Randomized Clinical Trial of Deep Brain Stimulation for Poststroke Pain

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Objective: The experience with deep brain stimulation (DBS) for pain is largely based on uncontrolled studies targeting the somatosensory pathways, with mixed results. We hypothesized that targeting limbic neural pathways would modulate the affective sphere of pain and alleviate suffering.

Methods: We conducted a prospective, double-blinded, randomized, placebo-controlled, crossover study of DBS targeting the ventral striatum/anterior limb of the internal capsule (VS/ALIC) in 10 patients with poststroke pain syndrome. One month after bilateral DBS, patients were randomized to active DBS or sham for 3 months, followed by crossover for another 3-month period. The primary endpoint was a ≥50% improvement on the Pain Disability Index in 50% of patients with active DBS compared to sham. This 6-month blinded phase was followed by an 18-month open stimulation phase.

Results: Nine participants completed randomization. Although this trial was negative for its primary and secondary endpoints, we did observe significant differences in multiple outcome measures related to the affective sphere of pain (eg, Montgomery–Åsberg Depression Rating Scale, Beck Depression Inventory, Affective Pain Rating Index of the Short-Form McGill Pain Questionnaire). Fourteen serious adverse events were recorded and resolved.

Interpretation: VS/ALIC DBS to modulate the affective sphere of pain represents a paradigm shift in chronic pain management. Although this exploratory study was negative for its primary endpoint, VS/ALIC DBS demonstrated an acceptable safety profile and statistically significant improvements on multiple outcome measures related to the affective sphere of pain. Therefore, we believe these results justify further work on neuromodulation therapies targeting the affective sphere of pain.

Neuropathic pain, defined as “pain initiated or caused by a primary lesion or dysfunction in the nervous system,”¹ is common in the general population, with an estimated prevalence of 8% among adults enrolled in a family practice.² It can be associated with pathology of the peripheral nervous system or the central nervous system (typically referred to as central pain). When central pain is associated with stroke, typically involving the somatosensory thalamic nuclei or the somatosensory ascending pathways, it is commonly referred to as poststroke pain syndrome (PSPS). PSPS is commonly characterized by hemiparesis associated with severe unremitting anesthesi dolorosa and is known to be particularly refractory to pharmacological, interventional, and surgical treatment modalities.³

Treating patients with PSPS can be extraordinarily frustrating for both the patient and the physician. To date, interventional and neurostimulation-based treatment modalities (eg, deep brain stimulation [DBS], spinal cord stimulation, and motor cortex stimulation) have

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.24927
Received Jan 12, 2017, and in revised form Mar 27, 2017. Accepted for publication Mar 29, 2017.

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focused almost exclusively on modulation of pain transmission through ascending pathways (e.g., lateral spinothalamic tract). The primary endpoint is typically analgesia, with efficacy defined as a reduction of ≥50% in pain magnitude reported by the visual analog scale (VAS) in 50% of patients. Despite significant advances, the majority of patients undergoing surgical intervention for the management of medically refractory PSPS fail to experience significant long-term benefits.

Traditionally, neurostimulation therapies for pain attempt to interrupt or modulate the sensory-discriminative pathways. However, our current scientific understanding of pain, described by the neuromatrix theory, indicates that the overall pain experience (and consequently disability) is determined by the integration of nociceptive inputs with the affective and cognitive spheres of pain processing. In this study, we departed from an analgesia-based approach and focused on neural networks related to the control of emotion and behavior. This approach was based on the hypothesis that modulation of the affective sphere of pain would relieve pain-related disability, with or without a reduction of pain intensity.

To test this conceptual approach, we conducted the first federally funded prospective, double-blind, placebo-controlled, crossover trial of DBS for neuropathic pain. We targeted the ventral striatum/anterior limb of the internal capsule (VS/ALIC), given its well-established role in the control of emotion and behavior and the previously documented safety and efficacy of VS/ALIC DBS for the treatment of obsessive–compulsive disorder (OCD) and treatment-resistant depression (TRD). This trial included 10 patients with PSPS who had hemibody pain and anesthesia dolorosa secondary to a contralateral lesion.

