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Cerebral stimulation for the affective component of neuropathic pain

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Abstract

Objective—To review the current state of cerebral stimulation for neuropathic pain and to propose that cerebral stimulation should aim at the affective sphere of chronic pain rather than solely focusing on the primary sensory-discriminative sphere.

Methods—The past and current goals of cerebral stimulation are reviewed as well as its limitations. A novel deep brain stimulation approach is proposed to evaluate this conceptual shift from somatosensory to affective sphere of pain targeting

Approach—Thalamic and other central pain syndromes are typically intractable to current treatment methods, including cerebral neuromodulation of somatosensory pathways, leading to long-term distress and disability. Our modern understanding of chronic pain pathophysiology is based largely on the neuromatrix theory, where cognitive, affective and sensory-discriminative spheres contribute equally to the overall pain experience. During the last decade, the safety and feasibility of chronic stimulation of neural pathways related to mood and affect has been explored with promising results. Here, we propose a novel approach to modulate the affective sphere of chronic pain by targeting similar networks in patients with treatment-refractory central pain. Our

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Authorship: Drs. Machado, Baker and Malone contributed with the initial idea and concept of targeting neuromodulation in the networks related to the affective sphere of chronic pain. Dr. Machado wrote the initial draft with Dr. Ela Plow and this was extensively edited by Dr. Baker and Dr. Malone until a final version was achieved. Drs. Plow and Malone are working with Dr. Machado (the study PI) in advancing these concepts with invasive and non-invasive stimulation. Their contributions were key to the final manuscript. . All authors approved the final manuscript.

Conflicts of Interest Authors Andre G. Machado and Kenneth B. Baker have conflict of interest related to intellectual property assigned to Cleveland Clinic companies IntElect Medical, Cardionomics and ATI. The Conflict of Interest committee has managed these conflicts and a research plan has been approved.

Andre G. Machado was a consultant, member of the Member of Scientific Advisory Board and owner of stock or stock options for Intelect Medical / Boston Scientific (Intelect was recently purchased by Boston). This conflict ended in the beginning of 2011. Dr. Machado also owns stock or stock options for Cardionomics and ATI, and serves as a consultant for Monteris.

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primary goal is not to produce (or measure) analgesia, but rather to modulate the affective burden of chronic.

Discussion—Cerebral neuromodulation for neuropathic pain has had limited efficacy thus far. Shifting our aim to neural networks related to the affective sphere of pain may allow us to reduce pain conditioning and pain-related disability. Our ultimate goal is to promote rehabilitation from chronic pain - social and occupational.

Introduction

Chronic pain is a leading cause of disability, resulting in enormous impact to individual health and the economy. Although back pain is perhaps the most common chronic pain disorder, as the second leading complaint in outpatient consults and the third in hospital admissions¹, there are multiple pain syndromes that contribute to the overall burden of pain related disability. Neuropathic pain, defined as “pain initiated or caused by a primary lesion or dysfunction in the nervous system”² has an estimated prevalence of 8% among adults enrolled in a family practice³. Central pain, otherwise known as post-stroke pain, is a less common form of neuropathic pain⁴ that can be particularly devastating, due to its severity and refractoriness to management⁵. Management of central pain has interested neurosurgeons for several decades, but remains a challenge⁶⁻⁷. This is likely due to the medical refractoriness of the disorder, lack of other therapeutic options as well as presence of an associated CNS lesion. Surgical management of these disorders is challenging and often frustrating, with several failed brain targets evaluated to date. However, the mechanistic hypothesis behind all of the targets evaluated thus far has emphasized modulation of the somatosensory pathways to produce analgesia, with outcomes generally based upon measurements made using a numerical pain scale. We think it is time to depart from this approach. Psychological factors are known to influence recovery, recurrence rates and the probability of returning to work for patients with chronic pain syndromes⁸⁻¹¹. Indeed, our understanding of chronic pain physiopathology is not limited to the sensory pathways but, rather, includes significant involvement of neural networks related to its cognitive and affective spheres. This is corroborated by the prior experience with ablative stereotactic procedures for chronic pain, in selected patients¹². Although ablative procedures continue to be a relevant technical option in stereotactic and functional neurosurgery¹³, the reversibility of neuromodulatory techniques is an important safety feature. This can be particularly beneficial when exploring new targets and indications. As such, we propose a novel approach, utilizing neuromodulatory techniques such as deep brain stimulation (DBS) to target the networks related to the affective sphere – the suffering - of chronic pain. The goal also differs from simple analgesia. Instead of measuring outcome as a percentage of patients with greater than 50% pain relief, our intent is to reduce pain anticipation, suffering and, most importantly, pain related disability. If this approach proves to be successful in the most treatment-refractory conditions, it may also be a useful alternative or adjunct in the management of other disabling pain conditions.

