Occipital nerve stimulation for headache disorders

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Abstract

Occipital nerve stimulation (ONS) was originally described in the treatment of occipital neuralgia. However, the spectrum of possible indications has expanded in recent years, to include primary headache disorders such as migraine and cluster headache. Retrospective and some prospective studies have yielded encouraging results and evidence from controlled clinical trials is emerging, offering hope for refractory headache patients. In this paper we discuss the scientific rationale to use ONS to treat headache disorders, with emphasis on the trigeminocervical complex. ONS is far from a standardized technique at the moment and the recent literature on the topic, both with respect to the procedure and its possible complications, is reviewed. An important way forward in the scientific evaluation of ONS to treat refractory headache is the clinical phenotyping of patients, to identify patients groups with the highest likelihood to respond to this modality of treatment. This requires multidisciplinary assessment of patients. The development of ONS as a new treatment for refractory headache offers an exciting prospect to treat our most disabled headache patients. Data from ongoing controlled trials will undoubtedly shed new light on some of the unresolved questions.

Key words

Occipital nerve stimulation; refractory headache; cluster headache; migraine; hemicrania continua; neuropathic pain

Refractory headache

Despite a growing armamentarium of drugs, headache disorders can be refractory to medical treatment. The term intractable headache has often been used interchangeably with refractory headache, although the latter is now preferred.[1] Even though refractory headache is a well recognized occurrence in clinical practice, little research has been performed on the topic and it is not defined in the International Classification of Headache Disorders second edition (ICHD-II).[2] A globally accepted definition does not exist today, but there have been a few attempts by the International Headache Society (IHS) and the American Headache Society to develop operational definitions, such as for migraine and cluster headache.[1, 3] Patients with refractory headache should have failed adequate trials of conventional drugs, because of unsatisfactory or lack of therapeutic effect, intolerable side-effects, or contraindications to use.[3] As the concept of refractory headache is particularly developed for the purpose of controlled clinical trials that involve experimental medication, invasive therapies or implantable devices, it implies disability.[3] Patients with refractory headache lack a significant effect of drug treatment, but otherwise have very different conditions. Headache disorders are not part of a 'continuum', but should be classified according to the ICHD-II, which is a hierarchical classification system (up to 4 digits) with diagnostic criteria and has three main categories: primary headaches, secondary headaches and cranial neuralgias.[2] There is a need for appropriate specific treatments for the various subtypes of refractory headache, and studies are urgently required. Or to quote Dr. Jes Olesen: "No research can be done on a disease that is not defined… it is difficult to define a disease on which no research has been done".[4] Developing the concept of refractory headache is necessary for referral to empiric treatment as well as inclusion in future clinical trials. Defining refractory headache inevitably leads to the discussion of non-pharmacological options and may also create a basis for reimbursement of the medical costs of emerging interventional therapies. The conventional management

options for medically intractable chronic headache syndromes are often limited and have been reviewed elsewhere.[5-6] Various surgical procedures are offered to patients and neurostimulation procedures are of increasing interest. Peripheral nerve stimulation is a minimally invasive and reversible procedure, and is increasingly employed in the treatment of certain forms of chronic neuropathic pain, where it is certainly preferred over nerve ablation procedures. Many targets for treating headache disorders and facial pain with neurostimulation have been described, including motor cortex, hypothalamus, thalamus, periaquaeductal grey, trigeminal tract, trigeminal nerve or ganglion, supra- and infra-orbital nerves, vagus nerve and cervical spinal cord, but in recent years the main focus has been on stimulation of the occipital nerves in several headache disorders, including migraine and cluster headache.

