REVIEW ARTICLE

Neuromodulation and palliative medicine

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ABSTRACT The palliative care population is generally vulnerable to experiencing medication-induced adverse effects and drug-drug interactions. Neuromodulation may offer particular advantages over systemic medications in this population. Although brain electrical stimulation has not been adequately trialed or in some cases even tried at all for management of a variety of symptoms, it is conceivable that in the future that it may be a potential therapeutic option in efforts to palliate various severe refractory symptoms.

KEY WORDS Palliative care; neuromodulation; pain; brain; electrical; stimulation; nausea; dyspnea; delirium

Ann Palliat Med 2012;1(1):58-64. DOI: 10.3978/j.issn.2224-5820.2012.03.06

Neuromodulation continues to be among the fastest growing areas of medicine. The International Neuromodulation Society (INS) has defined neuromodulation as a field of science, medicine, and bioengineering that encompasses implantable, electrical or chemical; for the purpose of improving quality of life and functioning of humans (1). Among a variety of neuromodulation techniques/approaches, the use of brain neuromodulation has been recently blossoming with respect to emerging potential applications. Brain neuromodulation generally involves cortical and sub-cortical neurostimulation in efforts to alleviate problems detracting from quality of life and/or optimal functioning.

Currently, the most common application of brain electrical stimulation (BES) is the use of deep brain stimulation (DBS) for the treatment of movement disorders (e.g., parkinson's disease, dystonia, essential tremor). Additionally, spinal cord stimulation as well as stimulation in the periphery has been utilized to provide analgesia in a variety of painful conditions. Thus, some may consider that neuromodulation techniques are already part of the armamentarium of potential available therapeutic options being offered to patients for palliation (not cure) of significantly distressing symptoms.

In the future it is possible that potential therapeutic applications may include: depression and epilepsy (vagal nerve stimulation is already being utilized for this), obsessive-compulsive disorders, eating disorders, impulsivity disorders, addiction, obesity, tinnitus, blood pressure control and traumatic brain injury. Conceivably, BES may eventually be able to be utilized as an integral therapeutic option for palliation of significantly distressing and refractory symptoms in the palliative care population are intuitive, since this population is generally comprised of older adults with diminished organ reserve, patients on multiple medications and therefore particularly vulnerable to drug-drug interactions, and patients more susceptible to drug-induced adverse effects.

With respect to DBS, five hypotheses have emerged as potential popular explanations contributing to the mechanism of action of DBS. They involve DBS effects on local changes in the stimulated brain nuclei and distal changes in efferent outputs, and target nuclei of the stimulated brain nuclei: (I) inactivation of action potential generation in efferent outputs (depolarization block); (II) activation of neuronal terminals that inhibit and/or excite efferent outputs (synaptic modulation); (III) depletion of neurotransmitter in terminals of efferent outputs (synaptic depression); (IV) anti-oscillatory action on nasal ganglion circuitry (network jamming or modulation); and (V) sustained enhancement of neurotransmitter release (synaptic facilitation) (2).

BES has been utilized for over half a century to study the brain regions pathways and neurotransmitters involved in addiction.

No potential conflict of interest.

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Submitted Mar 14, 2012. Accepted for publication Mar 21, 2012.
Available at www.amepc.org/apm

ISSN: 2224-5820

The use of BES to study many other conditions/symptoms has remained in its infancy. However, it appears conceivable that BES of various brain areas/pathways and/or their connectivity may modulate the intensity of various other issues such as pain, dyspnea, etc.

Neuromodulation and pain

The use of electricity for painful disorders has been employed for quite some time. It has been reported that in about 15 AD a man having an acute attack of severe painful gout of his toe suffered a sudden shock from accidentally stepping on a torpedo fish that dramatically reduced his gout pain (3). In 1967 it was shown that pain could be reduced by stimulating a periopheral nerve [e.g., Peripheral Nerve Stimulation (PNS)] or by the use of a spinal cord stimulator [e.g., spinal cord stimulation (SCS)].

Simpson and colleagues performed a systematic review of the literature and sought clinical and cost-effectiveness data for spinal cord stimulation (SCS) in adults with chronic neuropathic or ischemic pain with inadequate response to medical or surgical treatment other than SCS (4) From approximately 6,000 citations identified, 11 randomized controlled trials (RCTs) were included in the clinical effectiveness review: three of neuropathic pain and eight of ischemic pain (4). The evidence suggested that SCS was effective in reducing the chronic neuropathic pain of failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS) type 1. For ischemic pain, there may need to be selection criteria developed for critical limb ischemia (CLI) and SCS may have clinical benefit for refractory angina short-term (4).

