Received: April 23, 2020 Revised: June 12, 2020 Accepted: June 23, 2020

(onlinelibrary.wiley.com) DOI: 10.1111/ner.13247

Functional Magnetic Resonance Imaging Correlates of Ventral Striatal Deep Brain Stimulation for Poststroke Pain

Stephen E. Jones, MD, PhD*; Scott F. Lempka, PhD†; Raghavan Gopalakrishnan, PhD‡; Kenneth B. Baker, PhD§; Erik B. Beall, PhD*; Pallab Bhattacharyya, PhD*; Xuemei Huang, MS*; Jian Lin, MS*; Jacqueline Chen, PhD*; Mark J. Lowe, PhD*; Donald A. Malone, MD¶; Andre G. Machado, MD, PhD‡**

ABSTRACT

Objective: Deep brain stimulation (DBS) for pain has largely been implemented in an uncontrolled manner to target the somatosensory component of pain, with research leading to mixed results. We have previously shown that patients with poststroke pain syndrome who were treated with DBS targeting the ventral striatum/anterior limb of the internal capsule (VS/ALIC) demonstrated a significant improvement in measures related to the affective sphere of pain. In this study, we sought to determine how DBS targeting the VS/ALIC modifies brain activation in response to pain.

Materials and Methods: Five patients with poststroke pain syndrome who were blinded to DBS status (ON/OFF) and six age- and sex-matched healthy controls underwent functional magnetic resonance imaging (fMRI) measuring blood oxygen level-dependent activation in a block design. In this design, each participant received heat stimuli to the affected or unaffected wrist area. Statistical comparisons were performed using fMRI z-maps.

Results: In response to pain, patients in the DBS OFF state showed significant activation ($p < 0.001$) in the same regions as healthy controls (thalamus, insula, and operculum) and in additional regions (orbitofrontal and superior convexity cortical areas). DBS significantly reduced activation of these additional regions and introduced foci of significant inhibitory activation ($p < 0.001$) in the hippocampi when painful stimulation was applied to the affected side.

Conclusions: These findings suggest that DBS of the VS/ALIC modulates affective neural networks.

Keywords: Chronic pain, DBS, deep brain stimulation, fMRI, poststroke pain syndrome

Conflicts of Interest: Stephen E. Jones is a consultant for Monteris, on the advisory board for Eisai, has received research support from Biogen, St Jude, and the NIH, and has received speaker fees and travel from Siemens, St Jude Hospital, and Radnet. Scott F. Lempka is a shareholder and scientific advisory board member of Presidio Medical, Inc. Andre G. Machado is a consultant for Abbott, has received research support from the NIH, St Jude Medical, and Enspire DBS, has distribution rights from intellectual property from Enspire and Cardionomics, and has received fellowship support from Medtronic. The remaining authors have no competing interests to declare.

Address correspondence to: Stephen E. Jones, MD, PhD, Imaging Institute, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195, USA. Email: joness19@ccf.org

* Imaging Sciences, Imaging Institute, Cleveland Clinic, Cleveland, OH, USA;
† Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA;
‡ Center for Neurological Restoration, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA;
§ Department of Neurosciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA;
¶ Department of Psychiatry, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA; and
** Department of Neurosurgery, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/WileyCDA/Section/id-301854.html

Source(s) of financial support: This work was supported by the National Institutes of Health Office of the Director (New Innovator's Award, DP2OD006469).

INTRODUCTION

Deep brain stimulation (DBS) has been explored as a potential treatment for refractory chronic pain since the 1970s. Traditionally, DBS is used to target the ascending somatosensory pathways or descending inhibitory pathways in an effort to modulate the sensory-discriminative sphere of pain. The most common target areas have been the sensory nuclei of the thalamus and the endorphin-releasing areas, such as the periventricular gray area or the periaqueductal gray area. Unfortunately, clinical outcomes associated with DBS of these traditional target areas have been mixed (1,2). Although some studies reported improvements in pain measured by the visual analog scale, large case series and industry-sponsored studies aimed at evaluating the long-term effects of DBS found limited benefits (3,4). Many of these studies have likely been met with mixed results due to limitations in the study design. Several of these studies were performed during the early development of DBS with a lack of well-defined patient-selection criteria, surgical target identification, and electrode and stimulator technology (5). Recent systematic reviews suggest that future studies should focus on specific pain diagnoses and consider randomized placebo-controlled designs (6,7).

