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# Neurostimulation as an intervention for treatment resistant depression: From research on mechanisms towards targeted neurocognitive strategies

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**Abstract**

Despite the fact that several interventions for major depression have proven efficacy, a substantial number of patients are or become treatment resistant to various forms of pharmacotherapy and psychotherapy. Biological interventions that directly target brain activity such as electroconvulsive therapy are used to treat these patients, but some of these interventions are unlikely to be easily accepted because of their more invasive nature or side-effects. The efficacy of non-invasive neurostimulation with a favorable side effect profile, such as repetitive Transcranial Magnetic Stimulation, could not be sufficiently demonstrated for treatment resistant depressed patients (TRD). We argue that research on the working mechanisms of these neurostimulation techniques is necessary to develop more efficient treatment protocols. After an overview of current neurostimulation approaches to treatment resistance and the introduction of a neurobiological and a cognitive framework of depression, we provide an integrative review of research on both the neurobiological and cognitive working mechanisms of neurostimulation in TRD, with a specific emphasis on the work of our lab. Thereafter, we describe our own studies and studies from other labs on new neurocognitive interventions. Finally we discuss how all this knowledge can be used to further develop new strategies to deal with treatment resistance, in combining neurostimulation and cognitive interventions.

*Keywords: Treatment Resistant Depression; tDCS; rTMS; Neurocognitive Training; Neurostimulation; Cognitive Control*

# Neurostimulation as an intervention for treatment resistant depression: From research on mechanisms towards targeted strategies

## Introduction

Major depressive disorder (MDD) is highly prevalent and is associated with serious personal suffering and societal costs (Kessler et al., 2010). The conceptualization of MDD as a psychological disorder has inspired the development of various forms of psychotherapy such as Cognitive Behavior Therapy (CBT), whereas the conceptualization of depression as a disorder of the brain has stimulated the use of different forms of pharmacotherapy such as Selective Serotonin Reuptake Inhibitors (SSRI). Many of these interventions have proven efficacy (Cuijpers et al., 2013) but relapse or recurrence rates are very high (Beshai, Dobson, Bockting, & Quigley, 2011). Moreover, in spite of the correct use of pharmacological or psychotherapeutic approaches, a substantial number of patients become treatment resistant (up to 15%) (Burrows, Norman & Judd, 1994; Fava, 2003). Neurobiological interventions that directly target brain activity such as *Transcranial Magnetic Stimulation* (TMS) are frequently used when patients do not respond to pharmacological interventions or psychotherapy. However, an important question is whether there is enough evidence to justify the application of these interventions for treatment resistant depression (TRD). We argue that research on the working mechanisms of neurostimulation may be necessary for the development of more efficient treatment protocols. After an overview of current neurostimulation approaches to treatment resistance and the introduction of a neurobiological and a cognitive framework of depression, we provide an integrative review of research on both the neurobiological and cognitive working mechanisms of neurostimulation in TRD, with a specific emphasis on the work of our lab. Thereafter, we describe our own studies and studies from other labs on new neurocognitive interventions. Finally we discuss how all this knowledge can be used to

further develop new strategies to deal with treatment resistance, in combining neurostimulation and cognitive interventions.

## Neurostimulation Approaches to Treatment Resistance

*Electroconvulsive Therapy* (ECT) is a biological intervention that has been used for several decades to treat patients with TRD (Kosel, Frick, Lisanby, Fisch, & Schlaepfer, 2003). In ECT, generalized seizures are electrically induced by electrodes focally placed on the scalp. ECT revealed to be a possible alternative for pharmaco-resistant patients, but during the course of such treatment general anesthetics have to be administrated multiple times, and in particular bi-temporal ECT may cause memory and learning impairments (Rami-Gonzalez et al., 2001). Although ECT has proven efficacy at the short term, based on a meta-analysis, it has been shown that despite continuation therapy with pharmacotherapy, the risk of relapse within the first year following ECT is substantial (> 50%), with the greatest risk for relapse within the first 6 months (>37%) (Jelovac, Kolshus, & McLoughlin, 2013).

A variant of ECT is *Magnetic Seizure therapy* (MST). In MST, which has fewer cognitive side effects, focal seizure activity is induced by TMS (Lisanby, Luber, Schlaepfer, & Sackeim, 2003). In a small open label pilot clinical trial (N=13), 38,5 % of the depressed patients showed clinical response at the end of the study (Fitzgerald et al., 2013). This procedure may hold promise, but research on the use of MST is still very scarce and more research is needed to determine its antidepressant properties and its utility for TRD (Wani, Trevino, Marnell, & Husain, 2013).

