Idiopathic Parkinson’s disease and chronic pain in the era of deep brain stimulation: a systematic review and meta-analysis

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OBJECTIVE Pain is the most common nonmotor symptom of Parkinson’s disease (PD) and is often undertreated. Deep brain stimulation (DBS) effectively mitigates the motor symptoms of this multisystem neurodegenerative disease; however, its therapeutic effect on nonmotor symptoms, especially pain, remains inconclusive. While there is a critical need to help this large PD patient population, guidelines for managing this significant disease burden are absent. Herein, the authors systematically reviewed the literature and conducted a meta-analysis to study the influence of traditional (subthalamic nucleus [STN] and globus pallidus internus [GPI]) DBS on chronic pain in patients with PD.

METHODS The authors performed a systematic review of the literature and a meta-analysis following PRISMA guidelines. Risk of bias was assessed using the levels of evidence established by the Oxford Centre for Evidence-Based Medicine. Inclusion criteria were articles written in English, published in a peer-reviewed scholarly journal, and about studies conducting an intervention for PD-related pain in no fewer than 5 subjects.

RESULTS Twenty-six studies were identified and included in this meta-analysis. Significant interstudy heterogeneity was detected (Cochran’s Q test p < 0.05), supporting the use of the random-effects model. The random-effects model estimated the effect size of DBS for the treatment of idiopathic pain as 1.31 (95% CI 0.84–1.79). The DBS-on intervention improved pain scores by 40% as compared to the control state (preoperative baseline or DBS off).

CONCLUSIONS The results indicated that traditional STN and GPI DBS can have a favorable impact on pain control and improve pain scores by 40% from baseline in PD patients experiencing chronic pain. Further trials are needed to identify the subtype of PD patients whose pain benefits from DBS and to identify the mechanisms by which DBS improves pain in PD patients.

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KEYWORDS deep brain stimulation; Parkinson’s disease; chronic pain; central pain; peripheral neuropathy; neuropathic pain; allodynia; functional neurosurgery

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Conventional pain treatment in PD patients includes analgesics such as nonsteroidal antiinflammatory drugs and opioids, physical and occupational therapies, and optimization of dopaminergic medications. More recently, traditional deep brain stimulation (DBS), targeting the subthalamic nucleus (STN) and globus pallidus internus (GPi), has shown some promise in improving pain outcomes in this patient population. While traditional DBS is very effective in restoring motor function, its efficacy is not fully recognized for chronic pain and other nonmotor symptoms in PD. Thus, while there is a critical need to help this large PD patient population, guidelines for managing this significant disease burden are absent. Herein, we systematically reviewed the literature and conducted a meta-analysis to study the influence of traditional (STN and GPi) DBS on pain in patients with PD.

Methods
Systematic Literature Search
Two authors (O.F., K.Y.) independently performed a systematic search of the PubMed, MEDLINE, Scopus, and Web of Science databases according to the PRISMA guidelines to access studies examining the relationship between DBS and PD-related pain. Electronic bibliographic searches were conducted for the years from 1950 to 2021 using medical subject headings (MeSH) terms and keywords that included the following: 1) “Parkinson’s” AND “pain” AND “Deep Brain Stimulation”, OR 2) “Parkinson’s” AND “pain” AND “neuropathy”, OR 3) “Parkinson’s” AND “pain” AND “neurostimulation”, OR 4) “Parkinson’s” AND “pain” AND “Neurostimulation.” The selection of included articles, extraction of data, and evaluation of methodological quality were conducted independently by the two authors. The selected records reported the incidence, pathophysiology, classification, and treatment of pain in the setting of PD. The effect of traditional DBS on PD-related pain was also carefully studied. Further inclusion criteria were articles written in English, published in a peer-reviewed scholarly journal, and about studies conducting an intervention or treatment, rehabilitation, or epidemiological examination of PD-related pain in no fewer than 5 patients. Records that consisted of animal studies, reviews, descriptive articles, case reports, book chapters, and technical notes were individually identified and excluded from the meta-analysis.

