Use of Cortical Stimulation in Neuropathic Pain, Tinnitus, Depression, and Movement Disorders

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Published online: 3 June 2014

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Abstract Medical treatment must strike a balance between benefit and risk. As the field of neuromodulation develops, decreased invasiveness, in combination with maintenance of efficacy, has become a goal. We provide a review of the history of cortical stimulation from its origins to the current state. The first part discusses neuropathic pain and the nonpharmacological treatment options used. The second part covers transitions to tinnitus, believed by many to be another deafferentation disorder, its classification, and treatment. The third part focuses on major depression. The fourth section concludes with the discussion of the use of cortical stimulation in movement disorders. Each part discusses the development of the field, describes the current care protocols, and suggests future avenues for research needed to advance neuromodulation.

Key Words Cortical stimulation · neuropathic pain · depression · tinnitus · movement disorders

Introduction

Medical treatment must strike a balance between benefit and risk, efficacy and invasiveness. Few other fields illustrate this conundrum as well as neuromodulation. Reliance on chemical treatment, with a multitude of side effects, forced the development of alternate methods [1]. Nonpharmacological treatments of neurologic disorders include deep brain stimulation

(DBS), epidural cortical stimulation (ECS), and transcranial magnetic stimulation (TMS).

As technology, including delivery systems and imaging techniques, improved over the last century, the field has been able to maintain the efficacy of treatment while decreasing the invasiveness of the procedures in several key areas of neuromodulation. In this chapter we will review the history of cortical stimulation and advancements in treatment of neuropathic pain, tinnitus, depression, and movement disorders.

Neuropathic Pain

Pain out of proportion to the external stimuli or chronic pain without stimuli loses its evolutionary advantage, thus becoming an incredible burden to the patient. At costs exceeding \$US600 billion annually, chronic pain has been labeled a major health priority, affecting more of the population than diabetes, cancer, and heart disease combined [2]. The disorder is detrimental to physical and psychological wellbeing, worsening outcomes of many other concomitant diseases and increasing suicide attempts 2-fold [3, 4].

While medical treatment remains the first-line therapy for pain, electrical modulation of the nervous system has been used for centuries. As mentioned by Whitaker et al. [5] and Schwalb and Hamani [6], *Torpedo nobiliana*, the dark electric ray inhabiting the Atlantic Ocean, was suggested as a treatment of headache and gout by 1st-century CE Romans. The ancient remedies, and most of the treatments that followed, have by and large preceded the theories that would eventually explain the beneficial effects.

The ancient dogma of the brain being an inert and homogeneous organ, prevalent for 2 millennia, delayed the research in the field of cortical stimulation [7]. Such belief was supported by well-intended, but poorly designed experiments continuing into the 1860s. The work of Pierre Flourens and

Electronic supplementary material The online version of this article (doi:10.1007/s13311-014-0283-0) contains supplementary material, which is available to authorized users.

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other notable physiologists, in part on pigeons, used cortical stimulation and ablation. These studies failed to evoke muscle twitching and seemed to support the equipotential nature of the brain [8].

The credit for the first successful cortical stimulation in humans is given to Giovanni Aldini (1762–1834), who, in 1802, was able to elicit contralateral facial grimace by electrical stimuli applied to recently beheaded prisoners [9]. The work on motor pathways by Luigi Rolando in the early 19th century and the publications of Paul Broca in language center localization [10] from 1861 onwards continued the debate against the dogma of the inert brain.

The first widely accepted report of cortical stimulation in alive mammals occurred in 1870 with the seminal canine experiments of Gustav Fritsch and Eduard Hitzig [11]. The ability to produce graded motion of the limbs by varying the intensity of cortical electrical stimulation led to attempted experiments in humans.

By 1874, Roberts Bartholow reported successful stimulation in a 33-year-old woman dying of an erosive skull cancer. It is debated whether, owing to the depth of the needles inserted, the physician was actually stimulating the corticobulbar fibers of the post central gyrus, or the subcortical structures of the caudate nucleus and thalamus. Bartholow's distinction is also dubious due to the rapid progression from electrical stimulation to likely status epilepticus, eventual coma, and death of the patient several days later [9].

