Chapter 16
Neuromodulation in Classical Trigeminal Neuralgia and Painful Trigeminal Neuropathy

Turo Nurmikko and Mark Obermann

16.1 Central Neuromodulation

Central neurostimulation is mainly used to treat otherwise intractable chronic pain including trigeminal neuralgia and painful trigeminal neuropathy, but extending to many other chronic pain conditions. It is often reported effective, but the available evidence is restricted to small trials, case series or even single case reports. The different stimulation techniques used are not in any way specific to facial pain or trigeminal nerve pathology. Most studies employ the unspecific nature of these neuromodulation techniques and investigate different disorders with the only similarity of trigeminal pain or even chronic pain in parts. There are invasive (i.e. surgical) and non-invasive neuromodulation techniques with different safety profiles that have to be considered.

The rationale for central neuromodulation in trigeminal neuralgia and painful trigeminal neuropathy is sensitization of trigeminal-nociceptive pathways due to repetitive painful input, resulting in hyperexcitability of the nociceptive trigeminal system via second order wide dynamic range (WDR) neurons in lamina V of the dorsal horn and the trigeminal nerve nuclei [1]. Neuroplastic changes within the primary somatosensory cortex, insula, anterior cingulate and thalamus further support central adaptive processes that may facilitate refractory and/or chronic facial pain [2].

T. Nurmikko
Neuroscience Research Unit, The Walton Centre NHS Foundation Trust, Liverpool, UK

M. Obermann (✉)
Center for Neurology, Asklepios Hospital Seesen, Seesen, Germany

West German Headache Center, University of Duisburg-Essen, Essen, Germany
e-mail: mark.obermann@uk-essen.de

G. Lambru, M. Lanteri-Minet (eds.), *Neuromodulation in Headache and Facial Pain Management*, Headache, https://doi.org/10.1007/978-3-030-14121-9_16

16.1.1 Transcranial Magnetic Stimulation

Single pulse transcranial magnetic stimulation (sTMS) or repetitive transcranial magnetic stimulation (rTMS) were used to treat different chronic pain conditions [3, 4]. The exact location, stimulation intensity, frequency and duration widely vary throughout the different studies, making them less comparable and much harder to replicate. Optimal stimulation paradigms to achieve an optimal treatment response still need to be characterized for any particular pain condition. Repetitive TMS over the contralateral facial motor cortex was used to treat various facial pain conditions including traumatic or inflammatory trigeminal neuropathy, trigeminal neuralgia, post-stroke pain, and persistent idiopathic facial pain [3–6]. Stimulation of the motor cortex with 10 Hz over nine consecutive days in patients with persistent idiopathic facial pain showed a pain relief in 28 of 46 patients ($p < 0.001$). Patients with a mean pain history of less than 5 years showed the best treatment response [7]. A different collection of patients showed pain decreased on average at day 15 post treatment independent from the underlying disorder with a mean pain score decrease of at least 30% in 73% of patients. This response rate decreased over time, and reached a low of 40% at 180 days [3]. In a sham-controlled rTMS study using 10 min 20 Hz stimulation of the hand area of the motor cortex in 24 patients with trigeminal neuralgia over five consecutive days showed a reduction of pain scores in the real rTMS treated patients compared to controls. This treatment effect lasted 2 weeks after the last stimulation was applied [5]. One case report reported a treatment effect of rTMS in a patient with trigeminal neuralgia and failing response to previous medical and surgical therapies. This patient received a total of 35 sessions of rTMS distributed unevenly over 1 year and experienced temporal pain relief for up to 3–4 weeks following treatment [6].

Few side effects of rTMS were reported including feelings of light-headedness, temporary hearing problems, mild headaches, tingling in the face, jaw, or scalp. The relatively small risk of seizures caused by TMS has to be considered. In summary, transcranial magnetic stimulation is an effective, non-invasive, well-tolerated treatment option for otherwise intractable neuropathic pain that should be taken into consideration, but requires proper, controlled clinical trials in the future.

16.1.2 Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) modulates the cortical excitability of the stimulated cortex depending on the direction of electric current that is applied (e.g. anodal or cathodal) [8]. Its main effect is thought to be a modulation of the membrane potential of neurons [9, 10], mediated by N-methyl-D-aspartate receptors (NMDA-R) [11]. tDCS applied cortical excitability can spread to distant brain areas possibly along interconnections between the stimulated and adjacent regions [12]. Anodal tDCS is mainly used to reduce pain perception in different disorders [8].