**Patients and Methods**

**Study Design and Participants**

This study was a 6-month, randomized, double-blind, placebo-controlled, crossover trial followed by an 18-month open stimulation phase (Fig 1). The study was conducted at a single hospital (Cleveland Clinic) in the United States. Patients with a clinical diagnosis of PSPS were eligible if they met the following inclusion criteria: hemibody pain and anesthesia dolorosa due to contralateral lesion(s) of the contralateral thalamic area and somatosensory pathways, 6 months or more of medically refractory severe pain, pain disability reported by the Pain Disability Index (PDI) > 30 points at the time of enrollment, an average daily pain for the past 30 days > 5 on a 0 to 10 scale, and failure to adequately respond to at least 1 antidepressant, 1 antiseizure medication, and 1 oral narcotic. Exclusion criteria included patients with severe, unmanaged psychiatric or cognitive comorbidities, and the usual contraindications for DBS or intracranial procedures. A complete list of inclusion and exclusion criteria and the study protocol can be found at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT01072656?term=machado) and in our prior report.

We evaluated patients at the senior author’s (AGM) outpatient clinic. If we thought a patient was potentially eligible for the study following prescreen, we extensively explained the study to the patient and his/her family. If the patient wished to provide written informed consent, we continued with the screening procedures. We thoroughly discussed the study and reviewed the entire consent form with patients who met criteria for enrollment. A staff bioethicist (PJF) served as the consent monitor for the study and independently evaluated each patient’s ability to understand the study prior to enrollment and signing of the informed consent form. A standardized checklist was utilized to confirm understanding (i.e., a modified version of the Dartmouth Informed Consent Evaluation Feedback Tool, used with permission). Participants had access to the bioethicist throughout the study and met with the bioethicist when making choices near the end of their participation.

This study was investigator-initiated (AGM). All study procedures were approved by the Cleveland Clinic Institutional Review Board and by a physician-sponsored Investigational Device Exemption from the U.S. Food and Drug Administration. All patients provided written informed consent before enrollment.

**Randomization and Masking**

We randomly assigned participants to either the stimulation on-first group (active DBS for the first 3-month period, followed
by sham [ie, 0V] stimulation for the second 3-month period) or
the stimulation off-first group (sham stimulation for the first
3-month period, followed by active DBS for the second 3-
month period). A computer-generated randomization sequence
was created by a biostatistician (B.H.) using block randomiza-
tion with a size of 2. The principal investigator (A.G.M.) was
unblinded to the treatment allocation and performed the stimu-
lator programming procedures. This unblinded clinician spent
equal time adjusting the stimulator of the participants at the
start of the active DBS or sham stimulation periods. Adjust-
ments were done in an identical manner during both blinded
periods. The electrical parameters were selected to avoid side
effects and to avoid any sensation of stimulation being per-
ceived by the participants to avoid potential unmasking of the
treatment allocation. All study personnel involved in outcome
assessments were masked to the treatment allocation.

Procedures
Patients were screened for eligibility, and after inclusion each
patient completed a baseline assessment. After baseline assess-
ment, patients underwent bilateral DBS lead implantations in
the VS/ALIC area following a frame-based technique similar to
the technique routinely used in DBS for movement disorders
(Fig 2).15 Briefly, we applied a stereotactic head frame (Leksell;
Elekta, Stockholm, Sweden) while the patient was under local
anesthesia or intravenous sedation with vital sign monitoring.
We then obtained a stereotactic computed tomographic (CT)
scan with the head frame in place. We coregistered this stereo-
tactic CT to a preoperative volumetric magnetic resonance
imaging scan in a commercially available surgical planning sta-
tion (StealthStation; Medtronic, Minneapolis, MN) and
designed the surgical plan consisting of the target, entry point,
and trajectory.

We used our previous experience with DBS for OCD and
TRD to determine the appropriate surgical targeting.13,16
We bilaterally implanted each electrode array (model 3387 or
3391, Medtronic) lead through the ALIC into the VS, with the
lead tip placed approximately 3 to 5mm ventral to the junction
between the ALIC and the anterior commissure. We had previ-
ously shown that targeting this area reliably elicits positive
changes in mood and anxiety in patients with OCD and
TRD.13,17,18

After lead implantation, we performed intraoperative
stimulation with the patient awake and able to answer ques-
tions. We used this intraoperative test to identify electrode loca-
tions that produced acute improvements in mood and
reductions in anxiety and/or pain, without significant adverse
effects. Targeting was determined based on the patient’s report
of qualitative improvement and/or lack of adverse effects in
response to stimulation from at least 1 electrode contact. Once
we identified an adequate lead location, we anchored the DBS
leads to the skull and closed the surgical sites with the patient
under sedation following standard DBS surgical techniques.15
We obtained a postoperative CT to verify the lead implant
location. We later connected the bilateral lead implants to a sin-
gle nonrechargeable implantable neurostimulator (Activa PC,
Medtronic) placed in an infraclavicular location with the
patient under general anesthesia.