In addition to PNS and SCS, BES also appears to provide analgesia in certain circumstances. Electrical stimulation is used worldwide to localize the epileptogenic cortex and to map the functionally eloquent areas in the context of epilepsy surgery or lesion resections, at least in part due to seminal work of Wilder Graves Penfield (1891-1976) at the Montreal Neurological Institute. Mazzola and colleagues reinvestigated this issue by analysing subjective and videotaped behavioural responses to 4,160 cortical stimulations using intracerebral electrodes implanted in all cortical lobes that were carried out over 12 years during the presurgical evaluation of epilepsy in 164 consecutive patients (5). Pain responses were scarce (1.4%) and concentrated in the medial part of the parietal operculum and neighbouring posterior insula where pain thresholds showed a rostrocaudal decrement. The medial parietal operculum and posterior insula are thus the only areas where electrical stimulation is able to trigger activation of the pain cortical network and thus the experience of somatic pain (5). However, there are multiple areas of the brain where electrical stimulation may contribute to providing clinically meaningful analgesia.

Two non-invasive techniques [transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS)] have emerged as interesting, potentially effective, and promising modalities for pain relief (6). Zaghi and colleagues performed a meta-analysis includes 18 studies, which together show that non-invasive brain stimulation is associated with an effect size of –0.86 (95% C.I., –1.54, –0.19) on a standardized pain scale ranging from 0 (no pain) to 10 (worst pain possible) (6).

Currently, 2 kinds of intracranial neurostimulation are used in attempts to control pain: motor cortex stimulation and deep brain stimulation (7). MCS has shown particular promise in the treatment of trigeminal neuropathic pain and central pain syndromes anecdotally such as thalamic pain syndrome. DBS may be employed for a number of nociceptive and neuropathic pain states, including cluster headaches, chronic low back pain, failed back surgery syndrome, peripheral neuropathic pain, facial deafferentation pain, and pain that is secondary to brachial plexus avulsion (7).

Deep brain stimulation (DBS) has shown promise as a treatment for peripheral neuropathic pain and phantom limb pain. Compared with DBS, motor cortex stimulation (MCS) is currently more frequently used, mainly because it is more easily performed, and has a wider range of indications (including central poststroke pain) (8). Controlled trials have demonstrated the efficacy of MCS in the treatment of various types of neuropathic pain, although these trials included a limited number of patients and need to be confirmed by large, controlled, multicenter studies (8).

The European Federation of Neurological Societies (EFNS) launched a Task Force to evaluate the evidence for these techniques and to produce relevant recommendations (9). They reported the following: spinal cord stimulation (SCS) is efficacious in failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS) type I (level B recommendation). High-frequency transcutaneous electrical nerve stimulation (TENS) may be better than placebo (level C) although worse than electro-acupuncture (level B). One kind of repetitive transcranial magnetic stimulation (rTMS) has transient efficacy in central and peripheral neuropathic pains (level B). Motor cortex stimulation (MCS) is efficacious in central post-stroke and facial pain (level C). Deep brain stimulation (DBS) should only be performed in experienced centres (9).

Electrical stimulation and pain

Deep brain stimulation was shown to provide analgesia in rodent

studies by stimulating the periventricular and periaqudectal gray (PVG/PAG) regions (10) and later in human studies in 1977 (11,12). DBS was also shown to provide analgesia by stimulating the ventral posterior lateral and medial (VPL/VPM) thalamic nuclei (13). Leone and colleagues reported on their positive experience of DBS of the posterior hypothalamus in chronic cluster headache (14). The appreciation that pain secondary to a thalamic lesion is generally refractory to thalamic stimulation (MCS) for pain secondary to a brain lesion (e.g., central pain) to a brain lesion (e.g., central pain) (15), or a trigeminal nerve lesion (e.g., neuropathic facial pain) (16) and/or other neuropathic pain states (17-19).