Data Synthesis and Statistical Analysis
Studies included in the meta-analysis were carefully evaluated, and their outcome measures were manually examined. The Oxford Centre for Evidence-Based Medicine levels of evidence (levels I–V) were used for quality assessment of the studies.20 Since the studies used different outcome measures, we used reported means and variances of the treatment and control groups (sham stimulation or before surgery) to calculate treatment effect sizes (Cohen’s d) and the standard error of the effect sizes.21 Some studies reported multiple outcome measures for pain and pain threshold. Those measures included quantitative sensory testing, which comprised nociceptive thermal and mechanical pain thresholds, visual analog scale (VAS), sharp/blunt discrimination testing, Rand SF-36 for bodily pain, non-motor symptoms scale (NMSS), numeric rating scale (NRS), Movement Disorder Society (MDS) Unified Parkinson’s Disease Rating Scale (UPDRS) part 1B for pain, UPDRS-III, 39-Item Parkinson’s Disease Questionnaire (PDQ-39) for bodily discomfort, and Kings Parkinson’s Disease Pain Scale (KPPS; Supplementary Table S1). Given the heterogeneity of pain measures, we calculated the effect size and standard deviation for each pain outcome separately and combined them by averaging to provide a single outcome value per study. The heterogeneity between studies was tested (Cochran’s Q test), and study heterogeneity was estimated using tau² and I² indices. Statistical analysis was performed using metafor 3.0-222 and meta 4.19-0 packages in R version 4.0.4 (R Foundation for Statistical Computing).23 Results of the meta-analysis were presented as forest plots. A funnel plot was used to display publication bias.

Results
Systematic Search
After excluding duplicates, a total of 536 journal articles were identified and selected to match the topic of PD-related pain. After further exclusion according to our 10 additional criteria, a total of 28 original research studies were potentially eligible for inclusion in this study (Fig. 1); however, a study by Hwynn et al. and one by Jost et al. were excluded since the mean and standard deviation of pain outcome scores were not reported. Thus, 26 studies were included in the final analysis (Table 1). The average number of patients recruited per study was 30 (SD 16.9).

Summary of Findings
The 26 original research studies were examined. The average number of subjects per study was 28 (SD 15). Oshima et al. had the largest cohort at 69 patients.24 The most common control measure was internal control with preoperative baseline prior to DBS system implantation. The second most common control group was versus off testing in patients with implanted STN DBS systems. Nine-teen studies used the preoperative baseline as the internal control. Pain measurement scales were heterogeneous across studies. The most common outcome measurement tool was pain intensity measured using a VAS or its equivalent such as an ordinal numerical scale (e.g., a scale from 0 to 425 or a scale from 0 to 1026,27). The number of studies using this tool was 11. Other measures of pain outcomes included KPPS, quantitative sensory testing, nociceptive thermal pain threshold, Rand SF-36 for bodily pain, sharp/blunt discrimination, and mechanical pain thresholds.

Statistical Analysis
Significant interstudy heterogeneity was detected (Co-
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chran’s Q test p < 0.05), supporting the use of the random-effects model. The between-study heterogeneity (I²) was found to be almost 100 (Fig. 2). The random-effects model estimated the effect size of DBS for the treatment of idiopathic pain as 1.31 (95% CI 0.84–1.79). The large between-study variability is reflected in the funnel plot (Fig. 3). Percent pain improvement was calculated in each study by calculating the difference between intervention and control (stimulation off or preimplantation scores) and deriving the percent change from baseline. The term “baseline” was used to denote preoperative or DBS-off conditions. A simple average across studies showed that DBS improves pain scores by 40% (Table 1).

Discussion

This is the first and largest meta-analysis that examines the effect of STN and GPI DBS on PD-related pain. A total of 26 studies were included showing that the traditional STN and GPI DBS-on state can significantly reduce pain as compared to the DBS-off state or preoperative baseline pain. A recent systematic review that examined a total of 9 studies and focused only on the STN showed that STN DBS can be efficacious in reducing pain by improving levodopa-equivalent dosing, UPDRS-III scores, VAS scores, and Hoehn and Yahr Scale scores.35 Extended from this study, our primary aim was to quantify the degree of pain improvement following DBS, describe the degree of outcome measure heterogeneity present in the literature, and expand on our findings to lay a common path for future practice. Our results indicate that DBS has a positive effect on pain and pain perception. Although the interventions and pain scoring were highly variable, we demonstrated that DBS exerts a significant effect on

FIG. 1. PRISMA flow diagram for new systematic reviews showing the results of the conducted systematic search. *While all engine searches were based on MeSH terms, the PubMed search was based on keyword search. **Reports were excluded because they focused on topics outside of PD-related pain and DBS. Data added to the PRISMA template (from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71) under the terms of the Creative Commons Attribution License.
that DBS significantly improves comorbid pain in PD patients, although the results should be viewed with caution given the significant interstudy variability in testing pain and scoring it. A near 100% between-study heterogeneity reflects nonuniformity of pain diagnosis and scoring. A near 100% between-study heterogeneity reflects nonuniformity of pain diagnosis and scoring before and after the DBS-on intervention. The number of patients included in the studies was also highly heterogeneous, ranging from a minimum of 8 to a maximum of 69 subjects (mean 30 subjects, SD 16.9; Supplementary Table S1). Moreover, the included randomized controlled trials (RCTs) used various control conditions including preimplantation pain scores or pain scores during the DBS-off period, which was typically intercalated with one or more DBS-on periods. Therefore, for the purpose of this meta-analysis, we did not compare to a specific control condition and grouped all controls in one category labeled as the baseline control condition. Separating control conditions or choosing only one control condition significantly reduces the number of included studies and our power, limiting the interpretation of our results.