To potentially improve the success rate of DBS to treat chronic pain, we have proposed a change in how DBS is used to treat the chronic pain experience; this change expands upon our experience with DBS of the behavioral networks (8-10) and emphasizes modulation of the nonsensory pathways, in particular those involving the affective sphere of pain (1,11). Our goal was to reduce the affective (i.e., suffering) component of pain, thereby improving quality of life and pain-related disability without necessarily modulating pain intensity as typically measured with a Likert scale. There are many anatomical choices for DBS modulation of affective/nonsensory pathways.

Cortical control of emotion is manifested through processing within the cortico-striato-pallido-thalamocortical system and the circuit of Papez. In addition to projections from frontal and prefrontal cortical areas into the dorsal striatum, there are direct projections from the anterior frontal cortical areas and orbitofrontal cortical areas to the ventral striatum (VS). There are also direct projections to the thalamus via the anterior limb of the internal capsule (ALIC). We previously demonstrated that acute stimulation of the VS and the ventral ALIC produced changes in mood and behavior (9). DBS of the ALIC has been shown to be safe and effective for OCD (12,13) and was approved by the United States Food and Drug Administration under a Humanitarian Device Exemption. In an uncontrolled study, our multicenter collaborative group also reported the long-term benefits of VS/ALIC DBS in patients with treatment-resistant depression (10). Our group has direct experience implanting DBS leads in this location as well as experience titrating stimulation in a safe way to avoid side effects such as hypomania (1,2,10,11,13-15). It is also important to note that previous studies targeting the anterior cingulate cortex have demonstrated the potential of DBS of the affective sphere of pain to relieve pain and improve quality of life (16).

These previous experiences led to a prospective, double-blind, randomized, placebo-controlled, crossover trial of DBS targeting of the VS/ALIC in patients with intractable unilateral poststroke pain syndrome (17). In this first-in-humans trial, patients treated with DBS demonstrated a significant improvement in the Montgomery-Asberg Depression Rating Scale and the Beck Depression Inventory, suggesting that DBS can indeed modulate the affective sphere of treatment-refractory pain. In addition, we learned that implantation of these devices is safe in this patient population and is associated with improved quality of life (17).

To investigate the neural substrates of pain affect and its modulation by DBS of the ventral striatum, we previously studied the same patient cohort using an event-related magnetoencephalography (MEG) paradigm (18-20). Our findings were twofold. First, we found that in patients with poststroke pain, anticipatory brain response to a nonpainful stimulus was no different than pain anticipation, indicating a loss of salience (18-23). Second, we found that with DBS treatment, the abnormal anticipatory brain response to nonpainful stimuli in these patients was resolved, predominantly in the medial prefrontal and anterior cingulate areas (18). The present work expands on this previous investigation to include a complementary method, blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI), within the context of the same randomized, placebo-controlled clinical trial. While MEG provides excellent temporal resolution, fMRI yields excellent spatial resolution and allows us to further substantiate and corroborate our earlier MEG findings. To our knowledge, this is the first study using simultaneous DBS and fMRI to examine the neuromodulatory effects of long-term VS/ALIC DBS on the response to nociceptive stimuli in patients with chronic pain.

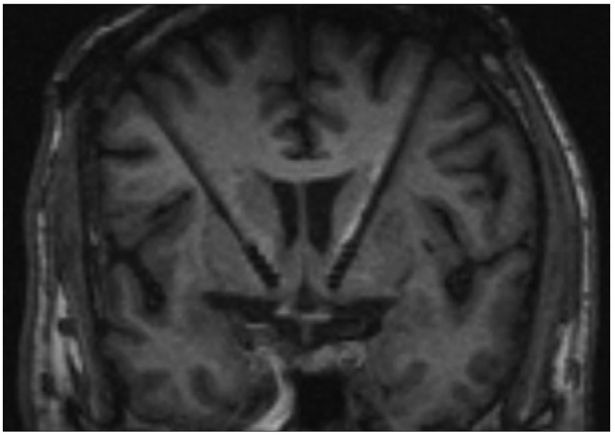

Figure 1 Axial oblique T1-weighted magnetization-prepared rapid gradient-echo image that is in-plane with bilateral deep brain stimulation electrodes targeting the ventral striatum/anterior limb of the internal capsule. The deeper contacts include the nucleus accumbens. The four electrode contacts are seen as small rounded enlargements at the end of the electrodes.

