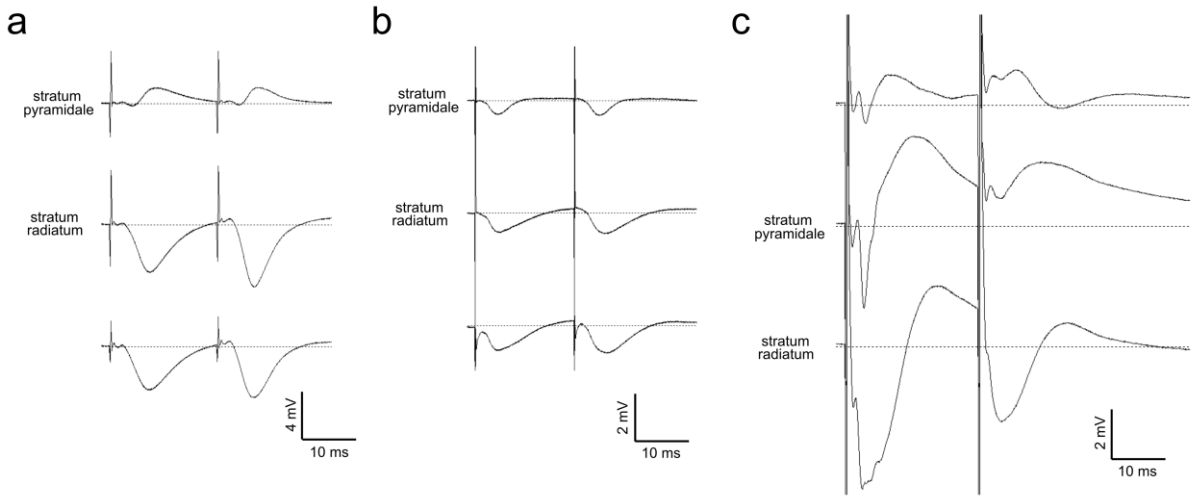


Figure S1. Low-intensity stimuli allowed to evaluate the localization of the stereotactically implanted AddSE. In 81% (13/16) of rats this confirmed cathode localization in the stratum radiatum with positive fEPSPs in the pyramidal cell layer and negative fEPSPs stratum radiatum **(a)**. In the remaining 19% (3/16) of rats, the fEPSP was negative both in the stratum radiatum and the pyramidal cell layer **(b)**. This response was similar to that obtained from the EpSE contact below the contact in the stratum radiatum and thus indicated a slightly deeper cathode localization in the dentate gyrus molecular layer with stimulation of perforant path fibers, as was confirmed by phase reversal of this negative response in the dentate gyrus molecular layer during surgery in a couple of additional rats. Despite the localization of the AddSE cathode in the stratum radiatum, typical analyzable input-output curves could not be obtained from this AddSE as higher-intensity EPs were composed of multiple components compatible with activation of nearby ortho- and antidromic neuronal elements **(c)**. The purpose of the AddSE, however, was to be used for DBS. In addition, the intensities used for DBS never exceeded those of the clearly monophasic low-intensity EPs.

PART III:
DISCUSSION & FUTURE PERSPECTIVES

CHAPTER 9

Discussion and future perspectives

Long-term outcome of hippocampal DBS in an uncontrolled trial

Despite optimal medical treatment, 30% of epilepsy patients do not achieve sustained seizure freedom [1, 2]. Temporal lobe epilepsy is the most common focal epilepsy in adults and is in particular refractory to pharmacological treatment [3, 4]. Resective surgery including anterior temporal lobectomy or selective amygdalohippocampectomy has a high success rate in these drug-resistant temporal lobe epilepsy patients [5-8]. However, many patients turn out to be unsuitable surgery candidates, are reluctant to undergo brain surgery, are not seizure-free or suffer from significant side effects such as memory loss after surgery. This leaves a large group of patients with uncontrolled seizures. DBS may be an alternative treatment for these patients. Especially the hippocampus seems an attractive stimulation target for these patients as electrophysiological, imaging and histopathological studies had previously demonstrated the involvement of the hippocampus in temporal lobe epilepsy [4, 9-12]. Its pivotal role is further confirmed by the long-term seizure freedom observed after selective amygdalohippocampectomy [11, 13, 14].

We evaluated the long-term outcome of 11 patients with drug-resistant temporal lobe epilepsy treated with hippocampal DBS [15]. This is the largest patient series on hippocampal DBS published so far (see Table 1). After a mean follow-up of 8.5 years (range 67-120 months), 6/11 patients had an excellent outcome showing a ≥90% reduction in seizure frequency, three of them being seizure-free for more than 3 years. Three patients showed moderate seizure reductions ranging between 40 and 70%, and 2/11patients were considered non-responders (<30% reduction in seizure frequency). Overall, the mean reduction in seizure frequency was 67%, the 50%-responder rate 73% and 27% of patients were seizure-free. These results are in line with those in previous and more recent trials on hippocampal DBS (see Table 1) [15-26]. In total 68 patients have been treated with hippocampal DBS so far, showing a weighted mean 66% reduction in seizure frequency, a 75% 50%-responder rate and a 25% seizure freedom rate. Similar results were also reported in (mesial) temporal lobe epilepsy patients treated with anterior thalamic DBS or responsive stimulation of the ictal-onset zone. Median reductions in seizure frequency were 44% (n=59) and 76% (n=33) after 1 and 5 years of ATN DBS, respectively [27]. At 5 years of follow-up, 19% of all patients treated with ATN DBS were seizure free for at least 6 months. The rate of seizure freedom amongst the temporal lobe epilepsy patients, however, was not reported nor was the exact duration of seizure freedom. Responsive stimulation of the ictal-onset zone in mesial temporal lobe epilepsy patients (n=82) was associated with a 67% median reduction in disabling seizures after 6 years of follow-up, with 65% of patients showing a ≥50% reduction in seizure frequency [28]. At 6 years of follow-up 21% of patients were seizure-free for at least 3 months. The proportion of patients experiencing sustained seizure freedom was not mentioned, but was lower as only 15% of patients were seizure-free for ≥1 year at any time during the 6-year evaluation period. Although it definitely needs further study, seizure freedom could occur somewhat more often with hippocampal DBS compared to ATN DBS and responsive ictal-onset zone stimulation. Without any doubt, however, these outcomes remain clearly inferior to those following resective surgery where long-term seizure freedom is observed in up to 70-80% of patients [5-8].

Study	Number of Patients	Follow-up (months)	% Seizure Reduction	Responder Rate	Seizure Freedom
Tellez-Zenteno et al. 2006*	4	3x 1	26%[§]	25%[§]	0%[§]
McLachlan et al. 2007*	2	3	33%[¶]	0%[¶]	0%[¶]
Velasco et al. 2007	9	18-84	84%	100%	44%
Boëx et al. 2011	8	12-74	67%	75%	25%
Vonck et al. 2013	11	67-120	67%	73%	27%
Min et al. 2013	2	18-36	78%	100%	0%
Wiebe et al. 2013*	2 (+4)	6	45%[+]	50%[+]	0%[+]
Cukiert et al. 2014	9	15-50	58%	78%	11%
Jin et al. 2016	3	26-43	93%	100%	0%
Lim et al. 2016	5	30-42	45%	60%	0%
Ding et al. 2016	5	18-24	96%	100%	80%
Cukiert et al. 2017*[#]	8 (+8)	6	71%[&]	75%[&]	38%[&]

* Randomized controlled trial; [#]outcome evaluated at month 5-6 compared to baseline; [§] 15, 0 and 0% respectively when comparing to sham stimulation; [¶] 29, 0 and 0% compared to sham stimulation; [+] 105, 50 and 0% compared to sham stimulation; [&] 64, 75 and 38% compared to sham stimulation

Table 1: Overview of trials on hippocampal DBS

None of our patients experienced permanent symptomatic neurological or systemic side effects. Complications related to the hardware and surgical procedure included an asymptomatic intracranial haemorrhage, a cable revision and a local infection not resolving by administration of systemic antibiotics urging temporary hardware removal. Similar surgical / hardware complications have been reported in other trials on hippocampal DBS, including skin erosions (n=3; 1 hardware removal), electrode dislocations necessitating a reimplantation procedure (n=2) and an infection around the pulse generator (n=1; 1 hardware removal) [15-26]. In the two largest trials on DBS, electrode implantation resulted in postoperative asymptomatic intracranial haemorrhage in 1.6% to 3.7% of the patients and 2.0% to 4.5% had postoperative soft tissue infections (9.4% to 12.7% after five years) [27-31]. As in our trial, none of the patient reported permanent symptomatic sequelae. None of the patient in our trial reported stimulation-related adverse events. Formal testing did not show neuropsychological deterioration, even in patients with bilateral hippocampal DBS [32]. This is in line with other trials on hippocampal DBS, although it should be noticed that formal neuropsychological testing was only performed in a small minority of patients [15-26].

Considering the refractory nature of the epilepsy of the patients included in the trials on hippocampal DBS, it is reasonable to state that the overall outcome of hippocampal DBS is quite favorable. Nevertheless, most patients do not become seizure-free and some patients even do not show any improvement upon initiation of DBS. Next to optimization of the stimulation protocol, the identification of factors associated with a poor or favorable outcome can help to increase the proportion of patients experiencing a beneficial outcome. Velasco and colleagues, one of the pioneers of the modern area of DBS in epilepsy, reported a significant worse and delayed efficacy of hippocampal DBS in the presence of hippocampal sclerosis [25]. Whereas 4/5 patients with a normal

MRI were seizure-free within 2 months, 4 patients with hippocampal sclerosis showed more gradual improvements with moderate 50-70% reductions after 6-8 months of DBS. The three patients with hippocampal sclerosis in our trial, however, did not display an inferior outcome compared to those with a normal MRI: 2 were seizure-free (one without active stimulation at the end of follow-up) and the other experienced a 50% seizure reduction. This is in line with other trials on hippocampal DBS showing similar outcomes in patients with and without hippocampal sclerosis [16, 17, 21] or even a more beneficial outcome in the hippocampal sclerosis subgroup [18, 19]. Boëx and colleagues did report the need for a larger area of stimulation and/or higher stimulation intensities in the presence of hippocampal sclerosis and hypothesized that suboptimal stimulation settings could be responsible for the less beneficial outcome in the hippocampal sclerosis patients of Velasco and colleagues [16]. In summary, based on current evidence the presence of hippocampal sclerosis should not be considered as an argument to refrain from hippocampal DBS.

A patient subgroup showing an excellent outcome were 4 patients with a unilateral focal ictal onset, defined as restricted to one or more contacts of a single depth electrode. Two of these were seizure-free and 2 experienced a ≥90% seizure reduction. A more variable outcome was observed in 5 patients with a regional unilateral ictal onset referring to a more widespread distribution of early ictal discharges involving several electrode contacts on different electrodes. One out of five patients was seizure-free, 2/5 showed a 70 and ≥90% seizure reduction and 2/5 were non-responders. This less favorable outcome is probably related to the fact that in patients with a regional ictal onset the electrodes are located and hence DBS is administered relatively more distant or in only a part of the epileptogenic region. Although not excluding more widespread effects, this finding is compatible with local and/or input-specific mechanisms of action of DBS. Both a focal and regional unilateral ictal onset do not necessarily exclude resective surgery, although less favourable outcomes have been reported in the latter [33]. In contrast, patients with a bilateral ictal onset are per definition no suitable candidates for curative resective surgery. From a clinical point of view hippocampal DBS is therefore an attractive alternative treatment especially for these patients. The 40-50% seizure reductions observed in the 2 patients with a bilateral ictal onset in our patient series are in this respect somewhat disappointing. Four other trials have previously evaluated the use of hippocampal DBS in patients with a bilateral ictal onset [16, 18, 22, 25]. Three of these included both patients with a uni- and bilateral ictal onset. Calculating the treatment effect for each group does not confirm the worse outcome in patients with a bilateral ictal onset observed in our study and shows even slightly superior results in this patient subgroup (unilateral versus bilateral ictal onset): 75 vs 96% in Velasco et al., 52 vs 77% in Boëx et al. and 65 vs 82% in Cukiert et al. [16, 18, 25]. Another potential treatment approach for patients with a bilateral ictal onset was reported by Ding and colleagues [19]. After failure of unilateral anterior lobectomy in 5 patients with intractable bilateral temporal lobe epilepsy, contralateral hippocampal DBS was initiated and resulted into seizure freedom in 4/5 patients and a 80% seizure reduction in the remaining patient. In conclusion, hippocampal DBS could play a significant role in the treatment of drug-resistant bitemporal epilepsy patients in the future.

Stimulation parameters used for DBS in epilepsy patients have mainly been chosen empirically. Of the different stimulation parameters, the stimulation frequency has been studied most intensively. We used high-frequency stimulation (130 Hz), which is similar to most of the other trials with DBS in epilepsy (>100-130 Hz) including all trials with ATN, STN and nucleus accumbens DBS, as well as most trials with hippocampal DBS and motor cortex stimulation [15-20, 22-26, 34-55]. This is probably related to previous experience in movement disorders including Parkinson's disease and essential

tremor where high-frequency stimulation has been found to be superior to lower stimulation frequencies [56-60]. On the other hand, lower stimulation frequencies were used in most trials with cerebellar stimulation (10 Hz) [61-64] and caudate nucleus DBS (4-8 Hz) [65], various studies on centromedian thalamic DBS (60-65 Hz) [66-70] and occasionally in hippocampal DBS [21] and motor cortex stimulation [38]. Various preclinical studies did find positive effects of low-frequency stimulation on reducing seizure(-like) activity [71]. Studies directly comparing the efficacy of low- to high-frequency stimulation are sparse. Boex and colleagus reported a suppression of interictal epileptiform discharges in 3/3 drug-resistant temporal lobe epilepsy patients with high-frequency hippocampal DBS (130 Hz), whereas low-frequency (5 Hz) stimulation increased these in 2/3 patients and had no effect in 1/3 patients [72]. High-frequency (130 Hz) hippocampal DBS was also more effective than low-frequency (5 Hz) stimulation in the rapid kindling rat model of epilepsy [71]. Lim and colleagues did not observe a major difference in seizure frequency reduction between high- (90-180 Hz) and low-frequency (5 Hz) hippocampal DBS in 3 patients [21]. Low-frequency DBS of the caudate nucleus was even found to be superior to high-frequency DBS in reducing interictal epileptiform discharges, indicating that the optimal stimulation frequency could be target-specific. This target-specificity was also observed in Parkinson's disease, where lower stimulation frequencies (20-80 Hz) are used for peduncolopontine DBS [73]. Child and colleagues even reported patient-specific optimal stimulation frequencies, with high-frequency motor cortex stimulation being superior to low-frequency stimulation in one epilepsy patient, whereas the opposite was observed in another patient [38].

The optimal stimulation intensity (determined by the output voltage / current and pulse-width, see Chapter 2) is another programmable stimulation parameter that has been less well studied. In previous trials, heterogeneous stimulation intensities have been used and yielded favorable results, with the voltage ranging between 0.5 and 14V (some studies expressed the output as current intensity, ranging from <0.5 to >7 mA) and the pulse width between 60 and 450 μs. In many of the initial studies, the intensity used was chosen relatively arbitrarily, although often at least based on previous experience with DBS in movement disorders. In other trials, the intensity was based on the threshold for conscious appreciation or on some vague neurophysiological parameters. From a safety point of view, too high stimulation intensities and longer pulse widths were avoided as these may induce seizures and cause irreversible tissue damage. After the initial trials had been published and shown positive results, more recent studies often based their protocol on the parameter settings used in these studies. We evaluated the relationship between the stimulation intensity and the clinical outcome to increase our knowledge on this issue. At maximum follow-up we did not observe a correlation between the output-voltage and the eventual outcome. This is in line with the open-label follow-up data of the SANTE trial, reporting no favorable trend towards any stimulation parameter when comparing responders and nonresponders at year 2 to 5 [27]. Although absent on a group level, there does seem to be a patient-specific optimal stimulation intensity (range). Increasing the stimulation voltage was not intimately associated with changes in seizure frequency in most patients in our trial. Two patients, however, became seizure-free shortly after stimulation voltage increments suggesting (not proving) a causal relationship. Improved seizure control by individually optimizing the stimulation parameters has also been reported in various other trials [16, 23, 27, 55, 67, 74]. The need for an individually optimized stimulation intensity is further supported by the reproducible increase in seizure frequency observed after a minor stimulation intensity increase in one other patient from our series. Similar increases in seizure frequency following stimulation intensity increments have been reported in various other trials

[17, 29, 55, 67]. Although only observed in a small minority of patients, it highlights the importance of employing a 'start low go slow' approach in analogy to the titration strategy used for antiepileptic drugs.

Another potential strategy to develop more efficacious stimulation protocols could be to combine DBS of the ictal onset zone and a remote network structure. Numerous studies have demonstrated the involvement of the contralateral medial temporal lobe in the epileptic network of unilateral temporal lobe epilepsy. Structural, metabolic/functional and nonepileptic clinical involvement of the contralateral medial temporal lobe has been shown [75-84]. Moreover, temporal lobe seizures often spread to the contralateral temporal lobe and there is evidence for both indirect (via the frontal lobes) and direct (dorsal hippocampal commissure, anterior commissure, corpus callosum) propagation pathways [10, 77, 85-101]. In our trial, contralateral and hence bilateral hippocampal stimulation was initiated in five patients with unilateral temporal lobe epilepsy in whom unilateral DBS failed to decrease seizures by ≥90% after 2.5-3 years. This resulted in improved seizure control in 3 of these patients. The 25, 75 and 83% reductions in seizure frequency with unilateral DBS increased to 95, 100 and 92% reductions with bilateral stimulation, corresponding to 93, 100 and 50% relative seizure reductions, respectively. Although the possibility of bitemporal lobe epilepsy with rare seizures originating from the contralateral temporal lobe cannot be ruled out with complete certainty, it seems unlikely to fully explain the observed improvements. Hence, we hypothesize that the improved seizure control results from the combined stimulation of the ictal onset zone and a remote network structure. To our knowledge, we were the first to investigate such a combined stimulation protocol. Except for Boex and colleagues who demonstrated the efficacy of unilateral DBS for bilateral temporal lobe epilepsy, previous trials had always evaluated the efficacy of uni- and bilateral stimulation for uni- and bilateral temporal lobe epilepsy, respectively [15-26]. Since the publication of our manuscript, however, bilateral DBS for unilateral temporal lobe epilepsy has been evaluated in three more trials. Lim and colleagues reported a similar efficacy of unilateral DBS in 2 clear-cut unilateral temporal lobe epilepsy patients (-48%) and bilateral DBS in 3 unilateral temporal lobe epilepsy patients with bilateral interictal epileptiform discharges (with or without contralateral hippocampal sclerosis) (-44%). Initiation of bilateral DBS in another trial in one patient with unilateral temporal lobe epilepsy showing an 88% seizure reduction with unilateral DBS was associated with only a subtle and clinically non-significant further -23% relative improvement [20]. Finally, Cukiert and colleagues reported no benefit of switching from uni- to bilateral hippocampal DBS in 2 unilateral temporal lobe epilepsy patients with bilateral interictal epileptiform discharges or bilateral hippocampal sclerosis who had previously not shown any improvement with unilateral DBS [17]. On the contrary, bilateral hippocampal DBS was clearly superior to unilateral DBS in the intraperitoneal kainic acid rat model of temporal lobe epilepsy [102]. This finding should be interpreted with caution, however, as the latter is rather a model of bilateral than unilateral temporal lobe epilepsy. Until now only one clinical trial has evaluated the combined stimulation of two different network structures. Additional ATN DBS was not associated with further improvement in three responders to nucleus accumbens DBS [45]. In conclusion, our results suggest a potential superior efficacy of combined stimulation of different stimulation targets involved in the epileptic network. However, more recent trials could not confirm this in some additional patients. Given the limited number of patients, more research is definitely indicated.

Another issue with regards to the stimulation protocol is whether stimulation pulses should be administered either continuously or intermittently and until now both paradigms have been used interchangeably. Most trials on hippocampal [16, 17, 19, 20, 22, 24], motor cortex [38, 103, 104] and

STN [34, 36, 37, 41, 48, 55] stimulation have used continuous stimulation protocols, whereas intermittent stimulation has been employed in the majority of trials on ATN [29, 42, 43, 46, 50, 105], CMT [54, 66, 68-70], nucleus accumbens [45, 52] and cerebellar [62-64] stimulation. However, continuous stimulation has also been investigated in trials on ATN [35, 49, 105] and CMT [39, 53, 67] DBS, and intermittent stimulation has also been explored in hippocampal DBS [21, 23, 25]. Both stimulation paradigms have been associated with significant reductions in seizure frequency, without good arguments to prefer one strategy above the other. Furthermore, intermittent has been administered with different duty cycles, including 1/1 min ON/OFF, 4/4 min ON/OFF, 8/8 min ON/OFF, 1/4 min ON/OFF, 1/5 min ON/OFF, 2 or 24 hours per day,… We investigated another intermittent stimulation paradigm that we called 'day-night cycling', consisting of 18 hours with DBS 'on' (6 am to 12 pm) followed by 6 hours with DBS 'off' (12 pm to 6 am). In 4/5 patients including one patient with nightly seizures this strategy did not affect seizure control, whereas in one patient it seemed to be associated with an increase in seizure frequency upon which continuous stimulation was successfully reinstalled. Previously, continuous stimulation has been compared to intermittent stimulation in the same patients in only one trial and no differences were found [21]. This preliminary evidence on the initiation of intermittent stimulation after a stable seizure frequency reduction has been reached with continuous stimulation offers the potential advantage to increase the battery life of the pulse generator. More interestingly, however, it suggests an outlasting effect of DBS in epilepsy.

This potential outlasting effect was further investigated by reviewing the evolution of the seizure frequency following intentional or accidental DBS discontinuation for at least one month in 7 DBS responders. Only in 2/7 patients this was associated with an immediate significant increase in seizure frequency. A subtler increase was observed in 1/7 patients, and in 2/7 patients the seizure frequency remained unchanged during several months without DBS. In one patient the seizure frequency did not increase for 17 months after which it gradually increased from 5 to 12-18 seizures per month. Upon reinstallation of DBS, his seizure frequency decreased for a second time. Finally, in 1/7 patients DBS discontinuation was associated with the introduction of clonazepam 1 mg, leading to sustained seizure freedom. These seizure frequency evolutions suggest that DBS in epilepsy could have both immediate direct effects requiring ongoing stimulation (3/7 patients) and longer-lasting effects not (immediately) subsiding upon DBS discontinuation as observed in 4/7 patients. Moreover, the pronounced effect of the very low dose of clonazepam in the last patient is possibly in part also mediated by long-lasting network changes induced by prior DBS. Our findings are in line with previous anecdotal reports describing immediate increases in seizure frequency [24, 25, 38, 40, 43, 103, 105] as well as outlasting effects [22, 35, 38, 51, 74, 104-107] after DBS discontinuation. We now evaluated and confirmed this in a larger patient group. Similar analyses were performed in two other trials. A more recent trial by Cukiert and colleagues reported the seizure outcome after battery depletion in a group of 9 patients [108]. An increase in seizure frequency was observed in 7/9 patients but in 5/7 patients the seizure frequency remained well below the baseline seizure frequency. In 2/9 patients, the seizure frequency was unaffected. Hence, similar to our findings they found evidence for both immediate (7/9 patients) and longer-lasting (7/9 patients) effects of DBS. Similar findings were reported by Boex and colleagues who observed an immediate increase in seizure frequency following DBS discontinuation in 2/4 patients and an unchanged seizure control in the 2 other patients [16]. The uncontrolled trial design cannot exclude the possibility that the outlasting effects result from a microlesion effect due to electrode implantation or the natural evolution of the disease [16, 109-115]. However, improved seizure control in many patients only occurs after initiation of stimulation. Moreover, the delayed

increase in seizure frequency in one of our patients indicates a potential reversibility of the DBS-induced outlasting effects, as has been reported previously [22, 25]. Also, an increasing efficacy over time is often observed in DBS trials, and therefore it is likely that DBS has true neuromodulatory properties resulting into a true outlasting effect. As outlined in Chapter 4 and below, these neuromodulatory effects have been suggested to result from neuroplasticity, neuroprotective and neurogenesis changes induced by DBS. The EP reductions clearly outlasting the duration of hippocampal DBS in our animal study in healthy rats provide one of the potential neurophysiological correlates for this clinical observation (see Chapter 8 and below) [116].