A considerable amount of research has been performed using TMS, a non-invasive neurostimulation technique that is increasingly used. Electrical stimulation is delivered by an electromagnetic coil placed above the scalp in which a high-intensity current is rapidly turned on and off, producing a time-varying magnetic field. This magnetic field passes freely through the skin, muscle and skull to the surface of the brain, where it induces weak electric currents to flow in the underlying neurons. These neurons will be induced to fire if stimulation is

provided above a given threshold. Delivering trains of high-frequency (HF) (≥ 1 Hz) repetitive TMS (rTMS) pulses produces an increase in local cortical excitability *after* stimulation, whereas low-frequency (LF) stimulation (0.1– 1.0 Hz) decreases cortical excitability (Fitzgerald, Fountain, & Daskalakis, 2006). Although rTMS has been investigated as a treatment tool for various psychiatric disorders, most research has been done in major depression. Treatment protocols for depression consist mostly of 5-25 sessions of HF-rTMS to the left dorsolateral prefrontal cortex (DLPFC) or LF-rTMS applied to its right counterpart. A meta-analysis of 34 studies comparing rTMS to sham treatment showed a moderate effect size of 0.55 on depressive symptoms (Slotema, Blom, Hoek, & Sommer, 2010), whereas another meta-analysis of 30 HF-rTMS studies found an effect size of 0.39 (Schutter, 2009). Although these effect sizes are comparable to psychotherapy and pharmacotherapy (Roshanaei-Moghaddam et al., 2011), it is important to consider long term effects and treatment resistance to psychotropic agents.

Disappointing effects of TMS on remission are illustrated by the results of a well-designed large scale (N = 190) prospective, multisite, randomized, sham-controlled, duration-adaptive intention-to-treat study in depressed patients. In a first phase, 3 weeks of daily weekday treatment (left DLPFC, 10 Hz) was followed by continued blinded treatment for up to another 3 weeks in improvers (patients who did not achieve full remission but a 30% reduction on the Hamilton Scale for Depression (HAM-D)) (George et al., 2010). The primary efficacy analysis of the initial intervention of 3 -6 weeks revealed a significant effect of treatment, but the number of remitters was modest (14.1% in the active and 5.1% in the sham condition), and importantly most remitters were not treatment resistant in the past. The latter is consistent with the results of another trial also suggesting that patients who have repeatedly failed other treatments tend to be less responsive to rTMS (Lisanby et al 2009). In the open-label follow-up second phase of 3-6 weeks treatment in patients who did not achieve a 30 %

reduction on their HAM-D score after the initial 3 week period of phase 1, only 30% remitted. The investigators correctly concluded that , although this kind of treatment produced a statistically significant effect on remission, the overall number of remitters and responders was less than one would like with a treatment requiring a daily intervention for 3 weeks or more. Moreover, few studies have assessed the long term effects of rTMS. In a large retrospective naturalistic study (Cohen, Boggio, & Fregni, 2009), a group of patients who remitted after both high and low frequency rTMS treatment were further followed up to 6 months. During this period there were no further rTMS sessions, and medication was never introduced or changed after rTMS treatment. Event-free remission was 75.3% at 2 months, 60.0% at 3 months, 42.7% at 4 months, and only 22.6% at 6 months. To summarize, although rTMS produces beneficial treatment effects in depression, the immediate effects on remission remain modest, the long term effects are limited, and treatment resistance seems to be a contra-indication.

Even though a systematic review and meta-analysis of randomized trials showed that the reduction of depressive symptomatology was significantly more pronounced in ECT as compared to HF-rTMS (Berlim, Van den Eynde, & Daskalakis, 2013), rTMS has a more favorable side-effect profile and better tolerability (Baker, Trevino, McClintock, Wani, & Husain, 2012). Moreover, long term effects of ECT are not established as well. A study of Eranti et al. (2007) confirmed that ECT - as compared to rTMS - leads to a larger decrease in depressive symptoms as measured with the HAM-D, but at 6 months group differences disappeared.

A recently developed variant of TMS is *deep TMS*. Deep TMS coils minimize the accumulation of electrical charge on the surface of the brain and maximize the electrical field deep in the brain by the summation of separate fields projected into the skull from several different points around its periphery (Roth, Amir, Levkovitz & Zangen, 2007). A review

comparing the efficacy and tolerability of deepTMS, rTMS and ECT in drug-free patients with pharmaco-resistant unipolar depression confirmed the superior efficacy of ECT as the most effective treatment option after 4 weeks of therapy. Deep TMS seems also to provide a substantial improvement of depressive symptoms but it is characterized by poorer tolerability, as witnessed by the highest dropout as compared to rTMS and ECT (Minichino et al., 2012).

Another technique that yields growing interest is *Transcranial Direct Current Stimulation* (tDCS), an easy to use, safe, low-cost method. tDCS differs from TMS in that it can manipulate the membrane potential of neurons, but is not capable of directly activating the neurons itself (Paulus, 2011). Therefore it is often referred to as neuromodulation, whereas rTMS is referred to as neurostimulation. However in the reminder of this paper we will refer to both techniques as neurostimulation. tDCS uses a constant low current (1–2 mA, e.g. during 20 minutes) delivered directly to the brain area of interest via electrodes positioned on the scalp, inducing intracerebral current flows. The device has an anodal electrode (the positively charged electrode) and a cathodal electrode (the negatively charged electrode). One electrode (anode) is placed over the region of interest and the other electrode, the reference electrode (cathode), is placed in another location to create a circuit. Anodal tDCS enhances excitability, whereas cathodal tDCS reduces excitability (Nitsche & Paulus, 2000; Nitsche et al., 2005).

