Deep brain stimulation of the dorsal anterior cingulate cortex for the treatment of chronic neuropathic pain

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Chronic neuropathic pain is estimated to affect 3%–4.5% of the worldwide population. It is associated with significant loss of productive time, withdrawal from the workforce, development of mood disorders such as depression and anxiety, and disruption of family and social life. Current medical therapeutics often fail to adequately treat chronic neuropathic pain. Deep brain stimulation (DBS) targeting subcortical structures such as the periaqueductal gray, the ventral posterior lateral and medial thalamic nuclei, and the internal capsule has been investigated for the relief of refractory neuropathic pain over the past 3 decades. Recent work has identified the dorsal anterior cingulate cortex (dACC) as a new potential neuromodulation target given its central role in cognitive and affective processing. In this review, the authors briefly discuss the history of DBS for chronic neuropathic pain in the United States and present evidence supporting dACC DBS for this indication. They review existent literature on dACC DBS and summarize important findings from imaging and neurophysiological studies supporting a central role for the dACC in the processing of chronic neuropathic pain. The available neurophysiological and empirical clinical evidence suggests that dACC DBS is a viable therapeutic option for the treatment of chronic neuropathic pain and warrants further investigation.

<http://thejns.org/doi/abs/10.3171/2015.3.FOCUS1543>

KEY WORDS deep brain stimulation; anterior cingulate cortex; chronic pain; neuropathic pain; ACC; dACC

CHRONIC pain affects approximately 100 million American adults each year and results in an annual incremental health care cost of \$560–\$635 billion.⁶⁶ The economic burden of chronic pain is multiplied when loss of productive work time is considered.¹⁴³ Chronic pain has been associated with impairment in cognition and attention,⁷⁸ development of psychiatric comorbidities such as depression and anxiety,⁴⁸ dependence on opioid analgesia, and decline in social functioning.⁵⁹ Further, many chronic pain states, such as neuropathic pain, remain difficult if not impossible to treat with available therapeutics.¹⁵⁹ For these reasons, the impact of chronic pain on public well-being cannot be overstated.

Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.”⁷⁸ When neuropathic pain extends beyond the period of injury and healing, it becomes chronic disease.^{45,70,74} The development of chronic neuropathic

pain is associated with alterations in function of the peripheral, spinal, and central pain pathways, which result in abnormal activity, leading to the development of allodynia, the experience of nonnociceptive stimuli as painful; hyperalgesia, an abnormally increased pain response to nociceptive stimuli; and spontaneous pain, which can be constant and debilitating.^{5,24,40,43,53,58,62} Chronic neuropathic pain arising from aberrant nervous system activity is particularly resistant to conventional medical therapies.¹⁸ Additionally, many of the medications used to treat neuropathic pain by modulating aberrant activity in the peripheral nervous system, such as carbamazepine, gabapentin, tricyclic antidepressants, serotonin- and norepinephrine-selective reuptake inhibitors, are associated with significant side effects, such as sedation and nausea.⁴⁵ These treatments, which act peripherally, are unable to address pathologic changes in the central nervous system, which are implicated in the development and maintenance of chronic pain.

ABBREVIATIONS ACC = anterior cingulate cortex; dACC = dorsal ACC; DBS = deep brain stimulation; DTI = diffusion tensor imaging; fMRI = functional MRI; IASP = International Association for the Study of Pain; IC = internal capsule; LTP = long-term potentiation; MRS = MR spectroscopy; PAG = periaqueductal gray; PVG = periventricular gray; VAS = visual analog scale; VPL/VPM = ventral posterior lateral and medial thalamic nuclei.

SUBMITTED February 1, 2015. **ACCEPTED** March 23, 2015.

INCLUDE WHEN CITING DOI: 10.3171/2015.3.FOCUS1543.