Numerous trials on DBS in epilepsy have reported increased efficacy over time [19-21, 25, 27-31, 40, 44, 50, 51, 54, 63]. The mean duration of follow-up in our study was 8.5 years which is to our knowledge the longest of all DBS trials in epilepsy. This makes our study suitable to evaluate a potential increasing efficacy over time. When studying the evolution of the mean seizure frequency in our study, a trend for increasing efficacy over time could indeed be appreciated (see figure 1). The limited number of patients included in our trial further allowed to investigate this trend in more detail on an individual patient basis. For a specific stimulation protocol efficacy tended to increase for up to 18-24 months. Further improvements beyond this time frame occurred in many patients but these seemed to be related to adjustments in the stimulation protocol (n=5, augmentation of stimulation voltage or initiation of bilateral DBS in unilateral epilepsy) or changes in the antiepileptic drug regimen (n=2-3). The uncontrolled open-label design of most studies cannot exclude some contribution of such changes in other trials reporting increasing efficacy over time. However, improvements have also been described with an unchanged therapeutic regimen. The most solid evidence on this issue probably comes from the two largest RCTs on cortical and deep brain stimulation, reporting an increasing effect size during the blinded evaluation period with fixed stimulation parameters and unchanged antiepileptic drug regimens [29, 31]. The potential biological mechanisms behind this increasing efficacy over time remain incompletely understood but are likely at least in part similar to those responsible for the outlasting effect observed after cessation of DBS, including neuroplasticity, neurogenesis and neuroprotective effects (see Chapter 4 and below).

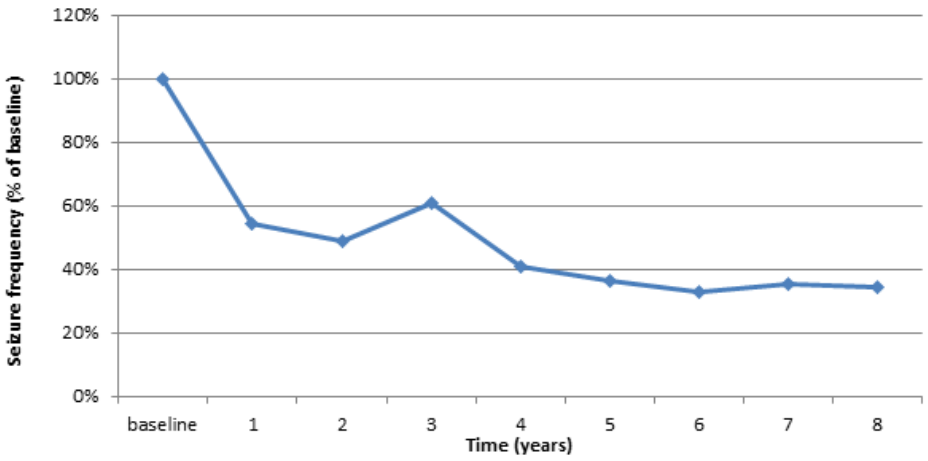


Figure 1: Evolution of the mean seizure frequency after initiation of hippocampal DBS, compared to the baseline seizure frequency. A 'last observation carried forward' approach is used for the missing data in year 3-4 for patient 7 and in year 7-8 for patient 11.

Systematic review and meta-analysis on deep brain and cortical stimulation in epilepsy

Notwithstanding that our and other uncontrolled nonblinded trials provide an invaluable source of knowledge even in the modern area of evidence-based medicine, these trials are at risk for many types of bias. We therefore critically reviewed the current evidence on deep brain and cortical stimulation in epilepsy by performing a systematic review and meta-analysis including only RCTs. The review was first published in 2014 and updated in 2017 [117, 118].

We identified 12 RCTs comparing active versus sham stimulation. Two of these were larger and included more than 100 patients: one trial on ATN DBS for (multi)focal epilepsy (n=109) and one trial on responsive stimulation of the ictal onset zone for patients with one or two epileptogenic regions (n=191) [29, 31]. All other trials were small: four trials on hippocampal DBS for medial temporal lobe epilepsy (n=15; 21 treatment periods due to the cross-over design in some trials), three trials on cerebellar stimulation for (multi)focal or generalized epilepsy (n=22; 39 treatment periods), two trials on centromedian thalamic DBS for (multi)focal or generalized epilepsy (n=20; 40 treatment periods) and one trial on nucleus accumbens DBS (n=4; 8 treatment periods).

For all these trials the published information and data was incomplete for a full judgement of the risk of bias and/or incorporation in the meta-analysis. Eight research groups provided us this unpublished additional data upon our request [22, 25, 29, 31, 45, 63, 66, 107]. Two research groups did not have time or could not provide us with the missing data [24, 26] and the two research groups of the oldest studies could not be reached anymore [62, 64]. Apart from some uncertainty about the risk of bias in these 4 trials, the risk of bias was in general judged as being low. Nevertheless, there was a high risk of selective reporting bias in three trials, a high risk of bias due to incomplete outcome data in one trial and an inadequate blinding procedure in another trial. Next to these 'classical' types of bias, we also evaluated the risk of an underestimation of the treatment effect due to changes in the antiepileptic drug regimen (present in one trial) and the risk of outlasting effects due to prior stimulation in cross-over trials without a sufficient washout period between the active and sham stimulation period. As outlined above, various trials have reported outlasting effects of DBS in epilepsy [15, 22, 25, 35, 38, 51, 74, 104-107] which could lead to an underestimation of the treatment effect in cross-over trials without a sufficient washout period. Washout periods were absent in four trials and judged to be too short (one month after three months of DBS) in one trial. We recognize that clear judgements on this issue are difficult and arbitrary as long as this outlasting effect is not investigated in more detail in randomized controlled conditions. We therefore rated the risk of bias in these five trials as 'uncertain' rather than 'high'.

The treatment effect was calculated and/or described for the following outcome parameters: seizure freedom (primary outcome measure), 50%-responder rate (primary outcome measure), percentage seizure frequency reduction, adverse events, neuropsychological outcome and quality of life. The quality of the evidence was rated for each outcome parameter per stimulation target according to the GRADE scoring system. Apart from some risk of bias in individual trials as described above, the main reason to downgrade the quality of the evidence was the limited number of trials and subjects leading to a considerable amount of uncertainty with regards to the observed effects. On the other hand, the GRADE score for the percentage seizure frequency reduction with ATN DBS and responsive stimulation of the ictal onset zone could be upgraded because of a clear trend for an increasing efficacy over time.

Moderate-quality evidence could not demonstrate statistically significant changes in the proportion of patients who were seizure-free (odds ratios (OR) 0.33, 95% confidence interval (CI) 0.01 to 8.36) or experienced a ≥50% reduction in seizure frequency (OR 1.20, 95% CI 0.52 to 2.80) after three months of ANT DBS. The observed effect sizes were in addition considered as being not clinically significant. In contrast, there is high-quality evidence showing a moderate but statistically significant -17.4% (95% CI -31.2 to -1.0) reduction in seizure frequency. DBS was associated with higher rates of self-reported depression (14.8 versus 1.8%, p=0.02) and subjective memory impairment (13.8 versus 1.8%) but fewer epilepsy-associated injuries (7.4 versus 25.5%, p=0.01) (moderate-quality evidence). Electrode implantation resulted in postoperative asymptomatic intracranial haemorraghe in 3.7% of patients, 4.5% had postoperative soft tissue infections increasing to 12.7% after five years and repeated surgery was required in 8.2% of subjects due to initial electrode implantation outside the target. None of these patients experienced permanent symptomatic sequelae. In contrast to the subjective impairments in memory and mood, neuropsychological testing results on the group level did not change (moderate-quality evidence). Finally, there is high-quality evidence that ATN DBS does not result into clinically meaningful changes in quality of life after three months of stimulation.

The quality of evidence on responsive stimulation of the ictal onset zone was in general similar to that on ATN DBS. There were neither clinically nor statistically significant changes in seizure freedom (OR 4.95, 95% CI 0.23 to 104.44) or the 50%-responder rate (OR 1.12 [95% CI 0.59 to 2.11]). Similar to ATN DBS, however, there is high-quality evidence showing a moderate -24.9% (95% CI -40.1 to -6.0) reduction in seizure frequency. There were no stimulation-related adverse events with responsive stimulation of the ictal onset zone (moderate-quality evidence). Surgical complications included postoperative asymptomatic intracranial haemorraghes (1.6%) and postoperative soft tissue infections (2.0%) increasing to 9.4% after five years. These complications never resulted into permanent neurological or other sequelae. The cranial implantation of the neurostimulator was the probable cause of most adverse events, including implant site pain (16% in the first year), procedural headache (11%), headache (9%) and dysaesthesia (6%). There is high-quality evidence that 3 months of responsive ictal onset zone stimulation does not cause clinically significant changes in the neuropsychological outcome or the quality of life.

With regards to hippocampal DBS in medial temporal lobe epilepsy, there were no statistically or clinically significant changes in seizure freedom (OR 1.03, 95% CI 0.21 to 5.15; moderate-quality evidence) or 50%-responder rate (OR 1.20, 95% CI 0.36 to 4.01; low-quality evidence). Similar to ATN and responsive ictal onset zone stimulation, however, a moderate but statistically significant -28.1% (95% CI -34.1 to -22.2) reduction in seizure frequency was found (moderate-quality evidence). There were no obvious stimulation-related adverse events or significant changes in the neuropsychological outcome and the quality of life but evidence on these issues is of only low to very low quality. In particular, possible memory deterioration with hippocampal DBS needs further study.

There is moderate-quality evidence that cerebellar stimulation does not result into significant increases in seizure freedom (OR 0.96, 95% CI 0.22 to 4.12). The 50%-responder rate (OR 2.43) was the highest amongst all different stimulation targets but 95% confidence intervals are wide (0.46 to 12.84) and evidence was of only low quality. Cerebellar stimulation was associated with a statistically non-significant -12.4% lower seizure frequency compared to sham stimulation (95% CI -35.3 to +10.6) (low-quality evidence). There were no stimulation-related adverse events (low-quality of evidence) but 6/22

patients needed repeated surgery due to electrode migration. The quality of the evidence on the neuropsychological outcome and quality of life was rated as very low.

One trial has studied nucleus accumbens DBS. It was methodologically well-designed but included only 4 patients (8 treatment periods), resulting into an overall low quality of evidence. Promising results were reported, but more trials are needed to allow a more accurate estimation of the 50%-responder rate (OR 10.0, 95% CI 0.53 to 189.15) and seizure frequency reduction (-33.8%, 95% CI -100 to +49.8%). The possible higher incidence of depression should be closely monitored.

The overall evidence on centromedian thalamic DBS is of only very low quality and more studies are required before judgements on its therapeutic potential can be made.

As outlined above, current evidence is strongly limited by the small number of trials and patients that have participated in RCTs on deep brain and cortical stimulation. More, larger and well-designed trials are needed. In addition, neuropsychological testing and assessment of quality of life was only performed in a subset of trials. Another very important shortcoming of the current evidence is the limited duration of the RCTs that have been performed with blinded evaluation periods ranging between one and three months except for one small trial on hippocampal DBS [26]. This is of particular concern as increasing efficacy over time has been reported during the blinded evaluation in the two largest RCTs [29, 31], during open-label follow-up after completion of RCTs [25, 27-31, 63, 66, 107] and in various uncontrolled open-label trials [15, 19-21, 40, 44, 50, 51, 54]. Comparing cortical or deep brain stimulation to best medical practice could overcome ethical issues associated with extended blinded evaluation periods. Furthermore, current evidence is limited to the type of patients that have been included in the RCTs: (multi)focal epilepsy for ATN and nucleus accumbens DBS, (multi)focal epilepsy with one or two epileptogenic regions for responsive ictal onset zone stimulation, medial temporal lobe epilepsy for hippocampal DBS and (multi)focal and generalized epilepsy for cerebellar and centromedian thalamic stimulation. Only one RCT on centromedian thalamic DBS included a substantial number of minors (5/13), reporting that skin erosion may be of particular concern in children under eight years of age due to the relatively large size of the pulse generator originally designed for an adult population. Evidence on ATN DBS is further limited to patients with normal mental capacities (intelligence quotient >70).

The absence of statistically or clinically significant effects on seizure freedom and the 50%-responder rate, as well as the only moderate 15-30% reductions in seizure frequency with ATN DBS, hippocampal DBS and responsive ictal onset zone stimulation are in contrast with he much more favorable results in uncontrolled open-label trials. For example, in uncontrolled open-label trials hippocampal DBS was associated with a weighted mean 66% reduction in seizure frequency, a 75% 50%-responder rate and a 25% seizure freedom rate. Similar reductions in seizure frequency and responder rates have also been reported in the vast majority of uncontrolled nonblinded trials on / follow-up of anterior thalamic DBS and responsive ictal onset zone stimulation (see Chapter 4) [27, 28, 30, 35, 42, 43, 46, 49-51, 105, 119].

Therefore, an important question is: why are the results reported in randomized controlled trials on deep brain and cortical stimulation so dramatically inferior to those observed in uncontrolled unblinded conditions? We believe that multiple factors could explain these discrepant results:

1) Placebo effect

The mere fact of being included in a trial is typically associated with the finding of clinical improvement of patients. Seizure frequency reductions are compared to sham stimulation in RCTs, filtering out the placebo effect. In contrast, the placebo effect can contribute to the observed improvements in uncontrolled trials in which seizure frequency is compared to the baseline seizure frequency. Placebo responses involve several mechanisms such as psychological influences including classical (Pavlovian) conditioning, patient expectations and the Hawthorne effect, i.e. the subjects' awareness of being studied impacts their behavior which can lead to improvement regardless of the treatment arm [120-122]. Multiple meta-analyses have estimated 50%-responder rates between 9.3 and 16.6% in the placebo arms of RCTs on antiepileptic drugs [123-125]. A similar 16-20% responder rate was observed in device trials evaluating repetitive transcranial magnetic stimulation in epilepsy [126].

2) Implantation and microlesional effects

Intracranial electrode implantation has been associated with reductions in seizure frequency prior to initiation of any stimulation [17, 18, 23, 29, 31, 42, 67, 105, 127]. A distinction should be made between implantation and microlesional effects. The implantation effect is per definition temporary typically lasting several weeks to months [17, 29, 31]. The biological mechanism behind the implantation effect is incompletely understood. It may be related to the effects of anesthesia, temporary disturbance of local neural activity, tissue edema or a local release of adenosine following electrode implantation [128]. Interestingly, craniotomy alone has been followed by seizure remission and trepanation was used as treatment of epilepsy by various ancient people [129]. On the contrary, microlesional effects are permanent. Sustained seizure freedom following electrode implantation in the context of diagnostic invasive EEG monitoring has been reported previously [111, 114]. Such sustained improvements are likely to result from the interruption of crucial seizure propagation pathways, actually mimicking very focal resective surgery and therefore only occurring if electrodes are by chance implanted exactly in very restricted epileptogenic regions. Implantation and microlesional effects may contribute to the overall improvements observed in uncontrolled unblinded trials whereas they are filtered out in RCTs as electrodes are also implanted in the sham stimulation group. Although implantation and microlesional effects are not believed to be the primary rational behind deep brain and cortical stimulation therapies, they nevertheless do contribute to temporary or sustained veritable clinical improvement.

3) Spontaneous evolution of the disease and changes in the antiepileptic drug regimen

Epilepsy is a dynamic disease and many patients have a fluctuating seizure frequency with spontaneous remissions followed by relapses [109, 110, 112, 120]. Patients are more likely to participate in clinical trials when their current seizure frequency is higher than their habitual seizure frequency. Spontaneous regression to their baseline frequency, a phenomenon referred to as 'regression to the mean', may be falsely ascribed to cortical or deep brain stimulation. RCTs control for this potential confounding factor but uncontrolled trials do not.

Improvements irrespective of the treatment under investigation could also occur due to changes in the antiepileptic drug regimen. This regimen is typically kept unaltered during RCTs, but such a rigorous approach is not feasible in uncontrolled trials with a long duration of follow-up. In a cohort of 139 drug-

resistant epilepsy patients, 448 medication changes were made during the 6.9 year follow-up period [113]. Eight per cent of these resulted in seizure freedom of at least 12 months and a further 17% was associated with a 50-99% seizure reduction. At the last follow-up, 19% of patients were seizure-free for at least 12 months and 29% showed a 50-99% improvement. Another trial evaluated the outcome of 34 drug-resistant epilepsy patients at an average of >4 years after they were considered unsuitable candidates for epilepsy surgery [115]. Seven patients (21%) achieved seizure remission for an average of 2.5 years and four of them attributed their remission to new antiepileptic drugs.

4) Increasing efficacy over time

As repeatedly described above, increasing efficacy over time has been reported during the blinded evaluation in the two largest RCTs [29, 31], during open-label follow up after completion of RCTs [25, 27-31, 63, 66, 107] and in various uncontrolled open-label trials including our trial on hippocampal DBS [15, 19-21, 40, 44, 50, 51, 54]. At the end of the blinded evaluation period of the SANTE trial on ATN DBS none of the patients were seizure-free and 30% experienced a ≥50% seizure reduction. These figures increased to 2% and 43% after one year of follow-up with an unchanged antiepileptic drug regimen, and further to 13% and 68% after five years of follow-up [27, 29]. Similar findings were observed for responsive stimulation of the ictal onset zone. The three-month seizure freedom and the 50%-responder rate were 2% and 29% during the blinded evaluation period, increasing to 7% and 55% after 2 years of follow-up [31]. At 6 years, these figures were 21% and 65% in patients with medial temporal lobe epilepsy whereas the 50%-responder rate in patients with neocortical epilepsy was 55% (exact figures on seizure freedom at last follow-up were not provided) [28, 30]. The most spectacular improvement was observed by Velasco and colleagues who reported seizure freedom in 4/9 patients after 18 months of hippocampal DBS (0/4 during the blinded evaluation period) and a ≥50% seizure reduction in all patients (1/4 during the blinded evaluation period) [25]. Although it is likely that other factors such as spontaneous evolution of the disease and changes in the antiepileptic drug regimen and the stimulation protocol contribute to the observed increasing efficacy over time, this trend has also been demonstrated during the blinded evaluation period of the two largest RCTs [29, 31]. In these trials the treatment effect increased from 10% and 9% at month 1 to 29% and 32% at month 3, respectively. These improvements occurred compared to sham stimulation and without adaptations in the antiepileptic drug regimen, strongly indicating a veritable increasing efficacy over time. However, RCTs with longer blinded evaluation periods are necessary to investigate whether and to what extent efficacy further increases under randomized controlled conditions after this three-month period.

5) Changes in the stimulation protocol

In general, RCTs use fixed stimulation parameter settings. In contrast, individual adjustments to the stimulation protocol are typically made during uncontrolled open-label follow-up. We and others have reported improved seizure control associated with such changes [16, 23, 27, 55, 67, 74]. It is therefore plausible that the individual stimulation parameter adaptations also contribute to the superior efficacy of DBS and cortical stimulation in uncontrolled compared to RCTs.

6) Cross-over design of multiple RCTs

A cross-over design was used in seven of the 12 RCTs. Four of these did not incorporate a washout period between the active and sham stimulation period [24, 62, 64, 107]. The washout period in the other three RCTs lasted one [45] or three [22, 66] months. As mentioned before, outlasting effects have been described in various trials on cortical and deep brain stimulation [15, 22, 25, 35, 38, 51, 74, 104-108]. Therefore, absent or too short washout periods could lead to carryover effects that would mask or reduce potential treatment effects. This is illustrated for the cross-over RCTs of McLachlan and colleagues in figure 2, where a treatment effect of -8% instead of -29% would have been observed if there would have been no washout period [22]. Indeed, a sensitivity analyses excluding RCTs with washout periods shorter than three months resulted in more pronounced treatment effects for cerebellar stimulation (responder rate OR 8.33, 95% CI 0.22 to 320; seizure frequency reduction -36.7%, 95% CI -95.5 to +21.2) and hippocampal DBS (responder rate OR 1.75, 95% CI 0.22 to 14.1; seizure frequency reduction -45.7%, 95% CI -89.5 to -5.5%). Of course, this issue is irrelevant in the absolute absence of any effect (e.g. for seizure freedom).

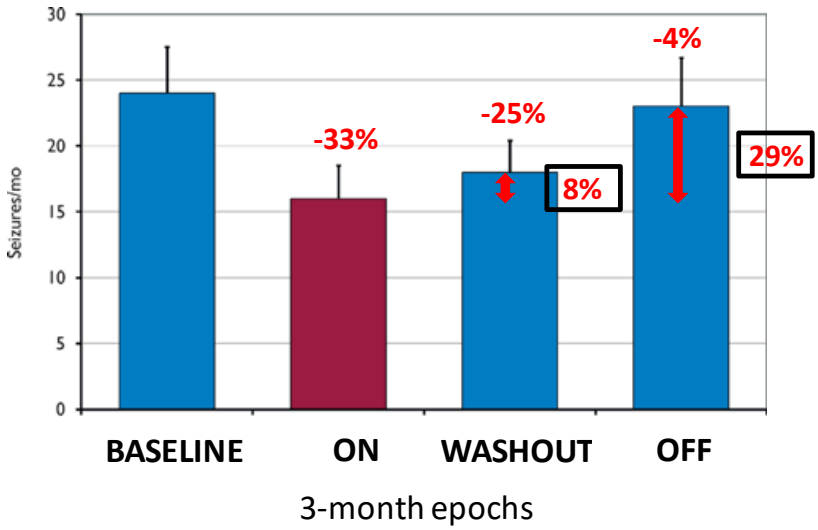


Figure 2: Illustration of the potential underestimation of the true treatment effect due to carryover effects in RCTs with a cross-over design and absence of or too short washout periods. In this example based on the data of McLachlan and colleagues [22], a -8% instead -29% treatment effect would have been reported in the absence of any washout period between active and sham stimulation. Values are mean +/- standard error of the mean.

In conclusion, it is likely that multiple factors overestimate the efficacy of DBS and cortical stimulation in uncontrolled trials whereas others may contribute to an underestimation of its full potential in RCTs performed so far.

Mechanism of action of DBS

The moderate efficacy of DBS in RCTs is probably the most important factor impeding a more widespread use in epilepsy. Even in uncontrolled open-label trials seizure freedom – the ultimate goal – is only achieved in a small minority of patients, leaving quite some room for further improvements. Optimizing patient selection, target identification and stimulation parameter setting are strategies to attain such progress. During my PhD, we evaluated the potential of high-frequency DBS in the central piriform cortex to suppress spontaneous seizures in the intrahippocampal kainic acid model of epilepsy as previous studies had demonstrated its involvement in the initiation and spreading of seizures [130-132]. Furthermore, there was preliminary but mixed evidence on potential beneficial effects of lesioning and low-frequency DBS of the piriform cortex in the kindling model of epilepsy (characterized by evoked but not spontaneous seizures) [133-137]. Although the results of our pilot trial could not exclude some beneficial effects of high-frequency DBS at the piriform cortex, it was very unlikely to be clearly more efficacious than DBS in other known stimulation targets and hence of limited clinical relevance [138]. We therefore decided to abandon this path.

When overlooking all unresolved issues with regards to DBS as a treatment for epilepsy and other neuropsychiatric diseases, we decided to focus further research on the mechanism of action of DBS. Increasing our knowledge on this issue would indeed allow to rationalize patient selection, stimulation parameters settings and stimulation target selection. Furthermore, it could also facilitate more appropriate designs of RCTs amongst others with regards to the trial duration and the introduction of washout periods in cross-over designs as the neurophysiological basis of the presumed increasing efficacy over time and outlasting effects remains poorly understood.

As outlined in Chapter 4, various mechanisms of action of DBS have been proposed. These include a depolarization block, synaptic depression, synaptic (GABAergic) inhibition, axonal conduction block, overriding of pathological activity by imposing new (stimulus-locked) activity, desynchronization and suppression of pathological oscillations, local increase in adenosine or extracellular potassium, neuroplasticity, neurogenesis and neuroprotective effects. Although these different mechanisms should not be mutually exclusive and can occur simultaneously as has been shown in some studies (e.g. partial axonal block and stimulus-locked neuronal activation in downstream network structures [139]), other studies have produced seemingly conflicting results highlighting the importance of the experimental setup. Effects found in *in vitro* preparations could differ from those *in vivo*, mechanisms demonstrated in anesthetized subjects might not reflect those present in the awake state and different stimulation protocols could result into different outcomes (especially the current amplitude is difficult to compare across studies).

We further elaborated on the mechanism of action of DBS by investigating how hippocampal EPs and EEG (local field potentilas, LFPs) are influenced by hippocampal high-frequency DBS in freely moving rats. Monosynaptically evoked potentials can be modulated by many of the proposed mechanisms of action including depolarization block, synaptic depression, synaptic inhibition, axonal conduction block and neuroplasticity. The recording of spontaneous EEG further allows to investigate possible desynchronization and suppression of oscillations in specific frequency bands. Hence, these techniques were deemed appropriate to further unravel the mechanism of action of DBS.

Both acute and chronic experiments were performed, aiming to evaluate both acute temporary effects as well as potential additional effects with longer stimulation durations given the reported increasing efficacy over time in various clinical trials on DBS. We further compared the effects of continuous to those of intermittent DBS to increase our knowledge on and rationalize the stimulation protocol.

Prior to the experiment we had to optimize both the configuration of our custom-made electrodes and the surgical procedure in order to obtain stable recordings of the PS and the fEPSP in freely moving animals. This optimization process eventually led to the successful obtainment of good-quality EPs in more than 35 consecutive implantations.