Ten patients with classical trigeminal neuralgia (mean age 63 years (range: 49–82 years)) were stimulated daily for 20 min over 2 weeks using anodal (1 mA)

or sham tDCS over the primary motor cortex (M1) in a randomized double-blind cross-over design. The impact on trigeminal pain processing was assessed with pain-related evoked potentials (PREP) and the nociceptive blink reflex (nBR) following electrical stimulation on both sides of the forehead before and after tDCS. Anodal tDCS reduced pain intensity significantly after 2 weeks of treatment by 18% (±SD 29%), while sham stimulation led to an 11% (±30.8%) increase of VAS. The attack frequency reduction was not significant. PREP showed an increased N2 latency and decreased peak-to-peak amplitude after anodal tDCS. TN patients with concomitant persistent facial pain did not respond to tDCS treatment [1]. A different study included 21 patients with different chronic pain conditions such as trigeminal neuralgia, post stroke pain, back pain, and fibromyalgia with tDCS treatment over five consecutive days. A positive effect on pain intensity was demonstrated, that persisted for at least 1 month [13]. Ten patients with secondary trigeminal neuralgia after oral surgery were treated over five consecutive days with good response to the stimulation [14]. Side effects of tDCS included headache, fatigue and itching around the electrode placement. Many older patients found it difficult to handle the tDCS device at home, which may limit its clinical application [1]. Further studies on the application site, frequency and stimulation paradigm need to follow before this non-invasive, elegant treatment option can be fully recommended.

16.1.3 Motor Cortex Stimulation

Invasive, intracranial motor cortex stimulation (MCS) requires the surgical placement of electrodes through a burr hole into the epidural space at the contralateral motor strip. In theory, stimulation then causes corticocortical feedback with inhibition of overactive nociceptive neurons in the sensory cortex and subsequent pain reduction [15].

Several studies testing MCS on patients with trigeminal neuropathic pain and trigeminal neuralgia were reported with sufficient pain relief in most patients ranging between 50% and 88% [16–18]. Most authors considered a >50% reduction of pain relief as effective. A case series that included four patients with trigeminal neuralgia and one with persistent idiopathic facial pain reported a decrease of pain intensity on a visual analogue scale (VAS) of 4.10, $p < 0.02$) at 3 months following MCS placement [16]. Patients with anaesthesia dolorosa had better outcome in this study. Other studies report anaesthesia dolorosa as risk factor of worse outcome, however [18]. A different study on invasive MCS investigated 36 patients with chronic trigeminal neuropathic pain and reported a significant pain reduction in 26 patients (72%) with a reduction of mean pain from 8.11 to 4.58 ($p < 0.05$) on a visual analogue scale (VAS) over a mean observational period of 5.6 years [15].

Treatment effects were described directly following surgery and lasting up to a mean of 3.6 years after the initial procedure demonstrating a sustained pain relief in successfully treated patients [19]. Adverse events were infection, epidural hematoma, and seizures (intra- and perioperatively) making this invasive treatment technique a feasible option that requires careful consideration of possible less invasive alternatives.

16.1.4 Deep Brain Stimulation

Treating pain with deep brain stimulation (DBS) first came up in the 1950s [20]. DBS is an invasive surgical technique where electrodes are placed intracranially to stimulate subcortical targets such as the sensory thalamus (ventral posterior lateral and medial), the periaqueductal (PAG) and periventricular grey (PVG), the hypothalamus, and the anterior cingulate cortex [21–23]. The exact pathophysiological mechanisms why DBS is effective in some chronic pain conditions remains unclear, despite the well-described pain transmission pathways. It is generally considered to be the last resort for the treatment of neuropathic pain, but may be beneficial for well-selected otherwise untreatable patients. Trigeminal neuropathy secondary to multiple sclerosis was treated with DBS to the hypothalamus. All five patients showed pain relief following DBS in the first division of the trigeminal nerve, but three patients had recurrence of pain in the second or third divisions at different time points after the procedure [22]. A meta-analysis on a multitude of chronic pain conditions evaluated the effectiveness of different stimulation sites with regard to pain character. In summary, sensory thalamic stimulation or stimulation of the PVG/PAG was more effective to treat patients with nociceptive pain (63%), while 47% of patients with deafferentation/neuropathic pain achieved long-term pain control [23]. Tolerance to the stimulation may occur in patients after several years leading to attenuation of the treatment effect. This may be resolved with changes in the stimulation settings or pause intervals without any stimulation. Some stimulators use smart adaptive stimulation paradigms to automatically counteract on this tolerance phenomenon [24].