MATERIALS AND METHODS

Ten patients were enrolled in a randomized controlled trial of VS/ALIC DBS for the treatment of poststroke pain syndrome (17). All patients had at least six months of contralesional hemibody pain following a stroke involving the sensory thalamic area or white matter above or below the sensory thalamic area. Ten healthy controls were also specifically recruited for comparison of fMRI findings only; these controls were age- and sex-matched to the study patients. In all patients, bilateral DBS leads (Model 3387; Medtronic, Minneapolis, MN, USA) were implanted into the VS/ALIC area (Fig. 1) using neurosurgical techniques described previously (1,2,11). All study procedures were approved by the institutional review board (IRB) with a physician-sponsored Investigational Device Exemption from the U.S. Food and Drug

Administration. Before enrollment, all patients provided written informed consent.

The prospective, randomized, double-blind, placebo-controlled, crossover trial consisted of an initial six-months double-blind stimulation phase in which patients were randomized to three months of active stimulation (i.e., DBS ON) or sham stimulation (i.e., DBS OFF) followed by a three-months crossover to the other treatment allocation. The blinded phase was then followed by an 18-months open stimulation phase (i.e., unblinded active DBS, no sham stimulation). We acquired fMRI images two months after randomization and two months after crossover.

Because of safety concerns regarding implanted DBS systems in MRI scanners, extensive end-to-end safety heating tests were performed before any human scans were carried out. All testing followed ASTM F 2182–02a guidelines, using a torso phantom containing a full mock-up of a complete DBS system. During MRI scans, temperatures near the surface of the DBS contacts were measured using fluoroptic temperature sensors as previously reported (24,25). Testing was performed in both DBS ON and OFF conditions and with the MRI-compatible heating stimulus hardware both active and inactive. None of the scan protocols produced significant heating near the electrodes (i.e., <1°C for all scans).

Participants were imaged under an IRB-approved protocol on a Siemens TIM Trio 3 T MRI scanner (Erlangen, Germany). After a standard anatomic T1-weighted magnetization-prepared rapid gradient-echo sequence was obtained (axial acquisition with 120 slices; repetition time/echo time/inversion time = 1900/1.71/900 ms; voxel size = 1 × 1 × 1.2 mm; scan time = 4 min 5 sec), 2 BOLD sensitive echo-planar imaging (EPI) scans for fMRI were performed (axial acquisition with 31 slices; repetition time/echo time = 2000/29 msec; voxel size = 4 × 4 × 4 mm; field of view = 64 × 64; 224 volumes; total scan time = 7 min 28 sec).

The fMRI paradigm consisted of painful heat stimuli to the affected or unaffected wrist area delivered using a contact heat-evoked potential stimulator of the Medoc PATHWAY system (Medoc Ltd, Ramat Yishai, Israel). During each scan, the heat stimuli were delivered in a block design comprising five cycles of heat (44.8 sec) followed by no heat (44.8 sec). Scans were repeated as necessary (e.g., because of excessive movement of the participant or failure of the heating equipment). Physiological monitoring was performed during scans to facilitate physiological noise correction. Immediately after each scan, participants reported the thermal pain intensity on a 0 to 10 rating scale (0 representing "no pain" and 10 representing "worst pain possible").

