Effect of low-frequency deep brain stimulation on sensory thresholds in Parkinson's disease

Abigail Belasen, BSc,¹ Khizer Rizvi, BS,¹ Lucy E. Gee, BS,^{1,2} Philip Yeung, BS,¹ Julia Prusik, BS,¹ Adolfo Ramirez-Zamora, MD,³ Era Hanspal, MD,³ Priscilla Paiva, MD,³ Jennifer Durphy, MD,³ Charles E. Argoff, MD,³ and Julie G. Pilitsis, MD, PhD^{1,2}

Departments of ¹Neurosurgery and ³Neurology, Albany Medical Center; and ²Center for Neuroscience and Neuropharmacology, Albany Medical College, Albany, New York

OBJECTIVE Chronic pain is a major distressing symptom of Parkinson's disease (PD) that is often undertreated. Subthalamic nucleus (STN) deep brain stimulation (DBS) delivers high-frequency stimulation (HFS) to patients with PD and has been effective in pain relief in a subset of these patients. However, up to 74% of patients develop new pain concerns while receiving STN DBS. Here the authors explore whether altering the frequency of STN DBS changes pain perception as measured through quantitative sensory testing (QST).

METHODS Using QST, the authors measured thermal and mechanical detection and pain thresholds in 19 patients undergoing DBS via HFS, low-frequency stimulation (LFS), and off conditions in a randomized order. Testing was performed in the region of the body with the most pain and in the lower back in patients without chronic pain.

RESULTS In the patients with chronic pain, LFS significantly reduced heat detection thresholds as compared with thresholds following HFS ($p = 0.029$) and in the off state ($p = 0.010$). Moreover, LFS resulted in increased detection thresholds for mechanical pressure ($p = 0.020$) and vibration ($p = 0.040$) compared with these thresholds following HFS. Neither LFS nor HFS led to changes in other mechanical thresholds. In patients without chronic pain, LFS significantly increased mechanical pain thresholds in response to the 40-g pinprick compared with thresholds following HFS ($p = 0.032$).

CONCLUSIONS Recent literature has suggested that STN LFS can be useful in treating nonmotor symptoms of PD. Here the authors demonstrated that LFS modulates thermal and mechanical detection to a greater extent than HFS. Low-frequency stimulation is an innovative means of modulating chronic pain in PD patients receiving STN DBS. The authors suggest that STN LFS may be a future option to consider when treating Parkinson's patients in whom pain remains the predominant complaint.

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KEY WORDS low-frequency stimulation; high-frequency stimulation; deep brain stimulation; quantitative sensory testing; mechanical detection thresholds; thermal thresholds; pressure pain thresholds; vibratory detection; chronic pain; functional neurosurgery

CHRONIC pain is a major nonmotor symptom of Parkinson's disease (PD). Approximately 40%–85% of patients with PD experience pain,^{3,14,33,41,55} and in some patients the pain can overshadow the motor symptoms of the disease.^{44,57} Early after a PD diagnosis, dopaminergic medications may provide some analgesic efficacy;²¹ however, up to 49% of patients believe their medications do not reduce the severity of their pain.⁴⁶ In

patients with more advanced disease, subthalamic nucleus (STN) deep brain stimulation (DBS), commonly used to treat the motor symptoms of PD, is gaining attention as an effective therapy for PD-related pain. Several studies have shown significant improvements in global pain scores 6 months to 1 year following DBS surgery,^{12,19,42,43,52} and a recent 8-year follow-up study suggests that preoperative pain can be well managed over time.²⁹ Although STN

ABBREVIATIONS DBS = deep brain stimulation; HFS = high-frequency stimulation; LFS = low-frequency stimulation; PD = Parkinson disease; QST = quantitative sensory testing; STN = subthalamic nucleus.

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DBS has been shown to be superior to high-dose levodopa treatment in controlling chronic pain,⁵⁴ the mechanism by which STN DBS improves pain remains unclear. Further, 74% of patients develop new-onset pain after STN DBS.⁸

Quantitative sensory testing (QST) provides an objective measure of pain perception through mechanical and thermal threshold assessment, which is used to clinically assess pain sensitivity and/or sensory dysfunction.¹ The effects of STN DBS on sensory thresholds are varied;^{12,26,46,52} however, a study of 25 PD patients has suggested that high-frequency stimulation (HFS) increases mechanical and thermal pain thresholds.^{26,37,53} Moreover, a recent study in 6OHDA (6-hydroxydopamine)-lesioned rats has suggested that both HFS and low-frequency stimulation (LFS) of the STN increase mechanical and thermal thresholds.²⁴ Thus, this work implies that pain may be modulated with LFS of the STN. Additionally, STN LFS has been shown to improve motor function in PD patients.^{30,38} We believe that LFS also provides an optional therapeutic strategy for alleviating pain in patients undergoing DBS. Here, we evaluate LFS delivered at 60 Hz and its effects on mechanical and thermal sensory and pain thresholds in PD patients with and without chronic pain.