Some clinical trials with multiple daily sessions yielded encouraging results in the treatment of depression. In a recent meta-analysis, active tDCS was found to be more effective than sham tDCS in reducing depression severity (Hedges' g = .743) (Kalu, Sexton, Loo, & Ebmeier, 2012). Nonetheless, as concluded by several authors, its clinical utility remains unclear because there are not enough studies with large representative samples and optimized protocols to confirm the efficacy of tDCS (Brunoni, Ferrucci, Fregni, Boggio, & Priori, 2012; Kalu, Sexton, Loo, & Ebmeier, 2012), particularly for patients with TRD

(Valiengo et al., 2013). Recently researchers are also experimenting with high density tDCS, which uses smaller electrodes to more precisely target specific brain areas (Datta et al., 2009).

The exact working mechanisms of all the abovementioned interventions, how they influence the brain circuitry involved in depression, remains poorly understood. Recent years have witnessed more targeted applications of neurostimulation to regions that have been implicated in disrupted emotion processing known to be involved in TRD, such as the subgenual cingulate cortex (Ressler & Mayberg, 2007). Chronic Deep Brain Stimulation (DBS) of subgenual areas has yielded limited but promising initial results in small samples of TRD patients (Mayberg et al, 2005; Holtzheimer et al., 2012). In a systematic review and exploratory meta-analysis based on four observational studies in severe chronic TRD, twelve-month response and remission rates were almost 40% and over 26% respectively (Berlim, McGirr, Van den Eynde, Fleck, & Giacobbe, 2014). However, this technique is invasive because it requires implanted electrodes and chronic application.

Another invasive method to treat pharmaco-resistant depressed patients is *Vagus Nerve Stimulation* (VNS), in which the vagus is stimulated by implanted electrodes. A review based on a limited number of studies shows that it yields reductions in depressive symptomatology and high rates of remission in TRD patients but again, this intervention requires invasive surgery and continuous application (Rush & Siefert, 2009).

To summarize, there are a number of biological treatment options for depressed patients who are not responsive to psychotherapy and pharmacotherapy that directly target brain activity, but many of these techniques are unlikely to be easily accepted by patients because (a) they require invasive interventions such as multiple anesthetics and surgery, (b) their efficacy is insufficiently demonstrated, or (c) they produce significant cognitive side effects. Given that we will argue (see further) that a combination of neurostimulation and cognitive interventions such as computerized cognitive control training might be an interesting option to

treat TRD, cognitive side effects are a contra-indication. Of all these neurobiological treatment techniques, rTMS and tDCS may be an excellent option for the combination with cognitive interventions because they are the least invasive and do not produce important side effects. Researchers have concluded that more research on the working mechanisms of these non-invasive neurostimulation techniques might be helpful to develop more efficient protocols (Fidalgo et al., 2014). We argue that we should take advantage of the increased understanding of the neurobiological and cognitive effects of neurostimulation.

In the next section we provide an overview of our studies investigating the (1) neurobiological and (2) cognitive mechanisms of neurostimulation in TRD patients, guided by a neurobiological and a cognitive framework of depression respectively.

## Treatment Mechanisms of Neurostimulation in TRD

### A Neurobiological Framework of Depression

Based on the observation that new depressive episodes are triggered by progressively milder stressors, it has been proposed that through stress-kindling new episodes are triggered more easily in response to stressors as compared with initial episodes (Monroe & Harkness, 2005). In this perspective, we argue that recurrent MDD may evolve towards chronicity and treatment resistance because the neurocognitive protective mechanisms underlying stress resistance decline with the number of episodes (De Raedt & Koster, 2010).

Depression has been conceptualized as a failure to recruit prefrontal top-down cognitive control to regulate emotion producing subcortical limbic activity (Phillips, Ladouceur, & Drevets, 2008). A meta-analysis of neuroimaging studies revealed evidence for the involvement of two neurocircuits in major depressive disorder. One network includes the dorsolateral prefrontal cortex (DLPFC) and dorsal (d) regions of the anterior cingulate cortex (ACC). These regions, among other regions which are implicated in attentional and cognitive control, are characterized by reduced activity during resting state, and return to normal with

successful treatment. A second network is centered on the medial prefrontal cortex and ventral subcortical regions such as the amygdala, which is hyperactive to emotional stimuli during depressive episodes, and also returns to normal after treatment (Fitzgerald, Laird, Maller, & Daskalakis, 2008). The amygdala is activated when people are confronted with emotionally challenging events (Zald, 2003), and is tightly connected to the ventral ACC. The ACC can be conceived as a bridge between subcortical emotion processing and prefrontal cognitive control, because it integrates signals from its ventral and dorsal parts (Bush, Luu, & Posner, 2000). The dorsal ACC sends signals to the DLPFC to enhance cognitive control (Hopfinger, Buonocore, & Mangun, 2000; MacDonald, Cohen, Stenger, & Carter, 2000) and studies suggest that the DLPFC initiates control over emotions by inhibition of the amygdala via other brain regions (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007).