To determine the chronic stimulation parameters in each
patient, we performed outpatient stimulation parameter titra-
tion for up to 7 visits over 2 to 4 weeks starting 1 month after
DBS implantation. We initially conducted a monopolar survey,
evaluating the acute effects of stimulation with each individual
electrode. Using a pulse width of 90 or 210 microseconds, we
gradually increased the pulse amplitudes to examine the effects
of acute stimulation on mood, anxiety, or suffering (integer rat-
ing on a 0–10 scale). Based on the results of the monopolar
survey and our experience with VS/ALIC stimulation, we also
tested bipolar and/or multipolar electrode combinations. We
retested electrode combinations that produced positive results
with the patients blinded to the stimulation state. We then
selected stimulation settings that produced the most consistent
positive effects with no or well-tolerated side effects for chronic
stimulation during the double-blind phase. Side effects that
were related to high stimulation amplitudes included hypomag-
nia, sensations of warmth/flushing, and euphoria.13,17 As part
of the study design, patients returned monthly for rating assess-
ments and device interrogation during the double-blind phase.
We allowed for modifications to stimulation settings (eg,
amplitude or pulse width) during the open-label phase to optimize efficacy.

Formal assessments were performed at each visit by clinicians and study personnel masked to the stimulation status. These assessments included sensory and motor neurological examinations, pain assessment, neuropsychological cognitive assessment, functional neuroimaging, and a battery of outcome measures. The neuropsychological assessment included California Verbal Learning Test, Wechsler Memory Scale–III, Delis–Kaplan Executive Function System, Wisconsin Card Sorting Test, Beck Depression Inventory (BDI), Beck Anxiety Inventory, Columbia-Suicide Severity Rating Scale, Montgomery–Åsberg Depression Rating Scale (MADRS), Positive and Negative Affect Schedule, and NEO Five-Factor Inventory. Additional outcome measures included PDI, Box and Blocks Test, Jepsen-Taylor Hand Function Test, VAS, Short-Form McGill Pain Questionnaire (McGill), and EQ-5D. During the blinded stimulation phase, we repeated tests and outcome measures at 1, 2, and 3 months after randomization and 1, 2, and 3 months after crossover (see Fig 1). We performed functional neuroimaging and neurophysiological studies (functional magnetic resonance imaging and magnetoencephalography) at baseline, 2 months after randomization, and 2 months after crossover.

Upon completion of the blinded stimulation phase, we reprogrammed all participants in an attempt to continuously optimize outcomes in an unblinded fashion. There was no sham stimulation after this point. Participants completed planned follow-up assessments at approximately 9, 12, 18, and 24 months as well as at additional time points as medically necessary. We repeated the same tests and outcome measures at each follow-up session noted above, and the functional neuroimaging measurements were repeated annually (ie, 12- and 24-month follow-up visits).

Outcomes
To evaluate whether modulation of the affective sphere of chronic pain would alleviate disability and promote independence, we selected the PDI as the primary outcome measure of this study. We defined the primary endpoint as a ≥50% improvement on the PDI in 50% of patients with active VS/ALIC DBS compared to sham stimulation. We included the following secondary endpoints: (1) ≥50% improvement on the PDI in 50% of patients at the 2-year follow-up (ie, at end of the open stimulation phase), (2) affirmative response to the prospect of undergoing the treatment again if the same outcomes were to be achieved, and (3) ≥50% reduction in pain intensity assessed by the VAS in 50% of the patients at the 2-year follow-up. As described in the Procedures section, we incorporated several additional outcome measures that included depression and anxiety rating scales as well as detailed pre- and postsurgical cognitive assessments, to monitor the safety of DBS implantation and chronic stimulation.

Statistical Analysis
Because this trial employed the crossover design in the blinded phase, we used linear mixed-effects models to analyze various continuous outcomes (ie, score on each outcome measure). These models included a participant-level random intercept to account for correlations of measurements from the same participant. For binary outcomes (eg, ≥50% improvement on PDI), we used mixed-effects logistic models. We obtained the least-square estimates (eg, mean PDI or probability of having ≥50% improvement) for the active and sham treatments and performed group comparisons with the appropriate contrasts. For the open phase, we calculated the changes from baseline to long-term follow-up visits for all participants and summarized the changes with means, standard deviations, and the number of participants with ≥50% improvement. We conducted all analyses with RStudio. We established statistical significance with 2-sided \( p < 0.05 \). Due to the small sample size \( (n = 9) \), we were unable to perform procedures to correct for multiple comparisons. This study was overseen by a Data Safety Monitoring Board (DSMB) consisting of a neurosurgeon and neurologist with expertise in their field of practice and in the conduct of clinical trials. No DSMB members were directly involved in the study or are authors of this article. This study is registered with ClinicalTrials.gov (number NCT01072656).