A. Acute temporary effects

The acute temporary effects of seconds to minutes of high-frequency stimulation on EPs have previously been investigated. All these studies were performed in *in vitro* preparations or in rats under urethane anesthesia. The complex three-dimensional architecture and physiological neuronal activity are lost in *in vitro* preparations. Urethane anesthesia is known to affect hippocampal neurotransmission as well as short- and long-term plasticity [140, 141]. In addition, stimulation parameters in anesthetized animals and especially in vitro setups may differ from these in freely moving rats.

We evaluated for the first time the effect of hippocampal DBS on hippocampal EPs in freely moving rats and identified three important findings [142]. Firstly, relatively low DBS intensities corresponding to 1.8% of the maximum EP intensity were required in freely moving rats in order to prevent seizure occurrence in freely moving healthy rats. Secondly, a temporally summated fEPSP was observed at stimulation onset, typically fading out within 100 to 200 ms. Thirdly, input-specific reductions of the 10% fEPSP slope were observed after 1 and 6 minutes of DBS. A 6.8% reduction was found 100 milliseconds after 1 minute of DBS and this reduction disappeared within 20 seconds. A similar 4.4 to 5.9% reduction was demonstrated after 6 minutes of DBS but this reduction lasted longer and only disappeared after 60 seconds. The higher intensity (25, 50 and 80%) fEPSP slopes, the PS amplitude, the fEPSP slope/PS amplitude and the fEPSP slope paired-pulse relationship did not show acute temporary effects.

The temporary EP reductions following high-frequency DBS are in line with the results of prior studies in *in vitro* preparations and urethane-anesthetized rats. Shen et al. demonstrated a 97% decrease of the excitatory postsynaptic current in the SNr following 2 seconds of 100 Hz STN stimulation in an *in vitro* preparation that lasted 2 minutes [143]. Anderson and colleagues reported a homosynaptic EP suppression after 1 to 30 seconds of 125 Hz stimulation in a thalamic slice preparation that required 2.1 seconds to recover [144]. In the *in vitro* study of Iremonger and colleagues, 30 seconds of 125 Hz high-frequency stimulation at the external capsule caused a profound (around 90% based on the illustrations in the manuscript, exact figures not mentioned in the text) depression of the excitatory postsynaptic current recorded in the primary motor cortex. Recovery took around 2 and 6 minutes after 30 seconds and 5 minutes of stimulation, respectively. Antidromic spikes could not fire with frequencies higher than 50-70 Hz. In another *in vitro* experiment in the lateral habenula EPSPs were strongly suppressed following 130 Hz stimulation [145]. Based on an illustration in the article, a 86% reduction that lasted less than 2 minutes was observed after 5 minutes of stimulation (more specific numbers not reported in the text). Eighty to 100 pulses at 100 Hz caused 48% and 69% reductions of

the EPSP and fEPSP in slices of the CA1 region of healthy rats [146]. Another *in vitro* study reported a 89% decrease of the EPSP following 1 to 5 seconds of 25-200 Hz stimulation in the neocortex, with around 70% recovery occurring within the first 20 seconds [147]. The number of spikes provoked by 100 ms of current injection was only affected after direct antidromic but not indirect orthodromic stimulation. Furthermore, axonal firing could not follow stimulation frequencies above 25 Hz indicating partial axonal block. Finally, in a series of experiments in the CA1 region of urethane-anesthetized rats Feng and colleagues observed complete suppression of the orthodromic population spike within 10 seconds of 100 Hz stimulation of the Schaffer collaterals [148, 149]. Whether the fEPSP also disappeared completely occurred was not described in detail. The antidromic population spike evoked by high-frequency stimulation in the alveus was strongly reduced (e.g. 84% at 100 Hz) and displayed an increased latency [139, 148, 149]. Half of the recovery occurred within 20 milliseconds indicating a prolonged refractory period. The remaining recovery took 2 to 7 minutes [148, 149]. Two of these studies have also tested the input-specificity of the observed EP reductions [144, 150]. Similar to our findings, both studies confirmed that only the stimulated pathway was affected by high-frequency stimulation.

Although the effects we reported were similar in nature, the magnitude of the EP reductions was much larger in previous studies. These reported 48-100% reductions whereas we observed 5-7% reductions of the 10% fEPSP slope only. Some factors could explain this difference. First, the first EPs in our study were measured 100 milliseconds after the final DBS pulse. During this short time course, partial recovery may already have occurred. For example, in the study of Feng and colleagues about half of the recovery of the antidromic population spike took place within 20 milliseconds [148]. In addition, the stimulation intensities were relatively higher in previous studies. For example, Feng and colleagues applied high-frequency stimulation with an intensity set at 75% of the maximal PS [148, 149]. In our study, stimulation intensity corresponded to 1.8% of the maximum EP intensity. This is probably by far the most important reason why the effect size in our experiments seemed smaller than in previous studies.

Initially we planned to set the stimulation intensity at 60% of the afterdischarge threshold because such an intensity has proven to reduce seizures in epileptic rats [102, 151]. However, as the afterdischarge threshold varied over time this required repeated seizure activity provocation. In addition, this intensity resulted into unexpected seizure provocation in 1/6 rats in a pilot study. Therefore, we decided to set the stimulation intensity just above the threshold evoking a clear summated fEPSP which we found to appear typically around this 60% afterdischarge treshold stimulation intensity and seizures were in addition most frequently being provoked in those rats with the largest difference between their 60% afterdischarge threshold and summated fEPSP threshold. This approach avoided the need for repeated seizure provocation. Moreover, from a physiological point of view it resulted into a more comparable stimulation intensity amongst rats in comparison to the varying 60% afterdischarge threshold and also guaranteed that the hippocampal network was indeed stimulated. As mentioned above, the summated fEPSP threshold corresponded to 1.8% of the maximum EP intensity. This seems quite low but at the same time it also corresponded to 66% of the afterdischarge threshold and seizures were nevertheless unintentionally provoked in 4.4% of all DBS sessions. Using higher stimulation intensities in a pilot study was even associated with higher seizure incidences: 2/6 rats with DBS at 72% and 4/6 with DBS at 85% of the afterdischarge threshold, respectively. Therefore, although 1-2% of the maximum EP intensity as DBS intensity may seem low,

higher intensities seem to be poorly tolerated in the in vivo unanesthetized situation due to seizure occurrence.

A temporally summated fEPSP at stimulation onset was also observed in the majority of previously published *in vitro* studies [143, 144, 146, 147, 150]. This summation probably results from repeated paired-pulse facilitations due to the successive administration of closely spaced stimulation pulses. Residual presynaptic calcium ions from a previous pulse are thought to be one of the main biological mechanisms causing paired-pulse facilitation, but other mechanisms include the saturation of presynaptic calcium buffers, the use-dependent facilitation of presynaptic calcium channels, the activation of calcium-dependent pathways leading to a higher neurotransmitter release and the modulation of presynaptic ionotropic and metabotropic receptors by their agonists released by presynaptic, postsynaptic or neighbouring (including glia cells) cells [152, 153]. In some rats this temporal summation transitioned into an epileptic seizure. This was the case when higher stimulation intensities were used in our pilot study, during determination of the afterdischarge threshold but also unintendedly in 4.4% and of rats during the experiment as mentioned above. In the vast majority of rats, however, the temporal summation decreased spontaneously and faded within 100 to 200 milliseconds.

The mechanisms constraining this temporal summation are likely – at least in part – the same as the ones causing the fEPSP slope reductions observed 100 milliseconds to 40 seconds after DBS. Various mechanisms that can provoke temporary EP reductions have described in DBS literature, including vesicle depletion, axonal block, synaptic GABAergic inhibition and a depolarization block [143-145, 147-150, 152, 154]. The input-specificity and the temporal dynamics including the duration of the outlasting effect observed in our study fit best with vesicle depletion and axonal conduction failure. With our study design it is not possible to further discriminate the relative contribution of each of these two mechanisms. In some of the previous studies authors assigned the observed EP reductions either completely to vesicle depletion [144, 145] or to axonal block [148, 149]. A potential involvement of both mechanisms cannot be excluded for any of these studies, however. Even in studies where the presence of axonal conduction failure was positively demonstrated by changes in the presynaptic fibre volley or the antidromic PS [146-150], some contribution of vesicle depletion cannot be excluded. The degree of axonal conduction failure could indeed not fully explain the extent of the observed EP reductions in some of these studies, providing evidence for the simultaneous occurrence of both mechanisms [146, 147, 150].

GABAergic synaptic inhibition is another potential mechanism of action of DBS that has been suggested by many authors [155-163]. This hypothesis is supported by the abundant presence of GABAergic inhibitory neurons in the basal ganglia network and the observed decrease in neuronal firing rate following DBS. In addition, Feng and colleagues have demonstrated the excitation of (probable) interneurons during high-frequency stimulation of the Schaffer collaterals [139]. Although this could in theory result into the GABAergic inhibition of pyramidal neurons, it is unlikely to be responsible for the observed EP reductions in our study for various reasons. First, GABAergic synaptic inhibition typically outlasts stimulation for 10 milliseconds to 1 second (and occasionally several seconds) [155, 156, 158-160, 163]. In our study, however, the fEPSP slope reductions only disappeared 40 to 60 seconds after the final DBS pulse. Secondly, the fEPSP slope reductions were input-specific in our study and this would not be expected if caused by interneuronal GABAergic inhibition. Thirdly, it is probable that the degree of paired-pulse recurrent and feedforward inhibition would be altered if GABAergic

interneurons were responsible for the observed EP reductions. In our study, however, the fEPSP slope paired-pulse relationship remained unaffected.

A fourth possible mechanism of action of DBS that could alter the EPs is a depolarization block. As described in Chapter 4, a depolarization block can be induced synaptically or nonsynaptically by direct modulation of somatic voltage-gated currents [164-166]. We did not find evidence in favor of this hypothesis in our study. The PS amplitude was not decreased as would be expected in the presence of a depolarization block. In addition, the synaptically mediated depolarization block in the study of Magarinos and colleagues was accompanied by a sustained depolarization which was not observed in our study [166]. The results of our study, however, cannot exclude the possibility of a directly, nonsynaptically induced depolarization block for a small proportion of neurons just adjacent to the stimulation electrode. Although the additional stimulation electrode was implanted the closest possible to the recording electrode (+/- 200 µm between the outer diameters), the 500 µm distance between the centers of both electrodes is longer than the 100 to 400 µm distance in the *in vitro* study of Garcia and colleagues [165]. Furthermore, the mean stimulation intensity in our study (84 µA) was much lower than in the study of Garcia and colleagues (100-1500 µA). Therefore, our stimulation intensities might have been too low to directly, nonsynaptically influence the neurons surrounding the recording electrode in a significant manner [167].

In theory, desensitization of postsynaptic AMPA receptors could also cause fEPSP slope reductions. In two *in vitro* experiments, however, the administration of cyclothiazide (which blocks AMPA receptor desensitization) failed to prevent the DBS-induced EP reductions [144, 150].

B. Effects of more prolonged DBS durations

An increasing efficacy over time of DBS in epilepsy has been observed both in several uncontrolled trials and during the blinded evaluation period of RCTs [15, 19-21, 25, 27-31, 40, 44, 50, 51, 54, 63, 66, 107]. Also in many other diseases treated with DBS maximum symptom relief is often only achieved after hours, days, weeks or months of DBS, e.g. for symptoms such as postural imbalance in Parkinson's disease, in dystonia patients, in obsessive-compulsive disorder, depression, Tourette's syndrome and cluster headache [15, 168-176]. Similarly, outlasting effects after accidental or intentional cessation of DBS have not only been observed in epilepsy [15, 22, 25, 35, 38, 51, 74, 104-108] but also in various other neuropsychiatric disorders treated with DBS, including dystonia, Tourette's syndrome and for axial symptoms in Parkinson's disease [118, 170, 177-181]. Both the delayed achievements of maximum symptom control and the outlasting effects suggest neuromodulatory changes induced by DBS. In addition, the positive correlation between the time required for symptom relief upon initiation and symptom recurrence after cessation of DBS [170, 181] suggests that common neurobiological mechanisms underlie both clinical observations. Although these mechanisms remain to be elucidated, it has been hypothesized that neuroplastiticy, neurogenesis and neuroprotective changes induced by DBS may be involved (see Chapter 4).

Various studies have evaluated the occurrence of neuroplasticity with DBS. Shen and colleagues evaluated the effects of one minute of DBS in a slice preparation of the STN. Fifty 100 Hz stimulation pulses alternated with 500 milliseconds-long pauses for one minute. Synaptic plasticity was observed in 17 out of 46 STN neurons. Four neurons showed short-term potentiation lasting less than 10 minutes, eight neurons displayed long-term potentiation and 5 neurons long-term depression, each

lasting more than 40 minutes [182]. One second of 100 Hz DBS in another *in vitro* experiment had no effect in STN slices from healthy rats but caused LTD lasting more than 30 minutes in STN slices from dopamine-depleted rats. The associated changes in the paired-pulse ratio indicated a presynaptic origin of the LTD [183]. Long-term depression lasting more than 40 minutes was also demonstrated in the striatum in another *in* vitro experiment following three times three seconds of 100 Hz DBS every 20 seconds at the cortex or the white matter connecting the striatum to the cortex [184]. LTD and LTP were also observed in various DBS targets in rats under urethane anesthesia. Three times 30 minutes of 130 Hz nucleus accumbens DBS caused NMDA-receptor dependent long-term potentiation in the orbitofrontal cortex lasting more than 90 minutes [185, 186]. These effects were inputspecific as the EPs in the orbitofrontal cortex evoked by thalamic stimulation were not affected, as well as region specific given the unaltered EPs in the medial prefrontal cortex evoked by nucleus accumbens stimulation. In another study, four times one second of 100 Hz DBS at the medial prefrontal cortex in urethane-anesthetized rats caused an NMDA-receptor dependent LTD in the dorsomedial striatum lasting more than 100 minutes [187].

It should be noted that we and others did not observe LTP in our acute experiments, as could be expected by some based on previous literature on the induction of LTP in the hippocampus. This probably results from the fact that a major requirement for the induction of LTP is not met: a synapse will only be potentiated if, and only if, it is active at a time when its dendritic spine is sufficiently depolarized [188-190]. The stimulation intensity in our study was only around 2% of the maximum EP intensity whereas much higher intensities are typically used for the induction of neuroplasticity. In the studies cited above a 50-100% EP intensities were used. With higher stimulation intensities, the postsynaptic cell is much more likely to fire. Another difference between our experiments and many of the studies where LTP and others types of neuroplasticity are induced, is that we used continuous stimulation whereas multiple shorter trains are frequently used in the latter. Introducing short pauses between successive stimulation trains may allow changes due to e.g. vesicle depletion and axonal block to recover, again increasing the likelihood of simultaneous occurrence of synaptic depolarization and postsynaptic neuronal firing.

A major limitation of the studies mentioned above is that they evaluated the effects of seconds to minutes of DBS only. Although the long-term plasticity observed in these studies could in theory potentially be responsible for some of the outlasting effects observed after DBS, they cannot explain the increasing efficacy observed with longer DBS durations in various clinical trials. To our knowledge, we were the first to study the neurophysiological effects of more prolonged DBS durations. This remarkable fact could be related to technical and practical issues, as it requires long-term stable EP recordings in freely moving animals. In addition, it could also result from the fact that DBS is worldwide most frequently used as a treatment for Parkinson's disease and essential tremor with the visually eye-catching tremor suppression occurring within seconds after turning stimulation on.

In our first study we evaluated the effects of 160 min of 1/9 and 6/4 min ON/OFF intermittent DBS and observed longer-lasting potentially cumulative input-specific EP reductions, with statistically significant 3-4% reductions of the 50 and 80% fEPSP slopes. Based on these results, a second study was initiated evaluating the effects of 2 days of continuous hippocampal DBS. Two days of continuous DBS caused marked fEPSP slope reductions. For example, the 10, 50 and 80% fEPSP slopes decreased by 70, 34 and 21%, respectively. Although the fEPSP slope reductions were relatively most pronounced for the lower EP intensities, absolute reductions were more equal among the different EP intensities.

This suggests that the neuronal elements closest the stimulation electrodes and/or their downstream targets were affected the most. The fEPSP slope reductions increased over time with stronger reductions after 2 days compared to 1 day of DBS. They also displayed long (5-7 days) outlasting effects. In this way these EP reductions provide a potential electrophysiological basis for the increasing efficacy over time and outlasting effects of DBS observed in numerous clinical trials, although more research is required to study the relationship between the observed EP reductions and the therapeutic effect of DBS.

The fEPSP slope reductions were associated with even more profound decreases of the PS amplitudes. For example, the 50 and 80% PS amplitude showed 86 and 51% reductions. However, the latter were only secondary to the fEPSP slope reductions as we did not find changes in postsynaptic intrinsic excitability. The fEPSP slope reductions were further accompanied by increases in the fEPSP paired-pulse slope ratio, but the fEPSP slope / fEPSP slope paired-pulse ratio relationship did not change. When DBS was administered via a different electrode as the one used for EP evocation, EPs were unaffected indicating that also the EP reductions observed with longer stimulation durations were input-specific.

With regards to the underlying neurobiological mechanism, we suggest that homeostatic plasticity may play a key role in the observed reductions in evoked activity. As outlined in Chapter 2, homeostatic plasticity refers to bidirectional changes in synaptic strength and/or intrinsic excitability aiming to stabilize the neuronal or network activity within a certain range preventing neurons or networks entering hyper- or hypo-active states [191-194]. Unlike Hebbian types of plasticity such as LTP and LTD which are rapidly induced, homeostatic plasticity typically requires hours to days of increased or decreased activity. It is probable that the DBS-induced continuous neuronal activation exceeds the homeostatic set point and hence recruits homeostatic plasticity machinery resulting into downscaled neuronal responses.

Homeostatic plasticity could counter the increased neuronal activation induced by DBS by various mechanisms. It may decrease synaptic strength and / or intrinsic excitability both at the pre- and postsynaptic level, or it could potentiate postsynaptic inhibitory GABAergic synapses [191-197]. We did not observe changes in postsynaptic intrinsic excitability as the PS amplitude / fEPSP slope relationship remained unaltered. The unaffected paired-pulse inhibition and the input-specificity of the observed effects also makes increased GABAergic inhibition less likely. Furthermore, the proportional increase of the fEPSP slope paired-pulse ratio associated with the decrease of the fEPSP slope (reflecting the unchanged fEPSP slope / fEPSP slope paired-pulse ratio relationship) indicates a reduction in probability of neurotransmitter release and hence a presynaptic origin of the fEPSP slope reduction [152, 182, 196, 198].

This presynaptic origin could result from a decreased presynaptic intrinsic excitability and/or a reduction in presynaptic neurotransmitter release as such (with intact or disproportional to potential changes in presynaptic excitabilitity). Homeostatic control of presynaptic neurotransmitter release was initially demonstrated at the neuromuscular junction but has also been shown in the mammalian central nervous system, including hippocampal synapses, and depends on the modulation of presynaptic calcium influx and the readily releasable pool of synaptic vesicles [191, 193, 199-202]. In an *in vitro* experiment in cultured CA1 neurons, for example, blocking of spiking activity by tetrodotoxin (a sodium channel blocker) or depressing the inhibitory tone by gabazine (a GABAa receptor

antagonist) resulted into bidirectional homeostatic plasticity of presynaptic neurotransmitter release by regulating presynaptic calcium currents and the size of the synaptic vesicle pool. These changes were mediated by P/Q-type voltage-gated calcium channels and independent of N-type voltage-gated calcium channel regulation [202]. Changes in intrinsic excitbality, on the other hand, are regulated by modulation of the intrinsic electrical properties of neurons, mainly inward and outward voltage-dependent sodium, potassium, calcium and other currents making neurons more or less excitable [193, 195, 203-205]. Our experiment does not allow to discriminate whether the observed EP reductions are mediated by a decreased intrinsic excitability, a reduction in neurotransmitter release or a combination of both. A prior study in rat organotypic hippocampal slices showed that both mechanisms can indeed be engaged in parallel, although changes intrinisic excitability occurred first [197].

In contrast to the reductions in evoked activity we did not find any changes in the spectrogram of the spontaneous hippocampal LFPs in both the acute and chronic experiments. This seems in contrast to numerous previous studies showing DBS-induced desynchronization of neuronal activity. As described in chapter 4, beta band oscillations are pathologically elevated in patients with and animal models of Parkinson's disease and correlate with symptom severity [206-214]. STN DBS has been shown to reduce these beta band oscillations in the STN, GPi and motor cortex [208, 215-221]. Similar suppressions of beta band activity were also observed with GPi DBS in the GPi and motor cortex [76, 222, 223]. The unaffected LFP spectrogram in our study could in part result from the fact that we recorded hippocampal LFPs after and not during DBS. Changes in the LFP spectrogram during DBS cannot be excluded based on the results of our experiments. However, this may not completely account for the discrepant results as the suppressed beta activity outlasted DBS for tens of seconds to minutes in some studies [215, 219]. For several reasons it is however more likely that the beta band reductions observed with DBS in Parkinson's disease are a secondary phenomenon and a consequence of other DBS-induced changes rather than its primary mechanism of action. First, similar reductions in beta band power have also been observed with dopaminergic drugs and correlated with clinical improvement [210, 224, 225]. Secondly, similar to our findings the EEG spectrogram was not altered by STN DBS in a study in healthy rats [209]. After the injection of a dopamine antagonist the resulting increased beta band oscillations were suppressed by STN DBS. Thirdly, DBS of the internal globus pallidus reduces theta oscillations in dystonia patients whereas the same intervention reduces beta power in Parkisonian patients [216, 226]. Such reductions are in accordance with the pathologically increase in alfa and theta versus beta power in patients with dystonia and Parkinson's disease, respectively [214, 226]. Also thalamic DBS reduces pathologically increased alfa and theta oscillations in essential tremor while it increases gamma power in Tourette's syndrome [227, 228].

C. Intermittent versus continuous stimulation

For nearly all indications, DBS is applied continuously in clinical practice. This seems a rational approach when the observed clinical improvements disappear rapidly upon cessation of DBS, such as tremor suppression in patients with Parkinson's disease or essential tremor [169, 175, 181]. Although requiring further investigation, these clinical effects may be associated with the acute temporary reductions observed in our acute experiments. Continuous DBS, however, may be less indispensable when clinical improvement is mainly based on DBS-induced neuroplasticity effects, provided that intermittent DBS induces similar neuroplasticity changes as continuous stimulation does. In this regard,

the demonstration of longer-lasting fEPSP slope reductions first in our acute experiments with 160 min of intermittent DBS with 1/9 and 6/4 min ON/OFF duty cycles, and later in our chronic experiments provide a potential neurophysiological basis for the use of intermittent DBS as an alternative to continuous DBS.

In our chronic experiments, we compared – to the best of our knowledge for the first time – the neurophysiological effects of sham, continuous and intermittent hippocampal DBS applied with two different duty cycles (1/5 and 1/29 min ON/OFF, respectively) in healthy rats. Compared to sham stimulation, both continuous and intermittent DBS provoked pronounced fEPSP slope reductions. The main finding of the experiment, however, was that the magnitude of these reductions was primarily dependent on the cumulative number of administered stimuli. Consequently, at identical time points after initiation of DBS the fEPSP slope reductions were most pronounced for continuous DBS, followed by 1/5 min intermittent DBS and eventually 1/29 min intermittent DBS. To what extent this dose-relationship continues and whether identical end stage plateau levels are reached, however, requires further study given the unexpectedly long ongoing slope reductions observed with intermittent 1/29 duty cycle DBS.

In theory the neuroplasticity effects of DBS could be the dominant mechanism of action for many of the neuropsychiatric disorders treated with DBS, as suggested by the increasing efficacy over time reported in dystonia patients, in obsessive-compulsive disorder, depression, Tourette's syndrome and cluster headache [15, 168-176]. Intermittent DBS may be a valuable and less energy consuming alternative for these patients. So far intermittent DBS has mainly been explored in epilepsy patients. Although RCTs are lacking, long-term seizure reductions were in general indeed comparable to those observed with continuous DBS (see above). The maintained seizure control after the introduction of day-night cycling in 4/5 epilepsy patients in our uncontrolled open-label trial on hippocampal DBS further supports this hypothesis [15]. Similar findings were reported by Lim and colleagues showing unchanged seizure frequencies after the introduction of intermittent DBS in patients previously treated with continuous DBS [105]. Both uncontrolled observations, however, only evaluated a shift to intermittent DBS after many years of continuous DBS and hence are not helpful to evaluate whether improved seizure control is achieved at a slower rate with intermittent compared to continuous DBS. Next to epilepsy, intermittent DBS has also been explored and shown promising results in depression and Tourette's syndrome [229-233]. In line with our data weekly increasing effect sizes with intermittent DBS and slightly smaller or similar final effects after two weeks of intermittent and continuous DBS have been shown in preclinical models of depression [229, 230, 233].