The fact that abnormalities in the abovementioned circuits are remediated after successful treatment (Fitzgerald et al., 2006) suggests that TRD might be characterized by an imbalance of ventral and dorsal systems. The connectivity network view, that a functional balance between ventral (ventral ACC) and dorsal compartments in the brain (dorsal ACC, DLPFC) may be necessary for maintaining homeostatic control over emotional information, has been confirmed by neuroimaging studies (for an overview, see Ochsner & Gross, 2005). Importantly, the subgenual cingulate region, which has been related to TRD (Mayberg, 2006; Baeken et al., 2010), has direct bidirectional connections to the amygdala and can be implicated in inhibitory control over the amygdala (Hamani et al., 2011). Depressed patients who are treatment resistant to CBT or pharmacotherapy exhibit pretreatment hypermetabolism at the interface of the pregenual and subgenual (sg)ACC (Konarski et al., 2009). The association of the sgACC with acute sadness (Mayberg et al., 1999; Smith et al., 2011), as well as with TRD (Ressler & Mayberg, 2007) is indicative of its crucial role in emotional reactivity. Consistent with this idea, in a study in which TRD female patients and

healthy controls were asked to passively view blocks of negative versus positive valenced baby faces while undergoing functional magnetic resonance imaging (fMRI), the depressed patients displayed higher bilateral sgACC activities in both emotional conditions as compared to the controls (Baeken et al., 2010).

We argue that neurostimulation of the DLPFC might produce beneficial antidepressant effects through its influence on the abovementioned circuits, including the ACC and amygdala. Antidepressant working mechanisms of neurostimulation in depression can be considered on a scale from molecular over neural systems to cognition-emotion interactions (De Raedt & Koster, 2010). We start with an overview of studies on the neurobiological mechanisms of action. Thereafter we introduce a cognitive framework emphasizing the relationship with the neurobiological approach, followed by a review of research on the influence of neurostimulation on cognitive functions and cognitive-emotion interactions. We will look at each of these mechanisms and emphasize their relationship.

**Molecular Approach to Working Mechanisms of Neurostimulation**

George, Taylor and Short (2013) have suggested that rTMS may act as a 'focal pharmacotherapy' in a similar way as SSRIs. When a neuron fires provoked by rTMS, neurotransmitters are released in the synaptic cleft, causing increased functional connectivity. In a study using the radioligand $^{123}$I-5-I-R91150 with single photon emission computed tomography in TRD patients, it could be demonstrated that the postsynaptic serotonin 5-$HT_{2A}$ receptors in dorsal regions of the prefrontal and the ACC are down-regulated compared to never depressed controls, whereas 5-$HT_{2A}$ receptor binding did not differ from controls in first-episode depressed patients (Baeken, De Raedt & Bossuyt, 2012). Based on these findings, the effect of 10 daily weekday HF-rTMS sessions applied to the left DLPFC on postsynaptic 5-$HT_{2A}$ receptor binding indices was examined in a group of antidepressant-free, pharmaco-resistant depressed (TRD) patients (Baeken et al, 2011). At baseline, the TDR

patients showed significantly less bilateral DLPFC and significantly higher left hippocampal 5-$HT_{2A}$ receptor binding as compared to healthy controls. Successful HF-rTMS treatment was associated with increased 5-$HT_{2A}$ receptor binding in the DLPFC bilaterally and decreased right hippocampal 5-$HT_{2A}$ receptor binding, which is in line with the idea that rTMS may act as a focal pharmacotherapy intervention.

**Neural Systems Approach to Working Mechanisms of Neurostimulation**

The fact that effects were also observed in remote brain areas (relative to the area targeted by neurostimulation) is in line with prior findings suggesting that rTMS also influences brain connectivity with other areas such as the contralateral stimulation side and the ACC (Paus, Castro-Alamancos, & Petrides, 2001; Paus & Barrett, 2004). Circuits including these regions are linked to crucial cognitive risk factors for recurrent depression, namely rumination, impaired attentional control, and cognitive reactivity (Marchetti, Koster, Sonuga-Barke & De Raedt, 2012). Baeken, De Raedt and co-workers (2009a) observed that successful HF-rTMS treatment in TRD patients caused metabolic increases (glucose metabolism measured with $^{18}$Fluorodeoxyglucose Positron Emission Tomography: $^{18}$FDG-PET) in dorsal subdivisions of the ACC, and that higher baseline metabolic activities in the DLPFC and the ACC are associated with better clinical outcome. The importance of looking at connectivity in circuits implied in TRD is underscored by research showing that limbic-cortical connections (DLPFC-Subgenual Cingulate Cortex-Orbitofrontal cortex) can differentiate responders to pharmacotherapy from non-responders (Seminowicz et al., 2004).