The work of such notable scientists as Hugliing Jackson, Sir Victor Horsley, and Wilder Penfield throughout the late 19th and early 20th centuries continued to advance the field by developing intraoperative electrocorticography, and mapping the motor and sensory homunculus [12].

Horsley, the famed British surgeon, is credited with the first symptomatic relief via neuromodulation of the cortex in humans. As in many other surgical fields, his first attempts were ablative procedures. These surgeries, carried out in the 1890s, disrupted the pyramidal system at the cortex, and, while providing some relief from pathologic movements, also left the patients with a significant paresis [6].

In 1960, almost 100 years after the experiments of Hitzig and Fritsch, Heath and Mickle introduced the concept of DBS in treatment of chronic pain [13–15]. While beyond the scope of this article, DBS was born out of cortical stimulation and now provides an invaluable treatment option to numerous patients. Yet early DBS procedures were costly, with morbidity rates approaching 20 % [1]. Some categories of chronic pain, thalamic pain syndromes in particular, seemed resistant to DBS, with significant improvement in only 20–30 % of cases treated with thalamic relay nucleus stimulation [16].

The return from the depths of the brain to the cortex for treatment of chronic pain occurred in the early 1990s, and continued the trend of decreasing the invasiveness while maintaining efficacy.

In 1991, Tsubokawa et al. [17] applied earlier studies of cats with deafferented spinothalamic tracts, and showed that ECS of the motor strip could cause long-term inhibition of the hyperactive thalamic neurons in humans. Pain control was reported as excellent or good in all 7 cases without morbidity. The source of the stimulation was placed intracranially yet extradurally, thereby decreasing the possibility of cortical injury.

In 1993, the follow-up experiment by same group showed that consistent pain relief was achieved in 5/11 patients at 2 years [18]. The level of stimulation needed to inhibit chronic pain was below that of producing contractions in the corresponding muscles, with some patients reporting only mild tingling or slight vibration in the previously painful areas.

The same year, Meyerson et al. [19] backed up the findings of Tsubokawa et al., with 5/10 patients improving with epidural cortical stimulation, with all responders having preoperative uncontrolled trigeminal neuropathic pain. The 5 non-responders included sufferers of chronic central pain after strokes and peripheral nerve injuries. The likely explanation at the time was the wide area of facial representation in the human cortex, making the targeting in those cases easier.

In 1998, Katayama et al. [20] went on to suggest that in poststroke pain syndromes the outcomes from cortical stimulation were significantly better if the strength deficit in the painful extremity was mild or absent, presumably owing to intact corticospinal tracts from the area of stimulation to the area of pain.

According to Lima and Fregni [21], > 1400 publications have dealt with the subject of cortical stimulation for pain with the consensus opinion for its benefit. Up to 70 % of patients reported the willingness to undergo ECS again to treat their pain [22].

Continuing reports of the benefits of cortical stimulation in chronic pain combined with improvement in imaging and, therefore, targeting, prompted an investigation into less invasive methods of stimulation such as TMS.

TMS uses coils placed on the surface of the patient's head to create electrical pulses, which, in turn, generate a strong, yet brief, magnetic field. With penetration of up to 8 cm into the cortex, the application of TMS ranges from research to brain mapping to evaluation of the central motor pathways [1]. While the discussion on the use of noninvasive stimulation to treat depression will follow, here we will concentrate on stimulation of the motor cortex in patients with chronic pain.

Several studies have shown that the primary motor cortex is the target providing the best response in relief of chronic pain [23, 24]. While the reasons for such response remain debated, the action potential created likely projects to pain-modulating areas of medial thalamus, periaqueductal gray, and anterior cingulate cortex [25]. The aforementioned areas, especially the cingulate gyrus, experience an increase in blood flow with TMS, and seem to improve the suffering aspect of chronic

pain [26]. Another possibility is the induction of central endogenous opioids, suggested by positron emission tomography (PET) studies after TMS [27]. Ongoing animal research also links the zona incerta, the electrical activity of which increases with TMS of the motor strip, with further downstream inhibition of the posterior thalamus [28].