Additionally, most of the studies recruited patients who were receiving concurrent medical treatment for pain, and the specifics of the medical management paradigms were not reported in most RCTs, as such management was not the primary aim. Thus, we could not clearly distinguish the direct effect of DBS treatment on PD-related pain without the caveat that medical management was often co-introduced during the treatment and control conditions.

Studying the effect of DBS on pain medication consumption could serve as an indirect indicator of pain control. Many of the included studies, especially those that compared DBS-on versus off testing, were not designed to track and compare pain medication consumption between the intervention and control sessions. In a study published by Smith et al., 16 patients were enrolled, and only 5 patients had pain medications recorded before and after DBS.30 Eleven patients had missing pain medication information preoperatively, postoperatively, or both. Of the 5 patients whose medications were reported before and after DBS, only 1 patient changed their medication dose, listing their medication used to lidocaine 5% external ointment preoperatively but not postoperatively. In another study by Pellaprat et al., there were no significant changes in the prescriptions of chronic analgesics and antidepressants; however, PD patients received significantly fewer prescriptions of benzodiazepines 12 months after STN DBS (25.9% vs 55.2% before, p = 0.001).30 However, no strong conclusion quantifying pain medication utilization before and after DBS can be drawn using our data set at this time. Such a question can be better addressed with an RCT specifically designed to study pain before and after DBS system implantation.

### First-Line Treatment

Our review of the literature substantiates that treatment of PD-associated pain begins with treating the disease itself. Pharmacological treatment consists of dopaminergic agents (carbidopa-levodopa, pramipexole, apomorphine, selegiline, and rotigotine) and nondopaminergic agents (nonsteroidal antiinflammatory drugs, opioids, and COX-2 inhibitors). In this setting, dopaminergic agonists are the most effective treatment, as they treat motor symptoms and pain such as pain from diabetic neuropathy, postherpetic neuralgia, and metastatic bone disease. Such findings further validate that dopamine plays an important role in mitigating pain perception; therefore, it would be logical to realize that neurodegenerative diseases involving dopaminergic circuits, such as PD, should manifest with a higher incidence of pain than normal controls or neurodegenerative diseases without dopamine degeneration. For example, studies have shown a reduction of mechanical pain thresholds in rodents with depleted striatal dopamine following 6-hydroxydopamine neurotoxin injections.36 However, other conflicting studies have shown that dopa-n
minergic agents can accentuate hyperalgesia by increasing sensory response to painful stimuli in PD patients regardless of the DBS setting (on vs off). We, therefore, conclude that the influence of striatal dopamine on the pain threshold can be multifactorial since dopamine improves the pathological motor symptoms and higher-order affective imbalances often seen with this disease.

**DBS and Pain in PD**

It is well established that STN and GPi DBS are effective in improving motor symptoms in PD. While the effects of DBS on nonmotor outcomes are less established, several reports have suggested a positive impact of DBS on nonmotor symptoms such as sensory, cognitive, and dysautonomic symptoms. In our meta-analysis, we found that multiple studies used different scales to measure pain in PD patients. Since most of the sample sizes were > 20, we used Cohen’s d to estimate the combined size effects of these different scales. The random-effects model estimated the effect size of DBS for the treatment of idiopathic pain as 1.3. According to the rules of thumb for Cohen’s d size effect estimates, d values of 0.2, 0.5, 0.8, 1.2, and 2 correspond to small, medium, large, very large, and huge size effects, respectively. Thus, effect size of DBS for the treatment of idiopathic pain would be considered very large.