D. Concluding remarks

We demonstrated DBS-induced input-specficic fEPSP slope reductions with two different time courses. Short-lasting temporary reductions were observed after 1 or 6 minutes of DBS and probably caused by vesicle depletion and/or axonal block. More prolonged stimulation durations resulted into more pronounced and over time increasing fEPSP slope reductions displaying long outlasting effects and being dependent on the cumulative number of administered DBS pulses. We suggest that these are an expression of presynaptic homeostatic plasticity although further study is necessary to demonstrate their true homeostatic nature. These two different time courses may parallel the different temporal patterns of clinical improvement observed with DBS. Our recordings were performed in freely moving

rats with stimulation parameter settings that have previously been shown to suppress seizures in epileptic rats, which adds strength to our findings.

In addition to vesicle depletion, axonal block and (homeostatic) neuroplasticity, stimulus-locked neuronal activity overriding pathological activity is also likely to be involved in the mechanism of action of DBS. Although we were not able to investigate this mode of action in our experiments, it has been shown in many previous studies [139, 209, 234-240]. The simultaneous occurrence of stimulus-locked neuronal firing and vesicle depletion and / or axonal block seems paradoxical at first sight but was previously demonstrated by Feng and colleagues. Despite the fact that high-frequency stimulation of the Schaffer collaterals completely abolished the initially evoked PS in the CA1 region, asynchronous increased neuronal firing of CA1 neurons was found [139, 149].

We did not observe desynchronization of neuronal activity in specific frequency bands and suggest that their presence in previous studies is rather a secondary phenomenon than a primary mechanism of action. Similar to most previously published reports, our findings in the hippocampus of freely moving rats do not support the occurrence of a depolarization block during DBS, although this cannot completely be excluded based on our results. We also did not find arguments suggesting a role of synaptic inhibition in the mode of action of hippocampal DBS. Nevertheless, synaptic inhibition could be involved in the mechanism of action of DBS in the basal ganglia network given the abundant presence of GABAergic neurons in these subcortical structures. However, in this context it is in fact no more than an alternative formulation of the induction-of-stimulus-locked-activity hypothesis. Finally, we did not evaluate potential neurogenesis and neuroprotective effects of DBS.

As outlined above, we were not able to analyze DBS-induced changes during DBS which is an important limitation. In addition, we cannot exclude the possibilities that our findings are restricted to the hippocampus of healthy rats or to the stimulation parameters that were used. For example, it is possible that EP modulations by DBS in the basal ganglia network differ from these in the hippocampus. While we have no reason to believe that within the high-frequency range the observed effects are specific to the 130 Hz frequency used in our experiments, the effects of low-frequency DBS are probably at least in part mediated by different mechanisms than high-frequency stimulation (e.g. no axonal block or vesicle depletion), although a long-lasting decreased excitability may be common to both paradigms. Overall, more research is needed to evaluate to what extent our results can be extrapolated to other brain regions such as the basal ganglia, to pathological brain tissue (with the possibility of disease-specific effects), to other stimulation parameters and to human subjects treated with commercially available hardware systems.

Although a definite relationship between the observed EP reductions in our experiments and the therapeutic effect of DBS remains to be proven, our findings could have various clinical implications. First, it could impact the design of clinical trials. As outlined above, the fEPSP slope reductions observed in our chronic experiments provide a potential electrophysiological basis for the observed increasing efficacy over time and outlasting effects of DBS observed in clinical trials. This adds strength to the importance of designing clinical trials with more prolonged blinded evaluation periods. Furthermore, it supports the use of RCTs with a parallel-group design and reinforces the need to introduce a sufficiently long washout if a cross-over design is incorporated. Secondly, in analogy to the approach used for antiepileptic drugs a ‘start low go slow’ is often employed for neurostimulation treatments. The EP reductions observed with more prolonged stimulation durations provide a rational basis for

this approach as stimulation intensities that could for example provoke seizures at the time of DBS initiation could be safe later on. Thirdly, the input-specificity of the EP reductions supports the importance of correct electrode implantation. Differences in the exact electrode location of the electrode could be responsible for the different outcomes observed in different patients. A clinical counterpart of this input-specificity was further suggested in our open-label trial on hippocampal DBS where patients with a focal ictal onset experienced the most favorable outcomes and where switching from uni- to bilateral hippocampal DBS improved seizure control in 3 out 5 patients. Both for hippocampal and ATN DBS the importance of the electrode location (in the range of millimeters) and the specific electrode contact selected for DBS has been shown [46, 241]. Fourthly, when the neuroplasticity effects of DBS are presumed to be the dominant mechanism of action, intermittent stimulation may be a valuable alternative to continuous stimulation. Intermittent stimulation may be applied from the onset of stimulation or after a stable relief of symptoms has been achieved.

Future perspectives

We reported excellent outcomes in our uncontrolled open-label trial on hippocampal DBS with 6/11 patients experiencing a ≥90% reduction in seizure frequency. Additionally, there is moderate- to high-quality evidence for statistically significant seizure reductions with ATN DBS, hippocampal DBS and responsive stimulation of the ictal onset zone. Deep brain and cortical stimulation may therefore be valuable treatment options for drug-resistant epilepsy patients. However, the observed reductions in seizure frequency in RCTs were relatively moderate, ranging from 17 to 28%, and statistically or clinically significant increases in the 50% responder rate or seizure freedom could not be demonstrated. In addition, the more favorable results obtained in uncontrolled unblinded trials are subjected to many types of bias. Finally, for many stimulation targets, outcome measures and patient populations, evidence is lacking or of only low to very low quality.

In essence, there are two factors that need be addressed to expand the role of deep brain and cortical stimulation in the treatment of drug-resistant epilepsy patients. First, there is a need for more high-quality evidence on their efficacy, safety and tolerability. Secondly, a better seizure outcome should be achieved.

The requirement for more high-quality evidence on deep brain and cortical stimulation in drug-resistant epilepsy patients can only be fulfilled by the conduction of more RCTs, given the limited number of RCTs which in addition often recruited only a small number of patients. This holds true for every stimulation target that has been investigated in randomized controlled conditions so far, but especially for hippocampal DBS, nucleus accumbens DBS, CMT DBS and cerebellar stimulation. Furthermore, some targets have yielded promising results in uncontrolled conditions but have not been studied in RCTs yet, e.g. subthalamic nucleus DBS, caudate nucleus DBS and motor cortex stimulation [36-38, 55, 65, 103, 104, 242]. A major limitation of the available evidence today is the short duration of the blinded evaluation period in RCTs performed so far, mainly ranging between 1 and 3 months and exceptionally lasting 6 months. As outlined above, an increasing efficacy over time has been reported during the blinded evaluation period in RCTs and in uncontrolled conditions [15, 19-21, 23, 25, 27-31, 40, 44, 50, 51, 54, 63, 66, 107]. Therefore, RCTs evaluating the long-term outcome of deep brain and cortical stimulation in controlled conditions are necessary. Another gap in the currently available evidence is that RCTs on invasive intracranial neurostimulation treatments mainly

recruited patients with (multi)focal epilepsy. Uncontrolled trials have shown promising results of STN and CMT DBS in patients with generalized epilepsy encouraging a methodologically more rigid evaluation in RCTs [34, 39, 54, 55, 68-70]. DBS and cortical stimulation also need to be studied in more detail in minors. So far, only one RCT recruited a substantial number of minors [107].

A major shortcoming to accurately identify the role of deep brain and cortical stimulation in the therapeutic landscape of drug-resistant epilepsy patients is the absolute lack of RCTs comparing DBS and cortical stimulation to other possible treatment options. In practice, the latter mainly include resective surgery, further trials with antiepileptic drugs and vagus nerve stimulation. Even in the absence of RCTs, it seems evident that resective surgery is clearly more efficacious than DBS and cortical stimulation with about 50% of patients remaining seizure-free as late as a decade after surgery [6, 243]. Although this may come at the cost of significant adverse events in a minority of patients, resective surgery remains the treatment of choice whenever possible. Many patients, however, turn out to be unsuitable candidates or refuse to undergo resective surgery. Whether these should be treated with antiepileptic drugs, vagus nerve stimulation or invasive intracranial neurostimulation has not been but should be studied in RCTs.

As mentioned in Chapter 3, the definition of drug-resistant epilepsy is not synonymous to the impossibility of becoming seizure-free with further trials with antiepileptic drugs. Moreover, such trials are in fact common practice in everyday clinical neurology. A meta-analysis evaluating the placebo-corrected net efficacy of adjunctive treatment with modern antiepileptic drugs showed that, compared to placebo, an additional 6% of patients became seizure-free and 21% of patients experienced a 50% seizure frequency reduction [244]. In practice, however, the choice between further trials with antiepileptic drugs and the initiation of deep brain and cortical stimulation is often bypassed by the fact that both options are not mutually exclusive. This does not discard, however, the need to investigate the additive value of deep brain or cortical stimulation in these situations as well as the exact point of time when they should be proposed.

A frequently encountered dilemma in tertiary epilepsy centers is whether unsuitable surgery candidates should proceed with either deep brain / cortical stimulation or vagus nerve stimulation. As ATN DBS is currently the only reimbursed invasive intracranial neurostimulation treatment in Belgium, this quandary is narrowed to ATN DBS versus VNS in our country. The lack of direct head-to-head randomized comparisons is a major gap in the currently available evidence and necessitates further study. Meanwhile, neurologists are forced to look at the treatment effects observed in the respective different RCTs to determine their treatment strategy, although it should be noted that such an approach is subjected to various confounding factors including differences in patient groups and therapeutic settings. In two large RCTs, VNS was associated with -18.4 and -12.7% seizure reductions [245, 246]. This is similar to slightly lower than the reductions observed with ATN DBS (-17.4%), responsive ictal onset zone stimulation (-24.9%) and hippocampal DBS (-28.1%). On the other hand, neither clinically or statistically significant changes could be demonstrated for the proportion of patients experiencing a 50% or greater reduction with ANT DBS (OR 1.20, 95% CI 0.52 to 2.80), hippocampal DBS (OR 1.20, 95% CI 0.36 to 4.01) and responsive stimulation of the ictal onset zone (OR 1.12, 95% CI 0.59 to 2.11) after three months of stimulation. In contrast, moderate-quality evidence has shown significantly higher 50% responder rates with high- versus low-stimulation (presumed ineffective) VNS, with an odds ratio of 1.73 (95%CI 1.13 to 2.64) corresponding to 24.9% versus 14.4% of patients [247]. Evaluating the reported 50% responder rates during long-term uncontrolled

unblinded follow-up, figures for VNS typically ranged around 50% (11 to 69%) which is slightly inferior than these observed with deep brain and cortical stimulation: 68% after 5 years of ATN DBS, 55 to 65% after 6 years of responsive ictal onset zone stimulation and 75% for hippocampal DBS [27, 28, 30, 248]. With regards to safety and tolerability, VNS requires a less invasive surgical procedure and is in general well-tolerated with only mild adverse events, including hoarseness, throat paresthesia or pain, coughing and dyspnea occurring during the stimulation ON periods that tend to improve over time [247, 249]. Deep brain and cortical stimulation are more invasive treatment options and associated with postoperative asymptomatic intracranial hemaemorrhage in 1.6 to 3.7% of patients and postoperative soft-tissue infections in 2.0 to 4.5% of patients (9.4 to 12.7% after 5 years). Nevertheless, no patient experienced permanent symptomatic sequelae. ATN DBS is associated with higher rates of subjective memory impairment and self-reported depression after three months of stimulation, clear stimulation-related adverse events were not reported for responsive stimulation of the ictal onset zone and data on the adverse events of hippocampal DBS are too sparse to make any judgement on this issue.

While awaiting RCTs directly comparing deep brain and cortical stimulation to VNS, I propose that in general VNS should remain the treatment of choice for the vast majority patients given its less invasive nature, the higher 50% responder rates observed in randomized controlled conditions and the mild side effect profile. This should, however, always be evaluated on an individual patient basis taking into account factors such as comorbidities (e.g. depression, cognition, …) and potential patient preferences (e.g. patients may be averse to hoarseness). After failure of VNS, the possibility of ATN DBS should in general be proposed to all patients. As a concluding remark, I mention that two RCTs comparing ATN DBS to VNS or 'usual treatment including VNS' are currently being conducted and the results of these and hopefully even more future trials should be closely monitored as they could change or reinforce the proposed treatment algorithm [250, 251].

We have emphasized the need for more double-blind RCTs to provide more evidence on the efficacy and safety of intracranial neurostimulation treatments for drug-resistant epilepsy and to fill the gaps in the currently available evidence. Preferably, these trials should:

1. Include a large number of patients. However, given the limited number of patients included in RCTs so far, RCTs with a smaller number of patients are also worthwile to be undertaken. Multicentre RCTs could overcome difficulties in patient recruitment.
2. Use a parallel-group design to bypass potential outlasting effects of stimulation. When a cross-over design is nevertheless used (e.g. due to difficulties in patient recruitment), a sufficiently long washout period should be introduced between the sham and active stimulation periods. The required duration of this washout period needs further study but we suggest at least a 3-month period without stimulation following three months of stimulation.
3. Introduce a sufficiently long time window between electrode implantation and initiation of the blinded evaluation period to avoid potential implantation effects during the blinded evaluation period complicating the interpretation of the observed treatment effects. A four-month period seems a reasonable duration for this time window [29, 31].
4. Assess and report all relevant outcome variables: seizure freedom, responder rate, seizure frequency reduction, adverse events, neuropsychological outcome and quality of life.

5. Investigate reported trends for increasing efficacy over time in randomized controlled conditions using more extended evaluation periods. Comparison to 'best medical treatment' could overcome ethical issues.

Obtaining high-quality evidence on all relevant outcome variables is an indispensable step for a more widespread use of cortical and deep brain stimulation in epilepsy. Merely this process of data collection, however, is not sufficient and efforts should also be made to optimize the efficacy and decrease the adverse events of this therapy. One possible strategy to achieve this is by a more thorough patient selection. The identificaction of factors predicting a favourable response could prevent the unnecessary hardware implantation in patients likely to be nonresponders and lead to a more convincing approach towards patients likely to benefit from the treatment. Our uncontrolled open-label trial suggests that patients with a focal ictal onset may be more likely to experience a ≥90% reduction in seizure frequency although this needs to be confirmed in larger trials. The initial impression that the presence of hippocampal sclerosis is associated with a worse outcome of hippocampal DBS was not substantiated in more recent trials. Overall, until now no factors have repeatedly and reliably been identified as predictive of a favorable or disadvantageous outcome. Given the limited number of patients treated with DBS and cortical stimulation so far, multicenter cooperation is probably indispensable and should be encouraged to retrospectively analyze all available data and identify such predictive characteristics.

The other main strategy to improve the outcome of patients treated with DBS and cortical stimulation is to optimize the stimulation protocol. This protocol includes both the stimulation target and the stimulation parameter settings. Various stimulation targets have been probed but the structure yielding the most beneficial outcomes remains unclear. Today, rather than the differences in outcome observed in uncontrolled trials, the main differences between these targets are the degree to which they have been investigated in RCTs and the currently available quality of evidence. The heterogenous patient groups included in different trials, however, preclude reliable comparisons. The importance of the exact electrode location even within a specific stimulation target has been suggested by retrospective outcome analyses of patients treated with ANT and hippocampal DBS. Lehtimaki and colleagues demonstrated that stimulation through electrode contacts with an actual location at the anterior aspect of the ANT were associated with a favourable outcome, whereas contacts at a more posterior and inferior aspect of the ANT were associated with a poor outcome [46]. In a series of 8 patients treated with hippocampal DBS, the active electrode contact was located within 3 mm of the subiculum in 6/6 responders, whereas this distance was more than 3 mm in 2/2 nonresponders [241]. The importance of an accurate electrode (contact) location is also in line with the input-specificity of the EP reductions observed in our experiments in healthy rats.

Next to the stimulation target, more research needs to be performed in order to identify the most efficacious stimulation parameter settings. As outlined above, very heterogeneous stimulation parameters have all yielded favorable results, making it difficult to identify the most efficacious settings. In analogy to previous experiences in movement disorders, there is preliminary evidence that high-frequency hippocampal DBS may be more efficacious than low-frequency stimulation [71, 72]. However, this superiority could be target-specific and low-frequency stimulation has been successfully used in various other targets in mainly uncontrolled conditions [21, 38, 61-65]. Futhermore, this superiority could also be patient-specific as observed in some previous trials [21, 38]. There is need for more RCTs evaluating the most optimal stimulation parameters settings or strategies (in case of

patient-specific protocols). Although it is realistic to compare for example high- to low-frequency DBS or continuous to intermittent stimulation, it should be kept in mind that the enormous amount of possible stimulation parameter settings and strategies makes it unfeasible to test them all in randomized controlled conditions in human patients. Preclinical studies in animal models of epilepsy could be an important aid in this search. Another possibitliy to bypass this issue is by rationalizing the stimulation protocol based on an increased knowledge of its mechanism of action.

We evaluated the effect of hippocampal DBS on intrahippocampal EPs and EEG. We demonstrated EP reductions with two different time courses, showing evidence for axonal block and / or synaptic depression as well as DBS-induced homeostatic neuroplasticity. We could not support previous studies demonstrating desynchronization of neural activity by DBS and suggest that these changes are mainly a secondary phenomenon. However, our experiments cannot exclude such changes during DBS and more studies are required to evaluate this possibility, especially given the numerous trials reporting DBS-induced neuronal activity in downstream targets making jamming of pathological activity likely to be involved in the mechanism of action of DBS. It would therefore be interesting to repeat our experiments and combine our setup with single-cell recordings both during and after DBS.

Another important issue warranting future research is the demonstration of a relationship between the EP reductions observed in our experiments and the therapeutic outcome. The dual neurophysiological effect of DBS with both short- and longer-lasting EP reductions is one of the main findings of my doctoral dissertation. To investigate the clinical counterpart of these dual effects, the final experiment of my PhD compared the therapeutic efficacy of continuous, intermittent 1/5 min ON/OFF and 1/29 min ON/OFF hippocampal DBS in the intraperitoneal kainic acid rat model of temporal lobe epilepsy. The aim was not only to compare the overall efficacy of these three stimulation regimens in terms of seizure reduction to increase our knowledge with regards to the most efficacious stimulation protocols, but also – and more interestingly – to investigate the relationship between the timing of seizure occurrence and the DBS ON and OFF times. Due to pneumocystis carinii lung infections after seven months, however, this study could unfortunately not yield interpretable results. Although labor-intensive and time consuming it seems worthwile to repeat this study as it could produce crucial insights into the mechanism of action of DBS in epilepsy, especially with regards to whether the temporary, the longer-lasting or a combination of both effects of DBS are mainly responsible for the antiepileptic effects.

Other limitations of our study necessitating more research are the facts that we evaluated the effects of hippocampal DBS only and in healthy rats solely. Future research should investigate whether similar EP reductions are found in other brain regions. Region-specific effects have been reported. For example, McCracken and colleagues evaluated the effects of nucleus accumbens DBS and found reduced evoked potentials in the orbitofrontal cortex but not in the medial prefrontal cortex [186]. Hence, it is possible that the effects of DBS in the hippocampus differ from those in the basal ganglia network where DBS is typically applied in movement disorders. For example, in analogy to the clinical observations, it could be that in the latter the temporary short-lasting effects are more important than the chronic neuroplasticity effects. Future research is also required to confirm the observed EP reductions in pathological brain tissue. For example, Yamawaki and colleagues showed presynaptic EP reductions after one second of high-frequency stimulation in the STN in slices from dopamine-depleted rats but not from healthy rats [183]. The occurrence of seizures could also influence the EP reductions observed in our experiments as well as their temporal dynamics. As a final step our findings need to

be confirmed in patients treated with DBS. It would be interesting to investigate the potential neurophysiological correlates of therapeutically effective and ineffectieve stimulation parameter settings. Furthermore, differences in DBS hardware characteristics such as electrode geometry could have important consequences.

Although increased understanding of the mechanism of action is necessary to rationalize the stimulation protocol, it seems unrealistic to completely unravel the mode of action of DBS and translate this knowledge into the most efficacious stimulation protocol in the short term. The identification of a biomarker predicting the final outcome of DBS could bridge the gap between the lack of a complete comprehension of the mechanism of action of DBS and the need for more efficacious stimulation protocols. Changes in evoked potentials as those encountered in our experiments could be such a biomarker but this needs more study. If this would be the case, however, it would allow a fast screening tool to evaluate different combinations of possible stimulation parameter settings.

REFERENCES

[1] Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012;78(20):1548-54.

[2] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342(5):314-9.

[3] Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology 1998;51(5):1256-62.

[4] Tatum WOt. Mesial temporal lobe epilepsy. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society 2012;29(5):356-65.

[5] Cohen-Gadol AA, Wilhelmi BG, Collignon F, White JB, Britton JW, Cambier DM, et al. Long-term outcome of epilepsy surgery among 399 patients with nonlesional seizure foci including mesial temporal lobe sclerosis. J Neurosurg 2006;104(4):513-24.

[6] de Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WF, Sander JW, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet 2011;378(9800):1388-95.

[7] Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain 2005;128(Pt 5):1188-98.

[8] Tellez-Zenteno JF, Hernandez Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. Epilepsy Res 2010;89(2-3):310-8.

[9] Blumcke I, Pauli E, Clusmann H, Schramm J, Becker A, Elger C, et al. A new clinico-pathological classification system for mesial temporal sclerosis. Acta Neuropathol 2007;113(3):235-44.

[10] King D, Spencer S. Invasive electroencephalography in mesial temporal lobe epilepsy. J Clin Neurophysiol 1995;12(1):32-45.

[11] Spencer D, Burchiel K. Selective amygdalohippocampectomy. Epilepsy research and treatment 2012;2012:382095.

[12] Swanson TH. The pathophysiology of human mesial temporal lobe epilepsy. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society 1995;12(1):2-22.

[13] Muhlhofer W, Tan YL, Mueller SG, Knowlton R. MRI-negative temporal lobe epilepsy-What do we know? Epilepsia 2017;58(5):727-42.

[14] Nascimento FA, Gatto LA, Silvado C, Mader-Joaquim MJ, Moro MS, Araujo JC. Anterior temporal lobectomy versus selective amygdalohippocampectomy in patients with mesial temporal lobe epilepsy. Arq Neuropsiquiatr 2016;74(1):35-43.

[15] Vonck K, Sprengers M, Carrette E, Dauwe I, Miatton M, Meurs A, et al. A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. Int J Neural Syst 2013;23(1):1250034.

[16] Boex C, Seeck M, Vulliemoz S, Rossetti AO, Staedler C, Spinelli L, et al. Chronic deep brain stimulation in mesial temporal lobe epilepsy. Seizure 2011;20(6):485-90.

[17] Cukiert A, Cukiert CM, Burattini JA, Lima AM. Seizure outcome after hippocampal deep brain stimulation in a prospective cohort of patients with refractory temporal lobe epilepsy. Seizure 2014;23(1):6-9.

[18] Cukiert A, Cukiert CM, Burattini JA, Mariani PP, Bezerra DF. Seizure outcome after hippocampal deep brain stimulation in patients with refractory temporal lobe epilepsy: A prospective, controlled, randomized, double-blind study. Epilepsia 2017;58(10):1728-33.

[19] Ding P, Zhang S, Zhang J, Hu X, Yu X, Liang S, et al. Contralateral Hippocampal Stimulation for Failed Unilateral Anterior Temporal Lobectomy in Patients with Bilateral Temporal Lobe Epilepsy. Stereotact Funct Neurosurg 2016;94(5):327-35.

[20] Jin H, Li W, Dong C, Wu J, Zhao W, Zhao Z, et al. Hippocampal deep brain stimulation in nonlesional refractory mesial temporal lobe epilepsy. Seizure 2016;37:1-7.