The potential for adverse events including death and the invasive nature of this procedure limit its use to otherwise treatment refractory and very disabled patients with trigeminal neuropathy preferably secondary to multiple sclerosis and with pain in the first division of the trigeminal nerve.

16.1.5 High-Frequency Spinal Cord Stimulation

Spinal cord stimulation (SCS) applies mild electric currents to the spinal cord through small electrodes placed in the epidural space near the targeted region. It is considered an ambulatory, minimally invasive surgical technique that was first developed in the 1960s. The patient will receive a temporary externalized SCS system, and if pain is reduced within the first 4 weeks by at least 50% the system will be implanted [25].

Spinal cord stimulation (SCS) in the high cervical (C1–2) region are based on prior studies on lesioning procedures of the nucleus caudalis dorsal root entry zone. However, evidence for successful therapy with SCS in patients with facial pain is controversial. Barolat et al. [26] reported the successful treatment of one left-sided trigeminal neuralgia patient with symptomatic TN due to multiple scle-

rosis. A different study on 41 patients with intractable upper limp and face pain reported that those patients with facial pain explicitly did not respond to high-frequency SCS with 10 kHz [27]. Cervicomedullary junction spinal cord stimulation was suggested effective in a retrospective analysis of patients with trigeminal neuropathic pain, post-herpetic neuralgia, trigeminal deafferentiation pain, occipital neuralgia, and post-stroke facial pain, while patients with occipital neuralgia did not respond to this particular stimulus location [27–29]. At the moment, spinal cord stimulation will require more properly controlled investigations before any treatment recommendation can be made for trigeminal neuralgia or painful trigeminal neuropathy.

16.2 Peripheral Neuromodulation

16.2.1 Trigeminal (Gasserian) Ganglion Stimulation

Promising early experience with deep brain stimulation, on the one hand, and transcutaneous nerve stimulation (TENS), on the other hand, led to a proposal that direct stimulation of the trigeminal ganglion and its rootlets could also alleviate chronic facial pain with acceptable risk and effectiveness [30, 31]. In the early years, improvisation was needed as no electrode designed for the purpose was available, although leads, receiver and later implantable pulse generators were available for spinal cord stimulation and deep brain stimulation. Although inspired by the Gate Control theory, the development of the methods has been on an empirical basis, with the main focus on technical demands and less so on mechanisms of action. It was shown, however, that trigeminal ganglion stimulation suppresses experimental pain-related cortical evoked potentials in patients with trigeminal neuropathy and increases their pain threshold in the dermatome being stimulated [32]. A PET study of ten patients revealed an increase of activation in ipsilateral rostral anterior cingulate cortex (ACC) and reduction in caudal ACC following 30 min of ganglion stimulation [33]. This is consistent with the generally accepted concept of the essential role of rostral ACC in pain modulation and that of caudal ACC in encoding pain [33].

Both craniotomy-based and percutaneous techniques have been in use since the late 1970s. Using an extradural subtemporal route, Meyerson and Håkansson [30] implanted a purpose built bipolar electrode consisting of two small platinum discs mounted on a silicone rubber strip which was sutured to the dura lying over Meckel's cave for permanent stimulation. Trial stimulation was carried out over some days to ensure pain relief is sufficient to warrant internalization. In positive cases, an extension lead was added and connected to the IPG placed under the clavicle. Prior to their craniotomy, four of the patients were successfully trialled using a percutaneous monopolar lead introduced to Meckel's cave, while seven more failed the test. A similar method was adopted by Lazorthes et al. [34] and Taub et al. [35].

The percutaneous method involves the introduction of a monopolar electrode into Meckel's cave using the Härtel method [32]. First introduced by Steude and

coworkers in the 1980s, the method has been improved over the years with the adoption of EM guidance as well as the 0.9 mm diameter electrode with an angled tip [36, 37]. Advocates of this method consider it as the 'gold standard', as it does not require a craniotomy, and is safe and effective in a significant percentage of patients.