Invasive neurostimulation for central pain and its current limitations

Several clinical trials and retrospective case series have examined the potential role of neurostimulation, including both motor cortex stimulation (MCS) and DBS, in the management of central pain^{6, 14-20}. Traditionally, DBS of the sensory thalamus has been reserved for neuropathic pain^{6, 15} while periventricular gray (PVG) DBS, the therapeutic effects of which are mediated at least in part by endorphin release^{16, 21}, has been thought to be most effective for nociceptive or axial pain. This dichotomy has been challenged recently however, with at least one group showing that PVG stimulation may be effective in neuropathic deafferentation syndromes¹⁴. Even though thalamic and central gray DBS has

shown promising results for managing chronic treatment refractory pain in some patients with peripheral deafferentation^{18, 22-23}, it has not proven consistently effective for patients with central pain¹⁹⁻²⁰. Recent work by the Oxford group has focused on PVG stimulation for central pain. In a non-controlled study, Nandi et al reported that six of eight patients reported “satisfactory” relief of pain, representing approximately 30% improvement from the preoperative baseline²⁴.

Motor cortex stimulation was proposed as a treatment for central pain, largely in response to growing frustration with inadequate DBS efficacy in this patient population²⁵⁻²⁶. However, the initial optimism derived from the preclinical model²⁵ and from the first clinical trial²⁶, was subsequently tempered when a trial comparing the effects of MCS on peripheral or central deafferentation in humans failed to observe efficacy in the latter group²⁷.

Subsequent, larger series of MCS continued to report some efficacy with this technique, particularly for trigeminal neuropathic pain. Nguyen and colleagues followed 32 patients for an average of 27 months, reporting that five of 13 patients with central pain and nine of 12 patients with facial pain presented with “good” pain relief²⁸. A gradual loss of efficacy was observed in six patients, however benefit was re-established through repositioning of the epidural leads assisted by neuronavigation. A similar decay of efficacy was also reported by Henderson and colleagues²⁹ and pain relief was recovered with intense programming. Nuti and colleagues³⁰ reported on a mean follow-up of four years in a series of 31 patients with central pain. Approximately 50% of patients reported greater than 40% pain relief in this non-controlled series. A two-center sham-controlled series of 10 patients was reported by Nguyen and colleagues, in which patients underwent two weeks of no stimulation or two weeks of active stimulation followed by double-blind cross-over. During the blinded phase, VAS pain scores reduced from a mean of 78 to 53 (32% improvement). Two of three patients with post-stroke pain did not respond. Although it was initially hypothesized that MCS would address the limitations of DBS in managing central pain, its effects largely replicated the results of prior DBS series, proving to be more effective for patients with peripheral deafferentation than central pain³¹⁻³². The gap between the promising results of MCS in the animal model and the clinical trials outcomes may be partially explained by the location of the central lesion. While the feline model tested the effects of MCS following spinal cord injury³³, the first human translation was attempted in patients with post-stroke pain²⁶⁻²⁷. Even though both represent CNS lesions per se, spinal cord injuries spare the corticothalamic pathways that are likely to contribute to the therapeutic mechanisms of MCS. Two decades following the first MCS studies, four decades after Akil’s central gray stimulation and five decades following the gate control theory we still do not have a reliable treatment for patients with chronic pain secondary to central lesions. The variety of brain regions that have been targeted and failed all have held the common goal of trying to produce analgesia through modulation of somatosensory pathways. In retrospect, it may be that the hypothesis itself was mis-postulated, with DBS or MCS doomed to fail in modulating a pathway that has been largely damaged in its central relay. This notion is underscored by the severity of pinprick anesthesia observed in many patients with thalamic pain syndrome.