Role of the Funding Source
This trial was an investigator-initiated study with no commercial sponsorship. During the funding reviewing period, the funding agency reviewed and approved the criteria for human subject enrollment and study procedures. The National Institutes of Health had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
From April 9, 2010 to September 27, 2013, we assessed a total of 69 patients for study eligibility (Fig 3). After an initial prescreen, 36 of 69 patients did not provide consent to perform the screening procedures for this study. After the screening procedures, 23 of 33 patients were excluded from the study; 6 patients did not consent to enrollment, 13 patients did not meet the inclusion criteria, and 4 patients were lost to follow-up. We enrolled 10 patients in this study. One participant was implanted with the DBS system, but dropped out of the study prior to the randomization phase. The remaining 9 participants completed the randomization procedure and were included in the primary endpoint analysis.

Table 1 shows the demographics and clinical characteristics for all 10 participants enrolled in the study. The mean age of the participants was 51.3 years (ranging from 41 to 60 years). The mean time since stroke was 4.7 years (range = 1–9 years), and the mean pain duration was 4.7 years (range = 1–9 years). The mean pain intensity of the participants was 8.5 on a 0 to 10 scale.
Chronic stimulation parameter settings for each patient are shown in Table 2.

The key clinical results are shown in Table 3. During the blinded stimulation phase, we did not observe a significant difference in pain-related disability as indexed by a \( >50\% \) improvement on the PDI (11% DBS ON vs 12% DBS OFF, odds ratio = 1.05, 95% CI = 0.96–1.15, \( p = 0.270 \)), but we did measure statistically significant improvements on the McGill Affective Pain Rating Index (39% DBS ON vs 18% DBS OFF, odds ratio = 0.35, 95% CI = 0.17–0.73, \( p = 0.005 \)) and the McGill Present Pain Intensity (10% DBS ON vs 3% DBS OFF, odds ratio = 0.27, 95% CI = 0.11–0.63, \( p = 0.002 \)).

We examined the quality of the study blind by having the participants and study personnel guess whether the stimulation was ON or OFF at each visit during the randomization phase. The participants and blinded study personnel correctly predicted the stimulation state at a rate of 69.8% and 56.6%, respectively (\( n = 53 \) guesses). The participants were able to correctly predict between active and sham stimulation at a rate significantly greater than due to chance alone (\( p = 0.004 \)). However, the blinded study personnel were unable to guess the correct state at a rate significantly greater than chance (\( p = 0.336 \)).

At the end of the 6-month blinded randomization phase, each participant entered an 18-month open phase in which unblinded active stimulation was applied. At the end of this open stimulation phase, approximately one-third of the participants maintained a \( >50\% \) improvement on the MADRS (3 of 9), BDI (4 of 9), and McGill Affective Pain Rating Index (3 of 9), respectively. Far fewer participants experienced a \( >50\% \) improvement on the PDI (1 of 9), McGill Sensory Pain Rating Index (1 of 9), VAS (1 of 9), and McGill Present Pain Intensity (0 of 9) at the end of the open phase.

Every participant was asked the following question at the end of the trial: “Would you undergo this procedure again if you were to get the same benefits you experienced?” More than half (5 of 9) of the participants responded positively. These 5 participants elected to continue DBS at the end of the trial, and their nonrechargeable implantable stimulator was replaced with a rechargeable stimulator for continued use. The remaining 4 of 9 participants elected to have their DBS systems removed before completing the 18-month open stimulation phase (see Fig 3).

We classified adverse events in the following categories: sleep and alertness changes, headache and worsened pain, fatigue and weakness, seizure, wound infection or redness, other infection, back disorders, abdominal and digestive disorders, other medical conditions, worsening of suicidal ideation, balance difficulties and falls, and other behavior changes (Table 4). A total of 88 adverse events were experienced in all 10 participants. All stimulation-related adverse events, such as insomnia, were transient and resolved with stimulator reprogramming. Only 14 of the adverse events were considered

FIGURE 3: Trial profile. VS/ALIC = ventral striatum/anterior limb of the internal capsule.
serious. Three of these serious adverse events were identified as related to the DBS therapy. One study-related serious adverse event included a seizure that was resolved with medication. The other 2 study-related serious adverse events occurred in the same participant and included wound dehiscence around a burr hole (resolved with surgery) and infection (resolved by removal of the DBS system). After the infection had cleared, we implanted a new DBS system in this participant and the participant reentered the trial at the beginning of the blinded phase. The remaining 11 serious adverse events were identified as unrelated to the DBS. All 14 serious adverse events were resolved.