Methods

Participants

Institutional review board approval was granted by Albany Medical College to conduct this study. All enrolled subjects had undergone STN implantation of a DBS device for the treatment of refractory motor fluctuations in PD. Those who qualified for surgical treatment had completed the Unified Parkinson's Disease Rating Scale (UPDRS) and neuropsychological testing as part of the routine preoperative workup. Patients who did not improve more than 30% on the Core Assessment Program for Surgical Interventional Therapies (CAPSIT) on/off medication testing were not considered acceptable surgical candidates and neither were those who demonstrated dementia, significant cognitive impairment, or unstable psychiatric disease at baseline testing. From a database of patients who had undergone STN DBS, patients were selected for study participation regardless of their pain status. Chronic pain, defined as 8 weeks of pain despite treatment, was self-reported by the patient at the time of testing. Subjects who could not complete testing because of language barriers and/or dementia were excluded from the study. Informed consent was obtained from all study participants prior to testing.

Outcome Measures

All patients completed the visual analog scale, McGill Pain Questionnaire, Oswestry Disability Index, and Pain Catastrophizing Scale and provided their pain medication usage. Quantitative sensory testing was performed to assess detection and pain thresholds for mechanical and sensory stimuli. Testing was conducted at 3 stimulation settings: 1) the patient's optimized HFS settings for the treatment of motor symptoms, 2) LFS at 60 Hz with the same pulse width and voltage, and 3) off stimulation, with the order of testing randomized. Both patient and exam-

iner were aware of the patient's stimulation setting during testing. A minimum of 10 minutes at the new setting was allotted in between each QST session. Testing was performed on the side of the body receiving therapeutic neuromodulation and at the site where the most pain was reported. If the patient did not report pain, QST was performed on the lower back given the high incidence of low-back pain in this population.⁸ Once an optimal spot for testing was determined, an "x" was drawn to ensure that all testing was performed on the same area.

Thresholds for mechanical sensation were detected using von Frey filaments, which allow forces between 0.25 and 512 mN to be applied to the skin with a consistent and uniform contact surface area and shape. Mechanical pain was detected using standardized 10- and 40-g weighted pinprick stimulators. Patients were asked to rate the pain felt after each 10- and 40-g pinprick on a scale of 0–10, with 10 being the highest level of pain. Pressure pain was detected through a standard pressure gauge device allowing 1–10 kg of pressure to be applied. Patients were asked to notify the researcher when the pressure became uncomfortable. Vibration detection was assessed using a Rydel-Seiffer tuning fork. Using the Medoc Pathway thermode (device range 0°C–50°C), we assessed cool and warm thermal detection and determined when the temperature became painful.

Data Analysis

For the demographic and medical information collected, statistical analysis was performed in SPSS (IBM SPSS Statistics for Windows, version 22.0, IBM Corp.) using paired t-tests and regression analysis to assess differences, in which $p < 0.05$ was considered significant.

Results

Demographics

Nineteen PD patients who had undergone surgery for STN DBS were included in this study. Thirteen patients had unilateral STN DBS surgery and 6 had bilateral surgery. Eleven patients reported chronic pain. Additional demographic information as well as the QST testing sites is listed in Table 1.

Results of Sensory Threshold Testing

Patients with chronic pain who received STN LFS had significantly reduced heat detection thresholds, compared with thresholds following HFS ($p = 0.029$) or in the off state ($p = 0.010$; Fig. 1A). In addition, LFS significantly increased mechanical detection thresholds ($p = 0.020$; Fig. 1B) and vibration detection ($p = 0.040$; Fig. 1C) compared with thresholds following HFS. In patients without chronic pain, LFS significantly increased mechanical pain thresholds in response to the 40-g pinprick as compared with HFS ($p = 0.032$; Fig. 1D). Combining all patients regardless of pain status, we found that LFS significantly reduced heat detection thresholds compared with HFS ($p = 0.044$). The mean mechanical and thermal detection values and p values are listed in Table 2.