Image analysis began with removal of the first four volumes to ensure a steady-state signal. Each scan was then retrospectively volume- and slice-wise motion-corrected for head motion using SLOMOCO (26). Total displacement was calculated using volumetric SLOMOCO z-translation parameters and used as the motion quality parameter. The fMRI data were considered motion corrupted if the maximum displacement of any voxel was greater than 1 mm or the mean displacement of parenchymal voxels was more than 0.2 mm. Scans exceeding either threshold were not included in the group analysis. Using the heating paradigm, we employed 3dDeconvolve in Analysis of Functional NeuroImages (AFNI) software (27) to create statistical maps, the specific output of which were voxel-based Student's t-scores. The subject's fMRI EPI images were aligned to their concurrent anatomic T1 image using the align_epi_anat.py routine from AFNI. The anatomic T1 image was then aligned to the template image, for which the MNI brain was used after transforming it into Talairach coordinates using symmetric image normalization (Syn) in Advanced Normalization Tools. The EPI images in T1 space were then transformed to final template space using the Advanced Normalization Tools transformation acquired in the previous step. A single participant had left-sided pain; in this patient, the normalized brain maps were left–right flipped so that data from all of the participants were aligned to a common side reflecting the affected hemisphere. The map was simply mirrored in the left–right direction about the center of the image in the normalized space. Thereafter, the individual fMRI t-maps were transformed to z-maps and averaged over all of the participants to produce an average z-map. A total of four single-condition z-maps were generated for each combination of the two condition variables (DBS ON versus DBS OFF) and for heating conditions (affected side versus unaffected side) (Fig. 2). The final Bonferroni-corrected p value was 0.05 (3dClustsim) after cluster analysis with single-voxel threshold, $p < 0.001$ and a cluster size requirement of 300.

RESULTS

Of the ten patients enrolled in the study, eight consented to the fMRI procedures. Of these, five participants met the motion criteria during all four fMRI sequences (right and left arm heating and DBS ON and DBS OFF conditions). Four participants had pain on the right side and the remaining participants had pain on the left side. The chronic stimulation parameter settings for each of these five participants are shown in Table 1. Six of ten healthy controls had satisfactory fMRI images during both the right and left arm heating sequences. Among the included patients and controls, all were right handed, with no significant differences in sex or age ($p = 0.27$).

Statistical maps of the BOLD response in study patients and healthy controls are shown in the top row of Figure 2. A predominant BOLD pattern seen in healthy controls was bilateral activation of foci within the insula and along the frontoparietal operculum, which includes the functional region S2 (label 1). Although activation was bilateral, we noted mild asymmetry with stronger activation on the side contralateral to heating stimulation. In addition, there was mild bilateral activation of the thalami (label 2) with stronger activation on the contralateral side.

In response to pain, patients with poststroke pain syndrome in the DBS OFF state (second row of Fig. 2) exhibited significant activation in the same regions as healthy controls (e.g., label 7), with more pronounced activation of the thalamic (label 5), insular, and opercular areas (label 4). Patients also showed activation in additional regions not significantly activated in the healthy controls, including in the orbitofrontal region (label 3) and diffusely over the superior convexity (magenta rectangle) cortical region. Also in contrast to healthy controls, patients demonstrated small foci of negative or inhibitory activation in the subgenual cortical regions (label 9). Relative to healthy controls, patients showed more foci of activation, both positive and negative, in the DBS OFF state.

In the DBS ON state (third row in Fig. 2), patients with poststroke pain syndrome showed fewer regions of positive BOLD activation than in the DBS OFF state. Fewer/smaller foci of significant activation were seen in the superior convexities with painful stimulation of both the affected and unaffected sides (see the five superior axial slices corresponding to the magenta rectangle in the second row of Fig. 2). In the DBS ON state, during painful