Discussion

In this prospective, randomized, double-blind, placebo-controlled, crossover trial, VS/ALIC DBS produced improvements on clinical outcomes related to the affective sphere of chronic pain in patients with PSPS. These improvements were significantly better than those observed with sham stimulation and occurred without significant changes in the sensory sphere of chronic pain. Analgesia-based treatment options have shown limited outcomes to treat central pain syndromes such as PSPS.6 We argue that analgesia may be an inappropriate treatment goal. The VAS is widely used and is the current standard in assessing pain relief following an intervention. Although the VAS is efficacious in monitoring acute pain, it can be misleading in the assessment of chronic pain, as reductions on the VAS are poorly correlated with patient satisfaction or disability.19 In light of these observations, we argue that neuromodulation therapies should focus on decreasing pain-related suffering or pain-related disability rather than pain intensity. Potential therapies that promote rehabilitation and reduce dependence for self-care should be considered valuable to both patients and society, even if patients still experience pain. We believe that chronic pain-related disability is not solely due to the pain intensity at a given point in time, but is related to the expectation of unrelenting pain that is not expected to resolve, thus adding to the suffering experience. Reducing pain anticipation related to the use of the affected limbs, which is aggravated by allodynia, as well as reducing the dread of pain may also reduce disability. Therefore, we propose a shift in surgical targeting,

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Stroke Location</th>
<th>Type of Stroke</th>
<th>Pain Side</th>
<th>Pain Duration, yr</th>
<th>Mean Pain Intensity, 0–10</th>
<th>Sensory Deficit in the Painful Zone</th>
<th>Motor Deficit in the Painful Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>M</td>
<td>Left thalamus</td>
<td>Ischemic</td>
<td>Right</td>
<td>3</td>
<td>7</td>
<td>Severe</td>
<td>Moderate</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>F</td>
<td>Right middle cerebral artery territory</td>
<td>Ischemic</td>
<td>Left</td>
<td>9</td>
<td>10</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>M</td>
<td>Right medulla</td>
<td>Ischemic</td>
<td>Left</td>
<td>9</td>
<td>6</td>
<td>Severe</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>M</td>
<td>Left brainstem</td>
<td>Hemorrhagic</td>
<td>Right (left face)</td>
<td>1</td>
<td>9</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>M</td>
<td>Left temporal stem</td>
<td>Hemorrhagic</td>
<td>Right</td>
<td>2</td>
<td>10</td>
<td>Severe</td>
<td>Moderate</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>M</td>
<td>Right thalamus</td>
<td>Ischemic and hemorrhagic</td>
<td>Left</td>
<td>1</td>
<td>10</td>
<td>Moderate</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>M</td>
<td>Left thalamus; left parietal white matter</td>
<td>Hemorrhagic</td>
<td>Right</td>
<td>3</td>
<td>7</td>
<td>Severe</td>
<td>Moderate</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>F</td>
<td>Left basal ganglia</td>
<td>Hemorrhagic</td>
<td>Right</td>
<td>9</td>
<td>9</td>
<td>Severe</td>
<td>Moderate</td>
</tr>
<tr>
<td>9</td>
<td>41</td>
<td>F</td>
<td>Left thalamus</td>
<td>Hemorrhagic</td>
<td>Right</td>
<td>4</td>
<td>9</td>
<td>Severe</td>
<td>Moderate</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
<td>F</td>
<td>Right basal ganglia</td>
<td>Hemorrhagic</td>
<td>Left</td>
<td>6</td>
<td>8</td>
<td>Severe</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Sensory deficits were defined as follows: Mild = subjective mild hypoesthesia, but able to distinguish sharp from dull; Moderate = inability to consistently distinguish between sharp and dull; Severe = anesthesia dolorosa. Motor deficits were defined as follows: None = 5/5; Mild = strength between 3 and 4/5; Moderate = strength between 2 and 3/5; Severe = hemiplegia or minimal movement of the upper extremity. F = female; M = male.
away from the neural networks that underlie the sensory-discriminative sphere toward the networks that mediate the affective–motivational sphere of chronic pain.10