DISCLOSURE The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Both internationally and in the United States, the use of deep brain stimulation (DBS) has been investigated for the treatment of chronic neuropathic pain that is refractory to conventional medical therapy.^{14,21,28,30,46,60,63,79,81,115,116,137} Investigations into the use of DBS targeting various areas of the brain, including the periventricular gray (PVG), sensory thalamus, and the internal capsule (IC), have yielded valuable information regarding patient selection, stimulation parameters, operative technique, and outcome measurement.⁸⁰ They have also served to highlight the complexity and burden associated with the management of chronic pain.

In this review, we briefly review the history of DBS for chronic pain and present evidence supporting DBS of the dorsal anterior cingulate cortex (dACC). We summarize important findings from recent neuroimaging and neurophysiology studies supporting a central role for the dACC in the development of chronic neuropathic pain and review existent literature on DBS of the dACC for this indication.

DBS for Chronic Pain: Subcortical Targets

The idea of using DBS to treat chronic pain has its origins in the development of the gate control theory of pain as described by Melzack and Wall in 1965.^{97,102} This theory, although now mostly supplanted by newer models such as the neuromatrix theory of pain,^{96,98–100} was instrumental in establishing the central nervous system as an active partner in the development of chronic pain states. Over the past 3 decades, multiple neural targets have been explored for chronic stimulation, including the periaqueductal gray (PAG) region,⁵⁷ the ventral posterior lateral and medial thalamic nuclei (VPL/VPM),^{114,123} the IC,¹ and, most recently, the dACC.

Under the US Medical Device Amendment of 1976, which compelled the US Food and Drug Administration to require DBS device manufacturers to conduct studies showing benefit of DBS for the treatment of chronic pain, 2 Medtronic-sponsored, open-label, multicenter trials were conducted. In the first of these trials, which enrolled 196 patients from 1989 to 1992, model 3380 DBS leads were implanted into either the VPL/VPM or the PAG.²⁹ This trial was supplanted by a second trial in 1992, utilizing lead model 3387, which had replaced model 3380. This second trial enrolled 50 patients between 1992 and 1995. Both trials were closed early due to slow enrollment and unexpectedly low efficacy, as determined by the limited reduction in pain scores postoperatively.

The criterion for success for the model 3380 trial was defined a priori as at least half of patients with internalized devices reporting $\geq 50\%$ pain reduction at 1 year. For the 3387 model, success was defined as at least half of the patients with internalized devices falling into 1 of 3 outcome categories at 1 year: excellent, $\geq 70\%$ pain relief with complete cessation of narcotic drugs; good, $\geq 50\%$ relief and no narcotic usage; moderate, 30%–49% pain relief and at least a 1-level decrease in analgesic usage. Any other result, including withdrawal from the study, was considered treatment failure. These values are in contrast to the 30% reduction criterion used commonly to evaluate efficacy of pharmaceutical pain relievers. For both studies,

only those patients who achieved a reduction in pain of $\geq 50\%$ during a test stimulation period immediately postoperatively with externalized leads went on to the next stage for full device internalization.

For the first trial, 46.1% of patients reported $\geq 50\%$ reduction in pain at 1 year and 17.8% at 24 months, and for the second trial, 16.2% had 50% reduction at 1 year and 13.5% at 24 months. Neither study achieved the a priori criteria for success. No major reduction in narcotic medication usage was observed in either trial. Additionally, withdrawals and dropouts accounted for 70%–73% of patients at the 24-month outcome point, with a higher proportion of responders represented in this group. The weakness of these results led the device manufacturer to reconsider pursuit of marketing approval for the treatment of chronic pain.

