ADVANCES IN INVASIVE AND NON-INVASIVE BRAIN STIMULATION IN PARKINSON'S DISEASE: FROM BASIC SCIENCE TO NEW TECHNOLOGIES

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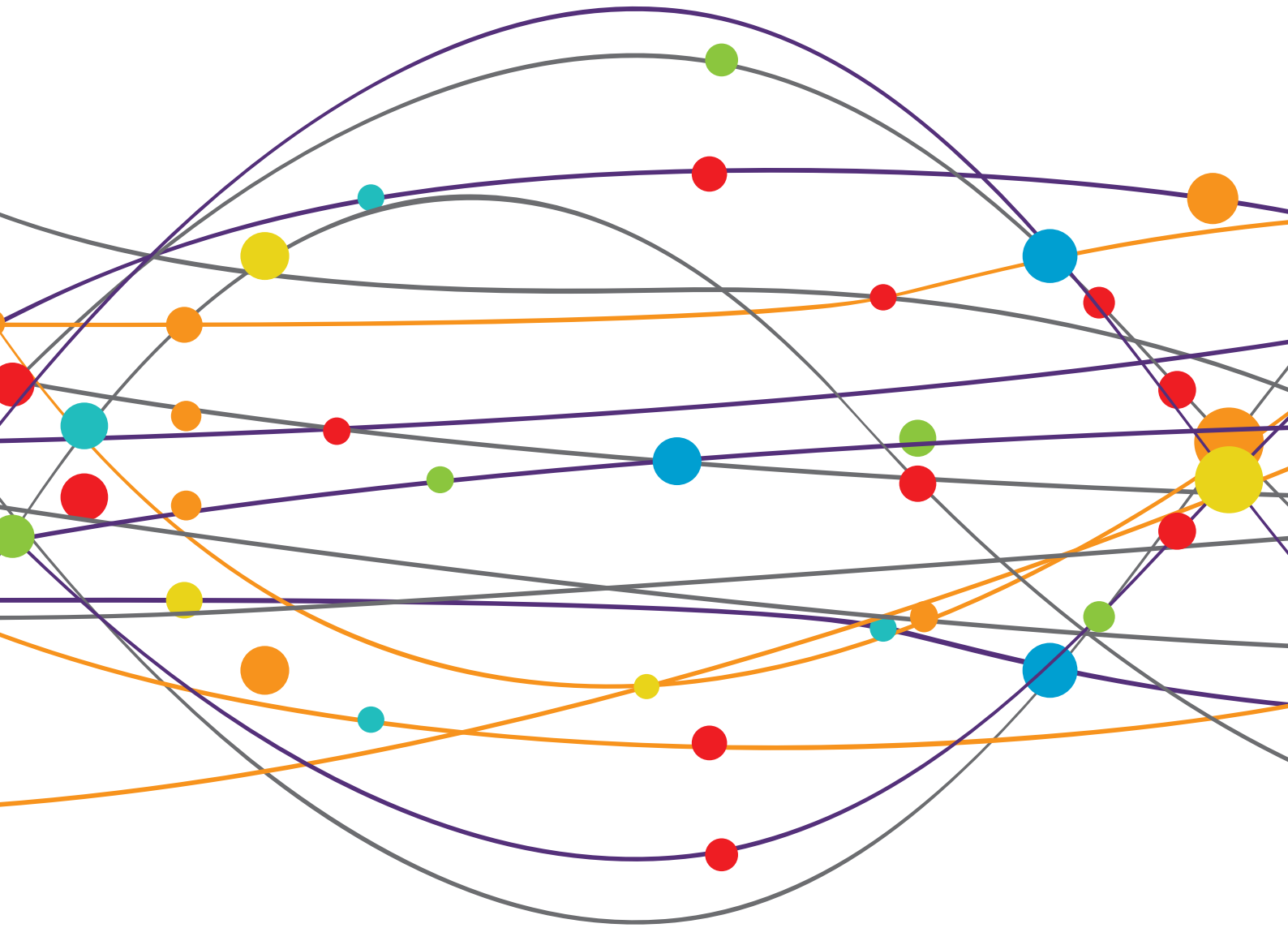

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ADVANCES IN INVASIVE AND NON-INVASIVE BRAIN STIMULATION IN PARKINSON'S DISEASE: FROM BASIC SCIENCE TO NEW TECHNOLOGIES

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EDITORIAL
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Editorial: Advances in Invasive and Non-invasive Brain Stimulation in Parkinson's Disease: From Basic Science to New Technologies

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Keywords: Parkinson's disease, brain stimulation, local field potential (LFP), transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), sleep disturbance, deep brain stimulation (DBS)

Editorial on the Research Topic

Advances in Invasive and Non-invasive Brain Stimulation in Parkinson's Disease: From Basic Science to New Technologies

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Parkinson's disease (PD) is the second most prevalent neurodegenerative disease, substantially impacting quality of life and economic burden. Currently available treatments, including pharmacological interventions, rehabilitation, and brain stimulation, undoubtedly help to reduce disease symptoms. This Frontiers of Neurology unique Research Topic brings us several new insights into improving brain stimulation interventions.