Both open and percutaneous ganglion stimulations are almost exclusively used for chronic painful trigeminal neuropathy and persistent idiopathic facial pain. Diagnoses range from painful trigeminal neuropathy of various aetiologies (e.g. PHN, posttraumatic neuropathy) to idiopathic facial pain conditions (e.g. post sinus or dental surgery). Neither intervention is used for uncomplicated trigeminal neuralgia.

Meyerson and Håkansson [30] reported a good outcome in 11 of 14 patients who underwent open implantation at a follow-up of 1–7 years. Of note, following a percutaneous trial stimulation of the ganglion, 65% were not considered candidates for the permanent implant. A similar approach was chosen by Lazorthes et al. [34] who trialled 21 patients with a percutaneous lead and only found five suitable for a permanent implant: three underwent the open procedure with two of them reporting a good outcome at 18 and 30 months. Taub et al. [35] subjected 34 patients with chronic trigeminal neuropathy to a percutaneous trial, 22 of whom received a permanent implant with 10 reporting benefit at a mean follow-up of 22 months. In total, of 76 patients reported in these three case series, 23 (30%) benefited long term. Complications included infection and technical breakdowns requiring replacement of the system and transient cranial nerve dysfunction. It appears that this method never became popular and over time was replaced by percutaneous trigeminal ganglion stimulation. Only recently, a modest response was reported in three patients with trigeminal neuropathy when used in conjunction with sphenopalatine stimulation [38].

Percutaneous Gasserian ganglion stimulation that avoids the need for open craniotomy has seen technical improvements over the years, with adoption of a custom-made electrode and guidance of the implantation procedure with a 3-D real-time electromagnetic navigation system [37]. The largest case series published to date includes 321 patients; long-term (5–25 years) follow-up is available for 235 patients. Sustained pain relief (>50%) was reported by 58% [32]. Results from two small case series are similar, but based on a shorter follow-up. Young [39] reported a >50% improvement in facial pain in 52% at a follow-up ranging from 12 to 45 months. Kustermans et al. [37] reported 'some benefit' in 46% at 24-month follow-up. As with the craniotomy approach, a percutaneous trial is used to identify likely long-term responders with the rate of responders varying 52–100% between centres. This was lowest in the large case series [32] and may reflect a more stringent selection criterion. Reported complications vary substantially—while Mehrkens and Steude [32] saw an occasional local uncomplicated infection in their large case series, Kustermans et al. [37] reported some form of complication in 82%. It should be stated, however, that the latter authors listed various forms of physical discomfort from the system as well a mechanical malfunction and dislocation of the system that will have inflated their numbers. Of interest, intraoral erosion was seen in four of their patients, requiring reimplantation. Post-herpetic neuralgia appears resistant to trigeminal ganglion stimulation, irrespective of the method used [32, 40].

16.2.2 Peripheral Nerve Field Stimulation

The first description of percutaneous peripheral nerve stimulation for facial pain appears from Wall and Sweet [41]. Among their eight patients with variable, mostly neuropathic pain conditions, there was a 62-year-old man with trigeminal neuralgia, whose infraorbital nerve was stimulated using a pair of wires in a G22 hypodermic needle placed at the infraorbital foramen. During electrical stimulation that was sufficient to elicit some paraesthesia, no pain paroxysm could be evoked by brushing the trigger zone in the patient's hard palate. Case series soon followed taking advantage of existing stimulators designed for spinal cord stimulation, tunnelled subcutaneously and horizontally both supraorbitally and infraorbitally and connected to an implantable pulse generator (IPG) [42, 43]. The relatively promising early results did not, however, lead to an extensive adoption of the method and only a few other case series have since appeared in literature [44]. No controlled trials have been published.

In this method, the stimulating electrode is introduced into the subcutaneous space from a small incision below the hairline either above or below zygoma and guided by a bent Tuohy needle. The electrode is pushed gently along a horizontal trajectory to lie above or below the orbit, depending on primary pain area. Two electrodes are required to be tunnelled separately if the pain includes both the ophthalmic and maxillary divisions of the trigeminal nerve. Stimulation of the mandibular division is rarely used due to concerns of electrode migration caused by jaw movement. The electrodes cross the nerve trunk and many of the branches of each nerve, rather than are placed next to a nerve as in ordinary peripheral nerve stimulation. (Note that when stimulating the mandibular nerve, Klein et al. [45] placed the electrode so that it would target the branches of the mandibular nerve only). The lead is secured with a fixation anchor to skin or fascia [44–46] or directly sutured to the fascia at the temporal incision site [44]. After trial stimulation, the system is internalised in responders with an extension lead connected to an IPG placed on the abdominal or chest wall. Trial stimulation using an external stimulator for several days is routine; 38–90% are selected for permanent stimulation, and no demographic or clinical features are predictive.