A number of limitations have been identified in the design and execution of the studies described above. First, these studies consisted of a collection of prospective case series from participating centers. These series were neither randomized nor case controlled. Subjects were drawn from a heterogeneous pain population, with a large variety of syndrome types and etiologies. Interventions varied between VPL/VPM and PAG stimulation in an uncontrolled manner, and no uniform stimulation parameters were employed. Additionally, a variable number of electrodes were used per patient. Use of validated outcome measurement tools was limited to the administration of the visual analog scale (VAS) score during the 3387 trial only. All other measurements of pain reduction upon which assessment of efficacy was based were subjective and unblinded.¹¹³

As a result of these studies, DBS for chronic pain has remained “off-label” in the United States, and, as a result, very little additional formal study has been undertaken. Most of the current literature on DBS for chronic pain has come from investigators in the United Kingdom, Europe, and Canada. These more recent studies have benefited from improved imaging techniques, updated DBS device design, and procedural refinement. In addition, continued work to determine which chronic pain etiologies are most responsive to this therapeutic intervention has led to improvements in patient selection. Finally, advances in the neuroscience of pain have opened up the possibility of new neural targets, such as the dACC, which hold promise for effective pain relief for some chronic pain patients.^{67,68,71,75–77,83,85,90,107,120,121,128,130,149,163–166,}

The Role of the dACC in Pain Processing

An extensive body of literature has been devoted to understanding the role of the dACC in human cognition. The dACC has been implicated in circuits involving decision making, emotional salience, learning, reward processing, empathy, attention, intention, addiction, and the affective aspect of pain.^{7,11,13,31,44,47,52,55,69,72,127,126,138,152–154,157} This region has been targeted successfully with lesioning techniques for the treatment of affective disorders,^{9,141} obsessive-compulsive disorder,¹³⁶ and chronic refractory pain,¹⁵² highlighting the diversity of neurological processes with which it is involved. Modern imaging techniques have demonstrated the extensive functional and anatomical con-

nections traveling to, from, and through this region, which underlie these diverse processes.^{3,8,93,103,108,109,117,118,131,137,150}

In 1962, Foltz and White published their seminal paper, "Pain 'Relief' by Frontal Cingulotomy," which ignited interest in discovering the role of cingulotomy in the treatment of chronic refractory pain.⁵¹ Drawing on lessons from early psychiatric neurosurgery, and particularly on observations made of the effect of lobotomy on pain perception and autonomic function, Foltz and White hypothesized that transection of the cingulum bundle might benefit those patients with a disproportionately large affective component to their pain. In the discussion of their findings, they reported a universal decrease in the distress associated with chronic pain.

The initial results regarding the use of cingulotomy for the treatment of refractory pain described above were replicated and expanded by numerous investigators, including Ballantine and Hurt at the Massachusetts General Hospital in Boston, who introduced a stereotactic approach in 1966.^{9,25,162} Stereotactic cingulotomy, which allows for more precise targeting, continues to be in use today for the treatment of malignant and nonmalignant chronic pain. Although slight variations have been reported, the target is commonly described as being located 7 mm from the midline, 20 mm posterior to the anterior tip of the frontal horns of the lateral ventricle, and 1 mm above the roof of the ventricles, bilaterally.¹⁴⁰ This region corresponds to Brodmann areas 24 and 32 and has been variably called either the dACC or the dorsal anterior midcingulate cortex (daMCC) in the literature.

The empirical work identifying the dACC as a target for treatment of chronic pain is supported by more recent imaging and neurophysiological evidence describing the role of the anterior cingulate in the perception of pain. The development of imaging modalities such as diffusion tensor imaging (DTI), functional MRI (fMRI), positron emission tomography, and voxel-based morphometry has allowed investigators to better characterize the structure and function predicted by these early studies, confirming the central role of the dACC in the perception of chronic pain, and allowing an increasingly nuanced therapeutic approach.⁸ Studies using fMRI have consistently demonstrated increased activation of the dACC during both empathic and experienced pain,¹¹¹ supporting a hypothesis that the dACC is implicated in the affective component of pain.