Lee and colleagues assessed the analgesic effects of periaqueductal gray (PAG) stimulation in the spared nerve injury (SNI) model of neuropathic pain of the rat. Spontaneous rapid paw withdrawal movements were used as the index of spontaneous pain. Deep-brain stimulation in the PAG was performed in rats 3 weeks after SNI. Significant analgesic effects on spontaneous pain behavior were observed at the same stimulation parameter that reversed the reduced mechanical threshold of the von Frey test. Both analgesic effects lasted 30-40 min beyond the 3 min stimulation period. In summary, PAG stimulation was effective in alleviating spontaneous pain and mechanical allodynia in the SNI rat (20). Thus, it would appear that electrostimulation of the PAG significantly enhances conditioned pain modulation (CPM) [formerly referred to as diffuse noxious inhibitory control (DNIC)], therefore, PAG electrostimulation appears to enhance descending inhibitory pain pathways. It remains to be seen if BES may also be able to inhibit descending facilitatory pain pathways.

Jung and colleagues performed thirty-two electrophysiological and psychophysical experiments in 16 healthy volunteers (21). Painful electrical test stimulation (0.125 Hz, 60 pulses) and conditioning electrical low-frequency stimulation (LFS) (1 Hz, 1200 pulses) were applied by a concentric electrode to the right hand. Test stimulation series were performed before (Pre) and after LFS (Post) or no stimulation period (Control). The strongest decrease in LFS-induced pain perception was shown after LFS ($P<0.01$). Topographic distribution of cortical potentials revealed reproducible negative (N1, N2) and positive (P2) components. Dipole magnitude analysis showed a significant difference between Post LFS and Post Control for P2 ($P<0.01$). P2 dipole location analysis yielded a significant posterior ($P<0.05$) shift following long-term depression (LTD) induction (21). Thus, data reveal central changes of pain processing after LTD induction (21).

Longo *et al.* found that viewing the body reduces acute pain (22). Participants rated nociceptive laser stimuli as less painful when viewing the stimulated hand in a mirror-box, versus an object at the same location (22). Mancini *et al.* subsequently replicated this effect using contact heat pain thresholds (23). In 2012, Longo and colleagues induced acute pain with an infrared laser while human participants looked either at their stimulated right hand or at another object (24). Behavioral results confirmed the expected analgesic effect of seeing the body, while fMRI results revealed an associated reduction of laser-induced activity in ipsilateral primary somatosensory cortex (SI) and contralateral operculoinsular cortex during the visual context of seeing the body. Longo *et al.* specifically evaluated two known cortical networks activated by sensory stimulation: (I) a set of brain areas consistently activated by painful stimuli (the so-called "pain matrix"), This putative "pain matrix" has been identified as a set of brain regions activated by nociceptive inputs (25,26), including brainstem and thalamic nuclei, somatosensory areas SI and SII, insular, and anterior cingulate cortices and (II) an extensive set of posterior brain areas activated by the visual perception of the body ("visual body network") (24). Connectivity analyses via psychophysiological interactions revealed that the visual context of seeing the body increased effective connectivity (i.e., functional coupling) between posterior parietal nodes of the visual body network and the purported pain matrix (24). Increased connectivity with these posterior parietal nodes was seen for several pain-related regions, including somatosensory area SII, anterior and posterior insula, and anterior cingulate cortex. These findings suggest that visually induced analgesia does not involve an overall reduction of the cortical response elicited by laser stimulation, but is consequent to the interplay between the brain's pain network and a posterior network for body perception, resulting in modulation of the experience of pain (24). Perhaps electrostimulation of certain occipital regions may help ameliorate pain.

Electrical stimulation and nausea or vomiting

The pathophysiology of nausea/vomiting may involve activation of various receptors in the area postema/chemoreceptor trigger zone [e.g., neurokinin (NK-1), serotonin ($5\text{-}HT_3$), histamine, muscarinic, dopamine (D_2)] as well as modulation of vagal afferent input. Therefore, electrical stimulation directed at modulating neural activity in these regions may potentially be beneficial in the future for palliation of severe refractory nausea/vomiting in the palliative care population.

Electrical stimulation and dyspnea

Dyspnea is defined by the American Thoracic Society as the

"subjective experience of breathing discomfort (27). There are three separable sensations that contribute to dyspnea: air hunger, work/effort, and tightness. This may not be a complete list as the neural mechanisms of dyspnea are still being defined (28).