Data from psychosurgical interventions support this shift from focusing on the sensorineural components to the affective–motivational sphere of pain. Anterior capsulotomy is a stereotactic procedure in which the reciprocal projections between the orbitofrontal cortex and the thalamus are lesioned. This procedure has been shown to alleviate obsessive symptoms and anxiety20 and demonstrates the relevance of the fibers projecting through the ALIC in the control of emotion and behavior. Radiofrequency ablation of the anterior cingulate has also shown the ability to alleviate symptoms in OCD as well as pain in chronic cancer and noncancer pain.20–23 Although these ablative procedures can be effective, there are significant concerns for cognitive changes at follow-up and the risk for deterioration of executive function.24

DBS is a reversible and adjustable therapy that allows for adverse effects to be managed and clinical efficacy to be optimized. Although our study represents the first randomized placebo-controlled trial of DBS for neuropathic pain, previous studies used DBS of the anterior cingulate cortex to target the affective sphere of chronic pain.25–28 These studies illustrated the potential for DBS of the affective sphere of pain to improve physical function and/or bodily pain.

In this study, we targeted the affective sphere of chronic pain via DBS of the VS/ALIC. Nuttin and colleagues pioneered DBS of the ventral ALIC for treating OCD, which led to further clinical testing.12 DBS of the ALIC was shown to be safe and effective for OCD, with no permanent adverse effects or loss of executive function,16 and was approved by the U.S. Food and Drug Administration under a Humanitarian Device Exemption. Our multicenter collaborative group reported long-term effects of VS/ALIC DBS in patients with TRD that produced significant reduction in the main outcome measures during an uncontrolled study.13 A subsequent study evaluated the specific areas of the ALIC associated

### TABLE 2. Chronic Stimulation Parameter Settings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Lead Hemisphere</th>
<th>Active Electrodes</th>
<th>Pulse Amplitude, V</th>
<th>Pulse Width, μs</th>
<th>Pulse Frequency, Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>Right</td>
<td>C(+) 10(−) 11(−)</td>
<td>2.3</td>
<td>90</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>C(+) 2(−) 3(−)</td>
<td>2.3</td>
<td>90</td>
<td>130</td>
</tr>
<tr>
<td>3</td>
<td>Right</td>
<td>C(+) 8(−) 9(−)</td>
<td>3.2</td>
<td>90</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>C(+) 0(−) 1(−)</td>
<td>3.2</td>
<td>210</td>
<td>130</td>
</tr>
<tr>
<td>4</td>
<td>Right</td>
<td>10(−) 11(+)</td>
<td>2</td>
<td>210</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>2(−) 3(+)</td>
<td>2</td>
<td>210</td>
<td>130</td>
</tr>
<tr>
<td>5</td>
<td>Right</td>
<td>C(+) 8(−)</td>
<td>3.5</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>C(+) 0(−)</td>
<td>3.5</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>Right</td>
<td>C(+) 10(−) 11(−)</td>
<td>4</td>
<td>60</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>C(+) 2(−) 3(−)</td>
<td>4</td>
<td>60</td>
<td>130</td>
</tr>
<tr>
<td>7</td>
<td>Right</td>
<td>C(+) 11(−)</td>
<td>1</td>
<td>210</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td>Right</td>
<td>C(+) 8(−) 9(−)</td>
<td>3.5</td>
<td>180</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>C(+) 2(−) 3(−)</td>
<td>3.5</td>
<td>180</td>
<td>130</td>
</tr>
<tr>
<td>9</td>
<td>Right</td>
<td>C(+) 10(−)</td>
<td>6</td>
<td>60</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>C(+) 1(−)</td>
<td>6</td>
<td>60</td>
<td>130</td>
</tr>
<tr>
<td>10</td>
<td>Right</td>
<td>C(+) 9(−) 10(−)</td>
<td>4.5</td>
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<td>130</td>
</tr>
<tr>
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<td>C(+) 9(−) 10(−)</td>
<td>4.5</td>
<td>90</td>
<td>130</td>
</tr>
</tbody>
</table>

For the active electrodes, + and − refer to the electrode polarity. C represents the case of the implantable pulse generator. For right-side leads, the electrodes are numbered 8 to 11, with 8 being the most distal electrode. For left-side leads, the electrodes are numbered 0 to 3, with 0 being the most distal electrode.

N/A = not applicable.
with chronic changes in mood and anxiety. Computer models of VS/ALIC DBS in patients with TRD demonstrated that clinical response was associated with activation of the pathways that course laterally and medially to the VS or dorsally and laterally to the nucleus accumbens. In this study, we proposed stimulation of these pathways for modulating the affective sphere of chronic pain.