Occipital nerve stimulation: history

Occipital nerve stimulation, or ONS, has been pioneered by Dr. Weiner and Dr. Reed, Departments of Neurosurgery and Anesthesiology of the Presbytarian Hospital of Dallas, for the treatment of "C2-mediated headache" after they described a case series of 13 patients with intractable occipital neuralgia in 1999.[7-8] The first use of ONS for headache was however reported in 1977 including 6 patients, but no specific diagnoses were provided.[9] Also in 1985, ONS treatment for a patient with occipital neuropathy was described in a case series of patients with painful neuropathies treated with peripheral nerve stimulation.[10] Initially, cuff electrodes, twined around the nerve, were used, but Weiner and Reed used subcutaneous cylindrical electrodes implanted at the occipitocervical junction. Beneficial effects of ONS were reported in more cases and case series, but the headache diagnosis sometimes remained as vague as 'Head pain that involved the C2 distribution with or without pain in other regions of the head' or 'C2-mediated occipital headaches'.[8, 11] Patients with primary headaches often

report pain that involves not only the front of the head, innervated by the first (ophthalmic) division of the trigeminal nerve, but also the back of the head, mainly innervated by the greater occipital nerve that is a branch of the C2 spinal root. Eight patients of Weiner and Reed' s series were further evaluated as part of a PET study.[12] All eight were reclassified as chronic migraine patients according to the ICHD-II. In the past few years, the application of ONS has been widened to include a large number of primary and secondary headache disorders, such as migraine, chronic cluster headache, new daily persistent headache, hemicrania continua, chronic posttraumatic headache, chronic headache attributed to whiplash injury, cervicogenic headache, and occipital neuropathy.[13-19] Identification of specific headache diagnoses that respond to ONS remains a challenge.[13] Recently, ONS has been evaluated in clinical trials in migraine and chronic cluster headache. The ONSTIM (Occipital Nerve Stimulation for the Treatment of Intractable Migraine) trial in migraine has only been published in abstract form.[18] There are two published trials in chronic cluster headache, one prospective and one retrospective, but these trials are uncontrolled as they offer no comparison to sham.[15, 17]

Occipital nerve stimulation: technique

ONS is a minimal invasive procedure, with a stimulator implanted uni- or bilaterally at the level of the occipitocervical junction, such that stimulation causes slight paresthesia in the distribution of the occipital nerves after adjusting stimulation parameters such as pulse width, frequency and amplitude (Figure 1). Even though these are the basic characteristics of ONS, many technical variations exist, and there is a need for standardization.[20]

Medial approach or lateral approach

The original technique described by Weiner and Reed used a lateral incision close to the mastoid process and a lead was advanced in the subcutaneous tissue towards the midline at

the C1 level under fluoroscopy control.[7] Later on, a medial approach was described with a midline incision.[21] There are many arguments in favor of the medial approach. Firstly, there is more subcutaneous fat at the midline which allows to make a subcutaneous pocket large enough for adequate fixation of the lead and leaving a loop to minimize lead dislocations. Secondly, especially patients who wore glasses complained of pain at the site of the incision with the lateral technique. Finally, bilateral electrodes can be implanted with a single incision.

Types of devices

No specific electrodes were developed yet for ONS. At present ONS is typically performed with electrodes normally used for spinal cord stimulation. ONS electrodes exist as paddle or cylindrical electrodes. One advantage of these electrodes is that electrodes for bilateral stimulation can be inserted through one midline incision. The paddle electrodes require more surgical dissection, but are associated with less scar tissue formation around the electrode, better stimulation field and less change of migration.[22] Silicone anchors and strain relief loops to reduce risk of migration are put in place. The ONS electrodes are connected to implantable pulse generators (IPG's), that can be non-rechargeable (life span 2-5 years) or rechargeable. The IPG's can be implanted in the subclavicular, abdominal, or gluteal area. A recent development as an alternative to electrodes is the BION device.[19, 23] It is a rechargeable, telemetrically programmable, and current-controlled mini-neurostimulator. It has a cylindrical shape and is 27 mm in length and 3 mm in diameter. If bilateral ONS is required, a bion device should be implanted on the left and on the right.