Painful trigeminal neuropathy is the main indication for this method, although some groups have also experimented it in patients with other conditions, including headache and trigeminal neuralgia [45, 46]. Given the availability of many other treatments with a substantial record of success in the latter conditions, it must be assumed that it is used only exceptionally for the latter conditions. However, for trigeminal neuropathy that notoriously lacks effective treatment, percutaneous peripheral nerve stimulation appears a promising approach. In open-label small cohort studies, albeit all retrospective, the majority of patients report substantial (>50%) long-term pain relief with low levels of adverse events (Table 16.1).

Although generally well tolerated, lead-associated skin erosion, local infection and discomfort associated with IPG are relatively common adverse effects. Ellis et al. [44] reported the need for surgical revision in one-half of their patients with a mean follow-up of 15 months. Recently, wireless systems and miniature-sized implants have been

Table 16.1 Peripheral nerve field stimulation for trigeminal nerve pain (published case series ($N = \geq 3$), 2004–2016)

Authors	Study type	Number trial stimulations	Number permanent implants	Overall efficacy	Responder (>50% pain relief)	Follow-up	Revision surgery/ removal	Major complications
Johnson and Burchiel [42]	Case series	11	10	n/a	70%	24 months	2	Wound breakdown (2), discomfort with extension lead (1)
Slavin et al. [54]	Case series	15	9	n/a	56%	Mean, 44 months	3	Wound breakdown, local infection
Stidd et al. [55]	Case series	3	3	60–100%	100%	6–27 months	1	Electrode migration
Feletti et al. [47]	Case series	4	4	56–100%	100%	12–32 months	1	Infection (1)
Ellis et al. [44]	Case series	28	13	72% 'improved'	n/a	Mean, 15 months (0.5–55 months)	12	Electrode/extension lead malfunction (12)
Klein et al. [45]	Case series	10	8	57–100%	100%	Mean 11 months (5–28 months)	2	Electrode malfunction (1), wound breakdown
Jakobs et al. [46]	Case series	8	7	50–100%	100%	Mean 15 months (6–29 months)	1	Infection (1)

developed but their application to facial pain and long-term effectiveness have not been established. To date, they have not become mainstream treatment [48, 49].

16.2.3 Other Neuromodulation

Non-invasive vagal stimulation showed reduction of allodynia in a rodent model of trigeminal neuropathic pain [50], but to date, there are no published clinical trials in humans. By contrast, invasive vagal stimulation for epilepsy is rarely associated with the development of trigeminal nerve pain [51]. No trials or case series have been published on the use of sphenopalatine ganglion stimulation despite its efficacy in cluster headache. A beneficial effect on painful trigeminal neuropathy from occipital stimulation has been anecdotally reported [47, 52]. Although transcutaneous nerve stimulation has been used for neuropathic pain in general, no systematic studies have appeared in literature supporting its use, and in the authors' experience, any limited effectiveness is offset by the unpleasantness of the need to apply the electrodes on the skin of the face. While acupuncture for trigeminal nerve pain is widely practised in many countries, a review of ten clinical trials, all published in Chinese, was criticized for poor methodological quality [53].

16.3 Discussion

Several neuromodulation methods ranging from non-invasive applications to those requiring major surgery have been described for the treatment of painful trigeminal neuropathy—less so for trigeminal neuralgia. In special circumstances, for example, recurrent trigeminal neuralgia after neuroablative procedures or microvascular decompression, or in patients with inoperable middle or posterior fossa tumour or MS, they may offer a reasonable option [46]. Problematically, to date, all evidence for the efficacy of neuromodulation in trigeminal nerve pain comes from low-quality studies, that is, mostly retrospective small case series. Nevertheless, years of experience involving patients with disabling facial pain refractory to other treatments should not be discounted. Mini-invasive neuromodulation (peripheral nerve and trigeminal ganglion stimulation) appears to provide similar long-term pain relief as invasive central neuromodulation with lesser risk and may therefore be considered as a preferential treatment in trigeminal neuropathy. In disabled patients who fail to respond to this treatment, invasive central neuromodulation (DBS, MCS) remains an option. Non-invasive interventions (TMS, tDCS) show short-term effectiveness but long-term data are virtually non-existent and therefore they should be offered only as part of a research study.