[21] Lim SN, Lee CY, Lee ST, Tu PH, Chang BL, Lee CH, et al. Low and High Frequency Hippocampal Stimulation for Drug-Resistant Mesial Temporal Lobe Epilepsy. Neuromodulation 2016;19(4):365-72.
[22] McLachlan RS, Pigott S, Tellez-Zenteno JF, Wiebe S, Parrent A. Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: impact on seizures and memory. Epilepsia 2010;51(2):304-7.
[23] Min B, Guoming L, Jian Z. Treatment of mesial temporal lobe epilepsy with amygdalohippocampal stimulation: A case series and review of the literature. Exp Ther Med 2013;5(4):1264-8.
[24] Tellez-Zenteno JF, McLachlan RS, Parrent A, Kubu CS, Wiebe S. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. Neurology 2006;66(10):1490-4.
[25] Velasco AL, Velasco F, Velasco M, Trejo D, Castro G, Carrillo-Ruiz JD. Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. Epilepsia 2007;48(10):1895-903.
[26] Wiebe S, Kiss Z, Ahmed N, Andrade D, Brownstone R, Del Campo M, et al. Medical vs electrical therapy for mesial temporal lobe epilepsy: a multicenter randomized trial. Epilepsy Curr 2013;13:289.
[27] Salanova V, Witt T, Worth R, Henry TR, Gross RE, Nazzaro JM, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology 2015;84(10):1017-25.
[28] Geller EB, Skarpaas TL, Gross RE, Goodman RR, Barkley GL, Bazil CW, et al. Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. Epilepsia 2017;58(6):994-1004.
[29] Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51(5):899-908.
[30] Jobst BC, Kapur R, Barkley GL, Bazil CW, Berg MJ, Bergey GK, et al. Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas. Epilepsia 2017;58(6):1005-14.
[31] Morrell MJ, Group RNSSiES. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 2011;77(13):1295-304.
[32] Miatton M, Van Roost D, Thiery E, Carrette E, Van Dycke A, Vonck K, et al. The cognitive effects of amygdalohippocampal deep brain stimulation in patients with temporal lobe epilepsy. Epilepsy Behav 2011.
[33] Spencer S, So N, Engel J. Depth electrodes. In: Engel JJ, editor Surgical treatment of the epilepsies (2nd edition), New York, United States: Raven Press; 1993, p. 359-76.
[34] Alaraj A, Comair Y, Mikati M, Wakim J, Louak E, Atweh S. Subthalamic nucleus deep brain stimulation: a novel method for the treatment of non-focal intractable epilepsy. Presented as a poster at Neuromodulation: defining the future Cleveland, OH June 8-10, 2001.
[35] Andrade DM, Zumsteg D, Hamani C, Hodaie M, Sarkissian S, Lozano AM, et al. Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy. Neurology 2006;66(10):1571-3.
[36] Capecci M, Ricciuti RA, Ortenzi A, Paggi A, Durazzi V, Rychlicki F, et al. Chronic bilateral subthalamic stimulation after anterior callosotomy in drug-resistant epilepsy: long-term clinical and functional outcome of two cases. Epilepsy Res 2012;98(2-3):135-9.
[37] Chabardes S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid AL. Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. Epileptic Disord 2002;4 Suppl 3:S83-93.
[38] Child ND, Stead M, Wirrell EC, Nickels KC, Wetjen NM, Lee KH, et al. Chronic subthreshold subdural cortical stimulation for the treatment of focal epilepsy originating from eloquent cortex. Epilepsia 2014;55(3):e18-21.
[39] Cukiert A, Burattini JA, Cukiert CM, Argentoni-Baldochi M, Baise-Zung C, Forster CR, et al. Centro-median stimulation yields additional seizure frequency and attention improvement in patients previously submitted to callosotomy. Seizure 2009;18(8):588-92.

[40] Franzini A, Messina G, Marras C, Villani F, Cordella R, Broggi G. Deep brain stimulation of two unconventional targets in refractory non-resectable epilepsy. Stereotact Funct Neurosurg 2008;86(6):373-81.
[41] Handforth A, DeSalles AA, Krahl SE. Deep brain stimulation of the subthalamic nucleus as adjunct treatment for refractory epilepsy. Epilepsia 2006;47(7):1239-41.
[42] Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM. Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 2002;43(6):603-8.
[43] Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, et al. Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia 2004;45(4):346-54.
[44] Khan S, Wright I, Javed S, Sharples P, Jardine P, Carter M, et al. High frequency stimulation of the mamillothalamic tract for the treatment of resistant seizures associated with hypothalamic hamartoma. Epilepsia 2009;50(6):1608-11.
[45] Kowski AB, Voges J, Heinze HJ, Oltmanns F, Holtkamp M, Schmitt FC. Nucleus accumbens stimulation in partial epilepsy--a randomized controlled case series. Epilepsia 2015;56(6):e78-82.
[46] Lehtimaki K, Mottonen T, Jarventausta K, Katisko J, Tahtinen T, Haapasalo J, et al. Outcome based definition of the anterior thalamic deep brain stimulation target in refractory epilepsy. Brain Stimul 2016;9(2):268-75.
[47] Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, Chen JL, et al. Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. Epilepsia 2007;48(2):342-7.
[48] Loddenkemper T, Pan A, Neme S, Baker KB, Rezai AR, Dinner DS, et al. Deep brain stimulation in epilepsy. J Clin Neurophysiol 2001;18(6):514-32.
[49] Oh YS, Kim HJ, Lee KJ, Kim YI, Lim SC, Shon YM. Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients. Seizure 2012;21(3):183-7.
[50] Osorio I, Overman J, Giftakis J, Wilkinson SB. High frequency thalamic stimulation for inoperable mesial temporal epilepsy. Epilepsia 2007;48(8):1561-71.
[51] Piacentino M, Durisotti C, Garofalo PG, Bonanni P, Volzone A, Ranzato F, et al. Anterior thalamic nucleus deep brain Stimulation (DBS) for drug-resistant complex partial seizures (CPS) with or without generalization: long-term evaluation and predictive outcome. Acta Neurochir (Wien) 2015;157(9):1525-32; discussion 32.
[52] Schmitt FC, Voges J, Heinze HJ, Zaehle T, Holtkamp M, Kowski AB. Safety and feasibility of nucleus accumbens stimulation in five patients with epilepsy. J Neurol 2014;261(8):1477-84.
[53] Son BC, Shon YM, Choi JG, Kim J, Ha SW, Kim SH, et al. Clinical Outcome of Patients with Deep Brain Stimulation of the Centromedian Thalamic Nucleus for Refractory Epilepsy and Location of the Active Contacts. Stereotact Funct Neurosurg 2016;94(3):187-97.
[54] Velasco AL, Velasco F, Jimenez F, Velasco M, Castro G, Carrillo-Ruiz JD, et al. Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox-Gastaut syndrome. Epilepsia 2006;47(7):1203-12.
[55] Wille C, Steinhoff BJ, Altenmuller DM, Staack AM, Bilic S, Nikkhah G, et al. Chronic high-frequency deep-brain stimulation in progressive myoclonic epilepsy in adulthood--report of five cases. Epilepsia 2011;52(3):489-96.
[56] Kuncel AM, Cooper SE, Wolgamuth BR, Clyde MA, Snyder SA, Montgomery EB, Jr., et al. Clinical response to varying the stimulus parameters in deep brain stimulation for essential tremor. Mov Disord 2006;21(11):1920-8.
[57] Moro E, Esselink RJ, Xie J, Hommel M, Benabid AL, Pollak P. The impact on Parkinson's disease of electrical parameter settings in STN stimulation. Neurology 2002;59(5):706-13.
[58] Pedrosa DJ, Auth M, Eggers C, Timmermann L. Effects of low-frequency thalamic deep brain stimulation in essential tremor patients. Exp Neurol 2013;248:205-12.

[59] Timmermann L, Wojtecki L, Gross J, Lehrke R, Voges J, Maarouf M, et al. Ten-Hertz stimulation of subthalamic nucleus deteriorates motor symptoms in Parkinson's disease. Mov Disord 2004;19(11):1328-33.
[60] Ushe M, Mink JW, Tabbal SD, Hong M, Schneider Gibson P, Rich KM, et al. Postural tremor suppression is dependent on thalamic stimulation frequency. Mov Disord 2006;21(8):1290-2.
[61] Cooper IS, Amin I, Gilman S. The effect of chronic cerebellar stimulation upon epilepsy in man. Trans Am Neurol Assoc 1973;98:192-6.
[62] Van Buren JM, Wood JH, Oakley J, Hambrecht F. Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. J Neurosurg 1978;48(3):407-16.
[63] Velasco F, Carrillo-Ruiz JD, Brito F, Velasco M, Velasco AL, Marquez I, et al. Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. Epilepsia 2005;46(7):1071-81.
[64] Wright GD, McLellan DL, Brice JG. A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. J Neurol Neurosurg Psychiatry 1984;47(8):769-74.
[65] Chkhenkeli SA, Chkhenkeli IS. Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain in patients with intractable epilepsy. Stereotact Funct Neurosurg 1997;69(1-4 Pt 2):221-4.
[66] Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, et al. Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 1992;33(5):841-51.
[67] Valentin A, Garcia Navarrete E, Chelvarajah R, Torres C, Navas M, Vico L, et al. Deep brain stimulation of the centromedian thalamic nucleus for the treatment of generalized and frontal epilepsies. Epilepsia 2013;54(10):1823-33.
[68] Velasco F, Velasco M, Ogarrio C, Fanghanel G. Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia 1987;28(4):421-30.
[69] Velasco F, Velasco M, Velasco AL, Jimenez F. Effect of chronic electrical stimulation of the centromedian thalamic nuclei on various intractable seizure patterns: I. Clinical seizures and paroxysmal EEG activity. Epilepsia 1993;34(6):1052-64.
[70] Velasco F, Velasco M, Velasco AL, Jimenez F, Marquez I, Rise M. Electrical stimulation of the centromedian thalamic nucleus in control of seizures: long-term studies. Epilepsia 1995;36(1):63-71.
[71] Wyckhuys T, Raedt R, Vonck K, Wadman W, Boon P. Comparison of hippocampal Deep Brain Stimulation with high (130Hz) and low frequency (5Hz) on afterdischarges in kindled rats. Epilepsy Res 2010;88(2-3):239-46.
[72] Boex C, Vulliemoz S, Spinelli L, Pollo C, Seeck M. High and low frequency electrical stimulation in non-lesional temporal lobe epilepsy. Seizure 2007;16(8):664-9.
[73] Thevathasan W, Debu B, Aziz T, Bloem BR, Blahak C, Butson C, et al. Pedunculopontine nucleus deep brain stimulation in Parkinson's disease: A clinical review. Mov Disord 2018;33(1):10-20.
[74] Valentin A, Selway RP, Amarouche M, Mundil N, Ughratdar I, Ayoubian L, et al. Intracranial stimulation for children with epilepsy. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society 2017;21(1):223-31.
[75] Araujo D, Santos AC, Velasco TR, Wichert-Ana L, Terra-Bustamante VC, Alexandre V, et al. Volumetric evidence of bilateral damage in unilateral mesial temporal lobe epilepsy. Epilepsia 2006;47(8):1354-9.
[76] Bar-Gad I, Elias S, Vaadia E, Bergman H. Complex locking rather than complete cessation of neuronal activity in the globus pallidus of a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primate in response to pallidal microstimulation. J Neurosc 2004;24(33):7410-9.
[77] Bernasconi N, Bernasconi A, Andermann F, Dubeau F, Feindel W, Reutens DC. Entorhinal cortex in temporal lobe epilepsy: a quantitative MRI study. Neurology 1999;52(9):1870-6.

[78] Bonilha L, Halford JJ, Morgan PS, Edwards JC. Hippocampal atrophy in temporal lobe epilepsy: the 'generator' and 'receiver'. Acta Neurol Scand 2011.
[79] Dupont S, Samson Y, Van de Moortele PF, Samson S, Poline JB, Hasboun D, et al. Bilateral hemispheric alteration of memory processes in right medial temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 2002;73(5):478-85.
[80] Jokeit H, Ebner A, Arnold S, Schuller M, Antke C, Huang Y, et al. Bilateral reductions of hippocampal volume, glucose metabolism, and wada hemispheric memory performance are related to the duration of mesial temporal lobe epilepsy. J Neurol 1999;246(10):926-33.
[81] Knake S, Salat DH, Halgren E, Halko MA, Greve DN, Grant PE. Changes in white matter microstructure in patients with TLE and hippocampal sclerosis. Epileptic Disord 2009;11(3):244-50.
[82] Lee JW, Andermann F, Dubeau F, Bernasconi A, MacDonald D, Evans A, et al. Morphometric analysis of the temporal lobe in temporal lobe epilepsy. Epilepsia 1998;39(7):727-36.
[83] Seeck M, Lazeyras F, Murphy K, Naimi A, Pizzolatto GP, de Tribolet N, et al. Psychosocial functioning in chronic epilepsy: relation to hippocampal volume and histopathological findings. Epileptic Disord 1999;1(3):179-85.
[84] Zubler F, Seeck M, Landis T, Henry F, Lazeyras F. Contralateral medial temporal lobe damage in right but not left temporal lobe epilepsy: a (1)H magnetic resonance spectroscopy study. J Neurol Neurosurg Psychiatry 2003;74(9):1240-4.
[85] Adam C. [How do the temporal lobes communicate in medial temporal lobe seizures?]. Rev Neurol (Paris) 2006;162(8-9):813-8.
[86] Bertashius KM. Propagation of human complex-partial seizures: a correlation analysis. Electroencephalogr Clin Neurophysiol 1991;78(5):333-40.
[87] Catenoix H, Magnin M, Guenot M, Isnard J, Mauguiere F, Ryvlin P. Hippocampal-orbitofrontal connectivity in human: an electrical stimulation study. Clin Neurophysiol 2005;116(8):1779-84.
[88] Colnat-Coulbois S, Mok K, Klein D, Penicaud S, Tanriverdi T, Olivier A. Tractography of the amygdala and hippocampus: anatomical study and application to selective amygdalohippocampectomy. J Neurosurg 2010;113(6):1135-43.
[89] Eross L, Entz L, Fabo D, Jakus R, Szucs A, Rasonyi G, et al. Interhemispheric propagation of seizures in mesial temporal lobe epilepsy. Ideggyogyaszati szemle 2009;62(9-10):319-25.
[90] Gloor P, Salanova V, Olivier A, Quesney LF. The human dorsal hippocampal commissure. An anatomically identifiable and functional pathway. Brain 1993;116 (Pt 5):1249-73.
[91] Lacruz ME, Garcia Seoane JJ, Valentin A, Selway R, Alarcon G. Frontal and temporal functional connections of the living human brain. Eur J Neurosci 2007;26(5):1357-70.
[92] Lieb JP, Dasheiff RM, Engel J, Jr. Role of the frontal lobes in the propagation of mesial temporal lobe seizures. Epilepsia 1991;32(6):822-37.
[93] Napolitano CE, Orriols MA. Graduated and sequential propagation in mesial temporal epilepsy: analysis with scalp ictal EEG. J Clin Neurophysiol 2010;27(4):285-91.
[94] Palmini AL, Gloor P, Jones-Gotman M. Pure amnestic seizures in temporal lobe epilepsy. Definition, clinical symptomatology and functional anatomical considerations. Brain 1992;115 (Pt 3):749-69.
[95] Rosenzweig I, Beniczky S, Brunnhuber F, Alarcon G, Valentin A. The dorsal hippocampal commissure: when functionality matters. J Neuropsychiatry Clin Neurosci 2011;23(3):E45-8.
[96] Sindou M, Guenot M. Surgical anatomy of the temporal lobe for epilepsy surgery. Adv Tech Stand Neurosurg 2003;28:315-43.
[97] Spencer SS, Spencer DD, Williamson PD, Mattson R. Combined depth and subdural electrode investigation in uncontrolled epilepsy. Neurology 1990;40(1):74-9.
[98] Spencer SS, Williamson PD, Spencer DD, Mattson RH. Human hippocampal seizure spread studied by depth and subdural recording: the hippocampal commissure. Epilepsia 1987;28(5):479-89.
[99] Wilson CL, Engel J, Jr. Electrical stimulation of the human epileptic limbic cortex. Adv Neurol 1993;63:103-13.

[100] Wilson CL, Isokawa M, Babb TL, Crandall PH. Functional connections in the human temporal lobe. I. Analysis of limbic system pathways using neuronal responses evoked by electrical stimulation. Exp Brain Res 1990;82(2):279-92.
[101] Wilson CL, Isokawa M, Babb TL, Crandall PH, Levesque MF, Engel J, Jr. Functional connections in the human temporal lobe. II. Evidence for a loss of functional linkage between contralateral limbic structures. Exp Brain Res 1991;85(1):174-87.
[102] Van Nieuwenhuyse B, Raedt R, Delbeke J, Wadman WJ, Boon P, Vonck K. In search of optimal DBS paradigms to treat epilepsy: bilateral versus unilateral hippocampal stimulation in a rat model for temporal lobe epilepsy. Brain Stimul 2015;8(2):192-9.
[103] Valentin A, Ughratdar I, Cheserem B, Morris R, Selway R, Alarcon G. Epilepsia partialis continua responsive to neocortical electrical stimulation. Epilepsia 2015;56(8):e104-9.
[104] Valentin A, Ughratdar I, Venkatachalam G, Williams R, Pina M, Lazaro M, et al. Sustained Seizure Control in a Child with Drug Resistant Epilepsy after Subacute Cortical Electrical Stimulation (SCES). Brain Stimul 2016;9(2):307-9.
[105] Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, Chen JL, et al. Long-term anterior thalamus stimulation for intractable epilepsy. Chang Gung Med J 2008;31(3):287-96.
[106] Davis R, Emmonds SE. Cerebellar stimulation for seizure control: 17-year study. Stereotact Funct Neurosurg 1992;58(1-4):200-8.
[107] Velasco AL, Velasco M, Velasco F, Menes D, Gordon F, Rocha L, et al. Subacute and chronic electrical stimulation of the hippocampus on intractable temporal lobe seizures: preliminary report. Arch Med Res 2000;31(3):316-28.
[108] Cukiert A, Cukiert CM, Burattini JA, Lima Ade M. Seizure Outcome After Battery Depletion in Epileptic Patients Submitted to Deep Brain Stimulation. Neuromodulation 2015;18(6):439-41; discussion 41.
[109] Callaghan B, Schlesinger M, Rodemer W, Pollard J, Hesdorffer D, Allen Hauser W, et al. Remission and relapse in a drug-resistant epilepsy population followed prospectively. Epilepsia 2011;52(3):619-26.
[110] Callaghan BC, Anand K, Hesdorffer D, Hauser WA, French JA. Likelihood of seizure remission in an adult population with refractory epilepsy. Ann Neurol 2007;62(4):382-9.
[111] Katariwala NM, Bakay RA, Pennell PB, Olson LD, Henry TR, Epstein CM. Remission of intractable partial epilepsy following implantation of intracranial electrodes. Neurology 2001;57(8):1505-7.
[112] Kwan P, Sander JW. The natural history of epilepsy: an epidemiological view. Journal of neurology, neurosurgery, and psychiatry 2004;75(10):1376-81.
[113] Neligan A, Bell GS, Elsayed M, Sander JW, Shorvon SD. Treatment changes in a cohort of people with apparently drug-resistant epilepsy: an extended follow-up. J Neurol Neurosurg Psychiatry 2012;83(8):810-3.
[114] Schulze-Bonhage A, Dennig D, Wagner K, Cordeiro J, Carius A, Fauser S, et al. Seizure control resulting from intrahippocampal depth electrode insertion. J Neurol Neurosurg Psychiatry 2010;81(3):352-3.
[115] Selwa LM, Schmidt SL, Malow BA, Beydoun A. Long-term outcome of nonsurgical candidates with medically refractory localization-related epilepsy. Epilepsia 2003;44(12):1568-72.
[116] Sprengers M, Raedt R, Larsen LE, Delbeke J, Wadman W, Boon P, et al. Long-lasting decreased excitability induced by hippocampal deep brain stimulation in freely moving rats. In preparation, will be submitted to Brain.
[117] Sprengers M, Vonck K, Carrette E, Marson AG, Boon P. Deep brain and cortical stimulation for epilepsy. Cochrane Database Syst Rev 2014(6):CD008497.
[118] Sprengers M, Vonck K, Carrette E, Marson AG, Boon P. Deep brain and cortical stimulation for epilepsy. Cochrane Database Syst Rev 2017;7:CD008497.
[119] Cooper IS, Upton AR. Therapeutic implications of modulation of metabolism and functional activity of cerebral cortex by chronic stimulation of cerebellum and thalamus. Biol Psychiatry 1985;20(7):811-3.

[120] Goldenholz DM, Moss R, Scott J, Auh S, Theodore WH. Confusing placebo effect with natural history in epilepsy: A big data approach. Ann Neurol 2015;78(3):329-36.
[121] McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. J Clin Epidemiol 2014;67(3):267-77.
[122] Rajagopal S. The placebo effect. Psychiatr Bull 2006;30:185-8.
[123] Burneo JG, Montori VM, Faught E. Magnitude of the placebo effect in randomized trials of antiepileptic agents. Epilepsy & behavior : E&B 2002;3(6):532-4.
[124] Guekht AB, Korczyn AD, Bondareva IB, Gusev EI. Placebo responses in randomized trials of antiepileptic drugs. Epilepsy & behavior : E&B 2010;17(1):64-9.
[125] Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. PLoS Med 2008;5(8):e166.
[126] Bae EH, Theodore WH, Fregni F, Cantello R, Pascual-Leone A, Rotenberg A. An estimate of placebo effect of repetitive transcranial magnetic stimulation in epilepsy. Epilepsy & behavior : E&B 2011;20(2):355-9.
[127] Krishna V, King NK, Sammartino F, Strauss I, Andrade DM, Wennberg RA, et al. Anterior Nucleus Deep Brain Stimulation for Refractory Epilepsy: Insights Into Patterns of Seizure Control and Efficacious Target. Neurosurgery 2016;78(6):802-11.
[128] Chang SY, Kim I, Marsh MP, Jang DP, Hwang SC, Van Gompel JJ, et al. Wireless fast-scan cyclic voltammetry to monitor adenosine in patients with essential tremor during deep brain stimulation. Mayo Clin Proc 2012;87(8):760-5.
[129] Lesser RP. Remission of intractable partial epilepsy following implantation of intracranial electrodes. Neurology 2002;58(8):1317.
[130] Laufs H, Richardson MP, Salek-Haddadi A, Vollmar C, Duncan JS, Gale K, et al. Converging PET and fMRI evidence for a common area involved in human focal epilepsies. Neurology 2011;77(9):904-10.
[131] Loscher W, Ebert U. The role of the piriform cortex in kindling. Prog Neurobiol 1996;50(5-6):427-81.
[132] McIntyre DC, Gilby KL. Mapping seizure pathways in the temporal lobe. Epilepsia 2008;49 Suppl 3:23-30.
[133] Ghorbani P, Mohammad-Zadeh M, Mirnajafi-Zadeh J, Fathollahi Y. Effect of different patterns of low-frequency stimulation on piriform cortex kindled seizures. Neurosci Lett 2007;425(3):162-6.
[134] Kelly ME, Staines WA, McIntyre DC. Secondary generalization of hippocampal kindled seizures in rats: examining the role of the piriform cortex. Brain Res 2002;957(1):152-61.
[135] Schwabe K, Ebert U, Loscher W. Bilateral lesions of the central but not anterior or posterior parts of the piriform cortex retard amygdala kindling in rats. Neuroscience 2000;101(3):513-21.
[136] Schwabe K, Ebert U, Loscher W. Effects of lesions of the perirhinal cortex on amygdala kindling in rats. Epilepsy Res 2000;42(1):33-41.
[137] Yang LX, Jin CL, Zhu-Ge ZB, Wang S, Wei EQ, Bruce IC, et al. Unilateral low-frequency stimulation of central piriform cortex delays seizure development induced by amygdaloid kindling in rats. Neuroscience 2006;138(4):1089-96.
[138] Sprengers M, Raedt R, Siugzdaite R, Van Nieuwenhuyse B, Descamps B, Dauwe I, et al. Consequences of kainic acid-induced piriform cortex lesions and therapeutic potential of piriform cortex deep brain stimulation in the intrahippocampal kainic acid model. Frontiers in Human Neuroscience, conference abstract Belgian Brain Council 2014: Modulating the brain: facts, fiction, future doi: 103389/conffnhum20142140.
[139] Feng Z, Wang Z, Guo Z, Zhou W, Cai Z, Durand DM. High frequency stimulation of afferent fibers generates asynchronous firing in the downstream neurons in hippocampus through partial block of axonal conduction. Brain Res 2017;1661:67-78.
[140] Riedel G, Seidenbecher T, Reymann KG. LTP in hippocampal CA1 of urethane-narcotized rats requires stronger tetanization parameters. Physiol Behav 1994;55(6):1141-6.