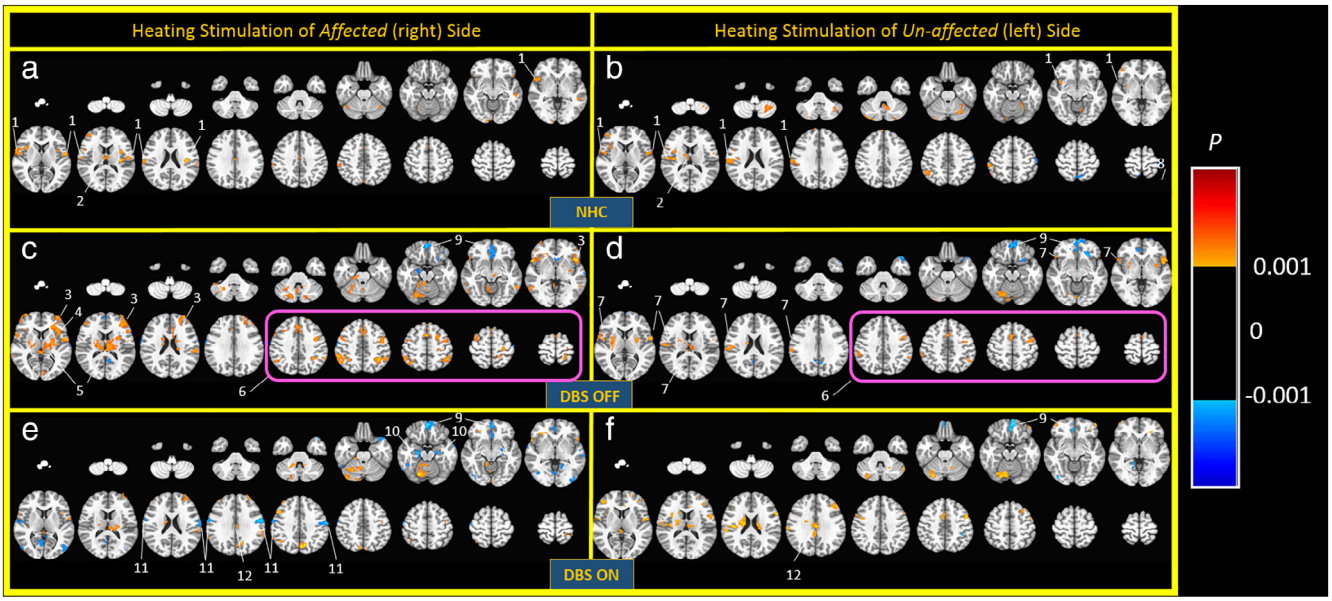

Figure 2 Statistical maps of BOLD activation in response to heating stimulus for normal healthy controls (NHC, top row), patients with poststroke pain syndrome with DBS OFF (second row), and patients with poststroke pain syndrome with DBS ON (third row). These maps represent different combinations of DBS state (healthy controls vs. DBS ON vs. DBS OFF) and side of heating stimulus with respect to the side of the body affected by chronic pain from a contralateral chronic infarction (affected side vs. unaffected side). Each map displays 18 axial slices spaced 8 mm apart. Regions with overlaid orange indicate positive BOLD response to heating stimulus (activation); regions of overlaid blue indicate negative BOLD response to heating stimulus (suppression). For each row, the Bonferroni-corrected p value was 0.05 for positive and negative activation (single voxel $p < 0.001$ with a cluster size of 300). Images are displayed using radiologic convention. Numbers indicate the specific brain regions described in the Results section. [Color figure can be viewed at wileyonlinelibrary.com]

stimulation of the affected side, foci of orbitofrontal activation (labels 3 and 4) and thalamic activation (label 5) were smaller than these foci in the DBS OFF state. In the DBS ON state, during painful stimulation of the unaffected side, significant increased activation was observed in the posterior cingulate region (label 12). Significant foci of activation were also observed in the cerebellum when painful stimulation was applied to either the affected or unaffected side. Multiple new foci of strong inhibitory activation were seen in the bilateral precentral gyrus (label 11), hippocampi (label 10), and multiple other locations. This was present predominantly on the affected side, with the unaffected side showing persistence of inhibition in the subgenual region (label 9).

DISCUSSION

DBS of the VS/ALIC has been proposed by our group as a method for managing the affective sphere of chronic pain, thus improving quality of life in patients with intractable pain syndromes. Poststroke pain syndrome is an excellent model in which to study the effects of this novel intervention, as the pain involved in this syndrome is unlikely to resolve spontaneously and is associated with a clear, imaging-identifiable etiology. The fMRI data presented here were collected during the double-blind phase of a randomized, controlled trial of VS/ALIC DBS in patients with intractable unilateral poststroke pain syndrome. The clinical outcomes of this trial supported our initial hypothesis that DBS of

Table 1 Chronic Stimulation Parameter Settings.