To our knowledge, this study represents the first prospective, randomized, double-blind, placebo-
controlled trial of DBS for neuropathic pain. We believe that our placebo-controlled study design represented an excellent method to generate class I evidence of neurostimulation for chronic pain. In this study design, it was important to evaluate the quality of the stimulation blinding during the randomized phase. Participants, but not the blinded study personnel, were able to correctly guess the treatment allocation at a rate significantly higher than chance (ie, 69.8%). These results suggest overall maintenance of the stimulation blind, but these results also suggest that the therapeutic benefit during active DBS or the lack of benefit during sham stimulation was sufficient to increase the likelihood of a participant guessing correctly.

We chose PSPS to test the effects of VS/ALIC DBS because these patients have severe refractory pain and are commonly referred for consideration for neurosurgical interventions. The severity and refractoriness of the pain often motivates both the patient and the physician to explore options such as motor cortex stimulation or thalamic DBS, despite the limited efficacy of these approaches for PSPS.3,6,8,31,32 Patients with PSPS are in need of new therapies aimed at alleviating suffering and disability. PSPS patients also provided a unique model to study the effects of neuromodulation of the brain networks related to the control of emotion and behavior. The integration between the affective–motivational, cognitive–evaluative, and sensory–discriminative spheres of chronic pain can make it difficult to study the isolated effects of neuromodulation of a single sphere. However, because PSPS patients have complete or near-complete damage to the sensory–discriminative pathways and because our double-blind study design reduced the cognitive–evaluative component, this study provided a good model to assess the near-isolated effects of DBS upon the affective–motivational sphere of chronic pain. We also selected a single target area in a homogenous patient population (single syndrome from a single etiology). Because we employed a crossover design, patients served as their own control. We believe that this type of systematic approach limits potential interpretational confounds, which is vital for the early investigation of any emerging therapy.

<p>| TABLE 4. AEs |
|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>AE</th>
<th>Patients, No. (%)</th>
<th>AEs, No. (%)</th>
<th>Study Related?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep and alertness changes, eg, insomnia, sleepiness, drowsiness, inability to concentrate</td>
<td>3 (30%)</td>
<td>8 (9%)</td>
<td>Yes (7/8); no (1/8)</td>
</tr>
<tr>
<td>Headache and worsened pain</td>
<td>6 (60%)</td>
<td>13 (15%)</td>
<td>Yes (6/13); no (7/13)</td>
</tr>
<tr>
<td>Fatigue and weakness</td>
<td>2 (20%)</td>
<td>5 (6%)</td>
<td>Yes (2/5); no (3/5)</td>
</tr>
<tr>
<td>Seizure</td>
<td>2 (20%)</td>
<td>2 (2%)</td>
<td>Yes (1/2); no (1/2)</td>
</tr>
<tr>
<td>Wound infection or redness: wound dehiscence and surgical site infection</td>
<td>3 (30%)</td>
<td>5 (6%)</td>
<td>Yes (2/5); no (3/5)</td>
</tr>
<tr>
<td>Other infection, eg, urinary tract infection, cellulitis staph infection, influenza, pneumonia</td>
<td>5 (50%)</td>
<td>12 (14%)</td>
<td>No</td>
</tr>
<tr>
<td>Back disorders: back problems and back surgery</td>
<td>3 (30%)</td>
<td>4 (5%)</td>
<td>No</td>
</tr>
<tr>
<td>Abdominal and digestive disorders, eg, acid reflux, nausea, vomiting, diarrhea, hernias, appendicitis, cholecystitis</td>
<td>4 (40%)</td>
<td>7 (8%)</td>
<td>Yes (3/7); no (4/7)</td>
</tr>
<tr>
<td>Other medical conditions, eg, diabetes, palpitation, urinary problems, sepsis, hypertension</td>
<td>4 (40%)</td>
<td>8 (9%)</td>
<td>No</td>
</tr>
<tr>
<td>Worsening of suicidal ideation</td>
<td>1 (10%)</td>
<td>1 (1%)</td>
<td>No</td>
</tr>
<tr>
<td>Balance difficulties and falls</td>
<td>5 (50%)</td>
<td>6 (7%)</td>
<td>Yes (2/6); no (4/6)</td>
</tr>
<tr>
<td>Other behavior changes, eg, libido change, hallucination, agitation, delirium, hypomania</td>
<td>7 (70%)</td>
<td>17 (19%)</td>
<td>Yes (5/17); no (12/17)</td>
</tr>
<tr>
<td>Total</td>
<td>10 (100%)</td>
<td>88 (100%)</td>
<td>Yes (28/88); no (60/88)</td>
</tr>
</tbody>
</table>