Using ordinary least-squares regression analysis, we evaluated each QST test on the 3 categorical factors (pa-

TABLE 1. Demographic distribution of PD patients with and without chronic pain

Patient No.	Age (yrs), Sex	Yrs Since Diagnosis	Chronic Pain	QST Testing Location
1	68, F	15	Yes	Lt dorsal medial hand
2	63, F	7	Yes	Lt low back
3	70, F	20	Yes	Lt low back
4	66, M	7	Yes	Lt posterior shoulder
5	55, M	20	Yes	Lt low back
6	71, F	17	Yes	Lt lat ankle
7	66, M	6	Yes	Rt posterior shoulder
8	58, M	5	Yes	Rt hip
9	61, M	11	Yes	Rt dorsal thumb
10	50, M	10	Yes	Bilat epigastric region
11	43, F	23	Yes	Lt anterior chest
12	71, F	71	No	Lt low back
13	75, F	75	No	Lt low back
14	36, M	36	No	Bilat low back
15	72, M	72	No	Bilat low back
16	67, F	67	No	Bilat low back
17	57, M	57	No	Bilat low back
18	79, M	79	No	Lt low back
19	68, M	68	No	Bilat low back

tient sex, pain status, and testing site) for significance. At the 5% level of significance, there was a statistically significant difference between male and female patients receiving HFS or LFS for both the pressure pain and 40-g pinprick tests. Specifically, women were more sensitive to pressure pain and less sensitive to mechanical pain. We also found a significant difference between testing the lower back and other sites for patients receiving HFS or LFS for the 10-g Neuropen test and for patients receiving HFS for the 40-g Neuropen test. The lower back was less sensitive. Results are summarized in Table 3.

Discussion

In this study, we demonstrated that LFS, as compared with traditional HFS, can differentially alter sensory thresholds for specific sensory modalities. Low-frequency stimulation significantly reduced heat detection thresholds, regardless of patient pain status. However, when patients were analyzed by pain status, LFS had different effects, suggesting that pain status may play an important role in the mechanism underlying low-frequency DBS symptom relief. Although chronic pain patients receiving LFS were less sensitive to mechanical and vibrational stimuli, they were more sensitive to heat. In contrast, patients without chronic pain who received LFS showed increased tolerance for mechanical pain, allowing this subset of patients to potentially exhibit greater pain relief than without the stimulator.

Mechanical and thermal detection thresholds were generally independent of patient sex; however, a stark differ-

FIG. 1. In PD patients with chronic pain, LFS significantly reduced heat detection thresholds (A) compared with HFS ($p = 0.029$) or no stimulation ($p = 0.010$), LFS increased mechanical detection thresholds (B) compared with HFS ($p = 0.020$), and LFS increased vibration detection (C) compared with HFS ($p = 0.040$). In PD patients without chronic pain, LFS significantly increased mechanical pain thresholds (D) compared with HFS ($p = 0.032$).

TABLE 2. Thermal and mechanical thresholds in patients receiving STN DBS*

Threshold	Patients w/ Chronic Pain (11 patients)				Patients w/o Chronic Pain (8 patients)				p Value, HFS vs LFS
	HFS	LFS	Off	p Value, HFS vs LFS	HFS	LFS	Off		
Cold detection	27.36364 ± 0.724731	28.66182 ± 0.479698	25.78455 ± 2.300776	0.119	28.03 ± 0.600538	27.98769 ± 0.637146	28.39231 ± 0.369884	0.916	
Heat detection	37.65364 ± 1.246518	36.33 ± 0.890095	37.80273 ± 1.028768	0.029	35.83538 ± 0.591267	35.22385 ± 0.377961	35.06462 ± 0.275673	0.365	
Cold pain	18.91182 ± 3.124763	22.14364 ± 2.997847	18.69364 ± 2.73834	0.143	20.07423 ± 2.692024	17.16077 ± 3.242687	15.24385 ± 3.277004	0.133	
Heat pain	42.33091 ± 1.820136	41.83 ± 1.535881	43.07818 ± 1.508293	0.400	39.85308 ± 1.131516	40.82923 ± 1.311222	41.64231 ± 1.515266	0.382	
Mechanical detection	3.431818 ± 0.34689	3.990909 ± 0.201614	3.816364 ± 0.250077	0.020	4.044615 ± 0.250273	3.791538 ± 0.286499	3.528462 ± 0.278956	0.333	
Pressure pain	2.472727 ± 0.324203	2.581818 ± 0.501601	2.236364 ± 0.329262	0.559	3.527273 ± 0.787874	3.290909 ± 0.727213	3.581818 ± 0.86805	0.328	
Mechanical pain, 10 g	0.2 ± 0.04671	0.2 ± 0.04264	0.209091 ± 0.031492	0.426	0.115385 ± 0.03729	0.130769 ± 0.042944	0.153846 ± 0.03859	0.721	
Mechanical pain, 40 g	0.427273 ± 0.077566	0.409091 ± 0.053009	0.409091 ± 0.062457	0.804	0.215385 ± 0.047833	0.338462 ± 0.072976	0.215385 ± 0.051697	0.032	
Vibration detection	0.636364 ± 0.15212	0.909091 ± 0.090909	0.727273 ± 0.140836	0.040	0.846154 ± 0.104154	0.846154 ± 0.104154	1 ± 0	1.000	