Brain stimulation is one of the fastest-growing neuroscience areas involving medical and bioengineering fields. Brain stimulation is inherently non-destructive, reversible, and, most importantly, adjustable. Whether invasive or non-invasive, the electrical intervention can modulate the nervous system function, leading to improved neurological symptoms and better quality of life.

Deep brain stimulation (DBS) has been clinically useful in the treatment of PD at all stages, especially in those patients with motor symptoms only partly controlled by dopaminergic drugs, such as severe rest tremor or off-period dystonia, and motor fluctuations. However, many DBS issues remain challenging, for instance, choosing a suitable stimulation target to maximize clinical outcomes, while minimizing side effects. As a highly heterogeneous disease, one DBS solution does not fit all patients.

Neurosurgeons commonly face the challenge of precisely localizing tiny surgical targets. Indeed, successful application of DBS relies on optimal lead placement, among several factors. In this regard, Shi et al. used microstimulation during microelectrode recordings to localize the subthalamic-substantia nigra border. The authors provided evidences that it can be easily and routinely employed to achieve better lead placement in the STN and superior therapeutic effectiveness.

There has been much debate on the best DBS target for PD. DBS targeting the subthalamic nucleus (STN) and the internal Globus pallidus (Gpi) reduces PD's motor and non-motor symptoms. Comparative studies suggested that STN and GPi DBS have similar outcomes. Nevertheless, GPi DBS likely causes less impact on both gait and cognition. Zeng et al. assessed the outcome differences of stimulating STN or GPi in the same individual. A significant improvement in motor symptoms occurred after STN stimulation. Effects of unilateral STN stimulation were seen

on both sides of the body, while unilateral GPi stimulation mainly acted on the contralateral side, thus providing evidence favoring STN DBS.

Adaptive DBS has gained space in the research and clinical fields. This novel approach might improve troublesome side-effects from conventional DBS, such as speech disturbances, disabling gait disorders, and behavioral changes. By enabling the recording of patient-specific local field potential (LFP) signals through electrode contacts adjacent to the stimulating electrode contact of the same DBS lead, adaptive DBS may allow for automated brain stimulation adjustment and better management of PD symptoms. This closed-loop approach demands familiarity with electrophysiological biomarkers associated with distinct clinical manifestations. On this field, Baumgartner et al. gifted us with a comprehensive review of the relationship between LFP oscillations in the STN and the sleep architecture of PD patients. This knowledge may allow future closed-loop optimization of electrical parameters to treat sleep dysfunction in PD.

Many factors may contribute to DBS outcomes in PD, and the genetic profile is undoubtedly one of them. About 25% of individuals undergoing DBS have a genetic form of PD. Given the individual variability in clinical evolution and surgical responses, it is reasonable to hypothesize that genetic variability may relate to distinct phenotypes and DBS outcomes. Accordingly, patients with LRRK2, parkin, VPS35, and SNCA mutations respond well to DBS treatment, whereas patients with glucocerebrosidase (GBA) mutations may disclose faster cognitive decline and poorer responses following DBS.

Beyond neuropathological issues, electrophysiological differences may justify differences in DBS outcome. David et al. analyzed the differences between left and right STN resting-state beta power in GBA mutation carriers with PD. The differences in peak beta ratio in GBA-mutation carriers correlated to the clinical findings, suggesting a distinctive physiologic signature from sporadic PD. Additional research on LFP attributes according to the PD genetic profile will provide resources for adaptive DBS programming.

DBS research may also explore alternative ways of electrical stimulation. An animal study by Wang et al. demonstrated the impact of coordinated STN DBS reset on motor parkinsonism. Preliminary evidence supports shuffled STN CR-DBS producing significantly better therapeutic effects on parkinsonian symptoms, with the additional gain of reducing side-effects by minimizing the current spread.

The systematic review, by Miao et al. on functional magnetic resonance imaging (fMRI) to investigate modulatory DBS effects on brain activity, shed light on DBS impact on functional connectivity. The authors reviewed studies on the mechanism of DBS action, the effects of chronic stimulation on motor networks, the impact on different inter-regional connectivity, the effects on non-motor symptoms in PD, and differences in levodopa and DBS actions on brain activity.