Neuroimaging of Chronic Pain

Melzack, having already introduced the concept of a *neuromatrix*, formulated his understanding of pain processing in the following way: "The anatomical substrate of the body-self, I propose, is a large, widespread network of neurons that consists of loops between the thalamus and cortex as well as between the cortex and limbic system. I have labeled the entire network, whose spatial distribution and synaptic links are initially determined genetically and later are sculpted by sensory inputs, as a neuromatrix."⁹⁹

The earliest neuroimaging studies of pain looked primarily at acute pain in healthy controls.^{10,35,38,91,122,158} In 2000, Peyron and colleagues undertook a thorough meta-analysis of the pain neuroimaging studies published be-

tween 1991 and 1999. The meta-analysis revealed a consistent pattern of activation in a diverse array of brain regions in response to acute pain. Most reliably, hemodynamic changes were observed in the bilateral insula, primary and secondary somatosensory regions, and the dACC, corresponding primarily to Brodmann area 24.¹¹⁷ These findings suggest that the experience of pain is a multimodal event, representing the output of a series of complex interactions between emotional processing, memory, cognitive, and sensory centers constituting a "pain neuromatrix."¹⁰¹ (Fig. 1).

More recent work has focused on understanding the brain's processing of chronic pain.^{3,4,23,104,106,148} Although execution and analysis of chronic pain imaging is complicated by heterogeneity of the clinical entities under study and inability to control experimental features, evidence for unique yet overlapping neurosignatures of various chronic pain disorders is amassing. A recent review by Apkarian discussed the findings of neuroimaging studies devoted to elucidating chronic pain states published over the past decade.⁴ He found that not only did each chronic pain syndrome evoke a unique pattern of activity but also that chronic pain generally activates brain regions that are more involved with emotional and motivational states than with acute nociception, such as the dACC.

The altered activity in chronic pain patients described above is complemented by changes in gray and white matter. Decreased gray matter density in areas involved in nociception has been reported in multiple chronic pain conditions.^{3,95} Mordasini and colleagues used voxel-based morphometry to investigate gray matter changes in 20 men with refractory chronic pelvic pain syndrome and 20 healthy age-matched controls. They identified a significant reduction in gray matter volume in the anterior cingulate cortex (ACC). Further, the reduction in gray matter volume in the ACC correlated with measures of bother or unpleasantness associated with the pain.¹⁰⁵ An additional study by Rodriguez-Raecke and colleagues monitored changes in brain morphometry in 20 patients with chronic pain due to hip osteoarthritis who underwent hip replacement.¹²⁵ When compared with controls preoperatively, patients with chronic pain were shown to have significantly less gray matter in the ACC, the insular cortex and operculum, the orbitofrontal cortex, and the dorsolateral prefrontal cortex, which corresponded to duration of pain. At the postoperative time point when the patients reported being pain free, an increase in gray matter was observed in the same area, suggesting that these changes may be at least partially reversible with appropriate analgesia. This observation suggests that changes in morphometry likely reflect long-term neuroplastic changes rather than neuronal loss. It also suggests that these changes are likely to have resulted from chronic pain and/or its functional and emotional consequences, rather than having predisposed the patient to the development of pathologic pain. The development and maintenance of neuroplastic changes in chronic pain is an area of active research and is discussed briefly below.⁹⁵

An additional body of literature has been devoted to exploring the utilization of advanced neuroimaging techniques to understand the specific contribution of the ACC to the experience of pain. Classically, the ACC has been

FIG. 1. Illustration based on the neuroimaging studies that suggest the experience of pain involves complex interaction between brain regions involved in emotional processing, memory, cognition, sensation, and motor planning. Ascending pain pathways are shown with *black arrows*. The classically described pathway (lateral spinothalamic tract, thalamus, primary sensory cortex) is one of these ascending pathways. *Blue arrows* represent descending modulatory pain pathways. Both the ascending and descending pathways involve regions of the brain involved in not just primary sensation but also emotional and cognitive processing. These associated regions include the dACC, dorsolateral prefrontal cortex (dlPFC), and amygdala (AMG). Labeled regions out of (lateral to) the midsagittal section are outlined with *dashed lines*. BG = basal ganglia; M1 = primary motor cortex; PB = parabrachial nuclei; PCC = posterior cingulate cortex; RM = rostral medulla; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; SMA = supplementary motor area; SPL = superior parietal lobule.