* Values expressed as the means ± standard error of the mean.

TABLE 3. Regression analyses p values for each QST test on patient sex, pain status, and testing site

Test	Frequency	Patient Sex	Pain Status	Testing Site
Cold detection	HFS	0.265	0.684	0.726
	LFS	0.742	0.148	0.293
Heat detection	HFS	0.267	0.964	0.152
	LFS	0.208	0.690	0.071
Cold pain	HFS	0.080	0.441	0.142
	LFS	0.168	0.070	0.160
Heat pain	HFS	0.372	0.850	0.103
	LFS	0.405	0.502	0.128
Mechanical detection	HFS	0.245	0.956	0.118
	LFS	0.850	0.391	0.569
Pressure pain	HFS	0.024	0.666	0.069
	LFS	0.011	0.456	0.064
Mechanical pain, 10 g	HFS	0.433	0.464	0.031
	LFS	0.402	0.395	0.0392
Mechanical pain, 40 g	HFS	0.002	0.088	0.000
	LFS	0.030	0.332	0.101
Vibration detection	HFS	0.692	0.907	0.314
	LFS	0.652	0.550	0.956

ence between men and women appeared to persist across stimulation settings for both pressure pain and mechanical pain with the 40-g pinprick. According to our results, men appeared to have a higher threshold for pressure pain than women for both HFS and LFS. On the other hand, women had a higher threshold for mechanical pain with the 40-g pinprick. Current literature has mixed results regarding sex differences in pain sensitivity. Some studies suggest that women have a less efficient pain inhibition capacity than men,^{23,27,28} while other studies report no change.^{2,22,35} One study suggests that behavioral and psychological factors may influence the perception of pain differently among men and women.¹⁰

Quantitative sensory testing location only had an influence on the 10-g and 40-g mechanical pain pinprick tests. According to our results, the lower back is less sensitive to mechanical pain. However, the correlation (r) between the patient's report of chronic pain and using the lower back as a testing site was -0.678, which indicates a strong relationship between patients without pain and less sensitivity in the lower back. This finding indicated that the lower-back test site may have influenced the results of these tests.

Little evidence exists for the efficacy of other common chronic pain treatments such as antiepileptics (for example, gabapentin, pregabalin), antispasmodics (for example, baclofen), antidepressants, or opioids for the treatment of PD-related chronic pain. However, in 2007, Djaldetti et al. did provide some evidence of pain relief after 6 weeks of duloxetine (serotonin-norepinephrine reuptake inhibitor) treatment in PD patients.¹⁸ Interestingly, the efficacy of STN DBS for the treatment of different types of pain is still debated. For example, in a cohort of 41 patients, significant improvements in dystonic and musculoskeletal

pain occurred at 1 year, while neuropathic and central pain remained unchanged.¹³ In another study, dystonic and central pain were relieved, while musculoskeletal and radicular pain were not.³²

Extensive evidence suggests that a variety of sensory functions are altered in PD, and recent studies have shown that patients and animal models exhibit lower mechanical^{42,46,48,60} and thermal^{21,42,46,48} thresholds than those in healthy controls. Unfortunately, treatment for PD-related pain is particularly difficult as it can manifest in a variety of ways (musculoskeletal, dystonic, radiculoneuritic, or central) and patients can suffer from pain from different origins at the same time.²⁰ Given that pain in PD is under-recognized, undertreated, and understudied, there is a critical need to develop new therapies in patients whose pain is refractory to dopaminergic medications or traditional STN HFS. Traditional STN DBS is delivered at a high frequency typically ranging from 130 to 185 Hz.⁵¹ However, recent literature has demonstrated the efficacy of STN LFS in improving motor function in PD patients.^{9,30,38,39,45,47,58}