Inspired by the idea that rTMS influences brain connectivity, and the apparent role of the sgACC in emotional reactivity in TRD, Baeken et al. (2014) examined the effects of HF-rTMS over the left DLPFC on resting state functional connectivity (fc) fMRI of the sgACC in TRD patients. First, at baseline, HF-rTMS responders compared to non-responders showed stronger fc anti-correlation between the sgACC and the left superior medial prefrontal cortex

compared to non-responders, which is similar to findings in other treatment modalities. Furthermore clinical response to HF-rTMS was associated with restored fc between sgACC and areas in the prefrontal cortex. The idea that these biological characteristics are related to functional mechanisms of decreased reactivity to stressful information is underscored by a study in which TRD patients received a single session of left-sided HF-rTMS to investigate the effects on the Hypothalamic Pituitary Adrenal axis. Although there were no changes in subjectively experienced mood, salivary cortisol concentrations, which is a measure of the physiological stress response, decreased significantly both immediately and 30 minutes after one active HF-rTMS session and not after sham (Baeken et al., 2009b).

**A Cognitive Framework of Depression and the Relationship with the Neurobiological Approach**

As proposed in the cognitive theory of depression (Beck, 1967; Clark, Beck & Alford, 1999), information-processing is guided by schemas, which are memory structures containing information about the self, the world, and the future based on prior experiences. Specific attentional biases for depressogenic information filter external information leading to subjective negative experience. Importantly, these negative experiences further develop the maladaptive schemas causing a vicious cycle maintaining the disorder (Eysenck, 1997; Teasdale & Barnard, 1993). Numerous studies using different experimental paradigms have demonstrated that depression is characterized by attentional biases for negative information at later stages of information processing (for a review, see De Raedt & Koster, 2010). It has been demonstrated that this problem reflects difficulties to inhibit negative information (Goeleven, De Raedt, Baert, & Koster, 2006, see also Joorman, 2004) or to disengage attention away from external negative information (Leyman, De Raedt, Schacht, & Koster, 2007). Although most of these studies have used visual cueing paradigms, evidence for control problems towards internal representations in depression could also be found (e.g. De

Lissnyder et al., 2012). Indeed, in cognitive psychology a distinction is made between external and internal attention (Chun, Golomb, & Turk-Browne, 2011). In the remainder of this chapter, for reasons of clarity, we will use the generic term “cognitive control”, to refer to internal executive functions (e.g. shifting and updating in working memory), and “attentional control” to refer to visuospatial attentional functions for external information (e.g. disengagement from negative information).

In several experimental studies using an internal shift task, it could be demonstrated that diminished cognitive control for mental representations – i.e. internal shifting impairments when negative information is held in working memory – is related to the tendency to ruminate (e.g. De Lissnyder, Koster & De Raedt, 2012). This impairment at baseline in a remitted depressed sample predicted depressive symptoms one year later, a relationship which was fully mediated by rumination (Demeyer, De Lissnyder, Koster, & De Raedt, 2012). Rumination, which has been defined as “behaviors and thoughts that focus one's attention on one's depressive symptoms and on the implications of those symptoms” (Nolen-Hoeksema, 1991, p. 569), is associated with depressive symptoms and is predictive of future depressive episodes and their duration (Nolen-Hoeksema, 2000), severity (Just & Alloy, 1997) as well as of recovery from depression (Kuehner & Weber, 1999). This indicates that rumination is an important cognitive vulnerability factor for depression. It has also been demonstrated that the DLPFC is implied in the neurocircuit associated with rumination (Vanderhasselt, Kuhn, & De Raedt, 2011). In healthy non-depressed individuals, those who tend to ruminate in daily life displayed higher DLPFC involvement when they successfully inhibit negative information during a cognitive control task (emotional GO/NOGO paradigm). These data suggest that healthy individuals who tend to ruminate need to recruit more cognitive control in order to disengage successfully from negative information. The fact that the involvement of dorsal areas might be a vulnerability factor is underscored by the

observation that rumination is also associated with volume and resting state reductions in brain areas that have been linked to cognitive control processes such as prefrontal areas and the ACC (Kuhn, Vanderhasselt, De Raedt & Gallinat, 2012).

To summarize, in TRD patients (see supra) abnormalities are observed in dorsal compartments at the level of neurotransmitters and at the level of connectivity with regions implied in cognitive and attentional control and rumination. This may explain how the neuroanatomical and functional correlates of treatment resistance may be related to core symptoms of depression such as rumination. This prompted us to develop a framework to explain the increasing vulnerability for depression after multiple episodes – which can lead to treatment resistance – integrating experimental psychopathology and neurocognitive research. The basic idea of this framework is that prolonged processing of self-referent material such as rumination - after the activation of negative schemas - is caused by impaired activity in dorsal prefrontal areas, mediated by the serotonergic system which is under control of the Hypothalamic Pituitary Adrenal (HPA) axis. The HPA axis – the hallmark of the stress response – stimulates the release of stress hormones (corticosteroids), and becomes increasingly impaired after periods of hypercortisolism during depressive episodes (van Praag, De Kloet & van Os, 2004), which means that it becomes more reactive to stressors (De Raedt & Koster, 2010).