DBS immediately modulates the cortico-basal ganglia-thalamocortical loop, leading to significant physiological modifications in the thalamus, globus pallidum, and cerebellum. The primary motor cortex activation changes correlate with motor symptoms and PD phenotypes. The impact of DBS on brain activity depends on several factors, such as programming parameters, subject's activity while being scanned, PD subtypes, and medication intake. Future use of fMRI should allow individualized surgical planning and help identify optimal anatomical targets as per symptoms. Overall, fMRI must enhance the understanding of DBS mechanisms in PD and help to improve clinical outcomes.

Non-invasive brain stimulation (NIBS), as theta-burst stimulation (TBS), proposes managing several PD symptoms. Furthermore, novel targets for rTMS, such as the prefrontal cortex, motor cortex, cerebellum, and spinal cord, focus on different symptoms like depression, apathy, motor symptoms, and gait disturbance. The mini-review performed by Wu et al. broadly discusses the role of rTMS and TBS in LID in PD. The authors explored the therapeutic mechanism of TMS in the management of LID, which involves understanding many neural circuits that take part in the occurrence of LID. Identifying brain regions involved in LID mechanisms is critical. The right stimulation target or combination of different areas might prolong therapeutic efficacy. Pan et al. highlighted the shortness of TMS efficacy protocols. They showed that high-frequency rTMS over the left dorsolateral-prefrontal cortex (DLPFC) only provides short-term improvements for alleviating fatigue in patients with multiple system atrophy.

Cheng et al. systematically and quantitatively analyzed the therapeutic effect of TBS for PD treatment. TBS leverages repetitive TMS due to its short time of single treatment and low stimulation intensity compared to traditional rTMS. Accordingly, TBS over the supplementary motor area significantly improved motor burden in the off-medication period. Additionally, intermittent TBS over the motor cortex and DLPFC impacted the slowing of gait and depression.

NIBS may change quantitative electrophysiological signs in PD patients. The scoping review of Costa et al. gathered evidence of the neurophysiological changes associated with NIBS in PD. They evidenced the NIBS' impact on the cortical activity as measured by electroencephalogram. On the other hand, the systematic review by Oliveira et al. found no significant short-term effect of tDCS on motor function, balance, gait, dyskinesia, or motor fluctuations in PD, regardless of brain area or targets stimulated. These opposite findings might reflect differences in the quality of the studies, the low number of studies, and especially variability in NIBS intervention.

NBIS new technologies, such as galvanic vestibular stimulation (GVS), are being increasingly explored in PD. Lee et al. investigated the behavioral GVS effects under different stimulation frequencies and the interaction between GVS effects and anti-parkinsonian medication. Clinical response varied considerably across participants under the tested conditions. Moreover, dopaminergic drugs significantly influenced GVS effects in PD patients. Kazemi et al. searched for EEG predictive measures of impaired motor vigor in PD, which may provide valuable leads for GVS modulation.

Finally, Pfeifer et al. shared the study protocol on clinical efficacy and dosing of vibrotactile coordinated reset stimulation (VCR) in PD symptoms. VCR is a non-invasive therapy that delivers gentle vibrations to the fingertips. VCR might

desynchronize abnormal brain rhythms within the sensorimotor cortex, thus relieving motor and non-motor symptomatology in PD.

From the evidence shown in this Research Topic, advances in brain stimulation are encouraging, but there are still many critical issues to address. We must fully clarify its mechanisms of action at the cellular level, its related neurophysiological events, and its impact on the regular and pathological neuronal networks. Besides, it is imperative to use multimodalities of PD biomarkers to better predict the outcome at the individual level as a tool for individualized medicine. Integrating neurophysiology, neuroimaging, and genomics into patient care is a highly strategic priority.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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ORIGINAL RESEARCH
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Microstimulation Is a Promising Approach in Achieving Better Lead Placement in Subthalamic Nucleus Deep Brain Stimulation Surgery

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Background: The successful application of subthalamic nucleus (STN) deep brain stimulation (DBS) surgery relies mostly on optimal lead placement, whereas the major challenge is how to precisely localize STN. Microstimulation, which can induce differentiating inhibitory responses between STN and substantia nigra pars reticulata (SNr) near the ventral border of STN, has indicated a great potential of breaking through this barrier.

Objective: This study aims to investigate the feasibility of localizing the boundary between STN and SNr (SSB) using microstimulation and promote better lead placement.