[141] Shirasaka Y, Wasterlain CG. The effect of urethane anesthesia on evoked potentials in dentate gyrus. Eur J Pharmacol 1995;282(1-3):11-7.
[142] Sprengers M, Raedt R, Larsen LE, Delbeke J, Wadman W, Boon P, et al. Deep brain stimulation reduces evoked potentials with a dual time course in freely moving rats: potential neurophysiological basis for intermittent as an alternative to continuous stimulation. Submitted to Epilepsia, under review (first submission October 17th, 2019; resubmitted February 6th, 2020).
[143] Shen KZ, Johnson SW. Complex EPSCs evoked in substantia nigra reticulata neurons are disrupted by repetitive stimulation of the subthalamic nucleus. Synapse 2008;62(4):237-42.
[144] Anderson TR, Hu B, Iremonger K, Kiss ZH. Selective attenuation of afferent synaptic transmission as a mechanism of thalamic deep brain stimulation-induced tremor arrest. J Neurosc 2006;26(3):841-50.
[145] Li B, Piriz J, Mirrione M, Chung C, Proulx CD, Schulz D, et al. Synaptic potentiation onto habenula neurons in the learned helplessness model of depression. Nature 2011;470(7335):535-9.
[146] Kim E, Owen B, Holmes WR, Grover LM. Decreased afferent excitability contributes to synaptic depression during high-frequency stimulation in hippocampal area CA1. J Neurophysiol 2012;108(7):1965-76.
[147] Schiller Y, Bankirer Y. Cellular mechanisms underlying antiepileptic effects of low- and high-frequency electrical stimulation in acute epilepsy in neocortical brain slices in vitro. J Neurophysiol 2007;97(3):1887-902.
[148] Feng Z, Yu Y, Guo Z, Cao J, Durand DM. High frequency stimulation extends the refractory period and generates axonal block in the rat hippocampus. Brain Stimul 2014;7(5):680-9.
[149] Feng Z, Zheng X, Yu Y, Durand DM. Functional disconnection of axonal fibers generated by high frequency stimulation in the hippocampal CA1 region in-vivo. Brain Res 2013;1509:32-42.
[150] Iremonger KJ, Anderson TR, Hu B, Kiss ZH. Cellular mechanisms preventing sustained activation of cortex during subcortical high-frequency stimulation. J Neurophysiol 2006;96(2):613-21.
[151] Van Nieuwenhuyse B, Vonck K, Raedt R, Meurs A, Wytse W, Boon PAJM. Deep Brain Stimulation Early during Epileptogenesis Modifies Disease Progression in the Hippocampus. Epilepsia 2012;53:26-7.
[152] Fioravante D, Regehr WG. Short-term forms of presynaptic plasticity. Curr Opin Neurobiol 2011;21(2):269-74.
[153] Zucker RS, Regehr WG. Short-term synaptic plasticity. Annu Rev Physiol 2002;64:355-405.
[154] Urbano F, Leznik E, Llinás R. Cortical activation patterns evoked by afferent axons stimuli at different frequencies: an in vitro voltage-sensitive dye imaging study. Thalamus Relat Syst 2002;1(4):371-8.
[155] Anderson ME, Postupna N, Ruffo M. Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. J Neurophysiol 2003;89(2):1150-60.
[156] Boraud T, Bezard E, Bioulac B, Gross C. High frequency stimulation of the internal Globus Pallidus (GPi) simultaneously improves parkinsonian symptoms and reduces the firing frequency of GPi neurons in the MPTP-treated monkey. Neurosci Lett 1996;215(1):17-20.
[157] Chan CS, Shigemoto R, Mercer JN, Surmeier DJ. HCN2 and HCN1 channels govern the regularity of autonomous pacemaking and synaptic resetting in globus pallidus neurons. J Neurosc 2004;24(44):9921-32.
[158] Dostrovsky JO, Levy R, Wu JP, Hutchison WD, Tasker RR, Lozano AM. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J Neurophysiol 2000;84(1):570-4.
[159] Filali M, Hutchison WD, Palter VN, Lozano AM, Dostrovsky JO. Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus. Exp Brain Res 2004;156(3):274-81.
[160] Lafreniere-Roula M, Kim E, Hutchison WD, Lozano AM, Hodaie M, Dostrovsky JO. High-frequency microstimulation in human globus pallidus and substantia nigra. Exp Brain Res 2010;205(2):251-61.
[161] Lee KH, Chang SY, Roberts DW, Kim U. Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. J Neurosurg 2004;101(3):511-7.

[162] Meissner W, Leblois A, Hansel D, Bioulac B, Gross CE, Benazzouz A, et al. Subthalamic high frequency stimulation resets subthalamic firing and reduces abnormal oscillations. Brain 2005;128(Pt 10):2372-82.
[163] Wu YR, Levy R, Ashby P, Tasker RR, Dostrovsky JO. Does stimulation of the GPi control dyskinesia by activating inhibitory axons? Mov Disord 2001;16(2):208-16.
[164] Beurrier C, Bioulac B, Audin J, Hammond C. High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. J Neurophysiol 2001;85(4):1351-6.
[165] Garcia L, Audin J, D'Alessandro G, Bioulac B, Hammond C. Dual effect of high-frequency stimulation on subthalamic neuron activity. J Neurosc 2003;23(25):8743-51.
[166] Magarinos-Ascone C, Pazo JH, Macadar O, Buno W. High-frequency stimulation of the subthalamic nucleus silences subthalamic neurons: a possible cellular mechanism in Parkinson's disease. Neuroscience 2002;115(4):1109-17.
[167] Ranck JB, Jr. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res 1975;98(3):417-40.
[168] Fasano A, Aquino CC, Krauss JK, Honey CR, Bloem BR. Axial disability and deep brain stimulation in patients with Parkinson disease. Nature reviews Neurology 2015;11(2):98-110.
[169] Herrington TM, Cheng JJ, Eskandar EN. Mechanisms of deep brain stimulation. J Neurophysiol 2016;115(1):19-38.
[170] Johnson MD, Miocinovic S, McIntyre CC, Vitek JL. Mechanisms and targets of deep brain stimulation in movement disorders. Neurotherapeutics 2008;5(2):294-308.
[171] Krack P, Hariz MI, Baunez C, Guridi J, Obeso JA. Deep brain stimulation: from neurology to psychiatry? Trends Neurosci 2010;33(10):474-84.
[172] Pedersen JL, Barloese M, Jensen RH. Neurostimulation in cluster headache: a review of current progress. Cephalalgia : an international journal of headache 2013;33(14):1179-93.
[173] Sachdev PS, Mohan A, Cannon E, Crawford JD, Silberstein P, Cook R, et al. Deep brain stimulation of the antero-medial globus pallidus interna for Tourette syndrome. PLoS One 2014;9(8):e104926.
[174] Servello D, Porta M, Sassi M, Brambilla A, Robertson MM. Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation. Journal of neurology, neurosurgery, and psychiatry 2008;79(2):136-42.
[175] Udupa K, Chen R. The mechanisms of action of deep brain stimulation and ideas for the future development. Prog Neurobiol 2015;133:27-49.
[176] Yianni J, Bain PG, Gregory RP, Nandi D, Joint C, Scott RB, et al. Post-operative progress of dystonia patients following globus pallidus internus deep brain stimulation. Eur J Neurol 2003;10(3):239-47.
[177] Hebb MO, Chiasson P, Lang AE, Brownstone RM, Mendez I. Sustained relief of dystonia following cessation of deep brain stimulation. Mov Disord 2007;22(13):1958-62.
[178] Houeto JL, Karachi C, Mallet L, Pillon B, Yelnik J, Mesnage V, et al. Tourette's syndrome and deep brain stimulation. Journal of neurology, neurosurgery, and psychiatry 2005;76(7):992-5.
[179] Motlagh MG, Smith ME, Landeros-Weisenberger A, Kobets AJ, King RA, Miravite J, et al. Lessons Learned from Open-label Deep Brain Stimulation for Tourette Syndrome: Eight Cases over 7 Years. Tremor Other Hyperkinet Mov (N Y) 2013;3.
[180] Ruge D, Cif L, Limousin P, Gonzalez V, Vasques X, Coubes P, et al. Longterm deep brain stimulation withdrawal: clinical stability despite electrophysiological instability. J Neurol Sci 2014;342(1-2):197-9.
[181] Temperli P, Ghika J, Villemure JG, Burkhard PR, Bogousslavsky J, Vingerhoets FJ. How do parkinsonian signs return after discontinuation of subthalamic DBS? Neurology 2003;60(1):78-81.
[182] Shen KZ, Zhu ZT, Munhall A, Johnson SW. Synaptic plasticity in rat subthalamic nucleus induced by high-frequency stimulation. Synapse 2003;50(4):314-9.
[183] Yamawaki N, Magill PJ, Woodhall GL, Hall SD, Stanford IM. Frequency selectivity and dopamine-dependence of plasticity at glutamatergic synapses in the subthalamic nucleus. Neuroscience 2012;203:1-11.

[184] Calabresi P, Maj R, Pisani A, Mercuri NB, Bernardi G. Long-term synaptic depression in the striatum: physiological and pharmacological characterization. J Neurosc 1992;12(11):4224-33.
[185] McCracken CB, Grace AA. High-frequency deep brain stimulation of the nucleus accumbens region suppresses neuronal activity and selectively modulates afferent drive in rat orbitofrontal cortex in vivo. J Neurosc 2007;27(46):12601-10.
[186] McCracken CB, Grace AA. Nucleus accumbens deep brain stimulation produces region-specific alterations in local field potential oscillations and evoked responses in vivo. J Neurosc 2009;29(16):5354-63.
[187] Braz BY, Belforte JE, Murer MG, Galinanes GL. Properties of the corticostriatal long term depression induced by medial prefrontal cortex high frequency stimulation in vivo. Neuropharmacology 2017;121:278-86.
[188] Andersen P, Morris R, Amaral D, Bliss T, O'Keefe J. The hippocampus book. New York, United States: Oxford University Press; 2007.
[189] Citri A, Malenka RC. Synaptic plasticity: multiple forms, functions, and mechanisms. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 2008;33(1):18-41.
[190] Nicoll RA. A Brief History of Long-Term Potentiation. Neuron 2017;93(2):281-90.
[191] Fernandes D, Carvalho AL. Mechanisms of homeostatic plasticity in the excitatory synapse. J Neurochem 2016;139(6):973-96.
[192] Lee KF, Soares C, Beique JC. Tuning into diversity of homeostatic synaptic plasticity. Neuropharmacology 2014;78:31-7.
[193] Turrigiano G. Too many cooks? Intrinsic and synaptic homeostatic mechanisms in cortical circuit refinement. Annu Rev Neurosci 2011;34:89-103.
[194] Turrigiano G. Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. Cold Spring Harb Perspect Biol 2012;4(1):a005736.
[195] Echegoyen J, Neu A, Graber KD, Soltesz I. Homeostatic plasticity studied using in vivo hippocampal activity-blockade: synaptic scaling, intrinsic plasticity and age-dependence. PLoS One 2007;2(8):e700.
[196] Goold CP, Nicoll RA. Single-cell optogenetic excitation drives homeostatic synaptic depression. Neuron 2010;68(3):512-28.
[197] Karmarkar UR, Buonomano DV. Different forms of homeostatic plasticity are engaged with distinct temporal profiles. Eur J Neurosci 2006;23(6):1575-84.
[198] Manabe T, Wyllie DJ, Perkel DJ, Nicoll RA. Modulation of synaptic transmission and long-term potentiation: effects on paired pulse facilitation and EPSC variance in the CA1 region of the hippocampus. J Neurophysiol 1993;70(4):1451-9.
[199] Branco T, Staras K, Darcy KJ, Goda Y. Local dendritic activity sets release probability at hippocampal synapses. Neuron 2008;59(3):475-85.
[200] Davis GW, Muller M. Homeostatic control of presynaptic neurotransmitter release. Annu Rev Physiol 2015;77:251-70.
[201] Gavino MA, Ford KJ, Archila S, Davis GW. Homeostatic synaptic depression is achieved through a regulated decrease in presynaptic calcium channel abundance. eLife 2015;4.
[202] Jeans AF, van Heusden FC, Al-Mubarak B, Padamsey Z, Emptage NJ. Homeostatic Presynaptic Plasticity Is Specifically Regulated by P/Q-type Ca(2+) Channels at Mammalian Hippocampal Synapses. Cell Rep 2017;21(2):341-50.
[203] Breton JD, Stuart GJ. Loss of sensory input increases the intrinsic excitability of layer 5 pyramidal neurons in rat barrel cortex. J Physiol 2009;587(Pt 21):5107-19.
[204] Desai NS. Homeostatic plasticity in the CNS: synaptic and intrinsic forms. J Physiol Paris 2003;97(4-6):391-402.
[205] Sanchez-Aguilera A, Sanchez-Alonso JL, Vicente-Torres MA, Colino A. A novel short-term plasticity of intrinsic excitability in the hippocampal CA1 pyramidal cells. J Physiol 2014;592(13):2845-64.

[206] Avila I, Parr-Brownlie LC, Brazhnik E, Castaneda E, Bergstrom DA, Walters JR. Beta frequency synchronization in basal ganglia output during rest and walk in a hemiparkinsonian rat. Exp Neurol 2010;221(2):307-19.
[207] Brown P. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. Mov Disord 2003;18(4):357-63.
[208] de Hemptinne C, Ryapolova-Webb ES, Air EL, Garcia PA, Miller KJ, Ojemann JG, et al. Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease. Proc Natl Acad Sci U S A 2013;110(12):4780-5.
[209] Dejean C, Gross CE, Bioulac B, Boraud T. Dynamic changes in the cortex-basal ganglia network after dopamine depletion in the rat. J Neurophysiol 2008;100(1):385-96.
[210] Kuhn AA, Tsui A, Aziz T, Ray N, Brucke C, Kupsch A, et al. Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. Exp Neurol 2009;215(2):380-7.
[211] Little S, Pogosyan A, Kuhn AA, Brown P. beta band stability over time correlates with Parkinsonian rigidity and bradykinesia. Exp Neurol 2012;236(2):383-8.
[212] Moran A, Stein E, Tischler H, Bar-Gad I. Decoupling neuronal oscillations during subthalamic nucleus stimulation in the parkinsonian primate. Neurobiol Dis 2012;45(1):583-90.
[213] Pollok B, Krause V, Martsch W, Wach C, Schnitzler A, Sudmeyer M. Motor-cortical oscillations in early stages of Parkinson's disease. J Physiol 2012;590(13):3203-12.
[214] Stein E, Bar-Gad I. beta oscillations in the cortico-basal ganglia loop during parkinsonism. Exp Neurol 2013;245:52-9.
[215] Bronte-Stewart H, Barberini C, Koop MM, Hill BC, Henderson JM, Wingeier B. The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation. Exp Neurol 2009;215(1):20-8.
[216] Brown P, Mazzone P, Oliviero A, Altibrandi MG, Pilato F, Tonali PA, et al. Effects of stimulation of the subthalamic area on oscillatory pallidal activity in Parkinson's disease. Exp Neurol 2004;188(2):480-90.
[217] Devos D, Labyt E, Derambure P, Bourriez JL, Cassim F, Reyns N, et al. Subthalamic nucleus stimulation modulates motor cortex oscillatory activity in Parkinson's disease. Brain 2004;127(Pt 2):408-19.
[218] Eusebio A, Thevathasan W, Doyle Gaynor L, Pogosyan A, Bye E, Foltynie T, et al. Deep brain stimulation can suppress pathological synchronisation in parkinsonian patients. Journal of neurology, neurosurgery, and psychiatry 2011;82(5):569-73.
[219] Kuhn AA, Kempf F, Brucke C, Gaynor Doyle L, Martinez-Torres I, Pogosyan A, et al. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. J Neurosc 2008;28(24):6165-73.
[220] Rosa M, Giannicola G, Servello D, Marceglia S, Pacchetti C, Porta M, et al. Subthalamic local field beta oscillations during ongoing deep brain stimulation in Parkinson's disease in hyperacute and chronic phases. Neurosignals 2011;19(3):151-62.
[221] Whitmer D, de Solages C, Hill B, Yu H, Henderson JM, Bronte-Stewart H. High frequency deep brain stimulation attenuates subthalamic and cortical rhythms in Parkinson's disease. Front Hum Neurosci 2012;6:155.
[222] McCairn KW, Turner RS. Deep brain stimulation of the globus pallidus internus in the parkinsonian primate: local entrainment and suppression of low-frequency oscillations. J Neurophysiol 2009;101(4):1941-60.
[223] McCairn KW, Turner RS. Pallidal stimulation suppresses pathological dysrhythmia in the parkinsonian motor cortex. J Neurophysiol 2015;113(7):2537-48.
[224] Levy R, Ashby P, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO. Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. Brain 2002;125(Pt 6):1196-209.

[225] Marceglia S, Foffani G, Bianchi AM, Baselli G, Tamma F, Egidi M, et al. Dopamine-dependent non-linear correlation between subthalamic rhythms in Parkinson's disease. J Physiol 2006;571(Pt 3):579-91.
[226] Barow E, Neumann WJ, Brucke C, Huebl J, Horn A, Brown P, et al. Deep brain stimulation suppresses pallidal low frequency activity in patients with phasic dystonic movements. Brain 2014;137(Pt 11):3012-24.
[227] Air EL, Ryapolova-Webb E, de Hemptinne C, Ostrem JL, Galifianakis NB, Larson PS, et al. Acute effects of thalamic deep brain stimulation and thalamotomy on sensorimotor cortex local field potentials in essential tremor. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2012;123(11):2232-8.
[228] Maling N, Hashemiyoon R, Foote KD, Okun MS, Sanchez JC. Increased thalamic gamma band activity correlates with symptom relief following deep brain stimulation in humans with Tourette's syndrome. PLoS One 2012;7(9):e44215.
[229] Falowski SM, Sharan A, Reyes BA, Sikkema C, Szot P, Van Bockstaele EJ. An evaluation of neuroplasticity and behavior after deep brain stimulation of the nucleus accumbens in an animal model of depression. Neurosurgery 2011;69(6):1281-90.
[230] Meng H, Wang Y, Huang M, Lin W, Wang S, Zhang B. Chronic deep brain stimulation of the lateral habenula nucleus in a rat model of depression. Brain Res 2011;1422:32-8.
[231] Okun MS, Foote KD, Wu SS, Ward HE, Bowers D, Rodriguez RL, et al. A trial of scheduled deep brain stimulation for Tourette syndrome: moving away from continuous deep brain stimulation paradigms. JAMA neurology 2013;70(1):85-94.
[232] Rossi PJ, Opri E, Shute JB, Molina R, Bowers D, Ward H, et al. Scheduled, intermittent stimulation of the thalamus reduces tics in Tourette syndrome. Parkinsonism Relat Disord 2016;29:35-41.
[233] Rummel J, Voget M, Hadar R, Ewing S, Sohr R, Klein J, et al. Testing different paradigms to optimize antidepressant deep brain stimulation in different rat models of depression. J Psychiatr Res 2016;81:36-45.
[234] Galati S, Mazzone P, Fedele E, Pisani A, Peppe A, Pierantozzi M, et al. Biochemical and electrophysiological changes of substantia nigra pars reticulata driven by subthalamic stimulation in patients with Parkinson's disease. Eur J Neurosci 2006;23(11):2923-8.
[235] Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. J Neurosc 2003;23(5):1916-23.
[236] Kita H, Tachibana Y, Nambu A, Chiken S. Balance of monosynaptic excitatory and disynaptic inhibitory responses of the globus pallidus induced after stimulation of the subthalamic nucleus in the monkey. J Neurosc 2005;25(38):8611-9.
[237] Li S, Arbuthnott GW, Jutras MJ, Goldberg JA, Jaeger D. Resonant antidromic cortical circuit activation as a consequence of high-frequency subthalamic deep-brain stimulation. J Neurophysiol 2007;98(6):3525-37.
[238] Maurice N, Thierry AM, Glowinski J, Deniau JM. Spontaneous and evoked activity of substantia nigra pars reticulata neurons during high-frequency stimulation of the subthalamic nucleus. J Neurosc 2003;23(30):9929-36.
[239] Montgomery EB, Jr., Gale JT. Mechanisms of action of deep brain stimulation(DBS). Neurosci Biobehav Rev 2008;32(3):388-407.
[240] Reese R, Leblois A, Steigerwald F, Potter-Nerger M, Herzog J, Mehdorn HM, et al. Subthalamic deep brain stimulation increases pallidal firing rate and regularity. Exp Neurol 2011;229(2):517-21.
[241] Bondallaz P, Boex C, Rossetti AO, Foletti G, Spinelli L, Vulliemoz S, et al. Electrode location and clinical outcome in hippocampal electrical stimulation for mesial temporal lobe epilepsy. Seizure 2013;22(5):390-5.
[242] Elisevich K, Jenrow K, Schuh L, Smith B. Long-term electrical stimulation-induced inhibition of partial epilepsy - Case report. J Neurosurg 2006;105(6):894-7.

[243] Wyllie E. Wyllie's treatment of epilepsy: principles and practice (6th edition). 6 ed. Philadelphia, United States: Wolters Kluwer; 2015.
[244] Beyenburg S, Stavem K, Schmidt D. Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: systematic review and meta-analysis. Epilepsia 2010;51(1):7-26.
[245] Group VS. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. Neurology 1995;45(2):224-30.
[246] Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998;51(1):48-55.
[247] Panebianco M, Rigby A, Weston J, Marson AG. Vagus nerve stimulation for partial seizures. Cochrane Database Syst Rev 2015(4):CD002896.
[248] Oliveira T, Francisco AN, Demartini ZJ, Stebel SL. The role of vagus nerve stimulation in refractory epilepsy. Arq Neuropsiquiatr 2017;75(9):657-66.
[249] Vonck K, de Herdt V, Sprengers M, Ben-Menachem E. Neurostimulation for epilepsy. Handb Clin Neurol 2012;108:955-70.
[250] Chabardes S. Deep brain stimulation of the anterior nucleus of the thalamus in epilepsy (FRANCE). https://wwwclinicaltrialsgov/ct2/show/NCT02076698 December 2015.
[251] Zhang B. Prospective randomized trial comparing vagus nerve stimulation and deep brain stimulation of the anterior nucleus of the thalamus in patients with pharmacoresistant epilepsy. http://chictrorgcn/showprojaspx?proj=10139, May 2015.

SUMMARY

Epilepsy is a disabling chronic neurological disorder characterized by the occurrence of unprovoked seizures. It affects around 50 million people worldwide and is ranked as the second most important neurological cause of disease burden in terms of disability-adjusted life years. Despite the availability of a continuously increasing number of antiepileptic drugs, around one third of patients do no achieve sustained seizure freedom with these drugs and are defined as being drug-resistant epilepsy patients. Whenever possible, epilepsy surgery is the first-line treatment for these patients. However, many drug-resistant epilepsy patients turn out to be unsuitable surgery candidates, are reluctant to undergo brain surgery or are not seizure-free after surgery. This leaves a large group of patients with uncontrolled seizures. Neurostimulation has been proposed as a promising treatment option for these patients. Analogous to antiepileptic drugs modulating the brain's chemistry, neurostimulation techniques deliver electrical or magnetic currents to modulate neuronal activity aiming to achieve seizure suppression.

One of these techniques is deep brain stimuliation (DBS), in which small electrical pulses are delivered directly to deep brain nuclei via stereotactically implanted depth electrodes. A closely related invasive neurostimulation technique is cortical stimulation where cerebral (such as the motor cortex) or cerebellar cortical regions are targeted by cortical electrodes. Given the limited number of mostly small and uncontrolled clinical trials, however, the precise role of deep brain and cortical stimulation stimulation in the treatment of drug-resistant epilepsy patients remains uncertain warranting further research. The primary aim of the first part of this thesis was to increase our knowledge on the efficacy, safety and tolerability of DBS in drug-resistant epilepsy.

In a first study we evaluated the long-term outcome of hippocampal DBS in drug-resistant medial temporal lobe epilepsy. Temporal lobe epilepsy is the most common focal epilepsy in adults and is in particular refractory to pharmacological treatment. We reported the outcome of 11 patients after a mean follow-up of 8.5 years (range 67 to 120 months), representing the largest patients series on hippocampal DBS published so far as well as the trial with the longest duration of follow-up. Six out of 11 patients had an excellent outcome showing a ≥90% seizure frequency reduction, with 3/6 patients being seizure-free for more than 3 years. Three patients experienced a moderate 40-70% seizure reduction and 2/11 patients were considered non-responders. The most beneficial outcomes were observed in patients with a unilateral focal ictal onset, all of them (n=4) experiencing a ≥90% seizure frequency reduction. In contrast to previous studies, the presence of hippocampal sclerosis (n=3) was not associated with a worse outcome. When unilateral DBS failed to decrease seizures by >90% after 3 years, a switch to bilateral DBS further improved the seizure outcome in 3/5 patients. Although there was no correlation on a group-level, increasing the stimulation intensity was associated with improved or worse seizure control in individual patients. The trial also suggested over time increasing and both immediate and stimulation outlasting effects of DBS. None of the patients reported permanent symptomatic side effects. In conclusion, the favourable results observed in this uncontrolled open-label study confirmed the promising potential of hippocampal DBS in drug-resistant epilepsy.

Notwithstanding that our and other uncontrolled open-label trials represent an invaluable source of knowledge, it should be noted that they are risk for many types of bias. To critically review the current evidence on deep brain and cortical stimulation in epilepsy, a systematic review and meta-analysis including only randomized controlled trials (RCTs) was performed.