described as consisting of 2 major subdivisions with distinct functions: the dorsal cognitive and the rostral-ventral affective divisions.¹⁵⁴ The cognitive division, which has abundant interconnections to and from the lateral prefrontal cortex, parietal cortex, and supplementary motor areas, has been ascribed a number of executive and evaluative functions, such as error processing, working memory, and anticipation.²² The affective subdivision, which includes rostral areas 24, 33, and 25, has significant connections to the amygdala and PAG and is thought to be involved in salience determination and emotional learning.⁴⁴ Although this view of functionally distinct subdivisions of the ACC has largely been replaced by more nuanced models,^{6,50,133,152,153} it continues to impact our understanding of the role of the dACC in the experience of pain.

Most commonly, the dACC is described as mediating the unpleasant or affective aspect of pain rather than the sensory-discriminative characteristics. This description is supported by a breadth of imaging studies that have shown that the dACC is activated during empathic pain as well as by the direct experience of pain.^{12,35,49,111,122,139} Several

thorough reviews have been published recently that discuss the neuroimaging evidence for the intersection of perceived and experienced pain in the dACC.^{84,132} This topic will not be covered extensively here, but evidence supports the view that the dACC is primarily involved in the motivational-affective evaluation of pain rather than in the detection of stimulus characteristics.

Despite major advancements in neuroimaging techniques, several important limitations should be noted in the imaging of chronic pain. First, the study of chronic pain is complicated by heterogeneity in pain location, inciting injury, duration of pain, and level of spontaneous pain.⁸² Samples are often small, and appropriate controls may be difficult to find. Additionally, it is often impossible and unethical to restrict the use of analgesia medication in chronic pain patients. The effect of these medications on imaging has not been fully determined. Further, individual differences in the anatomy of the cingulate cortex complicate group analysis and can make localization difficult.^{42,54} Finally, the cortical regions identified in pain contain mixed populations of neurons with different response

characteristics and firing properties. Changes in blood flow do not distinguish between activation of excitatory and inhibitory neurons, and limitations on voxel size mean that each image unit contains hundreds to thousands of neurons.³⁷ Painful mechanical and/or thermal stimulation likely activates multiple types of cells in a given region; this fact cannot be captured with sufficient granularity with current imaging techniques. Direct measures of neuronal activity are needed to corroborate neuroimaging findings.

Neurophysiology

Single-neuron recordings in awake humans provide the most direct evidence of cortical function. In 1999, Hutchison and colleagues identified neurons within the human dACC that respond selectively to thermal and mechanical stimuli in 11 patients undergoing cingulotomy for treatment of psychiatric disease.⁶⁵ Most of the cells identified responded selectively to 2 or 3 painful modalities but not to innocuous stimuli below the pain threshold. Additionally, in a patient, a neuron that responded to observation of painful stimuli being applied to another patient demonstrated activation during anticipation of receipt of the same stimuli. High-frequency electrical stimulation failed to elicit painful sensations. These results provide direct evidence that dACC neurons are involved in the processing of pain.

Additional information is provided by the use of magnetic resonance spectroscopy (MRS) to detect biochemical changes in the brain. MRS relies on analysis of the metabolites present in regions of the brain to detect changes associated with functional abnormalities. Siddall and colleagues used MRS to determine whether it was possible to discriminate subjects with chronic low-back pain from controls. MR spectra of the dACC, prefrontal cortex, and thalamus of 32 patients with low-back pain and 33 healthy controls were analyzed using pattern recognition techniques. The investigators found that they could reliably distinguish between subjects and controls with an accuracy of 100% using spectra obtained from dACC, 99% from the thalamus, and 97% from the prefrontal cortex.¹³⁷ Comparable results were reported in an MRS study of patients with spinal cord injury, suggesting that the changes observed may be generalizable to other chronic pain conditions.¹⁴² Recent animal studies suggest that these findings may reflect neuroplastic changes in the dACC that are common to multiple chronic pain etiologies.