Witjas et al. reported an 84.2% improvement in pain/sensory symptoms in 40 PD patients evaluated via a structured questionnaire designed to assess nonmotor fluctuation at 12 months’ follow-up after STN DBS. In a prospective study, Gierthmühlen et al. reported pain improvement after bilateral STN DBS without an objective change in pain sensitivity using quantitative sensory testing. The most common type of PD-related pain was nociceptive likely secondary to musculoskeletal and dystonic pain, which are easily attenuated after the improvement of rigidity by STN DBS. A prospective study by Cury et al. noted that the prevalence of pain decreased from 70% to 21% after bilateral STN DBS and that dystonic and musculoskeletal pain were the most improved subtypes. Although all PD patients with baseline pain off medication showed improvement at 8 years after STN DBS, new pain, especially the musculoskeletal type, developed in 79% of patients over time. Loher et al. evaluated a GPi DBS cohort of 19 subjects, harboring 9 unilateral and 10 bilateral implants, and showed that 74% and 90% of pain improved at 12 months, respectively. In another report, DiMarzio et al. showed that both STN (n = 12) and GPi (n = 6) DBS subjects had significant improvements in pain with stimulation, with greater improvement noted in the GPi cohort at 6 months.

A recent retrospective study by Gong et al. compared the impact of STN and GPi DBS on PD-related pain and found that the average NRS score significantly decreased in all 64 patients: 79% ± 27% NRS.
improvement for 36 STN DBS patients and 75% ± 27% NRS improvement for 28 GPI DBS patients. On the other hand, in a comparative study of nonmotor effects between two targets (40 STN and 20 GPI) by Dafsari et al., only STN DBS showed benefit in pain reduction.

Of the 26 studies included in our meta-analysis, 6 studies performed on- versus off-DBS testing in the absence of antiparkinsonian medications in order to isolate the effect of DBS on pain relief. While most studies showed a trend for improvement, only 3 of the 6 studies showed a statistically favorable effect of DBS on pain relief and pain thresholds. More importantly, because the levodopa-equivalent daily dose is generally decreased after STN DBS, it can be assumed that postoperatively observed clinical pain improvement is, in part, directly attributable to central STN neurostimulation and not solely restricted to pharmacological levodopa treatment.

It remains unclear whether pain reduction after STN DBS can be entirely attributed to motor improvement or whether DBS can exert central modulation of pain circuits. First, motor symptoms do not always correlate with the severity of pain, and second, the laterality of PD symptoms does not always correlate with pain localization. Though the mechanisms of pain relief with DBS in PD patients are not fully determined, pain relief can, in part, result from improved sensorimotor integration and increased sensory thresholds. STN DBS has differential effects on PD patients with or without pain, such as increasing the subjective heat pain threshold and reducing pain-induced somatosensory cortical activity. Adding to changes in sensory inputs, STN stimulation may indirectly elicit activation of the somatosensory cortex and improve sensory discrimination. Furthermore, affective aspects of pain could be modified by stimulating the limbic component of the STN, which influences activity of the nucleus accumbens. PD-related chronic pain can result from a process directly linked to degeneration of dopaminergic circuits or a secondary process that indirectly results from the PD phenotype. Primary pain syndromes of PD can result from a direct effect of neurodegeneration, reduced endogenous pain inhibition, and decreased pain thresholds. Such disturbances can manifest as affective, nociceptive, and deafferentation pain. On the other hand, secondary pain syndromes often result from 1) the association of PD with advanced age and 2) the sequelae of motor manifestation such as stooped posture, involun-

![Funnel plot of study data showing large between-study variability and a paucity of studies at the bottom of the plot. This indicates publication bias against small negative studies. The numbers below the circles represent the reference citations for the studies (e.g., 50 = Marques et al.). Figure is available in color online only.](image-url)
tary muscle contractions, increased baseline muscle tone, akathisia, and frequent falls.\textsuperscript{62,63} Experimentally isolating primary central causes of pain relief from secondary pain mitigation is a challenge since the two processes are dependent variables under the same treatment umbrella. It is, therefore, thought that pain in the PD population is often multifactorial and can result from one factor or, more often, an interplay between multiple processes that can influence the pain threshold and pain perception.

The studies indicated that both GPi and STN are equally effective in mitigating pain after DBS. It is worth noting, however, that most of the included studies focused on STN DBS. The minority of studies that included both GPi and STN DBS did not indicate any significant difference in PD-related pain relief between the two targets.\textsuperscript{48} We deduced that the influence of DBS on pain relief is likely multifactorial. It is likely taking place as a result of improved 1) rigidity and posture, 2) mitigation of dystonia, and 3) suppression of central pain circuits. From a rigidity standpoint, it is well known that both STN DBS and GPi DBS are equally effective in improving rigidity. From a dystonia perspective, it is well established that GPi DBS is effective against dystonia; however, STN DBS can also be effective against dystonia that is responsive to dopaminergic medications. From a central pain perspective, limited studies have shown mixed results when it pertains to central pain mitigation following DBS. For instance, a study by Cury et al. proposed that STN DBS surgery does not influence central or neuropathic pain,\textsuperscript{44} whereas a study by Kim et al. demonstrated that central pain improved in 92\% of a cohort following STN DBS.\textsuperscript{27} It is notable, however, that in a study published by Gong et al., both GPi and STN DBS had similar efficacy in relieving PD-related pain.\textsuperscript{48}