Our data are novel in showing that LFS can be used as an optional therapeutic strategy for pain relief in PD patients undergoing DBS. In addition, given our results, there could be a relationship between chronic pain in DBS and specific sensory threshold modalities. Among patients receiving STN DBS, mechanical pain changes were evident in those without pain, whereas thermal and mechanical changes were evident in those with pain. It is uncertain whether LFS is more sensitive to specific sensory modalities depending on whether or not there is chronic pain. However, our analysis suggests there may be some connection.

We acknowledge that QST has limitations. Its results may be subject to patient behavior, including boredom, distraction, or mental fatigue.⁵⁰ Although QST results have been shown to be reproducible over a period of weeks for healthy subjects,⁵⁰ we performed testing at a single visit. Moreover, we performed mechanical testing only once but thermal testing twice to minimize patient confusion when conducting these tests. In addition, the participants' self-assessments on their areas of chronic pain are subjective since their levels of current pain often change from day to day. This could cause a bias on their level of response to QST and stimulation setting changes. Moreover, neither patients nor examiners were blinded to the stimulation settings during testing. Changing the stimulation settings can have a profound effect on patient motor symptoms, and patients often felt when their stimulator settings were adjusted. We acknowledge this as a potential limitation of the study.

We examined alterations in sensory thresholds following acute LFS in PD patients with and without complaints of chronic pain. We did not address whether these patients would report changes in chronic pain since they were only stimulated with LFS for 15 minutes. However, sensory thresholds have been used as quantitative measures of changes in sensory processing in other studies and suggest changes in pain states.^{5–7,16,17,25,34,40,49,59} Although the analgesic effects of STN DBS in PD are not well understood, the current literature suggests that STN DBS

alters sensory processing in the central nervous system, including the basal ganglia,^{11,31,49} through increased pain thresholds.^{12,15,36} Since dopamine can also modify pain perception through increased pain thresholds in PD^{6,25,36} and levodopa dosing is typically reduced following STN DBS, it is conceivable that STN DBS modulates neurotransmission in midbrain circuits that are altered in PD.

Conclusions

In summary, although traditional STN HFS has proven efficacy in treating the motor symptoms of PD,⁴ patients can develop new pain symptoms or continue to have chronic pain.⁵⁶ Given the changes in sensory detection and pain thresholds in our patient cohort, we suggest that STN LFS may be a future option to consider in the treatment of PD-related pain refractory to other therapies. Further studies should address whether long-term STN LFS improves chronic pain status in these patients. In addition, patients receiving STN DBS who have a history of chronic pain may respond differently to specific mechanical and thermal stimuli compared with those who do not have chronic pain. Tailoring stimulation parameters to address specific symptoms of PD is critical for the optimization of DBS therapy.

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Disclosures

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Author Contributions

Conception and design: Pilitsis, Belasen. Acquisition of data: Pilitsis, Belasen, Yeung, Hanspal, Paiva, Durphy. Analysis and interpretation of data: Pilitsis, Belasen, Rizvi, Gee. Drafting the article: Pilitsis, Belasen, Rizvi, Gee, Yeung. Critically revising the article: Pilitsis, Belasen, Gee, Yeung, Ramirez-Zamora. Reviewed submitted version of manuscript: Pilitsis, Belasen, Rizvi, Gee, Prusik, Ramirez-Zamora, Hanspal, Paiva, Durphy, Argoff. Approved the final version of the manuscript on behalf of all authors: Pilitsis. Statistical analysis: Pilitsis, Belasen, Rizvi, Gee, Prusik. Administrative/technical/material support: Pilitsis, Gee, Prusik, Ramirez-Zamora, Hanspal, Paiva, Durphy, Argoff. Study supervision: Pilitsis, Prusik, Ramirez-Zamora.

Correspondence

Julie G. Pilitsis, AMC Neurosurgery Group, 47 New Scotland Ave., MC 10, Physicians Pavilion, 1st Fl., Albany, NY 12208. email: jpilitsis@yahoo.com.