AE = adverse event.
The results of this study suggest that VS/ALIC DBS can provide clinical benefit to patients with refractory PSPS. Although the primary endpoint (ie, 50% of patients achieve ≥50% improvement in PDI) was not achieved, DBS efficacy was demonstrated by significant improvements in indices of the affective component of pain, such as depression, anxiety, and quality of life (see Table 3). Furthermore, approximately half of the participants indicated that they would undergo the procedure again if given the same results and opted to continue DBS. Several participants also maintained ≥50% improvements in the MADRS, BDI, and McGill Affective Pain Rating Index at the 2-year follow-up. Significant improvements in outcomes measures sensitive to the affective aspect of pain, without a significant decrease in the sensory sphere of pain and pain intensity, suggest that VS/ALIC DBS successfully modulated the affective component of pain in patients with PSPS, corroborating our original hypothesis.

Despite the invasive nature of the DBS therapy, participants tolerated both the surgical procedure and the stimulation. However, we did observe a high incidence of seizures (20%; see Table 4) relative to the average rate (~2.4%) associated with DBS implantation. It is unknown whether this high incidence of seizures was related to the specific anatomical target and/or disease or whether it was simply due to a small patient population. We also frequently observed acute changes in mood and anxiety during stimulator programming sessions, but these undesirable changes were reversed through stimulation parameter adjustment. Stimulation parameter titration was a time-consuming process. Similar to DBS for other neurological disorders, we observed interpatient variations in the stimulation configurations and stimulation parameters (pulse amplitude, pulse width, pulse frequency) that provided the best outcomes (see Table 2). Variations in stimulation settings could have been due to slight differences in surgical targeting based on patient-specific anatomy, interpatient differences in sensitivity to the stimulation, stroke heterogeneity, and anatomical differences in the patient-specific fiber pathways.

Although there were several potential limitations to this study, the most significant limitation was the small sample size of 9 participants used in the statistical analysis that was inherent to the early phase of the investigation. The goal of this study was to provide pilot data to demonstrate the potential safety and efficacy of VS/ALIC DBS in modulation of the affective component of chronic pain. Despite our small sample size, we detected significant improvements in multiple outcome measures related to the affective aspect of chronic pain, suggesting a meaningful effect size. We believe that these significant improvements justify further investigation of this treatment approach.

In this article, we have presented the clinical results of our first-in-man clinical trial of VS/ALIC DBS to modulate the affective sphere of chronic pain. In future work, we will analyze functional neuroimaging and neurophysiological data (functional magnetic resonance imaging and magnetoencephalography) that were also obtained during this trial. We will use these data to develop objective biomarkers that could potentially improve patient selection and the corresponding response rate. We will also use these data to study the neural substrates underlying the effects of DBS on the affective dimension of pain. We hypothesize that clinically effective DBS will be associated with significant changes in the pain neuromatrix. Because pain anticipation is highly linked to pain chronification phenomena and to pain-related limited use of the affected extremities (and therefore linked to disability), we also believe that clinically effective VS/ALIC DBS will likely be associated with partial normalization of the neurophysiological correlates of pain anticipation.

In conclusion, VS/ALIC DBS was safe and effective in addressing the affective component of pain in patients with PSPS but not in reducing disability. We demonstrated that active versus sham VS/ALIC DBS produced significant improvements in multiple outcome measures related to the affective sphere of chronic pain. This trial represents a paradigm shift in chronic pain management by using neurostimulation to target brain structures related to the affective dimension rather than the sensory dimension of chronic pain. As pain clinicians, our ultimate goal is to reduce suffering. Our data suggest that neuromodulation trials may be most effective in reducing suffering by directly modulating the affective components of pain.

Acknowledgment
This work was supported by the NIH Office of the Director (New Innovator’s Award, DO006469A) and Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, Ohio.

We thank A. M. Noecker for assistance in generating Figure 2.

Author Contributions
Potential Conflicts of Interest

D.A.M. has received research support from Medtronic outside the submitted work. B.H. and P.J.F. report grants from the NIH during the conduct of the study. C.S.K. has a patent (US 8,538,536), “Methods of Improving Neuropsychological Function in Patients with Neurocognitive Disorders,” issued to Ali Rezai and Cynthia Kubu. A.G.M. reports distribution rights from intellectual property from Enspire DBS Therapy, Autonomic Technologies, and Cardionomics, and personal fees from St Jude Medical and Functional Neuromodulation, outside the submitted work.

References