Patient	Lead hemisphere	Active electrodes	Pulse amplitude (V)	Pulse width (μsec)	Pulse frequency (Hz)
1	Right	10(−) 11(+)	2	210	130
	Left	2(−) 3(+)	2	210	130
2	Right	C(+) 10(−)	6	60	130
	Left	C(+) 1(−)	6	60	130
3	Right	C(+) 11(−)	1	210	130
	Left	N/A	N/A	N/A	N/A
4	Right	C(+) 10(−) 11(−)	4	60	130
	Left	C(+) 2(−) 3(−)	4	60	130
5	Right	C(+) 8(−)	3.5	90	100
	Left	C(+) 0(−)	3.5	90	100

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 8–11 with 8 being the most distal electrode. For the left-side leads, the electrodes are numbered 0–3, with 0 being the most distal electrode.

the VS/ALIC can successfully modulate the affected sphere of pain and promote changes in quality of life (17). The present study is the first to use fMRI to examine the mechanisms underlying the effects of VS/ALIC DBS on the affective sphere of pain.

In this study, activation patterns in healthy controls indicated involvement of the affective networks in response to acute and expected painful stimuli and corroborated the validity of our experimental paradigm to examine these networks. Healthy controls showed bilateral activation of the insula and opercular areas. Even though there was mild asymmetry that favored a larger response contralateral to the painful stimulus, the effects on the affective networks were bilateral, consistent with previous research (28). As expected for somatosensory stimulation, we also noted activation of the thalami.

Relative to healthy controls, patients with poststroke pain syndrome and DBS OFF showed more foci of positive and negative activation, suggesting that painful stimuli elicit a greater response in patients than in healthy controls. Patients showed broader activation across cortical regions in response to painful stimuli; this activation extended from the premotor regions to the parietal cortical regions and also involved the opercular areas and thalami. In addition, there was marked activation of the insula and orbitofrontal areas, suggesting a strong involvement of affective and associative networks in response to pathological pain experience.

When fMRI scans were performed in the DBS ON state, we noted a significant reduction in the broad pattern of cortical overactivation seen in the DBS OFF state, as well as resolution of the strong orbitofrontal activation noted in the DBS OFF state. This finding suggests that DBS reduces abnormal cortical activation associated with the chronic pain state, thus shifting the activation pattern to more closely resemble that seen in healthy controls. These suppressive effects were greatest for heat stimulation of the affected side, with the greatest suppression seen in the convexity and regions of the insula, thalamus, and inferior frontal lobes. Stimulation on the affected side during DBS ON also led to robust negative BOLD activation, or inhibition, in the frontal regions. DBS was also associated with inhibition in the hippocampus, likely representing modulation of the affective networks projecting to and from the VS/ALIC. Although the data related to stimulation of the affected side are the most relevant from a therapeutic standpoint, we also noted strong BOLD activation of the cingulate cortex in response to heating of the unaffected side during DBS ON, a finding that is unique in this data set.

Our prior investigation with MEG showed that patients with poststroke pain do not neurophysiologically distinguish cues that represent pain vs. those that represent nonpainful stimuli (19). This trend was predominantly evident in the prefrontal and cingulate areas, indicating a cortical overactivation to incoming nonpainful stimuli. This observation parallels the clinical presentation of allodynia, a condition in which all sensory stimuli, irrespective of whether they are painful or not, are interpreted as painful. With DBS ON, we found that patients were able to differentially anticipate nonpainful stimuli, evidenced by resolution of cortical overactivation, indicating an "affective benefit" that restored salience, cognitive control, and emotional regulation (18). The findings of the current fMRI study corroborate our previous MEG investigation, both in terms of cortical overactivation in the DBS OFF state and in terms of reduction in the spread of cortical activation in the DBS ON state, potentially representing a partial restoration of the distinction between normal and pathological perception of pain. We also speculate that improved cognitive and emotional regulation restored by DBS could have resolved the widespread cortical activation in the pain matrix areas, including the orbitofrontal cortex, an area linked with fear and emotion (29).

The present work has several strengths. Because study participants and personnel were blinded to the DBS condition at the time of image acquisition, the risks for placebo-related or investigator-related bias were diminished. The inclusion of a healthy control group consisting of volunteers who underwent the same painful stimulation procedures during fMRI acquisition helped us to interpret the data, as results from the controls provided a point of reference regarding what we should expect in the pain-free brain. In addition, all study patients had the same well-characterized pain syndrome, improving the homogeneity of the sample.