For peripheral neuromodulation, technological advances may facilitate adoption of new methods more widely than to date. Miniature-sized electrodes implanted percutaneously next to a nerve under ultrasound control will simplify surgery.

Wireless systems have been developed to obviate the need for implantable IPGs. Non-invasive methods similarly are undergoing development; high-definition tDCS systems designed for home use with internet-based feedback controls will drastically reduce visits to the clinic. Whether or not these new methods become mainstream must, however, be based on outcomes from adequately powered controlled studies designed for well-defined craniofacial pain conditions.

References

1. Hagenacker T, Bude V, Naegel S, Holle D, Katsarava Z, Diener H-C, Obermann M. Patient-conducted anodal transcranial direct current stimulation of the motor cortex alleviates pain in trigeminal neuralgia. J Headache Pain. 2014;15:78.
2. Pradier B, Shin HB, Kim DS, St Laurent R, Lipscombe D, Kauer JA. Long-term depression induced by optogenetically driven nociceptive inputs to trigeminal nucleus caudalis or headache triggers. J Neurosci. 2018;38(34):7529–40.
3. Hodaj H, Alibeu J-P, Payen J-F, Lefaucheur J-P. Treatment of chronic facial pain including cluster headache by repetitive transcranial magnetic stimulation of the motor cortex with maintenance sessions: a Naturalistic Study. Brain Stimul. 2015;8:801–7.
4. Lipton RB, Dodick DW, Silberstein SD, Saper JR, Aurora SK, Pearlman SH, Fischell RE, Ruppel PL, Goadsby PJ. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. Lancet Neurol. 2010;9:373–80.
5. Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Long-lasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry. 2005;76:833–8.
6. Zaghi S, DaSilva AF, Acar M, Lopes M, Fregni F. One-year rTMS treatment for refractory trigeminal neuralgia. J Pain Symptom Manag. 2009;38:e1–5.
7. Lawson McLean A, Frank S, Zafar N, Waschke A, Kalff R, Reichart R. Time course of the response to navigated repetitive transcranial magnetic stimulation at 10 Hz in chronic neuropathic pain. Neurol Res. 2018;40(7):564–72.
8. Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, Paulus W, Hummel F, Boggio PS, Fregni F, Pascual-Leone A. Transcranial direct current stimulation: state of the art 2008. Brain Stimul. 2008;1:206–23.
9. Bindman LJ, Lippold OC, Redfearn JW. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J Physiol. 1964;172:369–82.
10. Creutzfeldt OD, Fromm GH, Kapp H. Influence of transcortical d-c currents on cortical neuronal activity. Exp Neurol. 1962;5:436–52.
11. Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain J Neurol. 2002;125:2238–47.
12. Lang N, Siebner HR, Ward NS, Lee L, Nitsche MA, Paulus W, Rothwell JC, Lemon RN, Frackowiak RS. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? Eur J Neurosci. 2005;22: 495–504.
13. Antal A, Terney D, Kühnl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. J Pain Symptom Manag. 2010;39:890–903.
14. Fricova J, Englerova K, Rokyta R. Noninvasive transcranial direct current stimulation (tDCS) for the treatment of orofacial pain. Neuro Endocrinol Lett. 2016;37:368–72.