Methods: We recorded neurophysiological data from 41 patients undergoing STN-DBS surgery with microstimulation in our hospital. Trajectories with typical STN signal were included. Microstimulation was applied near the bottom of STN to determine SSB, which was validated by the imaging reconstruction of DBS leads.

Results: In most trajectories with microstimulation (84.4%), neuronal firing in STN could not be inhibited by microstimulation, whereas in SNr long inhibition was observed following microstimulation. The success rate of localizing SSB was significantly higher in trajectories with microstimulation than those without. Moreover, results from imaging reconstruction and intraoperative neurological assessments demonstrated better lead location and higher therapeutic effectiveness in trajectories with microstimulation and accurately identified SSB.

Conclusion: Microstimulation on microelectrode recording is an effective approach to localize the SSB. Our data provide clinical evidence that microstimulation can be routinely employed to achieve better lead placement.

Keywords: deep brain stimulation, microstimulation, microelectrode recording, optimal lead placement, substantia nigra, subthalamic nucleus

INTRODUCTION

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-accepted therapeutic approach for controlling the motor symptoms of Parkinson's disease (PD) (1, 2). The efficacy of STN-DBS heavily relies on the influence by the appropriate placement of DBS electrodes relative to STN (3, 4). Previous studies suggested an optimal lead placement trajectory that travels through the entire dorsolateral portion of STN, with the tip of the distal contacts placed near the deep boundary of STN (3, 5, 6), which will enhance clinical outcomes (1, 2, 7, 8). However, the major challenge of this optimal lead placement is how to precisely localize STN, especially the ventral boundary (6, 9) of STN that is an almond-shaped nucleus embedded deeply in between the diencephalon and the midbrain and surrounded by multiple brain structures. Beneath the STN lies the substantia nigra (SN), which can be divided histologically into the dorsolateral substantia nigra pars reticulata (SNr) and the ventromedial substantia nigra pars compacta (6, 9). The ventral boundary of the STN is very close to SNr (6, 10), and the gap between them is only 0.5–1 mm or even smaller (6, 11). Due to insufficient imaging resolution and low signal-to-noise ratio (9, 11), conventional magnetic resonance imaging (MRI) strategies often fail in distinguishing STN from SNr.

Electrophysiological recording technique is often used to help distinguish the anatomical borders between the STN and SNr. Compared to the STN, SNr tends to have a neuronal activity featured by a higher and more regular firing frequency with a lower background noise level (3, 6, 10). Besides this, the appearance of the small inactive area (silent area) at the boundary between the STN and SNr (SSB) can also help identify the ventral border of the STN (5, 12). However, sometimes the inactive area is too small, if not missing, to be captured or noticed by intermittent electrophysiological recording, leading to a difficulty in recognizing the beginning of SNr (6, 11). In such cases, neurosurgeons often have to determine the implantation depth based on personal experiences along with the trial stimulation effects, which in many cases brings uncertainties to the efficacy of DBS.

Microstimulation is a train of electrical stimulation pulses with small electrical current delivered *via* the tip of a microelectrode, which is often used to pre-evaluate the stimulation effects of macroelectrodes (13, 14). A previous study has suggested that microstimulation can trigger different responses in STN and SNr (15). To further test this potential of microstimulation, we conducted this study and evaluated the feasibility of microstimulation in distinguishing the STN from SNr on patients who received STN-DBS surgery. Our data demonstrates that microstimulation is a promising tool in detecting SSB and guiding the placement of DBS leads.