Local or general anesthesia

Weiner and Reed described electrode placement under local anesthesia. Stimulation of the electrode during the procedure allowed the patient to indicate site of paresthesia and thus to verify correct electrode positioning relative to the occipital nerves. The procedure can also be performed under propofol sedation with a wake up during the procedure in order to check the

area of paresthesia. However, experienced physicians now perform the procedure under general anesthesia with the patient in the prone position and the head in a horseshoe headrest.[13, 24] They argue that the added risk of general anesthesia is more than outweighted by the reduction in postoperative lead migration, the main adverse event. Indeed, electrode migration may occur in up to 100% of individuals at three years follow-up,[11] but may be as low as 0% at three years under general anesthesia.[13]

Variability of the course of the greater occipital nerve

Important anatomic variability in the course of the occipital nerves exists, and in fact the classical descriptions do not seem to match recent data from cadaver studies.[25] Placement of the occipital nerve stimulator above the nuchal line, which is higher than in the classical descriptions, may be associated with less muscle spasm while still providing paresthesia.[26]

Occipital nerve stimulation: mechanisms of action

Anatomy of the nociceptive system of the head

Three pairs of occipital nerves, the greater, lesser and third occipital nerves, provide sensory innervation of the back of the head on either side. Nociceptive fibres project to the upper cervical spinal dorsal horns, that are continuous with the trigeminal nucleus caudalis, where nociceptive fibres of the trigeminal nerve synapse. Taken together, the upper cervical dorsal horns of C1-C3 and the trigeminal nucleus caudalis form the trigeminocervical complex (TCC; figure 2). From the TCC, nociceptive information is transmitted to higher centers in the brain. The TCC is a functional rather than an anatomic entity, and physiological studies in animals have pointed at convergence of trigeminal and upper cervical nociceptive information, and thus a loss of spatial specificity at the level of the second order neurons of the TCC.[27-29] The concept of a TCC is furthermore supported by human experimental evidence.[30-31] This functional continuum between occipital and trigeminal nociceptive input is important to

understand how pain from a source in the neck can be referred to the trigeminal territory (in cervicogenic headache) but it is equally important to note that primary headache disorders such as migraine and cluster headache, characterized by activation of the trigeminovascular system, often are characterized by pain in the trigeminal and occipital nerves' territory. The TCC itself is under the control of pain-modulatory structures, such as the periaquaeductal grey, the dorsolateral pontomesencephalic tegmentum and rostral ventromedial medulla oblongata. Together, these modulatory structures may generate both an anti-nociceptive or pro-nociceptive state of the TCC neurons.

Mechanim of action of ONS

ONS depolarizes the occipital nerves and anterograde impulses traverse in the sensory fibres towards the central nervous system. The beneficial effects of ONS in many different headache disorders suggest a non-specific pain relief mechanism, although the mechanism of action may in fact be different depending on the condition. As shown by Magis and colleagues[17] in patients suffering from chronic cluster headache, occipital nerve stimulation has neither a segmental nor a generalized analgesic effect.

At present, the exact central and/or peripheral mechanisms, as well as the neurotransmitter systems involved are unknown. ONS may have central and peripheral effects that modulate nociception. It has been shown that electrical stimulation may change excitability of the peripheral nerve fibres themselves.[32-33] Neurostimulation alters the conduction velocity and the amplitude of the A-α, A-β, and especially A-δ fibres (the latter being involved in nociception) in isolated rat cutaneous nerve.

The understanding of pain-modulatory mechanisms in the spinal cord as well as in the supraspinal structures has been greatly advanced by the 'gate-control theory' by Ronald Melzack and Pat D. Wall.[34] Although considerably extended and modified since 1965, this model in essence proposed that the transmission of pain in the spinal cord is modulated by

excitatory and inhibitory influences.[35] In accordance with the gate-control theory, an interplay of segmental spinal inhibiting effects and descending pain inhibitory pathways may also contribute to the analgesic effects of ONS. Given the loss of spatial specificity at the level of the trigeminocervical complex, electrical stimulation of the occipital nerve may have an anti-nociceptive effect in the territory of the trigeminal as well as the occipital nerves. There is some animal evidence to support this notion, as stimulation of the greater occipital nerve in the rat reduces calcitonin gene-related peptide in the jugular blood, which is a biomarker of inhibition of the trigeminal system.[36] A functional imaging study in chronic migraine patients supports the notion that ONS may influence supraspinal structures involved in central nociceptive trafficking, such as the dorsal rostral pons, the pulvinar nucleus of the thalamus and the anterior cingulate cortex.[12] More details on the possible mechanism(s) of action, especially on the TCC, have been covered elsewhere.[37] Interestingly, persistence of autonomic features has been described in one patient with hemicrania continua and one patient with chronic cluster headache after they obtained successful pain relief with ONS.[38]