Limitations of the work include its small sample size. Only nine out of ten patients completed the randomized phase of the clinical trial, and of these, only eight consented to participate in the fMRI experiments. In addition, the techniques for acquisition of the fMRI are complex and are substantially affected by motion artifacts; because of motion artifacts, we were able to include only five patients with poststroke pain syndrome and six healthy controls in the imaging analysis to achieve reliable statistical maps. Another limitation is the potential for selection bias, as patients exhibiting strong or exaggerated movements in response to painful stimuli would not have met the inclusion criterion regarding minimal movement. Thus, the final analyses excluded patients who might have had a differential response.

In conclusion, these findings suggest that DBS of the VS/ALIC modulates affective neural networks, corroborating our original hypothesis. DBS significantly reduced a pattern of overactivation of cortical regions seen in patients with chronic pain but not in healthy controls. Future studies in patients with more common pain syndromes are needed to determine whether these effects are specific to poststroke pain syndrome or whether they also occur in patients suffering from other types of chronic pain.

Authorship Statements

Dr. Machado, Dr. Beall, Dr. Bhattacharyya, Dr. Lowe, Dr. Lempka, Dr. Gopalakrishnan, Dr. Malone, and Dr. Machado designed and conducted the study, including patient recruitment. Dr. Jones, Dr. Beall, Dr. Lowe, Dr. Chen, Dr. Jian Lin, and Dr. Xuemei Huang performed the data collection and data analysis. Dr. Jones and Dr. Machado prepared the manuscript draft with important intellectual input from Dr. Lempka, Dr. Gopalakrishnan, Dr. Beall, Bhattacharyya, Dr. Chen, and Dr. Lowe. All authors approved the final manuscript. All authors had complete access to the study data. Megan Griffiths helped with editorial assistance.

How to Cite this Article:

Jones S.E., Lempka S.F., Gopalakrishnan R., Baker K.B., Beall E.B., Bhattacharyya P., Huang X., Lin J., Chen J., Lowe M.J., Malone D.A., Machado A.G. 2021. Functional Magnetic Resonance Imaging Correlates of Ventral Striatal Deep Brain Stimulation for Poststroke Pain.
Neuromodulation 2021; 24: 259–264