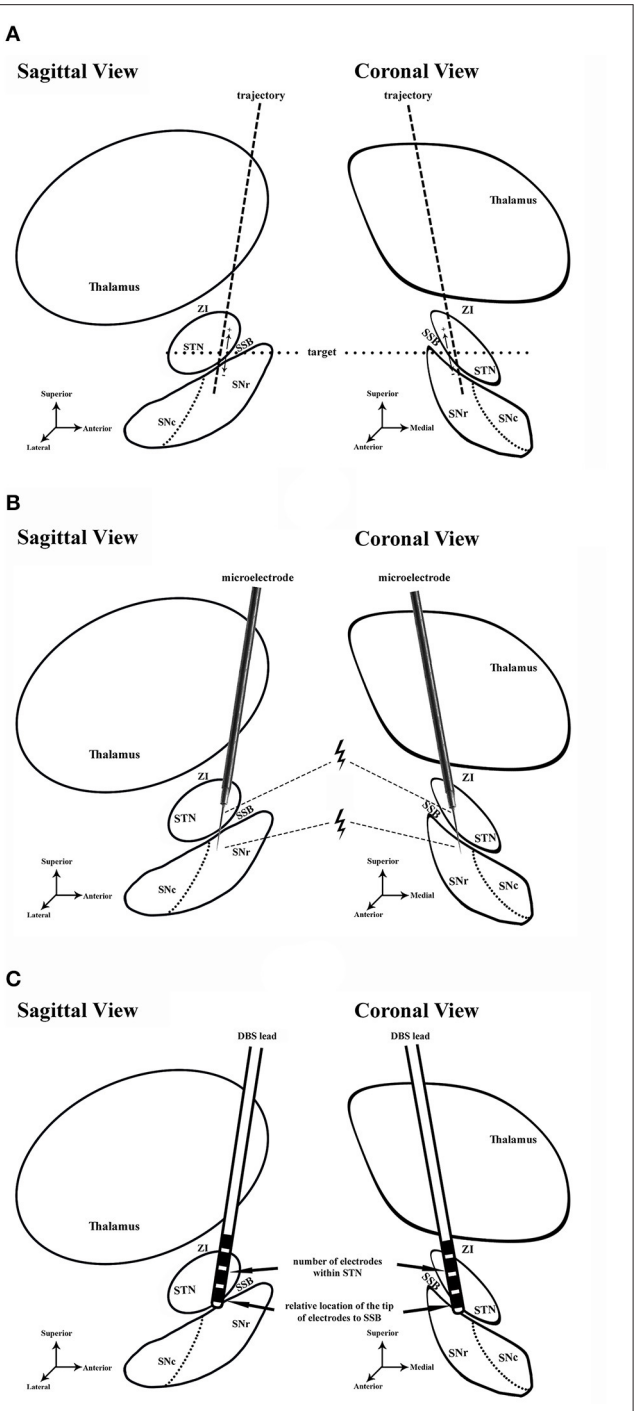

FIGURE 1 | Schematic diagram of the study. **(A)** Preoperative planning in sagittal and coronal views. Dash line, trajectory of lead placement. Dot line, the level of target. **(B)** Microelectrode recording and microstimulation during the DBS surgery. Microstimulation was conducted in the ventral STN and dorsal SNr. Thunder symbol, microstimulation near the exit of STN and entrance of SNr. **(C)** Assessment of lead placement. The number of electrodes in STN (arrow) and the relative location of the electrode tip to SSB (arrow) were assessed to evaluate the lead placement. STN, subthalamic nucleus; ZI, zona incerta; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta; SSB, boundary between subthalamic nucleus and substantia nigra; DBS, deep brain stimulation.

METHODS

Patients

The data analyzed in the study were recorded from patients who received microstimulation to determine SSB during unilateral or

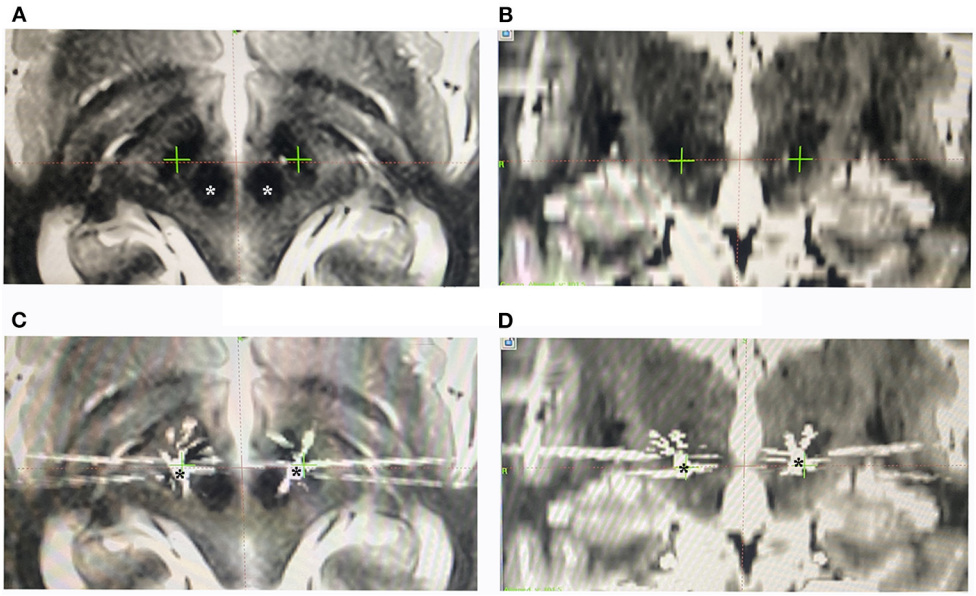

FIGURE 2 | Preoperative planning for lead implantation and postoperative verification of the lead location. **(A,B)**, Preoperative planning on MRI images using the SurgiPlan software, with the targets (green crosses) placed along the anterior edge of the red nucleus (white asterisk). **(C,D)** Postoperative verification of the lead location (black asterisk) using the SurgiPlan software to overlap postoperative CT images onto preoperative MRI images.