Occipital nerve stimulation: efficacy

The available data on ONS in primary headache disorders has recently been reviewed.[39] Results on ONS in refractory chronic migraine, often in the context of medication overuse, have been encouraging, with at least 50% improvement in more than 80% of patients. Encouraging but less impressive results have emerged from the ONSTIM (Occipital Nerve Stimulation for the Treatment of Intractable Migraine) trial data, which are only available in abstract form.[18] The ONSTIM trial is a prospective, multicentre, randomized, single blind, controlled feasibility study. The responder rate, defined as 50% drop in headache days per month or at least three-point drop (on a 0-10 scale) in overall pain intensity from baseline at 3-month follow-up, was 39% in refractory chronic migraine patients treated with ONS versus

8% in a control stimulation group and 0% in a medical management group. More randomized controlled trials, such as the PRISM trial, are ongoing in chronic migraine. In a retrospective series including 8 migraine patients, ongoing medication overuse was associated with a negative long-term outcome.[13]

In chronic cluster headache, a devastating condition, results have been variable, and in the two largest case series (one prospective and one retrospective), at least 50% improvement was noted in about 1/3 and 2/3 of patients respectively.[16-17] In the prospective study, a delay of 2 months or more between implantation and significant clinical improvement was noted, which suggests that ONS acts via slow neuromodulatory processes in chronic cluster headache.[17] It seems reasonable to propose a trial of occipital nerve stimulation in patients with drug-resistant chronic cluster headache before considering hypothalamic deep-brain stimulation.[40]

Hemicrania continua is characterized by an absolute response to indomethacin, but long-term use is often associated with side effects or indomethacin can be contra-indicated. More than 75 % of hemicrania continua patients have a robust response to ONS with at least 50% improvement after a mean follow-up of about a year.[19, 39]

Too few patients with paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and new daily persistent headache have been implanted to draw any conclusions.[13, 41]

As for the secondary headache disorders and cranial neuralgias, data from case reports and case series are available in chronic posttraumatic headache, chronic headache attributed to whiplash injury, cervicogenic headache, occipital neuropathic pain (ICHD-II 13.12) and occipital neuralgia.[13-14] In a retrospective case series, 8 patients with occipital neuropathic pain (ICHD-II 13.12) had an average overall percentage pain relief at long term follow-up of 80%.[13] All 8 patients experienced pain relief within a week after the start of ONS treatment, in some even within the first 24 hours. Most, but not all, of these patients reported that the

pain exacerbates very quickly, within ten minutes to one hour, after switching the stimulator off.

Occipital nerve stimulation: issues

There is a small, but growing body of evidence to support the efficacy of ONS in headache disorders. ONS should however still be considered an experimental therapy, as many questions remain unanswered yet. There are no good predictors of efficacy, including the response to occipital nerve block is not a good predictor[42] The presence of an occipital component to the pain seems to have been the rationale in the past, although this is not required based on the physiology of the trigeminocervical complex.[13] ONS has been used in many different situations, and identification of specific headache diagnoses, with a higher likelihood of responding to this modality of treatment, is required.[13] Multidisciplinary assessment of patients and clinical phenotyping of the headache syndrome, which may include an indomethacin test, is required in this respect. This requires harmonization of the classification systems of the International Association for the Study of Pain (IASP) and the IHS, which differ in many respects. Criteria for one condition may be different in the two classification systems, a typical example is occipital neuralgia. Medication overuse was associated with a less favourable outcome in migraine patients in a retrospective series.[13] It remains to be prospectively studied whether medication overuse is a predictor of negative outcome, but at present withdrawal from medication overuse is suggested prior to implantation as it may improve the patient's condition for a large part by itself.