REFERENCES

1. Machado AG, Baker KB, Plow E, Malone DA. Cerebral stimulation for the affective component of neuropathic pain. *Neuromodulation* 2013;16:514–518.
2. Plow EB, Pascual-Leone A, Machado A. Brain stimulation in the treatment of chronic neuropathic and non-cancerous pain. *J Pain* 2012;13:411–424.
3. Coffey RJ. Deep brain stimulation for chronic pain: results of two multicenter trials and a structured review. *Pain Med* 2001;2:183–192.
4. Levy RM, Lamb S, Adams JE. Treatment of chronic pain by deep brain stimulation: long term follow-up and review of the literature. *Neurosurgery* 1987;21:885–893.
5. Levy R, Deer TR, Henderson J. Intracranial neurostimulation for pain control: a review. *Pain Physician* 2010;13:157–165.
6. Deer TR, Grider JS, Lamer TJ et al. A systematic literature review of spine neurostimulation therapies for the treatment of pain. *Pain Med* 2020;21: 1415–1420.
7. Frizon LA, Yamamoto EA, Nagel SJ, Simonson MT, Hogue O, Machado AG. Deep brain stimulation for pain in the modern era: a systematic review. *Neurosurgery* 2020;86:191–202.
8. Lujan JL, Chaturvedi A, Malone DA, Rezai AR, Machado AG, McIntyre CC. Axonal pathways linked to therapeutic and nontherapeutic outcomes during psychiatric deep brain stimulation. *Hum Brain Mapp* 2012;33:958–968.
9. Machado A, Haber S, Sears N, Greenberg B, Malone D, Rezai A. Functional topography of the ventral striatum and anterior limb of the internal capsule determined by electrical stimulation of awake patients. *Clin Neurophysiol* 2009;120:1941–1948.
10. Malone DA Jr, Dougherty DD, Rezai AR et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry* 2009;65:267–275.
11. Plow EB, Malone DA Jr, Machado A. Deep brain stimulation of the ventral striatum/anterior limb of the internal capsule in thalamic pain syndrome: study protocol for a pilot randomized controlled trial. *Trials* 2013;14:241.
12. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet* 1999;354:1526.
13. Greenberg BD, Gabriels LA, Malone DA Jr et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Mol Psychiatry* 2010;15:64–79.
14. Dougherty DD, Rezai AR, Carpenter LL et al. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. *Biol Psychiatry* 2015;78:240–248.
15. Kubu CS, Malone DA, Chelune G et al. Neuropsychological outcome after deep brain stimulation in the ventral capsule/ventral striatum for highly refractory obsessive-compulsive disorder or major depression. *Stereotact Funct Neurosurg* 2013;91:374–378.
16. Boccard SGJ, Prangnell SJ, Pycroft L et al. Long-term results of deep brain stimulation of the anterior cingulate cortex for neuropathic pain. *World Neurosurg* 2017;106:625–637.
17. Lempka SF, Malone DA Jr, Hu B et al. Randomized clinical trial of deep brain stimulation for poststroke pain. *Ann Neurol* 2017;81:653–663.
18. Gopalakrishnan R, Burgess RC, Malone DA et al. Deep brain stimulation of the ventral striatal area for poststroke pain syndrome: a magnetoencephalography study. *J Neurophysiol* 2018;119:2118–2128.
19. Gopalakrishnan R, Burgess RC, Lempka SF, Gale JT, Floden DP, Machado AG. Pain anticipatory phenomena in patients with central poststroke pain: a magnetoencephalography study. *J Neurophysiol* 2016;116:1387–1395.
20. Gopalakrishnan R, Burgess RC, Plow EB, Floden DP, Machado AG. Early event related fields during visually evoked pain anticipation. *Clin Neurophysiol* 2016; 127:1855–1863.
21. Gopalakrishnan R, Burgess RC, Plow EB, Floden DP, Machado AG. A magnetoencephalography study of multi-modal processing of pain anticipation in primary sensory cortices. *Neuroscience* 2015;304:176–189.
22. Gopalakrishnan R, Machado AG, Burgess RC, Mosher JC. The use of contact heat evoked potential stimulator (CHEPS) in magnetoencephalography for pain research. *J Neurosci Methods* 2013;220:55–63.
23. Machado AG, Gopalakrishnan R, Plow EB, Burgess RC, Mosher JC. A magnetoencephalography study of visual processing of pain anticipation. *J Neurophysiol* 2014;112:276–286.
24. Bhattacharyya PK, Mullin J, Lee BS, Gonzalez-Martinez JA, Jones SE. Safety of externally stimulated intracranial electrodes during functional MRI at 1.5T. *Magn Reson Imaging* 2017;38:182–188.
25. Quirouet A, Bhattacharyya PK, Dielubanza EJ, Gill BC, Jones SE, Goldman HB. Sacral neuromodulation device heating during lumbar and pelvic magnetic resonance imaging-a phantom study. *Urology* 2017;107:61–66.
26. Beall EB, Lowe MJ. SimPACE: Generating simulated motion corrupted BOLD data with synthetic-navigated acquisition for the development and evaluation of SLOMOCO: a new, highly effective slicewise motion correction. *Neuroimage* 2014;101:21–34.
27. Cox RW, Hyde JS. Software tools for analysis and visualization of fMRI data. *NMR Biomed* 1997;10:171–178.
28. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. *N Engl J Med* 2013;368:1388–1397.
29. Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Prog Neurobiol* 2004;72:341–372.

COMMENT

Deep brain stimulation for pain historically had mixed results and lack of robust data to demonstrate efficacy. Trying to understand why some individuals benefit and not others may be key to effective patient selection. Jones et al have performed a novel study looking at how ventral striatal/ALIC DBS alters brain networks by looking at fMRI On vs Off stimulation. The numbers are small but the data is fairly unique. Their findings that certain limbic and frontal areas differed in pain patients may help to predict responders and the fact that DBS reduced an abnormally high activity in these areas lends some useful information as to the mechanisms of DBS in this cohort.

Alexander Green, MD, BSc, MBBS
Oxford UK