An analysis of literature from 2001 to 2013 [1], showed significant pain reduction in 12/15 single session publications and 6/9 trials of repeated TMS (rTMS) applications. Maintenance of clinical benefit is reported up to 2 weeks and, with follow-up sessions, some patients are able to maintain pain relief up to a month after the cessation of rTMS [29].

A thorough comparison between the invasive and noninvasive cortical stimulation was performed by Lima and Fregni in 2008 [21]. After a literature screen, 22 invasive studies and 11 noninvasive studies were analyzed, showing a statistically significant difference in the responder rate (73 % and 45 %, respectively). Comparing the noninvasive group with sham stimulation showed a significantly higher number of responders in the active treatment group. Follow-up was analyzed in the invasive group and showed a small, yet statistically significant, 10 % decrease in responder rate over time. Such an analysis was not possible in the noninvasive group owing to the overabundance of single-session TMS.

Further elucidation is needed in the concrete demarcation of the types of chronic pain and their response to each type to treatment. Currently, the value of TMS may be as an adjunct to medical therapy in less severe cases, as a predictor of eventual response to epidural cortical stimulation, or as a bridge to invasive stimulation [30–32]. With both strategies presenting valuable options, a thorough evaluation of the risks and the benefits of each should be guiding the choice of the physician in the spectrums of invasiveness and efficacy.

Tinnitus

Tinnitus is a difficult disorder to define and treat owing to the subjective nature of the symptoms and the range of potential causes. It is suggested to be in the spectrum of deafferentation disorders similar to neuropathic pain. Tinnitus is most commonly defined as perceived sound without external stimuli [33]. While controversy exists, most authors stress the difference between subjective (audible only to the patient) and objective tinnitus (audible to physician) [34], or, similarly, between neurophysiologic and somatic tinnitus [35].

Affecting 10–15 % of the adult population, tinnitus can cause insomnia, depression and other affective disorders [36]. Approximately a sixth of patients seek treatment owing to the severity of this condition. Some sources of somatic sounds, like vascular lesions and palatal myoclonus, can be addressed directly [37]. While some benefits are seen with antidepressants [38], masking [39, 40], and retraining therapies [41],

cortical stimulation has been investigated as a possible treatment for the patients with subjective or neurophysiologic tinnitus not responding to aforementioned strategies [42, 43].

Partial deafferentation of the auditory system is a useful theory to explain tinnitus. The loss of cochlear hair cells by chronic stressors of high intensity sounds, ototoxic drugs, and aging is potentially compensated by the central nervous system. Akin to phantom limb pain, the overactive system, while making up for decreased external input, can result in creation of spontaneous activity and may cause subjective perception of sound (tinnitus) [36, 44, 45].

Studies using electroencephalography [46, 47] and magnetoencephalography [48] show that tinnitus is correlated with a hyperactive auditory cortex focally in the area of the frequency of the pathologic sound. The auditory cortex, one of the easier areas of the auditory system to reach, is therefore a plausible target for cortical stimulation in tinnitus.

In 2003, Eichhammer et al. [49] showed such hyperactive areas in 2/3 patients with tinnitus and treated those 2 with rTMS, with reported short-term benefit.

In 2004, De Ridder et al. [50] reported on the suppression of intractable tinnitus in 1 patient with TMS of the reorganized area of auditory cortex. The shifted frequency map, targeted with functional magnetic resonance imaging (fMRI), corresponded to the frequency and severity of the tinnitus itself. After establishing clear benefit to the patient with rTMS *versus* sham stimulation, electrodes were implanted epidurally over the auditory cortex. Follow up at 10 months showed abolishment of the tinnitus.

Building on previous experience, in 2006 De Ridder et al. [43] reported on 12 patients with cortical stimulation for tinnitus. The results were beneficial in patients with pure tone tinnitus of recent origin, which was suppressed by rTMS preoperatively. Fregni et al. [51] replicated the findings of the noninvasive cortical stimulation, temporarily alleviating tinnitus symptoms using transcranial direct current stimulation.

In 2007, Friedland et al. [52] showed possible improvement in several patients with chronic epidural stimulation over the areas of auditory cortex with greatest hyperactivity. These results supported the theory of cortical plasticity induction by stimulation leading to the relief from tinnitus.