One of the main areas of disagreement between pain physicians and neurologists is the relationship between headache and the neck. Tenderness of the occipital nerves is seen as proof of origin of pain in the neck, but it is part of the phenotype of many headache disorders, such as migraine.[43] Similarly, a response to occipital nerve block has been described in

migraine and cluster headache.[44-45] Finally, even within the ICHD-II criteria, a lack of specificity to separate migraine from cervicogenic headache has been suggested.[46]

As for the technique itself, the overall complication rate is low, however re-interventions are frequent and due to lead fracture, connector leakage, and need for battery replacement. [13] The ideal positioning of the electrodes is still debated. Unpleasant local side effects may occur such as muscle spasm, local discomfort, a shock-like sensation at the electrode site as well as slight neck stiffness. Some have suggested an electrode placement higher at or above the nuchal line to avoid muscle spasms.[26] Both traumatic and spontaneous electrode migration are frequently reported, in some series in up to 100 % of cases at three year follow-up.[11] Lead pathway changes with movement have been modeled and IPG's in sites other than the buttock, including infraclavicular or low abdomen, may be associated with lower lead migration risk.[47] Two cases of occipital lead tip erosion have been reported.[48] There is no literature to show benefit of a trial period of ONS prior to implantation, although this is commonly performed (and may be required for reimbursement). The delay to clinical efficacy is variable between conditions, and may be up to weeks or months in cluster headache,[16-17] but can be experienced within a week in occipital neuropathy (ICHD-II 13.12).[13] A different mechanism of action of ONS in both conditions seems plausible but there is no physiological explanation yet. There are some arguments in favor of implanting bilateral stimulators in unilateral headache conditions, such as cluster headache, as development of contralateral attacks has been described in cluster headache patients after unilateral implantation.[17] The optimal stimulation parameters, such as pulse width, amplitude, frequency, are now determined by trial and error, although recently systematic study has begun with the BION device.[23] There are no data to correlate paresthesia maps with clinical outcomes.[49]

Suboccipital nerve stimulation is usually accompanied by local paraesthesia, which makes the inclusion of a sham trial or a placebo arm difficult in ONS studies. Many data are gathered

from retrospective series, which are associated with more sources of error. The results of the prospective ONSTIM trial in migraine are less impressive than what has been previously reported in retrospective series.[18]

Conclusion

ONS is a promising treatment, but far from proven.[37] Some have suggested ONS is a useful tool in the treatment of chronic severe headaches with at least Level IV (limited) evidence based on AHRQ criteria.[50] Patient satisfaction is generally high and ONS may have an effect even decades after onset of a headache disorder.[13] The concept of refractory headache and its subtypes need to be further refined. A multidisciplinary approach is necessary to allow scientific evaluation of ONS on the basis of a specific headache diagnosis. This requires harmonization of existing classifications of the IASP and IHS. Withdrawal from medication overuse, especially in migraine patients, is necessary prior to implantation and may account for a large part of the improvement by itself. Prospective trials with sham control are eagerly awaited to assess the contribution of placebo effect, regression to the mean and spontaneous improvement in the observed effects. Preliminary ONSTIM trial results suggest that ONS is more effective than placebo or medical therapy, and that greater occipital nerve block may not predict response to ONS.[18] Several clinical trials of ONS for chronic migraine are now in progress (NCT00286078; NCT00747812; NCT00200109).

Despite many unresolved questions, ONS is an exciting development with a huge potential to treat our most disabled and refractory headache patients, and is currently offered on a compassionate basis as an off-label treatment.

Figure legends

Figure 1: Bilateral occipital nerve stimulators in place (Courtesy of Dr. Jean-Pierre Van Buyten, Multidisciplinary Pain Centre AZ Nikolaas, Sint-Niklaas, Belgium).

Figure 2: Schematic drawing illustrating the functional anatomy of pain-modulatory pathways in the spinal cord and supraspinal structures. Nociceptive trigeminal fibres and C2-C3 afferents synapse and converge in the trigeminal nucleus caudalis (TNC) and dorsal horns of C2 and C3. The dorsal horns C1-3 and the TNC form a functional continuum, the trigeminocervical complex (TCC), from which information is relayed to higher centers of the brain, e.g. thalamus and cortex. Nociceptive and non-nociceptive information is relayed in the spinal dorsal horn where it is subject to segmental modulatory mechanisms either intrinsic or extrinsic from descending projections. The nociceptive input is transmitted to supraspinal relay sites, and is subject to inhibitory anti-nociceptive projections by pain modulatory-circuits in the brainstem (RVM, rostral ventromedial medulla; DLPT, dorsolateral pontomesencephalic tegmentum; PAG, periaqueductal gray). Pain processing on different levels may be modulated by neurostimulation of occipital nerves.