bilateral STN-DBS surgery as a treatment for PD or dystonia at Beijing Tiantan Hospital between October 2019 and December 2020. Their intraoperative electrophysiological recording data were reviewed so that trajectories with poor neural signal or trajectories in which electrodes deviated significantly from STN, as shown in postoperative reconstruction (see below), were excluded. The study was performed in accordance with the Declaration of Helsinki, and all procedures were approved by the Institutional Review Board of our hospital (permission no. KY2019-097-02). Informed written consents were acquired from all patients. This case series has been reported in line with the PROCESS Guideline (16).

Surgical Procedures and Microstimulation

All patients went through a routine neurological assessment conducted by movement disorder specialists, including the Unified Parkinson's Disease Rating Scale (UPDRS) for PD patients, the Unified Dystonia Rating Scale (UDRS), and multiple other scales and examinations, *etc.*, to confirm the diagnosis and indication for surgery (5, 12). The preoperative brain MRI scans of patients were acquired at admission using a 3-Tesla MRI scanner (SIGNA; GE Healthcare, Waukesha, WI, USA), including 3D-T1-weighted (slice thickness: 1 mm, repetition time: 9.4 ms, echo time: 4.3 ms, spacing between slices: 0), axial T2-weighted (slice thickness: 1 mm, repetition time: 7,881 ms, echo time: 104.9 ms, spacing between slices: 0), and coronal T2-weighted (slice thickness: 1 mm, repetition time: 8,947 ms, echo time: 102 ms, spacing between slices: 0) images. The patients received a unilateral (two cases) or bilateral (39 cases) DBS surgery. The procedures of the surgery were described in detail in previous studies (12, 17, 18). Targeting and trajectory planning were conducted on an image-based preoperative planning system (Leksell SurgiPlan 10.1, Elekta Instrument, Sweden) using the direct targeting method as described before (19–21) (**Figure 1A**, **Figures 2A,B**). On each side, after incising the scalp and making a burr hole under local anesthesia, a shielded tungsten microelectrode (Neuroprobe, Alpha Omega, Israel; an average impedance of 458 ± 183 kΩ) was inserted into the brain toward the target area driven by a microdrive (Drive Headstage, Alpha Omega, Israel). Electrophysiological signals were recorded to guide the implantation of the DBS leads (**Figure 1B**) using a Neuro Omega system (Neuro Omega, Alpha Omega, Israel). Microelectrodes were advanced at a step-size of 0.2–0.4 mm once the entrance of the STN was identified, and when the tips of the microelectrodes were near the bottom of the STN, the step-size was adjusted to 0.1–0.2 mm. The gap between the exit of the STN and the putative entrance of SNr was considered SSB. The thickness of the SSB was annotated.

We conducted microstimulation (0.5-s train at 200 Hz in frequency, 300 μA in amplitude, and 60 μs in pulse width) at every stop near the bottom of the STN to investigate the neuronal responses using a similar approach as described in previous literature (15) (**Figure 1B**). At every stop, the microstimulation was repeated two to four times. The recorded signal was examined to determine whether microstimulation induced the inhibition of neuronal firing. The inhibition period was defined as the time length between the end of the microstimulation train and the first spike afterwards. If

the inhibition periods were unidentifiable (lower than 50 ms) in the STN and much longer in SNr (longer than 50 ms, usually longer than 200 ms), the electrophysiological recording in this trajectory was considered concordant with the findings described in previous studies (15, 22); otherwise, it was considered discordant.

When a trajectory with satisfactory signal was obtained, a DBS lead was implanted along the same track for trial stimulation (**Figure 1C**). The therapeutic windows (*i.e.*, the range between the minimal intensity of stimulation required to obtain meaningful clinical benefits) and the intensity of stimulation at which the first persistent side effect occurred