Plasticity in the ACC

Recent work in rodent models of neuropathic pain have focused on long-term potentiation (LTP) in the ACC as a central mechanism for initiating and maintaining pathologic pain.^{15,26, 27,87,89,136,144,167} In a recent review summarizing the work in this area over the past decade, Zhuo describes at least 4 different forms of LTP involving both pre- and postsynaptic mechanisms, including increased presynaptic glutamate release and increased postsynaptic trafficking of the GluA1 α -amino-3-hydroxy 5-methyl-4-isoxazole propionate (AMPA) receptors to the cell membrane in level V ACC pyramidal neurons.¹⁶⁵ Initiation

and maintenance of LTP has been shown to be dependent upon increased phosphorylation of the atypical kinase, PKM ζ .^{73,87,88,134,155} Inhibition of PKM ζ activity resulted in diminished spontaneous pain behaviors and decreased glutamatergic transmission, suggesting that LTP of the ACC is essential for the establishment of pathologic pain states.

The findings described above also suggest a potential mechanism of action for the therapeutic effect of dACC DBS in chronic pain. In a rodent model of cortical infarct, Cooperrider and colleagues observed evidence of cortical reorganization, increased synaptic density, and up-regulation of markers of LTP following chronic electrical stimulation of the cerebellar output.³⁴ This study suggests that chronic stimulation has the potential to interrupt the pathologic changes in the dACC responsible for maintenance of chronic neuropathic pain by modulating the expression of mediators of neuronal plasticity.

Previous Studies of dACC DBS for Chronic Pain

The first case series of electrical stimulation of the anterior cingulate was published by Lewin and Whitty in 1960.⁸⁶ Based upon studies conducted in animals in which stimulation of the anterior cingulate was shown to alter autonomic function, these investigators conducted electrical stimulation of the ACC in 15 awake human subjects undergoing cingulotomy. During stimulation, patients were asked to engage in simple memory tests and calculations. Response to stimulation was monitored and recorded, although effects were sparse and inconsistent. Overall, the researchers observed only 8 positive responses to 92 bilateral stimulations. These responses consisted of momentary arrest of respiration in 3 cases of stimulation, momentary arrest of talking in 2 cases. Other responses included vomiting, regurgitating, tonic stiffening, and epigastric sensation. Overall, the researchers considered the results of their study to be largely negative and concluded, based on these results, that autonomic regulation was unlikely to be the usual function of these areas.

A second case report was published in 2007 by Spooner and colleagues, representing the first such report in which standard DBS electrodes were used to administer high-frequency electrical stimulation of the dACC to treat neuropathic pain. The patient described in this report had refractory neuropathic pain as a result of a complete spinal cord injury at the C-4 level, and had undergone numerous prior surgical and medical interventions without relief. DBS implantation of the bilateral cingulate cortex and unilateral PVG were undertaken, and a 1-week blinded stimulation period was completed prior to permanent implantation. Pain relief was assessed using the VAS and by tracking pain medication usage. Both PVG and dACC stimulation decreased VAS pain rating and led to a reduction in subcutaneous lidocaine usage. In addition, bilateral cingulate stimulation improved the patient's mood and reduced pain more completely than PVG stimulation. The investigators concluded that dACC stimulation does indeed target the affective component of pain, which can involve feelings of suffering, fear, anxiety, and depression.¹⁴¹

An additional case report of dACC DBS for chronic pain was published by Boccard et al.¹⁶ in 2013 as a prequel to the publication of a larger case series. The patient described in this case had suffered brachial plexus injury as a result of a motorcycle accident. Over the course of several years, he developed additional neuropathic pain in his legs and feet that was treated with laminoplasty, but this was shortly followed by the development of a progressive full-body pain that left him clinically depressed and suicidal. The patient opted to undergo dACC DBS, with good effect. Neuropsychological assessment at 1-year postimplantation showed no significant change in test performance apart from selective improvement on the Stroop color-word interference task. Follow-up assessment did reveal an increase in self- and caregiver-rated apathy and executive dysfunction scales on the Frontal System Behavior Evaluation Scale.