It has been previously hypothesized that low-frequency thalamocortical bursts can suppress specific spots of the auditory cortex and disinhibit the surrounding areas. The spontaneous firing of those areas may cause the positive symptoms of tinnitus [48, 53, 54]. A recent case study using magnetoencephalography and ECS allowed Ramirez et al. [36] to present data supporting the thalamo-cortical dysrhythmia theory of tinnitus.

Adding to the rTMS experience in the area, 2 randomized prospective placebo controlled trials in 2010 [55, 56], showed significant improvement up to 6 months.

Continuing research in the field is augmenting the number of potential targets for the treatment of tinnitus. In addition to primary and secondary auditory cortices, anterior and posterior cingulate cortices, and left frontal and parietal areas are now thought to contribute to conscious perception of, and attention to, the pathologic sound [57, 58]. The target used in treatment of depression, left dorsolateral prefrontal cortex (DLPFC), has been added to some rTMS protocols in the hope of optimizing the benefit from stimulation [59]. Attempts to treat patients with concurrent depression and tinnitus using both targets underscores the potential of the field and the complexity of the disorders facing the neurologic community [60].

To address the small sample size of the majority of aforementioned studies, a 2011 Cochrane review of tinnitus analyzed 223 patients in 5 randomized controlled trials of rTMS *versus* sham rTMS [61]. The recommendations included very limited support for the treatment of tinnitus with rTMS. While short-term safety and a significant reduction in the loudness of the sound were seen, more level I studies with a larger number of participants are needed to further elucidate the efficacy of rTMS for tinnitus.

Depression

Cortical stimulation for treatment-resistant depression (TRD) is an alternative management option that has shown promise in an area in which new strategies are desperately needed. TRD is defined as an inability to achieve a meaningful response or full remission with an antidepressant drug used at an adequate dose for an adequate duration of time in major depressive disorder (MDD) [62]. The sufferers of TRD have an increased risk of suicide, greater medical morbidity and mortality, and higher healthcare use and costs when compared with MDD responders [63–65]. By affecting up to 3 % of the US population, TRD presents a significant health burden to society [66].

The use of electrical stimulation to treat depression dates back to 1938 with the introduction of electroconvulsive therapy by an Italian neurologist Ugo Cerletti. Approximately 1 million patients worldwide are estimated to still undergo electroconvulsive therapy yearly, with great variability in indications and prevalence [67]. The majority of treatment in Africa and Brazil is performed for schizophrenia and psychosis. In the USA, depression is the primary diagnosis in 72–92 % of the 100,000 patients treated annually [67, 68]. Yet high rates of relapse and amnesia, combined with stigma of the procedure, have prompted a continuing search for alternative therapies [69].

The first successful TMS was performed by Anthony Barker at the Royal Hallamshire Hospital in England in 1985 [70]. Using pervasive evidence of hypoactive left

DLPFC and hyperactive right DLPFC in depressed patients, the last 2 decades have seen numerous large trials of TMS for TRD. Benefit from high-frequency stimulation over the left DLPFC, which increases cortical activity, and low-frequency stimulation, in turn suppressing activity over the right DLPFC, supports the previous PET and fMRI data [71–73].

Two large trials and numerous meta-analyses showed statistically significant antidepressant effects of TMS [71, 74–76]. The reasonable complication profile of TMS includes headaches, which respond to simple analgesics. While the production of a seizure remains a concern, such risk is minimal, if safety guidelines are followed [77].

In 2005, Mayberg et al. [78] reported on the feasibility of DBS for TRD. While beyond the scope of this article, such treatments continue to provide a valuable alternative and a direction for future investigation.

Unlike the multitude of depression targets in DBS, epidural and noninvasive cortical stimulations for depression focus on the DLPFC [71–73, 79]. Epidural stimulation, born out of the aforementioned research, can potentially improve on TMS treatment with continuous stimulation at increased intensity and a better defined target [69]. Cortical stimulation also eradicates the risk inherent to parenchyma penetration with DBS.

Using MRI and a frameless stereotactic navigation system, a craniotomy is performed to position epidural electrodes over the DLPFC. A postoperative computed tomography of the head is fused with the preoperative MRI to assure appropriate placement [69]. Kopell et al. [69] and Nahas et al. [80] have shown the feasibility of these implants. Stimulation was well tolerated, with the expected, yet low, chance of surgical complications of bleeding and infection.