Twelve RCTs were identified. Evidence of selective reporting was present in four trials and the possibility of a carryover effect complicating interpretation of the results could not be excluded in five cross-over trials without any or a sufficient washout period. Moderate-quality evidence could not demonstrate statistically or clincically significant changes in the proportion of patients who were seizure-free or experienced a 50% reduction in seizure frequency after one to three months of anterior thalamic DBS in (multi)focal epilepsy, responsive ictal onset zone stimulation in (multi)focal epilepsy and hippocampal DBS in (medial temporal lobe epilepsy). However, compared to sham stimulation moderate but statistically significant reductions in seizure frequency were found for anterior thalamic DBS (-17.4%, high-quality evdience), responsive ictal onset zone stimulation (-24.9%, high-quality evidence) and hippocamal DBS (-28.1%, moderate-quality evidence). Anterior thalamic DBS was associated with fewer epilepsy-associated injuries (7.4 versus 25.5%) but higher rates of self-reported depression (14.8 versus 1.8%) and subjective memory impairment (13.8 versus 1.8%). Responsive ictal onset zone stimulation seemd to be well-tolerated with few side effects. Both anterior thalamic DBS (moderate-quality evidence) and responsive ictal onset zone stimulation (high-quality evidence) were not associated with significant differences in formal neuropsychological testing results. There is insufficient evidence to make firm conclusive statements on the safety and tolerability of hippocampal DBS. There was no clinically meaningful impact on quality of life after three months of anterior thalamic DBS or responsive ictal onset zone stimulation (high-quality evidence). Other targets that have been studied in RCTs are the centromedian thalamic nucleus, the nucleus accumbens and the cerebellar cortex. Statistically significant effects could not be demonstrated but evidence was of only low to very low quality.

The results in RCTs are thus remarkably less favourable than those obtained in uncontrolled unblinded trials. Several factors could account for these discrepant results. The placebo effect, the implantation/ microlesion effect, medication-induced and spontaneous improvements probably overestimate the efficacy of DBS and cortical stimulation in uncontrolled trials. However, as a trend for increasing efficacy over time, results consistent with a possible outlasting effect after stimulation and further improvement due to optimization of stimulation parameter settings have been reported, the full potential of DBS and cortical stimulation may have been underestimated in RCTs due to their short duration, cross-over design and fixed stimulation protocol.

A major shortcoming for an increased use of DBS in epilepsy is the lack of knowledge on the optimal stimulation protocol. A better understanding of the mechanism of action of DBS could lead to a more rational selection of the stimulation parameter settings and the stimulation target. Despite extensive research, however, the mode of action of DBS remains incompletely understood. Furthermore, previous research has primarily focused on the investigation of the effects of seconds to minutes of DBS, while a progressively increasing efficacy over time has been reported in various clinical DBS trials (in epilepsy, dystonia, obsessive-compulsive disorder, depression, Tourette's syndrome, ...).

An interesting technique to further unravel this mechanism of action is the measurement of monosynaptically evoked field potentials (EPs) of a neuronal population following the administration of an electrical stimulus to its afferent axons. This technique allows to measure changes in postsynaptic input (field excitatory postsynaptic potentials, fEPSP), output (population spike, PS) as well as intrinsic excitability (PS-fEPSP relationship). The use of a paired-pulse protocol additionally provides information on changes in presynaptic calcium homeostasis, the readiliy releasable pool of vesicles and recurrent GABAergic inhibition. The aim of the second part of this thesis was to expand our

knowledge on the mechanism of action of DBS by evaluating the effect of hippocampal DBS on hippocampal evoked potentials and EEG in freely moving rats. Next to experiments evaluating the acute effects of DBS, we also evaluated – to the best of our knowledge for the first time – the electrophysiological effects of more prolonged DBS durations.

A remarkable finding was that, compared to previous DBS experiments in *in vitro* preparations or urethane-anesthetized animals, relatively low DBS intensities corresponding to only 1.8 to 2.1% of the intensity evoking a maximum EP had to be used in freely moving animals to prevent unintended seizure occurrence. Short-lasting fEPSP slope reductions were observed after 1 and 6 minutes of DBS, lasting less than 20 and 60 seconds respectively. These reductions were input-specific and there were no changes in postsynaptic intrinsic excitability, the fEPSP slope paired-pulse ratio or the EEG spectrogram. These findings are in line with the involvement of synaptic depression and axonal conduction block in the mechanism of action of DBS. We could not support the occurrence of synaptic inhibition, depolarization block or EEG desynchronization.

Longer-lasting and potentially cumulative effects were observed during 160 minutes of 1/9 and 6/4 minutes ON/OFF intermittent DBS. These effects were explored in more detail in 'chronic' experiments were DBS was administered continuously for 2 days. In these experiments, pronounced fEPSP slope reductions were found. These reductions progressively increased with longer stimulation durations and outlasted the stimulation duration for 5 to 7 days. The fEPSP reductions were input-specific and associated with marked PS amplitude reductions, but the latter was only a secondary phenomenon given the unaltered fEPSP slope / PS amplitude relationship. There were no changes in the fEPSP slope paired-pulse ratio or the EEG spectrogram. We propose that these reductions result from DBS-induced presynaptic homeostatic plasticity and may be the neurophysiological substrate of the increasing efficacy over time and of the outlasting effects observed in clinical trials.

One of the unresolved issues with regards to the stimulation protocol is whether continuous or intermittent stimulation should be used. Both stimulation regimens have been employed interchangeably in epilepsy patients without good arguements to prefer one strategy above the other. We evaluated the effect on hippocampal EPs of 6 and 10 days of intermittent DBS with 1/5 and 1/29 minutes ON/OFF duty cycles, respectively. Compared to continuous stimulation, the effects of intermittent DBS were less pronounced at identical time points, but when normalized to the cumulative number of DBS pulses administered, similar effects were observed. To what extent this dose-response relationship continues, however, needs further study.

In conclusion we demonstrated excellent outcomes with hipocampal DBS in drug-resistant temporal lobe epilepsy in our uncontrolled open-trial. In contrast, only moderate seizure reductions have been demonstrated in RCTs. More, large, and well-designed RCTs are necessary to increase the evidence on cortical and deep brain stimulation. Future research should also focus on the identification of the optimal stimulation parameters, the most efficacious stimulation target and the patients most likely to respond to DBS. Increased knowledge on the mechanism of action of DBS may provide a rational basis for these unresolved issues. We demonstrated DBS-induced EP reductions with 2 different time courses, including immediate short-lasting as well as progressively increasing longer-lasting effects. These dual effects may parallel the different temporal patterns of clinical improvement observed with DBS. However, more research is necessary to study the relationship of these EP reductions to the therapeutic outcome and to investigate DBS-induced changes during DBS, in other brain regions such

as the basal ganglia network, in pathological brain tissue and in human subjects treated with commercially available DBS systems.

SAMENVATTING

Epilepsie is een invaliderende chronische neurologische aandoening die gekenmerkt wordt door het optreden van spontane (niet-uitgelokte) epileptische aanvallen. Wereldwijd zijn er ongeveer 50 miljoen mensen die lijden aan epilepsie. Dit maakt van deze aandoening de tweede meest belangrijke neurologische oorzaak van verlies aan kwaliteitsvolle levensjaren ten gevolge van een combinatie van mortaliteit en morbiditeit. Hoewel het aantal beschikbare antiepileptische medicatie sterk is toegenomen, wordt ongeveer een derde van de epilepsiepatiënten hiermee niet aanvalsvrij. Deze patiënten lijden aan medicatieresistente epilepsie. Resectieve epilepsiechirurgie is bij geschikte kandidaten de eerstekeuzebehandeling voor deze groep patiënten. Bij velen blijkt dit echter niet haalbaar, anderen staan dan weer weigerachtig tegenover een invasieve ingreep of bereiken hiermee toch geen aanvalsvrijheid. Neurostimulatie kan een mogelijke oplossing bieden voor deze grote groep patiënten met ongecontroleerde aanvallen. Naar analogie met de effecten van antiepileptische medicatie op de chemische signaaltransmissie in de hersenen maken neurostimulatietechnieken gebruik van elektrische of magnetische stromen om de hersenactiviteit te moduleren met als doel de aanvallen hiermee te onderdrukken.

Eén van deze neurostimulatietechnieken is diepe hersenstimulatie (DHS). Hierbij worden kleine elektrische stroompjes direct toegediend ter hoogte van diepe hersenkernen via stereotactisch geïmplanteerde diepte-elektroden. Een andere maar nauw verwante invasieve neurostimulatietechniek is corticale stimulatie waarbij de cerebrale of cerebellaire cortex (bijvoorbeeld de motore cortex) gestimuleerd wordt via corticale elektroden. Wegens het beperkt aantal studies met bovendien doorgaans ook slechts relatief kleine patiëntenaantallen blijft de precieze rol van diepe en corticale hersenstimulatie in de behandeling van medicatieresistente epilepsiepatiënten evenwel onduidelijk. Het doel van het eerste deel van deze thesis was dan ook om meer kennis te verwerven over de doeltreffendheid, de veiligheid en de bijwerkingen van DHS bij patiënten met medicatieresistente epilepsie.

In een eerste studie onderzochten we de langetermijnresultaten van hippocampale DHS bij medicatieresistente epilepsie vanuit de mediale temporale kwab. Temporalekwabepilepsie is de meest voorkomende vorm van focale epilepsie bij volwassen en is typisch refractair aan medicamenteuze behandeling. Elf patiënten werden geïncludeerd in deze studie en gemiddeld gedurende 8.5 jaren (range 67 tot 120 maanden) opgevolgd. In vergelijking met andere studies omtrent hippocampale DHS is dit zowel de grootste patiëntengroep als de langste duur van opvolging tot dusver. Zes van deze elf patiënten rapporteerden een bijzonder gunstige evolutie met een aanvalsreductie van meer dan 90%, onder wie ook drie patiënten die meer dan drie jaar aanvalsvrij waren op het einde van de studie. Drie andere patiënten ondervonden een matig gunstig effect met aanvalsreducties tussen 40 en 70%, en twee patiënten ervaarden geen duidelijke beterschap sinds opstarten van DHS. De beste resultaten werden gezien bij de patiënten met een unilaterale focale ictale aanvang, zij beschreven allen (n=4) een aanvalsreductie van meer dan 90%. In tegenstelling tot eerdere studies bleek de aanwezigheid van hippocampaalsclerose (n=3) op beeldvorming niet geassocieerd met een minder gunstige uitkomst. Het opstarten van bilaterale hippocampale stimulatie bij vijf patiënten met een aanvalsreductie van minder dan 90% na 3 jaar unilaterale DHS leidde bij drie van hen tot een verdere verbetering. Hoewel er op groepsniveau geen correlatie was, bleek het verhogen van de stimulatie-intensiteit geassocieerd met een betere of slechtere aanvalscontrole in enkele individuele patiënten. De studie suggereerde met de tijd toenemende en zowel onmiddellijke als na uitzetten van de stimulatie langer aanhoudende

effecten van DHS. Geen enkele patiënt rapporteerde blijvende symptomatische bijwerkingen. Samengevat kunnen we stellen dat de resultaten van deze ongecontrolleerde niet-geblindeerde het veelbelovende potentieel van hippocampale DHS bij medicatieresistente epilepsie bevestigen.

Hoewel deze en andere ongecontrolleerde niet-geblindeerde studies een onmisbare bron van kennis vormen, dient opgemerkt te worden dat ze vatbaar zijn voor bias van allerlei aard. Om de huidige evidentie omtrent corticale en diepe hersenstimulatie kritisch in beeld te brengen, verrichtten we een systematische review en meta-analyse waarbij we ons uitsluitend baseerden op gerandomiseerde gecontrolleerde studies (*randomized controlled trials,* RCTs).

Twaalf RCT's werden geïdentificeerd. Argumenten voor een selectief rapporteren van de bekomen effecten waren aanwezig in vier van deze studies. Aangezien een aanhoudend effect na uitzetten van de stimulatie eerder beschreven is, werd de interpretatie van vijf cross-over studies zonder enige of met een te korte *wash-out* periode tussen de stimulatie- en de placebostimulatieperiode bemoeilijkt. Evidentie van matige kwaliteit kon geen klinisch of statistisch significante impact aantonen op het aantal patiënten die aanvalsvrij zijn of een meer dan 50% aanvalsreductie ervaren na 1 tot 3 maanden DHS ter hoogte van de anterieure thalame nucleus bij (multi)focale epilepsie, responsieve stimulatie van de ictale aanvangszone bij (multi)focale epilepsie of hippocampale DHS bij temporalekwabepilepsie. In vergelijking met placebostimulatie was er wel een statistisch significante doch matige reductie van de aanvalsfrequentie met anterieure thalame DHS (-17.4%, evidentie van hoge kwaliteit), met responsieve stimulatie van de ictale aanvalszone (-24.9%, evidentie van hoge kwaliteit) en met hippocampale DHS (-28.1%, evidentie van matige kwaliteit). DHS ter hoogte van de anterieure thalame nucleus ging gepaard met minder epilepsiegerelateerde verwondingen (7.4 versus 25.5%) maar ook met een toename van zelfgerapporteerde depressie (14.8 versus 1.8%) en subjectieve geheugenklachten (13.8 verus 1.8%). Responsieve stimulatie van de ictale aanvangszone leek goed verdragen te worden en gepaard te gaan met weinig bijwerkingen. Zowel bij anterieure thalame DHS (evidentie van matige kwaliteit) en bij responsieve stimulatie van de ictale aanvangszone (evidentie van hoge kwaliteit) waren er geen verschillen in formele neuropsychologische testresultaten. Er is onvoldoende evidentie om betrouwbare uitspraken te doen over de veiligheid en bijwerkingen van hippocampale DHS. Ten slotte is er evidentie van hoge kwaliteit dat zowel anterieure thalame DHS als responsieve stimulatie van de ictale aanvangszone niet leiden tot een klinisch betekenisvolle impact op de levenskwaliteit na drie maanden stimulatie. Andere targets die bestudeerd werden in RCT's zijn de centromediane thalame nucleus, de nucleus en accumbens en de cerebellaire cortex. Voor geen van deze structuren konden statistisch significante effecten worden aangetoond maar de evidentie hierbij is slechts van lage tot zeer lage kwaliteit.

De bekomen effecten in RCT's zijn dus opvallend minder goed dan deze in ongecontrolleerde niet-geblindeerde studies. Meerdere factoren kunnen deze discrepante resultaten verklaren. De aanwezigheid van een placebo-effect, een implantatie- of microlesie-effect, en spontane of door medicatie geïnduceerde verbeteringen leidden hoogstwaarschijnlijk tot een overschatting van het effect van DHS en corticale stimulatie in ongecontroleerde studies. Anderzijds is het aannemelijk dat de beperkte duur van de RCT's, het gebruik van een cross-over design en een vast stimulatieprotocol leidden tot een onderschatting van het volledige potentieel van DHS en corticale stimulatie in RCT's, daar een met de tijd progressief toenemende doeltreffendheid, een aanhoudend effect na stimulatie en een verdere verbetering mits optimaliseren van de stimulatieparameters beschreven zijn in eerdere studies.

Een belangrijke tekortkoming voor een wijdverspreider gebruik van DHS in epilepsie is het gebrek aan kennis omtrent het optimale stimulatieprotocol. Een beter inzicht in het werkingsmechanisme van DHS kan leiden tot een rationelere keuze van de stimulatieparameters en het stimulatietarget. Ondanks omstandig onderzoek blijft de kennis over dit werkingsmechanisme evenwel onvolledig. Eerder onderzoek hieromtrent focuste zich bovendien op de effecten van seconden tot minuten DHS, daar waar verschillende klinische studies een met de tijd toenemende doeltreffendheid hebben gerapporteerd (o.a. in epilepsie, dystonie, obsessief-compulsieve stoornis, depressie, syndroom van Tourette,…).

De techniek die in deze thesis gebruikt werd om het werkingsmechanisme van DHS verder op te helderen zijn monosynpatisch geëvokeerde potentialen (*evoked potentials,* EP's). Hierbij wordt het antwoord van een groep neuronen gemeten op de toediening een elektrische stimulus ter hoogte van zijn afferente axonen. Dit is een erg interessante techniek daar zij toelaat om veranderingen te meten in de postsynaptische input (excicatoire postsynpatische veldpotentialen, *field excitatory postsynaptic potentials,* fEPSP), de postsynaptische output (*population* spike*,* PS) en de intrisieke exciteerbaarheid (PS-fEPSP verhouding). Het gebruik van een protocol met gepaarde pulsen maakt het bijkomend mogelijk om inzicht te verwerven in mogelijke veranderingen in de presynaptische calciumhomeostase, de snel vrijstelbare poel van vesikels (*readiliy releasable pool of vesicles*) en de recurrente GABA'erge inhibitie. Het doel van het tweede deel van deze thesis was om de kennis over het werkingsmechanisme van DHS te vergroten door het bestuderen van het effect van hippocampale DHS op hippocampale EP's en hippocampaal EEG bij zich vrij bewegende ratten. Naast experimenten die het acute effect van DHS onderzochten werden – voor zover ons bekend voor het eerst – ook de elektrofysiologische effecten van langere periodes van DHS geëxploreerd.

Een eerste opvallende vaststelling hierbij was dat, in vergelijking met eerdere *in vitro* experimenten en studies bij dieren onder urethaananesthesie, relatief lage DHS-intensiteiten dienden te worden gebruikt (overeenkomend met slechts 1.8 à 2.1% van de intensiteit die aanleiding geeft tot een maximale EP) om het ongewild induceren van epileptische aanvallen in gezonde ratten te voorkomen. Kortdurende reducties van de fEPSP-helling werden aangetoond na 1 en 6 minuten DHS, dewelke respectievelijk minder dan 20 en minder dan 60 seconden aanhielden. Deze reducties waren input-specifiek en gingen niet gepaard met veranderingen in de postsynaptische intrinsieke excitaarbaarheid, de fEPSP-helling gepaarde-pulse ratio of het EEG spectrogram. Deze bevindingen wijzen op de betrokkenheid van synaptische depressie en een axonale geleidingsblok in het werkingsmechanisme van DHS. We vonden geen argumenten die het optreden van synaptische inhibitie, een depolarisatieblok of desynchronisatie van het EEG staven.

Langer durende en potentieel cumulatieve effecten werden gezien bij 160 minuten intermittente DHS met een 1/9 of 6/4 minuten AAN/UIT *duty cycle*. Deze effecten werden in meer detail bestudeerd in 'chronische' experimenten waarbij gedurende 2 dagen continu DHS werd toegediend. Dit leidde tot uitgesproken reducties van de fEPSP-helling. Deze namen progressief toe naarmate de stimulatieduur toenam en hielden nog 5 tot 7 dagen aan nadat de stimulatie gestopt was. Deze reducties waren input-specifiek en geassocieerd met sterke reducties van de PS-amplitude. Deze laatste betroffen evenwel een secundair verschijnsel aangezien er geen veranderingen optraden in de fEPSP-helling / PS-amplitude verhouding. Er was geen effect op de fEPSP-helling gepaarde-pulse ratio of op het EEG spectrogram. De geobserveerde EP-dalingen zijn ons inziens het gevolg van DBS-geïnduceerde presynaptische homeostatische plasticiteit en kunnen het neurofysiologisch correlaat zijn van de in

klinische studies gerapporteerde met de tijd toenemende doeltreffendheid en aanhoudende effecten na stopzetten van de stimulatie.

Een van de onduidelijkheden aangaande het stimulatieprotocol is of DHS bij voorkeur continu dan wel intermittent moet worden toegediend. In klinische studies met epilepsiepatiënten zijn beide tot op heden zonder doorslaggevende argumenten door elkaar gebruikt. We bestudeerden het effect op hippocampale EP's van 6 en 10 dagen intermittente DHS met respectievelijk een 1/5 en 1/29 minuten AAN/UIT *duty cycle*. In vergelijking met continue stimulatie waren de effecten van intermittente DHS op identieke tijdspunten minder uitgesproken, maar na normalisatie voor het cumulatief aantal toegediende DHS-pulsen werden gelijkaardige effecten vastgesteld. Toekomstig onderzoek moet uitwijzen tot op welk punt deze dosis-respons relatie verder aanhoudt.

Samengevat beschreven we uitstekende resultaten van hippocampale DHS bij patiënten met medicatieresistente temporalekwabepilepsie in een ongecontroleerde niet-geblindeerde studie. In RCT's konden daarentegen slechts matige aanvalsreducties worden aangetoond. Meer, grote en goed opgezette RCT's zijn nodig om de evidentie omtrent corticale en diepe hersenstimulatie verder uit te diepen. Toekomstig onderzoek moet zich bovendien richten op het identificeren van de meest optimale stimulatieparameters, het meest doeltreffende stimulatietarget en de patiënten bij wie het meeste baat van DHS kan worden verwacht. Een betere kennis over het werkingsmechanisme van DHS kan hiervoor een rationele basis bieden. We rapporteerden DHS-geïnduceerde EP-reducties met een tweeledig tijdsverloop: onmiddellijke kortdurende en progressief toenemende langer durende effecten. Dit duaal effect vormt een mogelijke verklaring voor de verschillende tijdspatronen waarmee klinische verbetering optreedt in patiënten die behandeld worden met DHS. Verder onderzoek is evenwel noodzakelijk om de relatie met het therapeutisch effect aan te tonen en om de effecten te bestuderen tijdens DHS, in andere hersenregio's zoals de basale ganglia, in pathologisch hersenweefsel en in patiënten die behandeld worden met commercieel verkrijgbare DBS-systemen.

DANKWOORD

Het dankwoord is een onontbeerlijk onderdeel van elke zichzelf respecterende doctoraatsthesis. Vaak wordt dit aangekondigd of omschreven als 'het meest gelezen hoofdstuk', wat aantoont dat het intermenselijke het wetenschappelijke overstijgt. Ik ben dan ook dankbaar voor deze gelegenheid om enkele mensen te mogen bedanken die me de voorbije jaren hebben bijgestaan.

Vooreerst zou ik graag mijn promotor en copromotor willen bedanken, **Prof. Dr. Kristl Vonck en Prof. Dr. Paul Boon**. Bedankt voor de kansen die jullie me hebben gegeven, jullie steun en vertrouwen de voorbije jaren betekenden veel voor mij. Prof. Vonck wens ik in het bijzonder te danken voor het vele en ongetwijfeld soms wat saaie naleeswerk, voor uw enthousiasme en ideeën, en voor uw gevatte tussenzinnen. Prof. Boon, ik herinner me mijn introductiegesprek nog goed. U opende voor mij de deur naar de wereld van het wetenschappelijk onderzoek. Ik heb veel respect voor hoe u het labo hebt gebracht tot waar het nu staat, een realisatie waarvoor veel verschillende kwaliteiten noodzakelijk zijn. Bovenal ben ik jullie echter dankbaar voor de nodige tijd en ruimte die jullie me gelaten hebben op de moeilijke momenten die onze familie de voorbije jaren gekend heeft.

Ook wens ik graag **Prof. Dr. Robrecht Raedt** te bedanken. Robrecht, iedereen die ooit in het 4BRAIN-labo gewerkt of stage gelopen heeft zal weten hoe cruciaal je rol in het labo is. Ik heb veel respect voor je wetenschappelijke kennis en kritische ingesteldheid. Ik herinner me de bij momenten hilarische nachtelijke uren in NERF te Leuven waarbij we afwisselend toezicht hielden op één enkele rat, wachtend op een eerste epileptische aanval die er uiteindelijk nooit kwam. Ook de tijd in Canada, de vele interessante en aangename gesprekken in het labo of elders, en in het bijzonder jouw hulp tijdens mijn marathonsessie operaties voor mijn laatste dierproef zal ik nooit vergeten.

Veel dank ook aan de leden van de peer review. **Prof. Dr. Jean Delbeke**, uw elektrofysiologische en materiaalkundige kennis zijn uniek, maar ook voor uw zachtaardige persoonlijkheid heb ik veel bewondering. **Prof. Dr. Wytse Wadman**, uw kennis en kritische ingesteldheid evenals uw directe doch steeds best bedoelde aanpak heb ik de voorbije jaren sterk weten te appreciëren. **Dr. Evelien Carrette**, bedankt voor je polyvalente bijdrages en hulp, je oprechte steun op de moeilijkere momenten en de aangename autoritten van en naar Eindhoven. Ook **Dr. Jeanelle Portelli** en **Prof. Dr. Bruce McNaughton** wens ik graag te bedanken voor hun tijdelijke bijdrages tijdens mijn doctoraat.

I would also like to thank all the members of the examination board: **chair Prof. Dr. Marie-Anne Vanderhasselt, secretary Prof. Dr. Christian Vanhove, Prof. Dr. Veerle De Herdt, Prof. Dr. Dirk De Ridder, Prof. Dr. Günther Deuschl and Prof. Dr. Bart Smolders.** Thank you for finding and taking the time to read my doctoral dissertation, to formulate stimulating questions and for your flexible and friendly attitude both in the process of planning and during the internal and public defense of my thesis.

Een bijzondere plaats in dit dankwoord komt toe aan mijn LCEN3-collega's **Annelies, Bregt, Ine B, Ine D, Lars, Leen, Lies, Lisa, Nathalie, Sofie C, Sofie D en Wouter.** Niemand volgde mijn doctoraatstraject van zo dichtbij als jullie, niemand anders kan beter inschatten wat zo'n traject inhoudt en niemand weet beter dan jullie hoe belangrijk we hierbij voor elkaar waren. Van collega's werden we vrollega's – een term die ik door jullie leerde kennen – en wanneer onze professionele wegen scheidden werden we uiteindelijk 'gewoon' vrienden. Bedankt voor alle mooie (en minder mooie) en grappige (en minder grappige) momenten die we samen mochten delen. 'Dr. S' is jullie heel dankbaar voor de steun en hulp

tijdens zijn doctoraatsjaren, maar ook nadien. Ik hoop dat we elkaar dan ook regelmatig zullen blijven zien. Een speciaal woord van dank zou ik ook willen richten aan Diego. Bedankt voor je permanente hulpbereidheid en uitleg, ook nog nadat je van labo veranderde, maar minstens evenzeer voor de vele aangename en interessante gesprekken tussendoor.