A new approach for targeting the brain for chronic pain disorders

Knowledge of the different effects of DBS and MCS for peripheral and central pain syndromes has advanced along neurosurgical experience over the last decades. At the same pace, our understanding of physiopathology of chronic pain has also advanced dramatically. While modern investigation of neuromodulation for pain was instigated by the gate control theory in 1965³⁴, the current systems level understanding of chronic pain is largely based on Melzack’s theoretical re-postulation of pain related networks in the neuromatrix³⁵. Under this ideology, sensory-discriminative pathways interact – with equal importance – with

affective-motivational and cognitive-evaluative spheres to create the final pain experience (figure 1). While targeting neural pathways related to the sensory-discriminative sphere remains valid and clinically effective³⁶ for some patients, it may not be a viable option for patients presenting with little or no residual neurological substrate to mediate the therapeutic effect. In such cases, targeting an anatomically spared pathway may be a reasonable option.

It is also time to reconsider analgesia as the treatment goal. The current yardstick for outcomes in pain neuromodulation studies is the visual analog (or equivalent) scale. While this tool remains useful for bedside monitoring of acute interventions for acute pain, it can be misleading when managing chronic pain and fails to correlate with patient satisfaction or disability³⁷. Instead of attempting to index analgesia by the percentage of reduction in pain intensity following intervention, a more reliable metric of therapeutic efficacy following neurostimulation would be improvement in pain-related disability³⁸⁻³⁹. Interventions that successfully facilitate rehabilitation and reduce dependence for self care should be regarded as valuable to patients and to society even if patients continue to report some persistence of measurable pain.

We postulate that chronic pain-related disability is not solely the result of the intensity of pain at a given point in time, but rather is profoundly influenced by the expectation of unrelenting pain. This is further aggravated by pain reinforcement caused by daily experiencing of allodynia when the affected side is used or touched. As such, reducing pain anticipation related to the use of the affected limb (or hemibody) and reducing pain fear – or dread – may also reduce disability. We propose that we shift our targeting choice away from neural pathways related to the sensory discriminative sphere of pain and focus on the neural networks related to the affective-motivational sphere. This is timely. We are now experiencing a renaissance of careful investigation of surgery for psychiatric disorders. Most relevant to this approach is the recent experience in DBS for obsessive compulsive disorder and depression.

Neural networks related to mood and affect: Recent DBS experience

Cortical control of emotion is manifested through processing within the circuit of Papez and the orbitofrontal cortico-striato-pallido-thalamo-cortical (CSPTC) system. The orbitofrontal cortex shares massive reciprocal excitatory projections with the thalamic mediodorsal nucleus, through the ventral anterior limb of the internal capsule (ALIC). This excitatory intercommunication is modulated by a longer loop, initiated by fibers that project from the orbitofrontal cortex to the ventral striatum, also passing through the ALIC. These fibers, in turn, connect with the ventral pallidum, which maintains inhibitory projections that further modulate thalamocortical activity⁴⁰. This circuitry is highly implicated in the control of emotion and behavior as well as in the pathogenesis of psychiatric disorders⁴¹. Anterior capsulotomy, a stereotactic procedure in which the reciprocal projections between orbitofrontal cortex and thalamus are lesioned, has been shown to alleviate obsessive symptoms and anxiety. This corroborates the importance of the fibers projecting through the ALIC in the control of emotion and behavior. The densely arranged fibers bundles through the ventral ALIC connecting the orbitofrontal cortex to the mediodorsal thalamic nucleus and to the ventral striatum, makes it an ideal stereotactic target. Other surgical targets need to also be taken in consideration, including the anterior cingulate areas. There is robust literature supporting the efficacy of radiofrequency cingulotomy for obsessive compulsive disorder^{13, 42}, chronic cancer pain^{12, 43} and chronic non-cancer pain⁴⁴. The procedure was also shown to be safe. In the Massachusetts General Hospital's series of more than 800 cingulotomies, there were no reported deaths and two intracranial hemorrhages. As for other ablative procedures aimed at non-motor networks, there is a concern for cognitive changes that may be observed on follow-up⁴⁵⁻⁴⁶. Nevertheless, the efficacy of cingulotomy in

alleviating pain conditions supports the concept of targeting subcortical networks related to affect and behavior with DBS for treatment-refractory neuropathic pain⁴⁷.