Interestingly, it has been shown that mood repairing psychological processes such as reappraisal of negative information are related to recruitment of the same dorsal areas. Healthy individuals who tend to use reappraisal to overcome negative affect in daily life were behaviorally faster and exerted more dACC activity when inhibiting a response to negative in favor of positive information (compared to inhibiting a positive in favor of a negative response) (Vanderhasselt, Baeken, Van Schuerbeek, Luypaert, & De Raedt, 2013).

In the next paragraphs we will explore the relationship between the neural systems that are influenced by rTMS of the DLPFC and emotional reactivity, attentional control, cognitive control and emotion regulation.

**Cognitive Approach to Working Mechanisms of Neurostimulation**

Based on a review (Pringle, Browning, Cowen, & Harmer, 2011), it has been hypothesised that pharmacotherapy (SSRIs) might act through its influence on attentional control over negative information. In a series of studies, it has been investigated whether HF-rTMS of the DLPFC might work through its influence on attentional and cognitive control. Vanderhasselt and co-workers examined the effects of a single session and 10 sessions during 2 weeks of HF-rTMS over the left DLPFC on attentional control using a task switching paradigm in TRD patients (crossover placebo-controlled double-blind design) (Vanderhasselt, De Raedt, Leyman & Baeken, 2009). After 2 weeks of stimulation, depressive symptoms improved in more than half of the therapy-resistant patients. After the single session, mood did not improve but attentional control was increased solely within the group of treatment responders. This suggests that rTMS activates a network implied in attentional control in TRD patients who show remission. Furthermore, it has been shown that deficiencies in cognitive control (as measured using ACC related Event Related Potentials (ERP) during a cognitive control task that requires conflict resolution) are correlated with the number of prior episodes, suggesting that with every episode control further declines (Vanderhasselt & De Raedt, 2009). In another small pilot study emotion specific results have been found. After two weeks of daily HF-rTMS of the left DLPFC, 9 out of 14 of severely depressed patients demonstrated clinical significant improvement, and these responders also demonstrated significant improvements in the inhibitory control for negative information (sad faces) (Leyman, De Raedt, Vanderhasselt & Baeken, 2011). This indicates that the antidepressant effect of rTMS may be related to decreased deficiencies in inhibitory control towards negative information.

However, in the latter study the changes in attentional processes might be caused by HF-rTMS induced symptom changes. Therefore it is also important to examine causal mechanisms in never depressed participants. By using a single placebo-controlled HF-rTMS session, De Raedt et al. (2010) experimentally manipulated activity within the right DLPFC of healthy participants to induce prefrontal asymmetry with higher right sided brain activity just as observed in depressed patients (Davidson, Pizzagalli, Nitschke, & Putnam, 2002), and examined changes in attentional control for emotional information (angry faces) using an emotional modification of a spatial cueing task during event-related fMRI. This stimulation of the right DLPFC resulted in impaired disengagement from negative information, just as observed in currently depressed patients (Leyman, De Raedt, Schacht & Koster, 2007). Moreover, this was associated with decreased activation in the right DLPFC, dACC and left superior parietal gyrus, combined with increased activity within the right amygdala during disengagement away from negative information. Depression specific attentional control deficiencies could be induced in healthy individuals, affecting regions that are implicated in the neurocircuits involved in emotion regulation but without any effects on mood. This underscores the possible causal influence of HF-rTMS of the DLPFC on attentional control, and that these mechanisms might be implied in the antidepressant outcome of rTMS.

## Combining Cognitive Interventions with Neurostimulation

So far we provided evidence that rTMS of the left DLPFC influences neurocircuits involved in rumination, cognitive control, attentional control and emotion regulation. Moreover, rTMS seems to act by restoring receptor sensitivities in postsynaptic receptor binding in the prefrontal cortex and connectivity between prefrontal areas and other areas implied in emotional reactivity and emotion regulation such as the ACC and the amygdala. Most importantly, rTMS seems not capable of causing stable remission in TRD despite the neurobiological and cognitive effects described in the former sections. This suggests that we

might do well to also influence the abovementioned cognitive and attentional control processes more directly in addition to the neurostimulation sessions. These cognitive processes (1) are known to be influenced by neurostimulation, and (2) are a vulnerability to depression. This could facilitate neuroplasticity, which is a core mechanism underlying new learning. Indeed, although the basic wiring of the central nervous system is genetically pre-programmed, its fine-tuning during the life span is experience-dependent (Post & Weiss, 1997). This experience-dependent neuroplasticity enables all forms of cognitive processes and changes of these processes. Neurons are able to modulate the strength and structure of their interconnections as a result of experience and training of specific behavior (Martin & Kandel, 1996; Krasne, 2002). In order for a treatment to be successful at the long term, changes at the structural and functional brain level related to cognitive and attentional control may be required. Although rTMS and tDCS are able to induce and modulate neuroplasticity (Kuo, Paulus & Nitsche, 2014), training (learning) may be a means to strengthen these effects, making them more specific to cognitive functions which are disabled in TRD. Thus, neuromodulation may cause unspecific neuroplasticity changes, whereas the combination with training might create more targeted neuroplasticity changes. The effects of neurostimulation could thus be boosted by combining these techniques with training of cognitive strategies that foster new learning and thus facilitate plasticity. In the next sections, we will focus on different specific targets for training: (1) cognitive control towards internal mental presentations and (2) attentional control, i.e. disengagement from negative external information. tDCS is particularly suitable to be combined with training because both procedures can be administered at the same time, whereas rTMS can be disruptive during stimulation (Fidalgo et al., 2014) (and training should thus start after rTMS). Moreover, there are indications that tDCS has similar effects on cognitive functions as rTMS (for a review, see Kuo & Nitsche, 2012).