The use of electrical stimulation to alleviate dyspnea may have many similarities with the use of electrical stimulation to alleviate pain. Both dyspnea and pain are alarming, unpleasant, and subjectively perceived physiological sensations (29-31) that contain an affective as well as a sensory dimension (32). Both are highly vulnerable to psychological influences (33-36). In particular, negative affect has been shown to be associated with increased reports of dyspnea as well as pain (37-43). Furthermore, similarities in the cortical processing of both sensations have been emphasized (29-31), including prominent activations of the insular cortex and anterior cingulate cortex (44). Despite the similarities between dyspnea and pain, our knowledge about interactions regarding their perception is markedly sparse. Studies have examined different aspects of the perception of both sensations within one experimental context (45-47). Electrical stimulation has been utilized in the periphery [e.g., transcutaneous electrical nerve stimulating (TENS)] to palliate pain and it is also conceivable that electrical stimulation may eventually have a role in the palliation of dyspnea. Jones and colleagues conducted a double-blind randomized controlled trial of forty-four subjects diagnosed with chronic obstructive pulmonary disease (COPD) to receive either acu-TENS or placebo-TENS on Dingchuan (EX-B1) acupuncture point for 45 minutes (48). An improvement in forced expiratory volume in 1 second (FEV1) and dyspnea visual analog score at the end of Acu-TENS treatment was associated with a concurrent increase in beta-endorphin level in patients with COPD (48).

Nishino and colleagues tested the hypothesis that an individual's pain sensitivity might parallel the individual's dyspnea sensitivity in 52 young healthy subjects (49). They found that an individual's pain threshold is correlated to the individual's dyspnea threshold, but the individual's pain tolerance is not consistently correlated to the individual's dyspnea tolerance (Nishino 2010) (49). Furthermore, there appear to be similarities and overlap with respect to the brain areas involved in the perception of pain and the perception of dyspnea.

The results of neuroimaging studies have shown that distinct brain areas process the dyspneic sensation, among which the anterior insular seems to be the most important (31).

Two major pathways have been suggested to process respiratory sensations to the cortex (50). The first pathway arises predominantly from respiratory muscle afferents, is relayed in the brainstem medulla, and projects to the ventroposterior thalamus area, from where thalamocortical projections ascend to the primary and secondary somatosensory cortex (31). In accordance with other interoceptive sensations, these structures might process the sensory or intensity aspects of dyspnea (51,52). The second pathway includes mainly vagal afferents from the lungs and airways, which are relayed in the brainstem medulla (31). Brainstem projections ascend to the amygdala and medial dorsal areas of the thalamus, and further to the insula and cingulated cortex (31). This predominantly limbic pathway might further include the hippocampus, operculum, putamen, and other prefrontal areas, and might be more associated with the affective components of the experienced breathlessness (50,53). In the future, it is conceivable that BES may be able to diminish the perception of severe distressing refractory dyspnea in certain refractory patients.

BES has not been well studied in efforts to alleviate dyspnea. DBS of subcortical brain areas such as the periaqueductal grey and subthalamic nucleus has been shown to alter cardiovascular autonomic performance, however, the supramedullary circuitry controlling respiratory airways is not well defined and has not been tested in humans (54). Hyam and colleagues used direct electric stimulation via DBS macroelectrodes to test whether airway resistance could be manipulated by these areas in awake humans (54). Thirty-seven patients with in-dwelling deep brain electrodes for movement disorders or chronic pain underwent spirometry according to the European Respiratory Society guidelines. Testing was performed randomly 3 times on stimulation and 3 times off stimulation; patients were blinded to the test. Thoracic diameter changes were measured by a circumferential pressure-sensitive thoracic band. Ten periaqueductal grey and 10 subthalamic nucleus patients were tested. To control for confounding pain and movement disorder relief, the sensory thalamus in 7 patients and globus pallidus interna in 10 patients, respectively, were also tested (54).

Peak expiratory flow rate (PEFR) increased significantly with periaqueductal grey and subthalamic nucleus stimulation by up to 14% ($P=0.02$ and 0.005, respectively, paired-samples Student t tests). Stimulation of control nuclei produced no significant PEFR change (54).

von Leupoldt and colleagues attempted to study the cortical areas associated with the processing of the affective unpleasantness of perceived dyspnea (55). Higher unpleasantness of dyspnea was associated with neuronal activations in the limbic system-that is, in the right anterior insula and in the right amygdala (respective Z values=3.93 and 3.15; $P<0.05$) suggesting that the unpleasantness of subjectively perceived dyspnea is processed in the right human anterior insula and amygdale (55). Thus, it may be possible in

the future to modulate perceived severe refractory dyspnea by placing electrodes by the anterior insula and/or amygdala and stimulating specific areas.