Deep brain stimulation has revolutionized the field of stereotactic and functional neurosurgery in large part because of its superior safety profile compared to ablative procedures such as thalamotomy or capsulotomy. Although effective, recent investigation has shown significant risk for deterioration of executive function following capsulotomy⁴⁸. DBS is reversible and adjustable, allowing for adverse effects to be managed and stimulation to be activated or deactivated as needed. Nutin et al pioneered DBS of the ventral region of the ALIC in a group of patients with OCD⁴⁹. The positive results led to subsequent exploration by other groups, demonstrating that DBS of the ventral ALIC region is safe and effective for OCD. Executive function has been prospectively assessed in patients undergoing long-term DBS of this area and permanent adverse effects were not seen⁵⁰.

In 2009 our group reported on the long-term effects of DBS of the ventral capsule and ventral striatal area (VC/VS) in patients with severe and treatment refractory depression⁵¹. This open label study showed a significant reduction in the two main outcome measures, the Montgomery-Asbrg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HDRS). The approximately 50% reduction occurred over three months and was sustained at 12-months of follow-up. Although confirmation from a controlled trial is still needed, the results are encouraging and demonstrate that it is feasible and safe to chronically modulate these networks in the human brain. Subsequent work in a subset of patients was conducted to evaluate the acute effects of stimulation in the VC/VS area and to study the topographic organization of the target region⁵². It was observed that the most ventral contacts of the quadripolar DBS lead were consistently associated with both acute and chronic changes in mood and anxiety. These contacts correspond to the topography of the ventral striatal and the ventral-most part of the anterior limb of the internal capsule (ALIC). Contacts positioned more dorsally in the ALIC typically were not associated with changes in affect and behavior. Interestingly, the effects on the network can be seen acutely during surgery and subsequently reproduced with stimulation of the same sub-regions during outpatient programming. Electrode contacts and corresponding settings that produce positive changes in mood and anxiety were successfully selected for long-term stimulation. A follow-up study utilizing DBS modeling techniques showed that, in the topography of the ventral anterior capsule, pathways that coursed laterally were more commonly associated with positive responses⁵³. We propose that the same pathways that have been safely targeted for OCD and depression may also be viable targets for modulating the affective sphere of chronic pain.

Deep brain stimulation of the ventral striatum and ventral capsular area for patients with chronic pain

As discussed above, we propose a conceptual shift in surgical target selection for central pain, one that moves away from emphasizing a compromised sensory-discriminative system and concentrates instead on networks related to the affective-motivational sphere of chronic pain. Such targets may be cortical (e.g., orbitofrontal, dorsolateral, insular, cingular) or subcortical, including the VC/VS area, mesial thalamus and Brodmann's areas 24 and 25.

Based on our experience with DBS of the VC/VS area, its safety in patients with OCD and treatment refractory depression and our recent work on the functional topography of the area, we proposed the VC/VS target as a new conceptual approach to the treatment of central pain (figure 2). We are currently conducting the first federally funded prospective, double-blinded, controlled trial of VC/VS DBS aimed at modulating the affective sphere of

thalamic pain syndrome⁵⁴. We recognize the significant leap that this clinical trial proposes, regardless of the prior demonstrations of safety of VC/VS DBS in other patient populations. In order to ascertain well informed consent of participants and proper oversight, the clinical study is conducted not only under Institutional Review Board approval but also with federal oversight via a physician sponsored Food and Drug Administration Investigational Device Exemption. The primary outcome measures of the study is the pain disability index, which was selected to evaluate if modulation of the affective sphere of pain will alleviate disability and promote independence. Other outcome measures are incorporated to monitor the safety of DBS implantation and chronic stimulation, including depression and anxiety rating scales as well as detailed pre- and post-surgical cognitive assessments. Patients are prospectively evaluated with magnetoencephalography and functional magnetic resonance imaging in order to evaluate possible mechanisms underlying clinical effects.

We anticipate that the results of this clinical trial will shed light on the role of the networks associated with mood and affect on the affective sphere of intractable chronic pain disorders. We expect that this structured evaluation of our conceptual approach will motivate our group and others to systematically evaluate targets related to the affective-motivational sphere in patients with central pain syndrome or other chronic pain disorders. We hope that future studies will be carried out in such fashion as to evaluate specific targets for specific pain disorders in controlled studies, thus avoiding the interpretational confounds imposed by studies that test a number of targets on heterogeneous populations. Further, we call upon our peers to favor quality of life and disability indices to measure the outcome of neuromodulatory interventions for chronic pain, thus retiring the visual analog pain scale as the yardstick of our field.