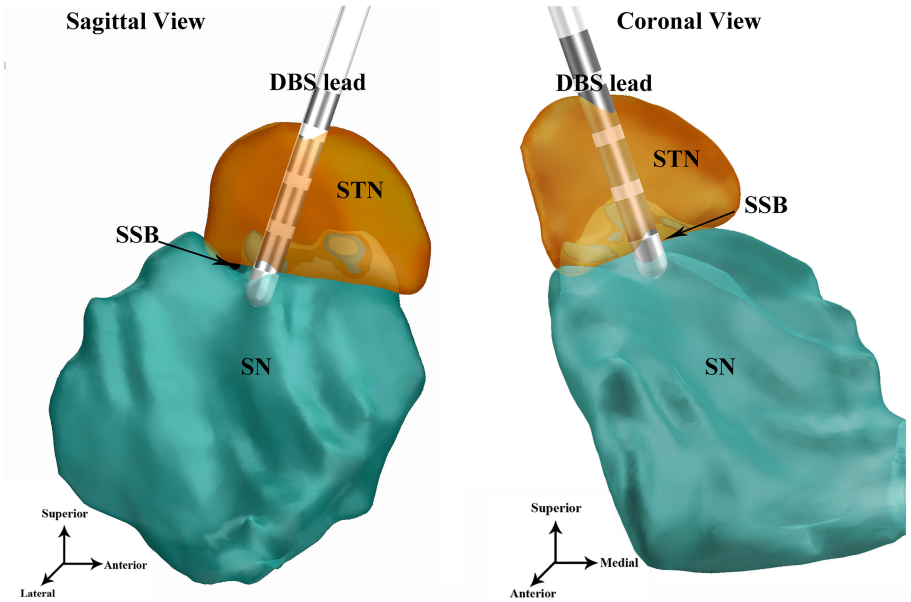

FIGURE 3 | An example of DBS lead reconstruction using the software Lead DBS. The electrode tip of the DBS lead is placed in or very close to SSB. DBS, deep brain stimulation; STN, subthalamic nucleus; SN, substantia nigra; SSB, boundary between subthalamic nucleus and substantia nigra.

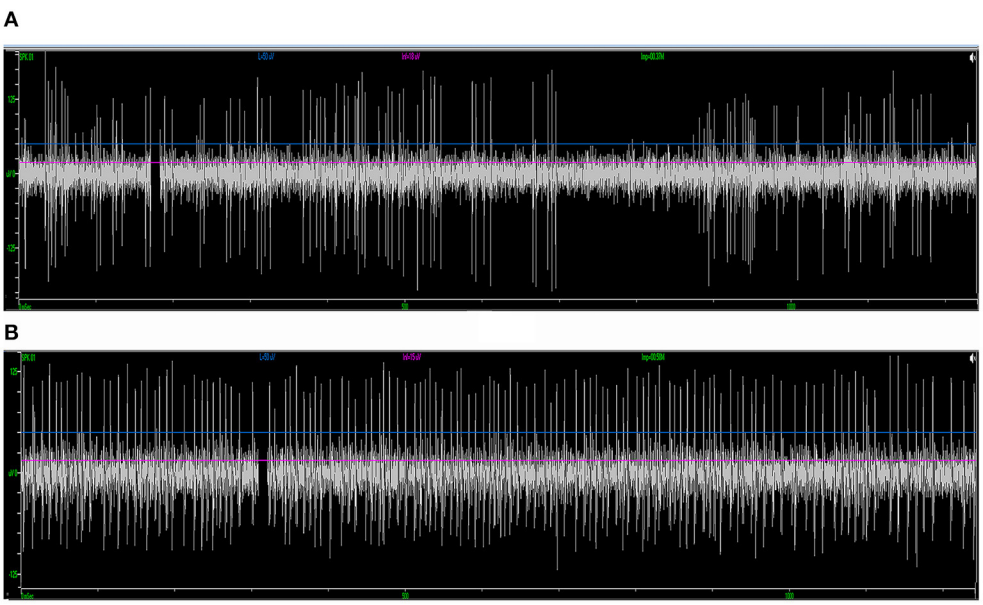

FIGURE 4 | Examples of standard STN and SNr signal in intraoperative microelectrode recording. **(A)** The typical STN signal is highlighted with a higher background noise level and irregularly firing neurons. **(B)** The SNr signal is featured by a lower background noise level with neurons that spike more regularly and frequently. STN, subthalamic nucleus; SNr, substantia nigra.

were noted. UPDRS or UDRS assessments were performed by a neurologist. The ultimate decision on the implantation depths of DBS leads in the track was made based upon the consensus among the neurosurgeons, a neurologist, and a neurophysiologist after considering the length of STN, the possible location of SNr, the intraoperative UPDRS/UDRS assessments performed by the neurologist, side effects, and the therapeutic window. The locations of the lead tips were noted for further verification.