Boccard and colleagues subsequently published a larger case series involving 16 patients, including the patient described above, who underwent dACC DBS.¹⁷ In this pilot series, 15 patients with refractory pain who underwent bilateral DBS implantation of the anterior cingulate were assessed postoperatively using multiple pain and quality of life measurement tools, including the VAS, the McGill Pain Questionnaire, the 36-item Short-Form Quality of Life Health Survey (SF-36), and the EuroQol-5 Domain Quality of Life Questionnaire (EQ-5D). No a priori level of improvement on any of the measurement tools was set to determine efficacy. Pain etiologies included failed back surgery syndrome, poststroke pain, brachial plexus injury, cervical spinal cord injury, head injury, and pain of unknown origin, and distributions varied from whole body to isolated limbs. Of the 15 fully implanted patients, 11 subjects were included in the final analysis.

In this study, the investigators observed a statistically insignificant overall improvement in the VAS of 24.5%, with a range of -41% to 100%. For 5 patients, average VAS scores dropped below 4 on a scale of 1-10, indicating mild pain, and 1 patient reported freedom from pain at 17 months after surgery. Statistically significant improvements were observed in the Physical Functioning and Bodily Pain domains of the SF-36, as well as on the EQ-5D, which evaluates 5 health dimensions including mobility, self-care, usual activities, pain, and anxiety. No major adverse events were discussed in this series, and it is unclear whether any unexpected stimulation effects, other than those discussed above, were observed. The investigators concluded that dACC DBS is a viable option for the treatment of medically refractory chronic pain.

In interpreting the results of this study, several important considerations arise. The first is that the population treated in this study is heterogeneous; patients with a number of chronic pain syndromes, arising through several different injury mechanisms, were included in this group. It is possible that certain pain etiologies may be more responsive to dACC DBS than others. Likewise, differences in anatomy, arising naturally or as a result of physiological postinjury changes, may alter responsiveness to DBS treatment. Additional study may determine that individualized targeting improves outcomes or that certain imaging features are predictive of good outcomes. Finally, as

discussed above, studies exploring the circuitry of pain perception have consistently identified the dorsal anterior cingulate as being involved in the “affective component” of pain. That is, activity of the dACC during painful stimulation has been associated with the negative emotional experience of pain rather than the nociceptive experience. Therefore, scales such as the VAS, which focus primarily on the nociceptive aspect of pain, may not adequately address changes in the perception of pain effected by this surgical intervention. It is possible that scales that aim to assess quality of life or the impact of pain on daily functioning may be more appropriate choices for adequate outcome assessment.

Interestingly, Parvizi and colleagues recently published a case study describing the subjective experience of the effects of electric brain stimulation of the dACC on 2 epilepsy patients.¹¹² Stimulation was delivered via implanted intracranial electrodes that were used clinically to identify epileptogenic foci. Upon application of stimulation, the investigators noted stereotyped cognitive, emotional, and autonomic reactions that they characterized as demonstrating a “will to persevere.” Patients described feeling a sense of foreboding that was accompanied by a belief that they would be able to overcome the obstacles facing them. The investigators used resting state fMRI to support the idea that this effect may result from activation of networks through the dACC that are involved in assigning salience. Although this study described the effects of acute stimulation rather than chronic stimulation as would occur with DBS, it corroborates a framework from which to understand how electrical modulation of the dACC might produce affective pain “relief.” The findings concord with the notion that the component of pain targeted by this therapeutic intervention is not the sensorial experience itself but rather the perceived emotional “burden” or “bother.”

Additional Considerations

The dorsal anterior cingulate has been implicated in a diverse range of cognitive, mood, and affective processes, raising concern about the potential for adverse effects related to chronic stimulation of the dACC.^{41,56,61,62,147} Little direct evidence of stimulation effects is available in the literature. Assessment and discussion of risk must draw on lessons extracted from the more robust cingulotomy and existing DBS literature.