15. Rasche D, Ruppolt M, Stippich C, Unterberg A, Tronnier VM. Motor cortex stimulation for long-term relief of chronic neuropathic pain: a 10 year experience. Pain. 2006;121:43–52.
16. Buchanan RJ, Darrow D, Monsivais D, Nadasdy Z, Gjini K. Motor cortex stimulation for neuropathic pain syndromes: a case series experience. Neuroreport. 2014;25:715–7.
17. Lefaucheur J-P, Drouot X, Cunin P, Bruckert R, Lepetit H, Créange A, Wolkenstein P, Maison P, Keravel Y, Nguyen J-P. Motor cortex stimulation for the treatment of refractory peripheral neuropathic pain. Brain J Neurol. 2009;132:1463–71.
18. Raslan AM, Nasseri M, Bahgat D, Abdu E, Burchiel KJ. Motor cortex stimulation for trigeminal neuropathic or deafferentation pain: an institutional case series experience. Stereotact Funct Neurosurg. 2011;89:83–8.
19. Kolodziej MA, Hellwig D, Nimsky C, Benes L. Treatment of central deafferentation and trigeminal neuropathic pain by motor cortex stimulation: report of a series of 20 patients. J Neurol Surg A Cent Eur Neurosurg. 2016;77:52–8.
20. Deer TR, Mekhail N, Petersen E, Krames E, Staats P, Pope J, Saweris Y, Lad SP, Diwan S, Falowski S, Feler C, Slavin K, Narouze S, Merabet L, Buvanendran A, Fregni F, Wellington J, Levy RM, Neuromodulation Appropriateness Consensus Committee. The appropriate use of neurostimulation: stimulation of the intracranial and extracranial space and head for chronic pain. Neuromodulation Appropriateness Consensus Committee. Neuromodulation. 2014;17:551–70.
21. Hosobuchi Y, Adams JE, Linchitz R. Pain relief by electrical stimulation of the central gray matter in humans and its reversal by naloxone. Science. 1977;197:183–6.
22. Kumar K, Toth C, Nath RK. Deep brain stimulation for intractable pain: a 15-year experience. Neurosurgery. 1997;40:736–47.
23. Nandi D, Smith H, Owen S, Joint C, Stein J, Aziz T. Peri-ventricular grey stimulation versus motor cortex stimulation for post stroke neuropathic pain. J Clin Neurosci. 2002;9:557–61.
24. Boccard SGJ, Prangnell SJ, Pycroft L, Cheeran B, Moir L, Pereira EAC, Fitzgerald JJ, Green AL, Aziz TZ. Long-term results of deep brain stimulation of the anterior cingulate cortex for neuropathic pain. World Neurosurg. 2017;106:625–37.
25. Simpson BA, Bassett G, Davies K, Herbert C, Pierri M. Cervical spinal cord stimulation for pain: a report on 41 patients. Neuromodulation. 2003;6:20–6.
26. Barolat G, Knobler RL, Lublin FD. Trigeminal neuralgia in a patient with multiple sclerosis treated with high cervical spinal cord stimulation. Case report. Appl Neurophysiol. 1988;51:333–7.
27. Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, Amirdelfan K, Morgan DM, Brown LL, Yearwood TL, Bundschu R, Burton AW, Yang T, Benyamin R, Burgher AH. Novel 10-kHz high-frequency therapy (HF10 Therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: the SENZA-RCT randomized controlled trial. Anesthesiology. 2015;123:851–60.
28. North RB, Kidd D, Shipley J, Taylor RS. Spinal cord stimulation versus reoperation for failed back surgery syndrome: a cost effectiveness and cost utility analysis based on a randomized, controlled trial. Neurosurgery. 2007;61:361–9.
29. Tomycz ND, Deibert CP, Moossy JJ. Cervicomedullary junction spinal cord stimulation for head and facial pain. Headache. 2011;51:418–25.
30. Meyerson BA, Håkanson S. Suppression of pain in trigeminal neuropathy by electric stimulation of the gasserian ganglion. Neurosurgery. 1986;18:59–66.
31. Meyerson BA, Håkansson S. Alleviation of atypical trigeminal pain by stimulation of the Gasserian ganglion via an implanted electrode. Acta Neurochir Suppl (Wien). 1980;30:303–9.
32. Mehrkens JH, Steude U. Chronic electrostimulation of the trigeminal ganglion in trigeminal neuropathy: current state and future prospects. Acta Neurochir Suppl (Wien). 2007;97:91–7.
33. Willoch F, Gamringer U, Medele R, Steude U, Tölle TR, PET Activation Study. Analgesia by electrostimulation of the trigeminal ganglion in patients with trigeminopathic pain: a PET activation study. Pain. 2003;103:119–30.
34. Lazorthes Y, Armengaud JP, Da Motta M. Chronic stimulation of the Gasserian ganglion for treatment of atypical facial neuralgia. Pacing Clin Electrophysiol. 1987;10:257–65.