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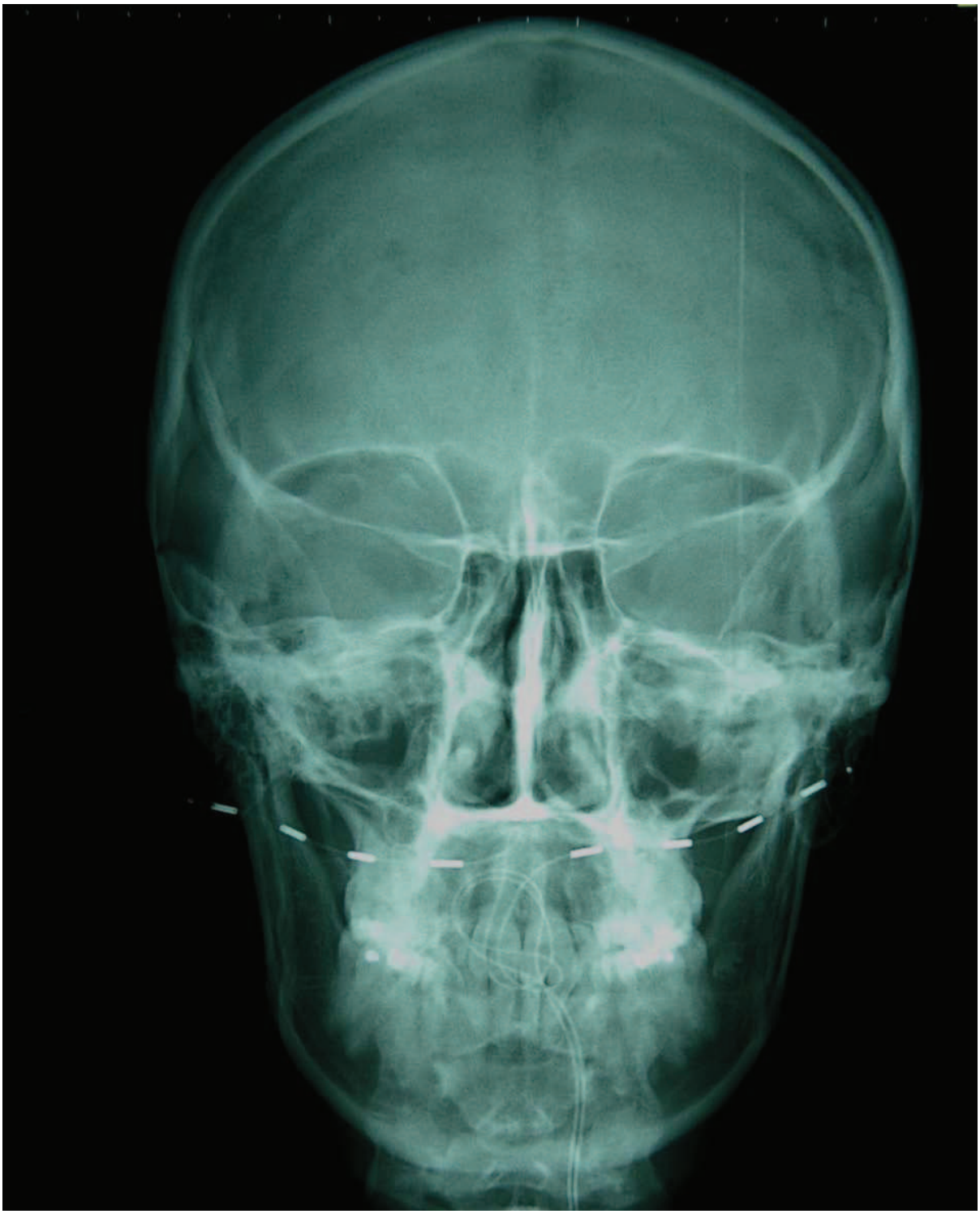