**Cognitive Control**

Siegle and colleagues (Siegle, Price, Jones, Ghinassi, Painter & Thase, 2014) used a DLPFC related cognitive control training (CCT) procedure to increase cognitive control, as an add-on to medication and psychotherapy in severely depressed patients (but not TRD). They applied six sessions of cognitive control exercises that consist of working memory training that engages the prefrontal cortex (Paced Auditory Serial Addition Task, PASAT, Gronwall, 1977) combined with attentional training for external auditory information (Papageorgiou & Wells, 2000) as an add-on to treatment-as-usual (TAU: medication & psychotherapy). As compared to TAU only, CCT + TAU resulted in decreased rumination, early reduction in depressive symptomatology, and less use of intensive outpatient services during the following year. In a subsample of six individuals, these authors also used fMRI assessment before and after the training. The results showed that after the intervention, depressed participants displayed decreased disruptions in both amygdala activity on an emotion task and in DLPFC activity on a cognitive task on which they were not trained (Siegle, Ghinassi & Thase, 2007). This is a first study showing that a combination of regular approaches and cognitive control training may have extra value in the treatment of depression. But what about medication resistant patients? Given that rTMS is capable to influence neurocircuits implied in cognitive and attentional control in TRD patients, but that TRD seems to weaken the effects of rTMS, a next step might be to use CCT as an add-on to neurostimulation in these patients. This might be a more potent strategy to influence depression vulnerability. In a pilot study, tDCS has been used to test this proof-of-principle.

Segrave and colleagues (Segrave, Arnold, Hoy, & Fitzgerald, 2013) used the abovementioned CCT (Siegle et al., 2014) in combination with tDCS of the left DLPFC during 5 consecutive daily sessions. Twenty-seven MDD patients were randomized into three conditions: tDCS combined with CCT, sham tDCS combined with CCT and sham CCT.

There was a similar reduction in depression severity at the end of the procedure in all three treatment conditions. However, only the tDCS plus CCT condition resulted in sustained antidepressant response at three weeks follow up, and the magnitude of this effect was greater than the one observed immediately following the treatment procedure. This provides a preliminary proof-of-principle for the use of concurrent CCT and tDCS, but the sample size was very small, these patients were not treatment resistant and the limited extra value could only be demonstrated at follow-up. In a similar double-blind trial (Brunoni et al., 2014), participants were randomized to sham tDCS and CCT (n=17) vs. active tDCS and CCT (n=20) during 10 consecutive workdays. Here, only the DLPFC-related working memory training (PASAT) was used. Both CCT alone and combined with tDCS were successful in decreasing depressive symptoms after the acute treatment period and at follow-up, with a response rate of approximately 25%. However, older patients and those who presented better performance in the task throughout the trial showed greater depression improvement in the tDCS with CCT treatment group.

Given that depression is characterized by emotion specific cognitive control problems, a crucial improvement may be to use a working memory paradigm that is emotion specific. In a placebo-controlled within subjects study in healthy individuals, anodal tDCS over the left DLPFC (cathode over the right supraorbital region) was applied during performance of an internal shift task (in which participants have to shift and update emotional information in working memory) during one session. Twenty minutes after neurostimulation, the occurrence of momentary self-referent ruminative thought was assessed during a rest period. The influence of tDCS (and not placebo) on ruminative thought was mediated by increased shifting ability away from negative to neutral information (Vanderhasselt, Brunoni, Loeys, Boggio & De Raedt, 2013). Although the task used in this study was not a training task but only a task to measure cognitive control, these findings in healthy individuals suggest that by

training the ability to update and shift away from negative representations in working memory, combined with tDCS, might help patients to specifically control their ruminative thoughts.

To summarize, combining cognitive training and neurostimulation may hold promise, but more research is needed to further elaborate these findings in depressed and TRD patients. Moreover, depression is not only characterized by cognitive control problems for internal mental representations, but also for external negative information (De Raedt & Koster, 2010) which will be discussed in the following paragraph.