Electrical stimulation and delirium

Delirium is a common clinical syndrome characterized by acute onset of disturbance in consciousness, with acute cognitive or perceptual alteration. It may be preceded by restlessness, anxiety, irritability, distractibility, or sleep disturbances. Disturbances in consciousness may include inattention or inability to focus on external stimuli and/or ideas. Cognitive alterations may affect orientation, memory, language, or executive thinking/decision making. Perceptual alterations may include illusions or hallucinations. Delirium has been classified into three clinical subtypes: hyperactive, hypoactive, and mixed (56). Mixed delirium may alternate between features of both hyperactive and hypoactive delirium (56). Hypoactive delirium is more difficult to recognize and may be misdiagnosed as depression or dementia (57). The pathophysiology of delirium remains elusive.

There are a number of neurotransmitters believed to be involved in the pathogenesis of delirium, including acetylcholine, serotonin, dopamine, and gamma aminobutyric acid (GABA) (58). There is evidence that delirium may be caused by widespread brain dysfunction rather than localized disruption (58). Neuroimaging studies conducted by Yokota *et al.* (59) using xenon-enhanced computed tomography (CT) scans showed that patients with delirium have a 42-percent reduction in overall cerebral blood flow (CBF) compared with baseline and that occipital and subcortical regions have greater decrease in CBF than other regions. In a single study with xenon-enhanced CT, global perfusion was decreased during delirium (59). If this finding can be replicated, it would suggest that delirium might result from brain dysfunction across multiple regions. A study by Fong *et al.* (60) also showed the same result of hypoperfusion with decreases in regional CBF in the brainstem and occipital lobe. In this study, 99 mTc HMPAO single-photon emission computed tomography (SPECT) scans suggested that frontal and parietal cerebral perfusion abnormalities occur in delirium in roughly half of the patients (60). Other studies that made use of SPECT imaging, mostly in patients with hepatic encephalopathy (a form of delirium caused by liver failure), revealed various hypoperfusion patterns, including involvement of the thalamus, basal ganglia, occipital lobes and anterior cingulate gyrus (61-63). The perfusion patterns reported were inconsistent, although some of the studies were statistically underpowered.

Certain specific brain structures, such as the thalamus and frontal and parietal cortex, appear to be particularly involved in contributing to delirium (64). Trzepacz proposed a neuroanatomic "pathway or neuromatrix" for delirium involving the thalamus, prefrontal cortex, fusiform cortex, posterior parietal cortex, and basal ganglia (65). Shioiri and colleagues examined whether any abnormalities in the white matter (WM) assessed by diffusion tensor imaging (DTI) predisposes patients to develop delirium after cardiac surgery and also analyzed other risk factors for delirium (66). Shioiri *et al.* concluded that the abnormalities in the deep WMs and thalamus (brain region abnormalities that were mainly accelerated by aging) may account for the vulnerability to postoperative delirium (66). Brain lesions, particularly strokes in certain brain areas -- most often limbic regions -- may potentially lead to hyperactive delirium or delirium-like states characterized predominantly by hyperactive agitation. The most common regions in which strokes and other pathology may lead to hyperactivity and agitation are the temporal lobes (right greater than left); fusiform and lingualgyri, caudate nucleus, and anterior cingulum (67). Munster and colleagues compared postmortem brain tissue from 9 cases with delirium to 6 age-matched controls without delirium and found an association between human brain activity of microglia, astrocytes, and interleukin-6 (IL-6) and delirium in elderly patients (68).

Although BES has not been utilized to ameliorate delirium, it is conceivable that in the future the use of BES in attempts to modulate the function of certain brain regions with possible resultant alterations of neural functions, neurotransmitter signaling and/or glial function may be of potential interest to researchers.

Summary

Since the palliative care population may be particularly vulnerable to the untoward effects of medications, and drug-drug interactions; it is conceivable that in the future, neuromodulation/brain electrical stimulation may be a potential therapeutic option in efforts to alleviate/palliate various severe distressing and refractory symptoms that detract from optimal quality of life.

Acknowledgments

The author would like to acknowledge Pya Seidner for her enormous efforts towards the preparation of this manuscript.

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Cite this article as: Smith HS. Neuromodulation and palliative medicine. Ann Palliat Med 2012;1(1):58-64. DOI: 10.3978/j.issn.2224-5820.2012.03.06