The basal ganglia circuitry has also been postulated to “gate” sensory processing. Studies have shown that basal ganglia dysfunction in PD leads to somatosensory deficits and abnormalities of sensorimotor integration and proprioception.\textsuperscript{54–60} This finding was corroborated by studies demonstrating decreased parietal N20 and frontal N30 somatosensory evoked potential components in patients with PD.\textsuperscript{70,71} Nonetheless, other studies have failed to replicate these findings.\textsuperscript{72,73} In a recent positron emission tomography study, a distinct reduction of frontal and parietal sensory evoked brain activation was found in those regions as well as the globus pallidus and putamen in patients with PD.\textsuperscript{74}

The conventional goal of traditional DBS (STN and GPi) is to alleviate the cardinal motor symptoms of PD. Mounting evidence shows that DBS can also provide therapeutic benefits for nonmotor PD symptoms. By systematically reviewing the literature and analyzing study results in the form of a meta-analysis, we showed that STN and GPi DBS exert a beneficial effect on PD-related pain. Extending from the results of this meta-analysis, care providers could consider including standardized pain scores in the routine screening process of PD candidates prior to DBS surgery. Patients could be consulted about the positive effect of DBS on pain control during the preoperative outpatient consultation visit. Programming sessions could also take standardized pain scores into consideration since pain is a significant factor in quality of life. Postoperative pain scores could be compared to the scores obtained prior to surgery, and big data sets across multiple centers could be stored and analyzed. Since little is known about the effect of DBS on specific etiologies of pain, collecting pain score data and categorizing patients by pain etiologies may prove helpful in further studying the effect of DBS on the specific pain etiology and subtype.

\section*{Study Limitations}

Scientific journals tend to represent positive results more often than negative ones. A negative study showing no pain benefit after DBS is less likely to get published than a positive study showing beneficial results. Hence, positive publication bias might have impacted our systematic review, as most of the published studies showed a significant beneficial effect of traditional DBS on pain. Most of the included studies utilized class III and IV evidence. From a design perspective, it is difficult to double blind the subject and examiner with on- versus off-stimulation paradigms. Similarly, it is not possible to double blind studies that compare pre- and post-DBS implantation. The studies also used different measurements of pain, control conditions, classification tools, and follow-up periods, which increased interstudy heterogeneity. Given the heterogeneous nature of pain in PD patients in the absence of a unified classification system to categorize and quantify pain, studies with better categorization and quantification of pain are warranted to examine more specifically the effect of DBS on the different components of pain in PD.\textsuperscript{49} It would be worth the effort to better understand the nature of the pain improvement and systematically quantify pain relief in order to provide better targeted treatment options that are tailored to a patient’s specific pain etiology. Even though most studies focused on STN DBS, a few included GPI DBS only or mixed subjects with STN and GPI implants. Finally, pain is hard to quantify objectively and can fluctuate between testing periods, especially if these periods are months and years apart.

\section*{Conclusions}

Pain is the most common nonmotor symptom of PD, with the musculoskeletal subtype being the most prevalent. Pain can precede motor manifestations by several years. There is increasing evidence that PD-related chronic pain can be alleviated with traditional DBS of the STN or GPi. Understanding basal ganglia circuitry and the pathophysiology of chronic pain in PD is key in providing optimal treatment. In this study, we analyzed the effect of STN and GPI DBS on comorbid pain in PD patients. Our results show that traditional STN or GPI DBS improves pain outcomes by 40\% in the PD population.

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\section*{References}


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Disclosures
Dr. Lozano is the scientific director of Functional Neuromodulation Ltd. and a consultant to Medtronic, Abbott, Boston Scientific, Insightec, and the Focused Ultrasound Foundation.

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Conception and design: Flouty, Yamamoto, Lozano. Acquisition of data: Flouty, Yamamoto. Analysis and interpretation of data: Flouty, Yamamoto, Germann, Harmsen. Drafting the article: Flouty, Yamamoto, Harmsen, Jung, Cheyuo, Zemmar, Milano, Sarica, Lozano. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Flouty. Statistical analysis: Germann. Administrative/technical/material support: Flouty, Yamamoto, Lozano. Study supervision: Flouty, Yamamoto, Lozano.

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