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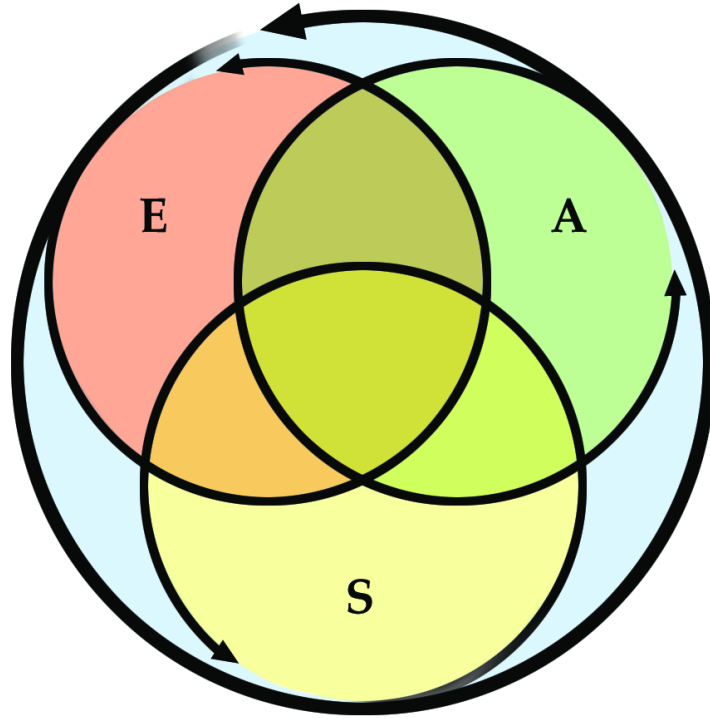


Figure 1.

Modified from Melzack et al 1999. Pain experience is not determined by the intensity of activation of somatosensory pathways only. Pain processing involves also affective and cognitive spheres of interpretation. For example, the context in which the painful stimulus occurs can dramatically change the final perception of pain. The affective sphere can gain greater importance in chronic pain, when the experience is no longer dependent on external stimuli. This is particularly relevant in chronic deafferentation pain, when patients experience unrelenting continuous pain as a result of the central deafferentation. A: Affective, E: Evaluative, S: Sensory

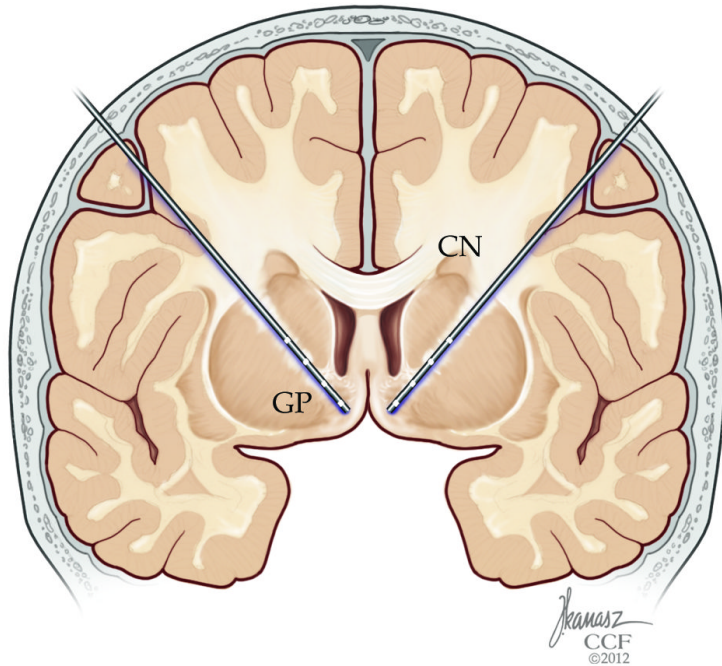


Figure 2.

Targeting of the ventral striatal and ventral capsular area has been shown to be safe in patients with obsessive compulsive disorder as well as treatment refractory depression. In open label studies, it was shown that it is possible to modulate networks related to mood and affect. This figure illustrates deep brain stimulation targeting along the anterior limb of the internal capsule into the ventral striatal area, as intended in the ongoing clinical trial.