35. Taub E, Munz M, Tasker RR. Chronic electrical stimulation of the gasserian ganglion for the relief of pain in a series of 34 patients. J Neurosurg. 1997;86:197–202.
36. Buyten J-P, Linderoth B. Invasive neurostimulation in facial pain and headache syndromes. Eur J Pain Suppl. 2011;5:409–21.
37. Kustermans L, Van Buyten J-P, Smet I, Coucke W, Politis C. Stimulation of the Gasserian ganglion in the treatment of refractory trigeminal neuropathy. J Craniomaxillofac Surg. 2017;45:39–46.
38. William A, Azad TD, Brecher E, Cherry T, Bernstein I, Bruce DM, Rohrer S, Smith Z, William M, Sabelman E, Heit G, Pezeshkian P, Sedrak M. Trigeminal and sphenopalatine ganglion stimulation for intractable craniofacial pain--case series and literature review. Acta Neurochir. 2016;158:513–20.
39. Young RF. Electrical stimulation of the trigeminal nerve root for the treatment of chronic facial pain. J Neurosurg. 1995;83:72–8.
40. Holsheimer J. Electrical stimulation of the trigeminal tract in chronic, intractable facial neuralgia. Arch Physiol Biochem. 2001;109:304–8.
41. Wall PD, Sweet WH. Temporary abolition of pain in man. Science. 1967;155:108–9.
42. Johnson MD, Burchiel KJ. Peripheral stimulation for treatment of trigeminal postherpetic neuralgia and trigeminal posttraumatic neuropathic pain: a pilot study. Neurosurgery. 2004;55:135–42.
43. Slavin KV, Wess C. Trigeminal branch stimulation for intractable neuropathic pain: technical note. Neuromodulation. 2005;8:7–13.
44. Ellis JA, Mejia Munne JC, Winfree CJ. Trigeminal branch stimulation for the treatment of intractable craniofacial pain. J Neurosurg. 2015;123:283–8.
45. Klein J, Sandi-Gahun S, Schackert G, Juratli TA. Peripheral nerve field stimulation for trigeminal neuralgia, trigeminal neuropathic pain, and persistent idiopathic facial pain. Cephalalgia. 2016;36:445–53.
46. Jakobs M, Unterberg A, Treede R-D, Schuh-Hofer S, Ahmadi R. Subcutaneous trigeminal nerve field stimulation for refractory trigeminal pain: a cohort analysis. Acta Neurochir. 2016;158:1767–74.
47. Feletti A, Santi GZ, Sammartino F, Bevilacqua M, Cisotto P, Longatti P. Peripheral trigeminal nerve field stimulation: report of 6 cases. Neurosurg Focus. 2013;35:E10.
48. Herschkowitz D, Kubias J. Wireless peripheral nerve stimulation for complex regional pain syndrome type I of the upper extremity: a case illustration introducing a novel technology. Scand J Pain. 2018;18:555–60.
49. Weiner RL, Garcia CM, Vanquathem N. A novel miniature, wireless neurostimulator in the management of chronic craniofacial pain: preliminary results from a prospective pilot study. Scand J Pain. 2017;17:350–4.
50. Oshinsky ML, Murphy AL, Hekierski H, Cooper M, Simon BJ. Noninvasive vagus nerve stimulation as treatment for trigeminal allodynia. Pain. 2014;155:1037–42.
51. Timarova G, Šteňo A. Late-onset jaw and teeth pain mimicking trigeminal neuralgia associated with chronic vagal nerve stimulation: case series and review of the literature. BMC Neurol. 2017;17:113.
52. Fontaine D, Bozzolo E, Chivoret N, Paquis P, Lanteri-Minet M. Salvage treatment of trigeminal neuralgia by occipital nerve stimulation. Cephalalgia. 2014;34:307–10.
53. Liu H, Li H, Xu M, Chung K-F, Zhang SP. A systematic review on acupuncture for trigeminal neuralgia. Altern Ther Health Med. 2010;16:30–5.
54. Slavin KV, Colpan ME, Munawar N, Wess C, Nersesyan H. Trigeminal and occipital peripheral nerve stimulation for craniofacial pain: a single-institution experience and review of the literature. Neurosurg Focus. 2006;21(6):E5.
55. Stidd DA, Wuollet AL, Bowden K, Price T, Patwardhan A, Barker S, Weinand ME, Annabi J, Annabi E. Peripheral nerve stimulation for trigeminal neuropathic pain. Pain Physician. 2012;15(1):27–33.