LCEN3 werd 4BRAIN en een nieuwe generatie doctoraatsstudenten kondigde zich aan. **Anirudh, Ann, Charlotte B, Charlotte G, Emma, Erine, Elien DC, Jana, Jeroen, Latoya, Marie en Simona en Silke**, door mijn focus op klinische activiteiten de voorbije jaren ken ik jullie iets minder goed dan jullie voorgangers, maar laat dat me er niet van weerhouden in elk van jullie aspecten te onderscheiden die ik bijzonder apprecieer. Ik kan alleen maar hopen dat jullie evenveel steun vinden bij elkaar als de LCEN3-collega's destijds, en hopelijk kunnen jullie binnenkort ook je doctoraat verdedigen. Een bijzonder woord van dank gaat hierbij naar mijn huidige bureaugenootjes **Ann, Elien DC en sinds kort ook Veerle.** Bedankt voor de gesprekjes tussendoor die het werken zo veel aangenamer maken, evenals de steun waar mogelijk.

Ik wens ook alle dierverzorgers in het **animalarium en Dr. Ingrid van Overbeke** te bedanken voor hun goede zorgen voor alle proefdieren.

Verder had ik ook de stafleden en consulenten uit de kliniek graag bedankt om me eerst tijdens maar vooral toch na mijn doctoraatsjaren de o zo boeiende klinische neurologie bij te brengen. Het helpen van de patiënt is en blijft het hoogste doel. Bedankt **Prof. Dr. Luc Crevits, Prof. Dr. Jan De Bleecker, Prof. Dr. Jan Debruyne, Prof. Dr. Veerle De Herdt, Dr. Dimitri Hemelsoet, Dr. Stephanie Hödl, Prof. Dr. Guy Laureys, Prof. Dr. Alfred Meurs, Prof. Dr. Koen Paemeleire, Prof. Dr. Patrick Santens, Dr. Anne Sieben, Dr. Tim Van Langenhove, Dr. Bruno Bergmans, Dr. Pascal Proot en Dr. Kristof Verhoeven.**

Ook de assistenten van de dienst neurologie had ik willen bedanken voor de vele mooie momenten die we samen hebben mogen beleven, voor jullie steun, en – ondanks de vele jaren – niet aflatende interesse in mijn doctoraat. Dit eerst tijdens mijn onderzoeksjaren, bedankt **Annelies, Anne-Sophie, Charlotte S, Eva, Evelien, Deborah, Jelle, Marieke, Riëm en Stefanie C**. Echter ook en minstens zoveel nadien tijdens mijn klinische jaren. Bedankt **Annelien, Frank, Pieter-Jan, Caroline, Vincent K, Antoon, Tim, Vincent VI, Zoë, Ann, Daan, Elien L, Elien DS, Griet, Alexander, Camille, Helena, Jonas en Arnout**. Ik ben zo vrij hier ook **Ine D, Liesbeth VH en Stefanie G** aan toe te voegen. Ik ben erg dankbaar om ook in de kliniek opnieuw met zo'n fijne collega's te hebben mogen samenwerken en opnieuw met velen van jullie de 'collega- vrollega-vriend'-evolutie te hebben mogen ervaren.

Graag had ik ook mijn huidige collega's van het **Perstim-team** bedankt. Ik ben ervan overtuigd dat onze aangename samenwerking de komende jaren nog tot mooie resultaten zal leiden.

Hoe harder ik werkte, hoe meer ik van de ontspannende momenten tussendoor genoot. Ik zou dan ook graag mijn **familie en vrienden** willen bedanken om er steeds voor me te zijn, niet in het minst op de moeilijke momenten die er de voorbije jaren geweest zijn. Ik prijs me erg gelukkig met jullie als familie en vrienden. Bedankt voor de gezellige avonden op café, restaurant of bij iemand thuis (iemand als in 'bij iedereen behalve bij mij', maar 'time for change has come'), de leuke reizen, de sportieve uitdagingen, de 'Dardennenweekends', jullie berichtjes tussendoor, en nog zo veel meer. Ook de **familie van Charlotte** zou ik graag bedanken om mij zo warm te ontvangen en voor de gezellige momenten die we samen al mochten beleven. De voorbije jaren heb ik helaas ook van enkele

familieleden die me dierbaar waren afscheid moeten nemen. **Ome Jean-Paul, Mamo, Bonne-Mamie en Daddy Jean,** ik draag jullie voor altijd mee in mijn hart.

Het laatste deel van mijn dankwoord brengt me bij de mensen die het allerbelangrijkste voor me zijn. **Papa, Gilles, Thibaut en Aurélie,** we hebben de voorbije jaren als gezin te veel moeilijke momenten moeten doorstaan. Ik had dit nooit zonder elk van jullie gekund. Jullie onvoorwaardelijke liefde, steun en appreciatie betekenen heel veel voor mij. Mijn bewondering voor ieder van jullie is bijzonder groot. Samen met mama hebben jullie me mee gemaakt tot wie ik nu ben. Gelukkig hebben we de voorbije jaren samen ook heel veel mooie momenten beleefd, met de geboorte van **Jérom** als onbetwistbaar hoogtepunt. Ik kijk er elke keer opnieuw naar uit een dag of avond met jullie door te brengen. Bedankt voor alles.

Naast enkele A1-publicaties heeft mijn doctoraatstraject me ook iets veel belangrijkers bijgebracht. **Charlotte**, ik ben zo blij dat ik jou heb mogen ontmoeten. Elke dag opnieuw prijs ik me gelukkig met jouw liefde en je steun. Bedankt ook voor je begrip en hulp op de momenten dat ik het erg druk had. Dat je me tussendoor ook nog aanmoedigde om te gaan fietsen, alleen omdat je weet hoeveel ik daarvan geniet, toont hoe graag je me ziet. Ik kan me geen leven zonder jou meer voorstellen. Bedankt om er steeds voor mij te zijn.

Mijn laatste woorden in dit dankwoord zou ik graag richten aan twee personen die me uitermate dierbaar zijn maar er helaas niet meer zijn. Aan jullie draag ik mijn thesis op. **Dieter**, ik had me een goede maand geleden nooit kunnen inbeelden dat je er vandaag niet zou bijzijn. Je hebt mijn zusje zo gelukkig gemaakt en daar ben ik je erg dankbaar voor. Ook voor mij, mijn vader en broers stond je altijd klaar met een helpende hand, een optimistische blik of vriendelijke woorden. Bij elk treffen genoot ik van je warme en oprechte aanwezigheid, je humor en – niet in het minst – je kookkunsten. Ik was zo fier toen je me samen met Aurélie vroeg om peter te worden van Jérom. Jou voortaan te moeten missen doet zo veel pijn.

Mama, mijn allerlaatste woorden zijn voor jou. Als er ergens in de hemel een plekje zou bestaan om vandaag mee te volgen, zat je ongetwijfeld op de eerste rij. Ik mis je elke dag opnieuw maar ben je bovenal ontzettend dankbaar voor de onmetelijke liefde die je mij gegeven hebt.

CURRICULUM VITAE

Personalia

Name	Mathieu J.Y.M. Sprengers
Date of birth	25th of July 1986
Nationality	Belgian
Address	Franklin Rooseveltlaan 150, 9000 Ghent, Belgium
Email	Mathieu.Sprengers@Ugent.be

Educational background

2004-2007	Bachelor of Science in Medicine Ghent University Graduation: Summa Cum Laude
2007-2011	Master of Science in Medicine Ghent University Graduation: Summa Cum Laude
2011-2020	Doctoral Schools Training Program Ghent University
2011-2019	Master after Master in Specialistic Medicine, Neurology Ghent University Hospital
2019	European Board of Neurology Examination Oslo, Norway Graduation: 91/100 (top score)

Postgraduate courses

2008	Permanent Training Programma ''Basic principles of electrocardiography'' Ghent University
2010-2011	Permanent Training Programme ''Sports Medicine'' Ghent University
2011	Spirometry in General Medicine Ghent Unversity
2011	Course in Laboratory Animal Science (FELASA C) Ghent University
2011	Workshop Cochrane Reviews The Dutch Cochrane Centre, Academic Medical Center, Amsterdam
2012	Good Clinical Practice (GCP) Training Ghent University Hospital

2012	Advanced Epilepsy Course Vlaamse Liga tegen Epilepsie
2012	Statistical analysis using SPSS, Advanced Course Ghent University
2012	Neurostimulation for Epilepsy – European Program J. Kiffin Penry Epilepsy Education Programs
2013	San Servolo Epilepsy Summer Course: Brain Exploration and Epilepsy Surgery International League Against Epilepsy
2018	Good Clinical Practice (GCP) Training (renewal) Ghent University Hospital

Postgraduate positions

10/2011 - 03/2016	PhD fellow (aspirant grant from Research Foundation Flanders) Laboratory for Clinical and Experimental Neurophysiology, Neurobiology and Neuropsychology (LCEN3), Ghent University
04/2016- 09/2019	Neurology Resident Ghent University Hospital
10/2019- 03/2023	(Postdoctoral) researcher Eindhoven University of Technology, the Netherlands
10/2019- 03/2023	Neurologist Ghent University Hospital

Publications in international peer-reviewed journals (A1)

Vonck K, Sprengers M, Carrette E, Dauwe I, Miatton M, Meurs A, Goossens L, De Herdt V, Achten R, Thiery E, Raedt R, Van Roost D, Boon P. A Decade of Experience with Deep Brain Stimulation for Patients with Refractory Medial Temporal Lobe Epilepsy. Int J Neural Syst 2013;23:1250034.

Sprengers M, Vonck K, Carrette E, Marson T, Boon P. Deep brain and cortical stimulation for epilepsy. Cochrane Database Syst Rev 2014;17(6):CD008497.

Van Nieuwenhuyse B, Raedt R, Sprengers M, Dauwe I, Gadeyne S, Delbeke J, Wadman W, Boon P, Vonck K. The systemic kainic acid rat model of temporal lobe epilepsy: long-term EEG monitoring. Brain Res 2015;1627:1-11.

Carrette S, Boon P, Sprengers M, Raedt R, Vonck K. Responsive neurostimulation in epilepsy. Expert Rev Neurother 2015;15(12):1445-54.

Thyrion L, Portelli J, Raedt R, Glorieux G, Larsen LE, Sprengers M, Van Lysebettens W, Carrette E, Delbeke J, Vonck K, Boon P. Disruption, but not overexpression of urate oxidase alters susceptibility to pentylenetetrazole- and pilocarpine-induced seizures in mice. Epilepsia 2016;57(7):e146-150.

Larsen LE, Wadman WJ, Marinazzo D, van Mierlo P, Delbeke J, Daelemans S, Sprengers M, Thyrion L, Van Lysebettens W, Carrette E, Boon P, Vonck K, Raedt R. Vagus Nerve Stimulation Applied with a Rapid

Cycle Has More Profound Influence on Hippocampal Electrophysiology Than a Standard Cycle. Neurotherapeutics 2016;13(3):592-602

Larsen LE, Lysebettens WV, Germonpré C, Carrette S, Daelemans S, Sprengers M, Thyrion L, Wadman WJ, Carrette E, Delbeke J, Boon P, Vonck K, Raedt R. Clinical Nerve Stimulation Paradigms Induce Pronounced Brain and Body Hypothermia in Rats. Int J Neural Syst 2017;27(5):1750016

Sprengers M, Vonck K, Carrette E, Marson AG, Boon P. Deep brain and cortical stimulation for epilepsy. Cochrane Database Syst Rev 2017;7:CD008497

Neumann AR, Raedt R, Steenland HW, Sprengers M, Bzymek K, Navratilova Z, Mesina L, Xie J, Lapointe V, Kloosterman F, Vonck K, Boon P, Soltesz I, McNaughton BL, Luczak A. Involvement of fast-spiking cells in ictal sequences during spontaneous seizures in rats w ith chronic temporal lobe epilepsy. Brain 2017 Sep;140(9):2355-69.

Garré J, Sprengers M, Van Melkebeke D, Laureys G. EBV-NMDA double positive encephalitis in an immunocompromised patient. J Neurol Sci 2019;396:76-77.

Van Lysebettens W, Vonck K, Larsen LE, Sprengers M, Carrette E, Bouckaert C, Delbeke J, Wadman W, Boon P, Raedt R. Hypothermia masks most of the effects of rapid cycling VNS on rat hippocampal electrophysiology. Int J Neural Syst 2019;29(9):1950008.

Van Iseghem V, Sprengers M, De Zaeytijd J, Sindic CJ, Willekens B, Dermaut B, Hemelsoet D, Laureys G. Biotinidase defiency: a treatable cause of opticospinal syndrome in young adults. Mult Scler Relat Disord 2019 Jul;32:64-65.

Sprengers M, Raedt R, Larsen LE, Delbeke J, Wadman WJ, Boon P, Vonck K. Deep brain stimulation reduces evoked potentials with a dual time course in freely moving rats: potential neurophysiological basis for intermittent as an alternative to continuous stimulation. Epilepsia 2020, Apr 16. doi: 10.1111/epi.16498 (online ahead of print).

Van Lysebettens W, Vonck K, Larsen LE, Stevens L, Bouckaert C, Germonpré C, Sprengers M, Carrette E, Delbeke J, Wadman W, Boon P, Raedt R. Identification of Vagus Nerve Stimulation Parameters Affecting Rat Hippocampal Electrophysiology Without Temperature Effects. Brain Stimul 2020; S1935-861X(20)30110-8.

Germonpré C, Proesmans S, Bouckaert C, Stevens L, Sprengers M, Vonck K, Carrette E, Wadman W, Boon P, Raedt R, De Herdt V. Acute symptomatic seizures following intracerebral hemorrhage in the rat collagenase model. Epilepsy Res 2020 Aug;164:106364.

Sprengers M, Raedt R, Larsen LE, Delbeke J, Wadman WJ, Boon P, Vonck K. Long-lasting decreased excitability induced by hippocampal deep brain stimulation in freely moving rats. In preparation for submission to Progress to Neurobiology.

Van Nieuwenhuyse B, Raedt R, Sprengers M, Dauwe I, Gadeyne S, Carrette E, Delbeke J, Wadman W, Boon P, Vonck K. Long-term hippocampal deep brain stimulation in a rat model for temporal lobe epilepsy contradicts seizures beget seizures hypothesis. In preparation, will be submitted to Science Translational Medicine.

Publications in national journals (A4)

Gadeyne S, Sprengers M, Vonck K. Neurostimulatie als behandeling voor refractaire epilepsie: een update. Epi-krant 2013;30(1):12-15.

Sprengers M, Ackerman T, Carrette E, Van Roost D, Boon P, Vonck K. Diepe hersenstimulatie en corticale stimulatie als behandeling voor refractaire epilepsie. Neuropraxis 2015; 19(3): 70-79.

Book chapters (B2)

Vonck K, De Herdt V, Sprengers M, Ben-Menachem E. Neurostimulation for epilepsy. In: Handbook Clinical Neurology 2012;108:955-70.

Sprengers M, Boon P, Vonck K. Hippocampal deep brain stimulation may be an alternative for resective surgery in medically refractory temporal lobe epilepsy. In: Case studies in epilepsy : common and uncommon presentations (2012):172-175.

Sprengers M, Carrette S, Vonck K, Boon P. Therapeutic stimulation of the ictal onset zone. Invasive studies of the human epileptic brain: principles and practice (2018): 476-485.

Papers in conference proceedings (P1)

Sprengers M, Raedt R, Meurs A, Carrette E, Van Roost D, Boon P, Vonck K. Invasive brain stimulation in the treatment of epilepsy. In: Recent Advances in Predicting and Preventing Epileptic Seizures (2013): 42-60.

Conference abstracts (C3)

Sprengers M, Vonck K, Carrette E, Meurs A, Van Roost D, Boon P. A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. Hyper-Interaction Viability Experiments Workshop, Abstracts 2012.

Sprengers M, Vonck K, Carrette E, Meurs A, Van Roost D, Boon P. A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. Front. Hum. Neurosci. Conference Abstract: Belgian Brain Council 2012.

Sprengers M, Vonck K, Carrette E, Meurs A, Van Roost D, Boon P. A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. Epilepsia 2012;53:176.

Sprengers M, Raedt R, Siugzdaite R, Van Nieuwenhuyse B, Descamps B, Dauwe I, Delbeke J, Wadman W, Boon P, Vonck K. Consequences Of Kainic Acid-Induced Piriform Cortex Lesions And Therapeutic Potential Of Piriform Cortex Deep Brain Stimulation In The Intrahippocampal Kainic Acid Model. Frontiers in Human Neuroscience 2014. doi: 10.3389/conf.fnhum.2014.214.00029

Van Nieuwenhuyse B, Raedt R, Sprengers M, Dauwe I, Gadeyne S, Delbeke J, Wadman W, Boon P and Vonck K. Hippocampal DBS affects disease development in the kainic acid rat model for temporal lobe epilepsy. Frontiers in Human Neuroscience 2014. doi:10.3389/conf.fnhum.2014.214.00013.

Neumann A, Luczak A, Steenland H, Sprengers M, Bzymek K, Xie J, Lapointe V, Navratilova Z, Kloosterman F, Vonck K, Boon P, McNaughton BN, Raedt R. Onset of spontaneous seizures in rat models for medial temporal lobe epilepsy is associated with changes in neural firing behavior in hippocampus but also in parietal association cortex. Epilepsy Currents 2014.

M. Sprengers, R. Raedt, R. Siugzdaite, B. Van Nieuwenhuyse, B. Descamps, I. Dauwe, J. Delbeke, W. Wadman, P. Boon and K. Vonck. The piriform cortex in the intrahippocampal kainic acid model: effects of lesions and deep brain stimulation on spontaneous seizures. Epilepsy currents 2014.

Van Nieuwenhuyse B, Raedt R, Sprengers M, Dauwe I, Gadeyne S, Delbeke J, Wadman W, Boon P, Vonck K. Hippocampal DBS affects disease development in the KA rat model for TLE. Epilepsy currents 2014.

Sprengers M, Raedt R, Larsen L, Van Lysebettens W, Daelemans S, Delbeke J, Wadman W, Boon P, Vonck K. Effects of hippocampal deep brain stimulation (DBS) on intrahippocampal evoked potentials (EPs) in freely moving rats. Epilepsy currents 2016.

Raedt R, Larsen LE, Van Lysebettens W, Wadman W, Delbeke J, Daelemans S, Sprengers M, Boon P, Vonck K. Vagus nerve stimulation profoundly decreases brain and core temperature in freely moving rats. Epilepsy currents 2016.

Van Lysebettens W, Vonck K, Larsen LE, Sprengers M, Carrette E, Delbeke J, Wadman W, Boon P, Raedt R. Vagus nerve stimulation induced hypothermia drives most of the effects on hippocampal electrophysiology in rats. Epilepsia 2018;59(S3):S237.

Oral presentations

A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. Hive Workshop 2012. April 28th 2012, Berlin, Germany.

Deep brain stimulation as a treatment option for pharmacologically refractory epilepsy. Lecture for Neurologists. June 14th 2012, Ghent University Hospital, Ghent, Belgium.

Long-term results with hippocampal deep brain stimulation for refractory medial temporal epilepsy Ghent International Epilepsy Workshop. October 26-28th 2012, Het Pand, Ghent, Belgium.

Neurostimulation techniques in epilepsy. 2nd Ghent Institute for Neuroscience Symposium. December 12th 2012, Het Pand, Ghent, Belgium.

Various topics in the intriguing world of epilepsy: a general introduction to clinical epilepsy, neurostimulation treatments and the paired-pulse stimulation protocol. Lethbridge Brain Dynamics. October 1st 2013, Lethbridge, Canada.

Deep brain stimulation as a treatment for refractory epilepsy. LCEN3 PhD project Workshop, February 13th 2015, Het Pand, Ghent, Belgium.

Van cyborg tot mens. Meeting of Minds for Youth. March 19th 2015, Ghent, Belgium.

Poster presentations

Sprengers M, Vonck K, Carrette E, Meurs A, Van Roost D, Boon P. A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. Hyper-Interaction Viability Experiments Workshop. April 27-28th 2012, Berlin, Germany.

Sprengers M, Vonck K, Carrette E, Meurs A, Van Roost D, Boon P. A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. 10th European Congres on Epileptology. September-October 2012, London, Great-Britain.

Sprengers M, Vonck K, Carrette E, Meurs A, Van Roost D, Boon P. A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. Belgian Brain Council Congress 2012. October 28th 2012, Liège, Belgium.

Sprengers M, Raedt R, Siugzdaite R, Van Nieuwenhuyse B, Descamps B, Dauwe I, Delbeke J, Wadman W, Boon P, Vonck K. Consequences Of Kainic Acid-Induced Piriform Cortex Lesions And Therapeutic Potential Of Piriform Cortex Deep Brain Stimulation In The Intrahippocampal Kainic Acid Model. Belgian Brain Council 2014. October 4th 2014, Ghent, Belgium.

Sprengers M, Raedt R, Siugzdaite R, Van Nieuwenhuyse B, Descamps B, Dauwe I, Delbeke J, Wadman W, Boon P, Vonck K. The Piriform Cortex In The Intrahippocampal Kainic Acid Model: Effects Of Lesions And Deep Brain Stimulation On Spontaneous Seizures. 68th Annual Meeting of the American Epilepsy Society. December 5-9th 2014, Seattle, USA.

Sprengers M, Raedt R, Larsen L, Van Lysebettens W, Daelemans S, Delbeke J, Wadman W, Boon P, Vonck K. Effects of hippocampal deep brain stimulation (DBS) on intrahippocampal evoked potentials (EPs) in freely moving rats. 17th Annual International Clinical Symposium Kempenhaeghe, March 2016, Kempenhaeghe Heeze, The Netherlands.

Sprengers M, Raedt R, Larsen L, Van Lysebettens W, Daelemans S, Delbeke J, Wadman W, Boon P, Vonck K. Effects of hippocampal deep brain stimulation on intrahippocampal evoked potentials in freely moving rats. 70th Annual Meeting of the American Epilepsy Society. December 2-6th 2016, Houston, USA.

Teaching and Students

2014-2015 **Guidance of the Research Internship** of Honours Project student Thomas Ackerman on the characterization of the intrahippocampal kainic acid epilepsy model and the effect of piriform cortex deep brain stimulation

2015 **Practical Session** on stereotactic brain surgery and the measurement of evoked potentials in rats to students of 1st Master Biomedical Sciences of the Ghent University

2015 **Lecture** for 14- to 18-year-old secondary school students 'Van cyborg tot mens' at the Meeting of Minds for Youth (MOM4Y)

2015-2016 **Guidance of the Research Internship** of Honours Project student Maaike Vierstraete on the initial experience with anterior thalamic deep brain stimulation at Ghent University Hospital

2014-2016 **Guidance of the Master Thesis** of Latoya Stevens on the effect of hippocampal neurostimulation on epileptic seizures in a rat model for temporal lobe epilepsy

2019-2020 **Guidance of the Research Internship** of Honours Project student Britt Debaene on transcranial direct current stimulation in epilepsy

2019-2020 **Guidance of the Research Internship** of Honours Project student Kato Van Rooy on transcranial direct current stimulation in epilepsy

Miscellaneous

Winner of Prices for Greek, Mathematics, French, History, Highest Grades in high school (2004, Sint-Barbaracollege, Ghent)

FWO aspirant grant 2011-2015

International League Against Epilepsy grant for participation at the 'San Servolo Epilepsy Summer Course: Brain Exploration and Epilepsy Surgery' (2014)

Research collaboration with Neuroelectronics Research Flanders (NERF, IMEC, Leuven, Belgium) (2012-2013)

Research collaboration with the Canadian Centre for Behavioural Neuroscience (CCBN, University of Lethbridge, Lethbridge, Canada) (2013, including a 5-week stay in Lethbridge)

Subinvestigator for multiple clinical trials investigating new drugs (epilepsy, multiple sclerosis) and deep brain stimulation (epilepsy)

Editorial board member of Tijdschrift voor Neurologie en Neurochirurgie (2012-2014)

Reviewer for Tijdschrift voor Neurologie en Neurochirurgie

Reviewer for Acta Neurologica Belgica

Reviewer for Cochrane Database of Systematic Reviews

Reviewer for Acta Neurologica Scandinavica

Reviewer for Brain and Behavior

Reviewer for Neuromodulation

Reviewer for Progress in Neurobiology

Reviewer for Epilepsia

Thesis submitted as fulfillment of the requirements
for the degree of Doctor in Medical Sciences

– 2020 –

ISBN 978-9-4640751-6-8

GHENT UNIVERSITY