A common criticism of the literature surrounding cingulotomy for refractory pain is that evaluation of the effects on patient mood, personality, and cognition has not been systematic. Negative effects on attention, executive function, and behavior have been noted in several studies, but few formal evaluations have been performed.^{20,33} Cohen and colleagues attempted to address the question of the neuropsychiatric impact of bilateral cingulotomy prospectively in a cohort of 12 patients with nonmalignant chronic pain. At the 1-year postoperative evaluation, the investigators found decreased intention and spontaneous response production as well as mildly compromised executive function. Deficits were identified in performance of the Stroop interference task and the Adaptive Rate Continuous Performance Test Inconsistency Index, which the

investigators classified as a task of sustained attention.³² A study by Yen and colleagues designed to assess neurocognitive effects of cingulotomy also noted a postcingulotomy deficit in performance on the Stroop task, although the effect was transient.¹⁶¹

In considering the lessons learned from cingulotomy in assessing the theoretical neuropsychiatric and cognitive risks of targeting the dACC for DBS, it is important to consider that the effects of DBS are likely the summation of modulating effects at both the neuronal and network levels.^{19,128,145,146,156,160} Stimulation is therefore hypothesized to impact not only the target and its immediately surrounding structures, but also neural networks that may have far-reaching branches.^{39,94,119} The extent of the neural activation associated with DBS was recently demonstrated by Riva-Posse and colleagues by applying DTI tractography and finite element models of electrical field propagation to create individualized maps of stimulation-induced activation in DBS patients.¹²⁴ Other studies have looked at markers of cortical activity such as neurotransmitter levels, changes in neuronal morphology, or cerebral blood flow for evidence of alteration in the activity of neural circuitry as a result of chronic neurostimulation, with similar conclusions.²

An additional factor to consider is the impact that chronic pain has on cognitive and emotional processing.^{78,110} The IASP published a clinical update on their website in 2007, reviewing the data surrounding the impact of chronic pain on cognitive functioning.⁷⁸ Two conclusions were drawn from their review of the literature: 1) chronic pain has a negative effect on cognition, and 2) cognitive impairment has the potential to impair patient communication of pain and reduce the effectiveness of cognitive therapies. The deficits noted most commonly in the literature involved attention, memory, verbal fluency, processing speed, and mental flexibility. The authors also pointed out the fact that analysis of the effect of chronic pain on cognition is confounded by commonly used medical treatments, such as opioid painkillers, which may independently impact cognitive functioning. Therefore, it is possible that DBS of the ACC may improve cognitive functioning by a 2-fold process, that is, by both alleviating the patient's pain and by reducing reliance on obtunding medications.

Conclusions

Chronic neuropathic pain is one of the most common and costly health complaints in the world today. It has the potential to interfere with all aspects of a patient's life, resulting in missed days of work, withdrawal from the workforce, greater health resource utilization, and strained interpersonal relationships. According to the American Academy of Pain Medicine, more than 1.5 billion people worldwide currently suffer from chronic pain, and 3%–4.5% of the worldwide population qualifies as having neuropathic pain, which often does not respond to available treatments.⁶⁶ Combating chronic pain is currently a national health initiative here in the United States.

The role of DBS in the treatment of chronic refractory neuropathic pain is currently unknown.³⁶ Advancements in neuroimaging and neuronal recording techniques over

the past decade have refined our understanding of neural circuitry and led to the identification of new targets for therapy. The dACC has long been an area of interest for the treatment of refractory pain. Recent pilot studies of DBS targeting the ACC for the treatment of chronic neuropathic pain have shown encouraging results in the alleviation of what is often an untreatable and disabling condition.

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Author Contributions

Conception and design: Russo. Acquisition of data: Russo. Analysis and interpretation of data: Russo. Drafting the article: Russo. Critically revising the article: Sheth. Reviewed submitted version of manuscript: Sheth. Approved the final version of the manuscript on behalf of both authors: Russo.

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