**Attentional Control**

As already mentioned, in many studies it has been observed that depression is characterized by biased visual attention for mood-congruent information, specifically difficulties with disengagement from negative information (for a review, see De Raedt & Koster, 2010). In this perspective, therapies could help patients to create new experiences by influencing how they perceive their environment, exposing them to schema incompatible information by using attention training to automatize attention away from negative towards positive information (Baert, Koster & De Raedt, 2011). In two experiments, one in dysphoric students and one in depressed patients, Baert and co-workers (Baert, De Raedt, Schacht & Koster, 2010), examined the effects of such an intensive internet delivered attention training procedure during 10 daily sessions. Whereas attention bias was not differentially influenced compared to a control procedure in both experiments, the undergraduates showing mild depressive symptoms improved on symptom severity in the active training condition. However, depressive symptoms increased after the training in the ones showing moderate to severe depressive symptoms. In depressed patients, no beneficial effects on top of therapy and medication (TAU) were observed. These results suggest that depressed patients might not benefit from attention training procedures to automatize attention away from negative towards

positive information. A recent meta-analysis confirms that there is currently no evidence for a beneficial effect of attentional bias retaining using visual cueing paradigms (Hallion & Ruscio, 2011).

Nonetheless, it could be demonstrated that a similar attention training procedure has beneficial effects in recovered depressed patients (Browning, Holmes, Charles, Cowen, & Harmer, 2012). Interestingly, Browning and colleagues have shown in healthy individuals that the modification of attentional bias by an attention training procedure (to train attentional disengagement away from negative information) altered DLPFC activation to emotional stimuli. This indicates that this form of training can influence brain processes which are dysfunctional in depression (Browning, Holmes, Murphy, Goodwin, & Harmer, 2010). Depressed patients might show no benefits of attention training because of dysfunctional activity in their DLPFC, which is related to this training. This means that combining attention training with neurostimulation may be beneficial.

In a recent study of Clarke and colleagues (in press) preliminary evidence is provided that anodal tDCS of the left DLPFC increases the effects of attention training in healthy participants. They induced attentional bias either towards or away from threat words, and participants received either tDCS or placebo during this training paradigm. Only participants receiving real tDCS showed more evidence of an attentional bias change in the targeted direction (towards or away from threat).

The results of another recent study in social anxious individuals provided further evidence that anodal tDCS applied to the left DLPFC may enhance the effects of attention training. Attention training (away from negative information), was combined with tDCS (both anodal and cathodal) versus sham stimulation. The only procedure that yielded effects was the anodal tDCS condition, which caused decreased total dwell time on angry faces as measured by eye movement registration (Heeren, Baeken,Vanderhasselt, Philippot, & De Raedt, 2014).

Although this latter study was conducted in social anxious individuals, and further research in depressed and TRD patients is thus needed, the results are indicative of the possibilities of combining attention training with neurostimulation. Given that both neurostimulation and attentional control training seem to target similar neurocircuits, combining them may have important added value. As suggested by Segrave, Arnold, Hoy and Fitzgerald (2013), stimulating brain circuits that are activated by cognitive procedures might produce better results as compared to stimulation alone. Moreover, by combining neurostimulation with more specific training procedures, patients also acquire new learning on how to use their improved brain functioning (e.g to disengage from negative thoughts or from external information). Despite the fact that there are currently no studies in TRD patients, the results of the abovementioned studies are encouraging for our approach.

## Conclusion and Implications for Future Research

Current invasive treatment options -including ECT- to deal with TRD are unlikely to be easily accepted by many patients and their caregivers because they produce cognitive side effects, require anesthetics or surgery, or their long term outcome is insufficiently demonstrated. The latter suggests that such biological treatment options remain insufficiently effective in diminishing underlying vulnerability factors. We argue that, in order to achieve long lasting treatment effects of neurostimulation applications, new learning to facilitate brain plasticity should take place. On the one hand, the effects of non-invasive neurostimulation on neuroplasticity could be fine-tuned by combining it with training strategies that activate the circuits implied in specific cognitive functions. On the other hand the positive effects of cognitive training could be facilitated by stimulating the circuits involved in the processes that are trained.

Based on this review, we propose that future research should be focused on the development of a new generation of treatment strategies combining biological and cognitive

interventions. To treat TRD with long term results, instead of using monotherapeutic interventions it could be necessary to influence its underlying pathophysiology by using a combination of different complementary strategies that are related to similar brain processes. In order for a treatment to be successful at the long term, changes at the structural and functional brain level associated with the disabled cognitive functions might be required, and the combination of neurostimulation and cognitive training could be a means to achieve this.

Novel therapeutic strategies should be further developed, combining neurostimulation techniques targeting specific parts of the brain with cognitive control training (i.e. working memory) to increase the ability to shift away from ruminative thinking, and attentional bias training to automatize attention away from negative information in the environment. Nonetheless, it is obvious that this research domain is still in its infancy. Therefore, an important avenue for further research is to develop new potent cognitive and attentional training procedures. Furthermore, the added value of these complementary techniques to increase response rates and reductions of relapse and long term effects in TRD patients, should be investigated. In addition, the necessary doses of training sessions should be established, and predictors of successful outcome need to be examined. Given the differences in neurobiological pathways for subtypes of depression (Sharpley & Bitsika, 2013), it is also crucial for this type of interventions to define what works best for whom.

To conclude, different strategies that target different aspects of similar underlying processes could be combined. This should enhance emotion regulation abilities to foster the development of more adaptive schemas of the self and the environment, and to ultimately increase resilience for future depressive episodes.

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