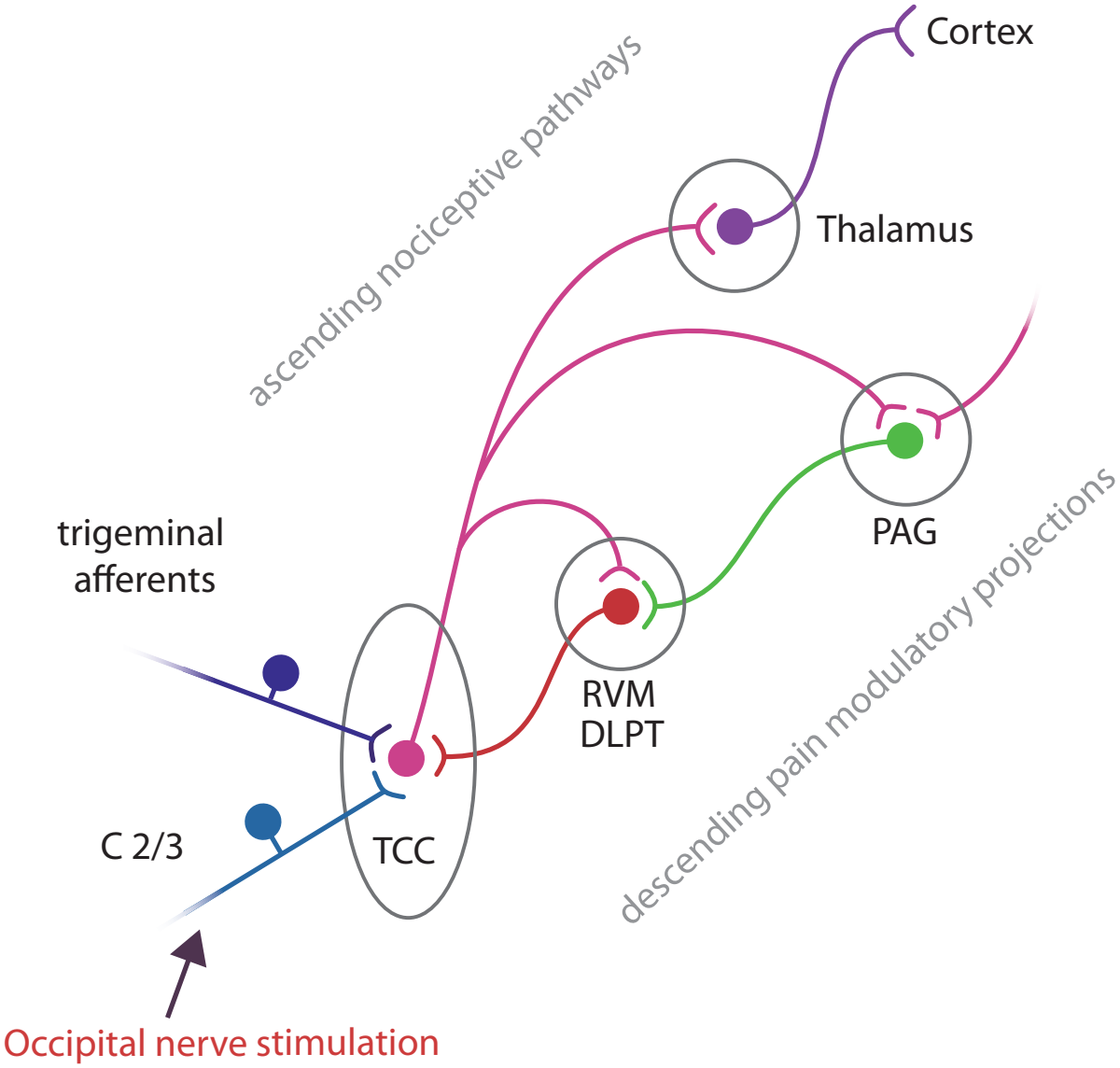
Cortex
ascending nociceptive pathways
Thalamus
PAG
trigeminal
afferents
RVM
DLPT
descending pain modulatory projections
C 2/3
TCC
Occipital nerve stimulation