TRD remains a common severe multifactorial disorder with few treatment options. While TMS for TRD is Food and Drug Administration approved, both ECS and DBS are important directions to pursue in the treatment of this illness.

Movement Disorders

Use of drugs in movement disorders is the frontline treatment of symptoms. Yet side effect profiles, especially in the elderly, adverse effects like dyskinesias, and complexities of some pharmacologic regimens, make cortical stimulation a tempting alternative [81].

An unfortunate accident reported by James Parkinson in 1817 [82] gave birth to the idea of cortical stimulation as treatment of movement disorders. A patient recovering from a cortical stroke experienced a transient improvement in tremor. Supporting evidence came in the early 20th century, as destructive lesions of the motor cortex and the corticospinal tract were reported by Patrick and Levy [83], Bucy and Case [84], and Walker [85] to improve tremor.

Using the neuropathic pain research that coincidently improved the motor symptoms of patients, the leaders in the field suggested that cortical stimulation could be used to treat movement disorders [86–90].

Ailments such as Parkinson disease (PD), dystonia, essential tremor, and multiple system atrophy have their pathology “surface” from the subcortical structures, allowing for methods of decreased invasiveness to treat the disorders at the level of the cortex. Numerous publications use fMRI [91, 92], electroencephalography [93, 94], and PET scans [95, 96] to show decreased activity of supplementary motor area and DLPFC in patients with PD. Yet similar areas show increased metabolic activity in dystonia [97]. The complexity of the pathologic circuits responsible is exemplified by the findings in the motor strip, which shows hypoactivation in early untreated PD [98] and hyperactivity in late stages [91].

Early results of rTMS for PD were mixed. In 2001, Boylan et al. [99] reported worsening of symptoms, while in 2003 Khedr et al. [100] showed a possible benefit of rTMS in PD. A 2005 meta-analysis by Fregni et al. [101] concluded that rTMS can be effective in motor symptoms improvement on the Unified Parkinson’s Disease Rating Scale compared with sham stimulation, although the effect was modest. As the studies analyzed used different stimulation targets, the debate over the best area of cortex to stimulate in movement disorders continues. Another meta-analysis by Elahi et al. [102] further delineated the positive effect of high-frequency rTMS *versus* sham TMS, while showing only inconclusive results in the low-frequency analysis. Such distinction is valid owing to the inhibitory nature of TMS at the primary motor strip at settings <1 Hz [103], and the excitatory effect at high frequency (10–20 Hz) settings [104]. Recent trials have attempted to pinpoint the area of stimulation in relation to the frequency needed to treat. Shirota et al. [105] showed that supplementary motor area stimulation at low frequency is beneficial, while high frequency showed no benefit over sham TMS.

The literature on ECS for movement disorders is sparse. Existing studies are limited by size, lack of randomization, and, at times, lack of objective evaluation. The first report of ECS, from Nguyen et al. [90], showed cessation of tremor in a patient with midbrain stroke. The large studies of Katayama et al. [87] focusing on neuropathic pain, showed motor improvements in 8/42 patients. Canavero et al. [106] and Pagni et al. [88] both reported improvements in series of 3 and 6 patients with PD, respectively. Multiple system atrophy patients are the one group so far with a clear lack of benefit from ECS [106, 107].

Cortical stimulation for movement disorders is a promising, yet young, field in need of large studies to clarify optimal stimulation areas for the variety of disorders, clinical profiles of likely responders, and specifications on stimulation settings.

Conclusion

Recent advances in technology have allowed for the move away from invasive procedures with the hope of maintaining efficacy. Cortical stimulation, with its decreased risks and comparable outcomes, is a valuable alternative in the field of neuromodulation. In the field of neuropathic pain, both TMS and ECS have been proven effective. Very limited support has been found for the use of rTMS in the treatment of tinnitus. In the case of depression, TMS is Food and Drug Administration-approved. The 2 more invasive alternatives of ECS and DBS are important future avenues to explore for TRD. Investigation into the use of cortical stimulation in movement disorders needs significant additional research before any recommendations can be made.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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