Lead Reconstruction

After surgery, a standardized postoperative computed tomography (CT) scan was conducted according to existing protocol (12). The postoperative CT was co-registered to the preoperative MRI to localize the electrodes and the tip of the contact array. A semi-automated Matlab toolbox, the Lead DBS toolbox (23), was used to visualize the leads in 3D virtual space (**Figure 3**). The precision of the reconstruction was verified by overlapping the postoperative CT upon the preoperative MRI (**Figures 2C,D**). The trajectories whose electrodes were obviously outside STN were excluded. The location of the lead was assessed according to the relative relationship between the tip of the contact array and SSB. The location of the lead was considered satisfactory if the ventral tip of the contact array was within or very close to SSB (*i.e.*, the distance between the tip of contacts and SSB was smaller than 1 mm) as revealed by Lead DBS and the notes of microelectrode recording. The number of contacts within the STN nucleus shown in the reconstructed images was counted. A contact was counted as half if only part of the contact was inside of the STN.

Statistical Analyses

We employed the Fisher exact test for categorical data and the *t*-test for continuous data to determine statistical significance. All statistical analyses were performed using R software (version 4.0.2) (24). The number of SSB identification was calculated for two groups (trajectories with macrostimulation *vs*. trajectories without microstimulation). The Fisher exact test was used to test the significance of proportion difference between groups with and without microstimulation. Descriptive statistics including means and standard errors were calculated. Unpaired two-tailed Student's *t*-test was used to test the significance of the mean difference between groups with identified SSB and without identified SSB.

RESULTS

Data Overview

Forty-one patients (16 males and 25 females; 31 PD and 10 dystonia cases in the cohort, with an average age of 58.2 ± 10.9 years) who underwent STN-DBS surgery (two unilateral and 39 bilateral) were included in the study. The average length of the disease was 8.5 ± 5.3 years. In total, 80 sessions of neural data that were recorded from microelectrodes implanted through different trajectories on these patients were analyzed. Typical STN signal was recorded in 50 trajectories (62.5%) (**Figure 4A**). In the rest of the 30 trajectories (37.5%), the signal was atypical inside the nucleus. In 56 trajectories (70.0%), putative SNr signal was identified at 1 mm above to 5 mm below the target, featured by a higher firing rate and a lower background compared to STN (**Figure 4B**). In the other 24 trajectories (30.0%), SNr signal was either not reached out for because a satisfactory coverage of STN was achieved or not identified during the microelectrode recording.

Inhibitory Responses Induced by Microstimulation in STN and SNr

Of the 39 patients who underwent bilateral surgery, 35 of them received unilateral and five received bilateral microstimulation. In total, 155 trials of microstimulation were applied in 45 trajectories (56.3%), while in the other 35 trajectories (43.8%) microstimulation was not conducted. No patient reported any discomfort with microstimulation, and no abnormal scenario (like seizure) was induced. In 38/45 trajectories with microstimulation (84.4%), STN signal could not be inhibited by microstimulation, while SNr presented a long inhibition period following microstimulation (566 ± 217 ms, **Figure 5**), which was in line with the previous study (15). By contrast, in three trajectories (6.7%), mild inhibitory responses were induced near the bottom of the STN (162 ± 77 ms), and a putative SNr signal could not be inhibited in the other four trajectories (8.9%).

Microstimulation Promotes the Identification of SSB

In our study, SSB was identified in 48/80 trajectories (60.0%), either purely by recognizing the exit of STN and the entrance of SNr in microelectrode recording or with the aid from microstimulation to test the inhibitory responses of STN and SNr. The average length of SSB was 0.87 ± 0.32 mm. No difference was detected between the length of SSB in trajectories with and without microstimulation ($P = 0.070$, **Figure 6A**). The identification rate of SSB was further compared between the tracks with and without microstimulation. Using microstimulation, SSB was identified in 33/45 trajectories (73.3%), which is significantly higher than those without microstimulation where SSB was found in only 15/35 trajectories (42.9%, $P = 0.011$, **Figure 6B**).

Imaging Reconstruction of DBS Leads

In 43/80 trajectories (53.8%), the distal tips of the contacts were placed within or very close to SSB, which is considered satisfactory, while in the other 37/80 trajectories, the distal tips of the contacts were at least 1 mm away from SSB (46.2%), which was considered unsatisfactory. In all trajectories, the mean number of contacts within STN was 2.4 ± 0.9. To determine whether the recognition of SSB might benefit the lead placement, we compared the relative location of the electrode tip and the number of contacts within STN between the trajectories whose SSB was identified and whose SSB was not identified. The percentage of a satisfying electrode tip location was 70.8% in trajectories with SSB identified and 28.1% in trajectories whose SSB was not identified ($P = 0.0002$, **Figure 7A**). On the other hand, the contact number within the STN in trajectories with the SSB identified was 2.6 ± 0.9, which was significantly higher than

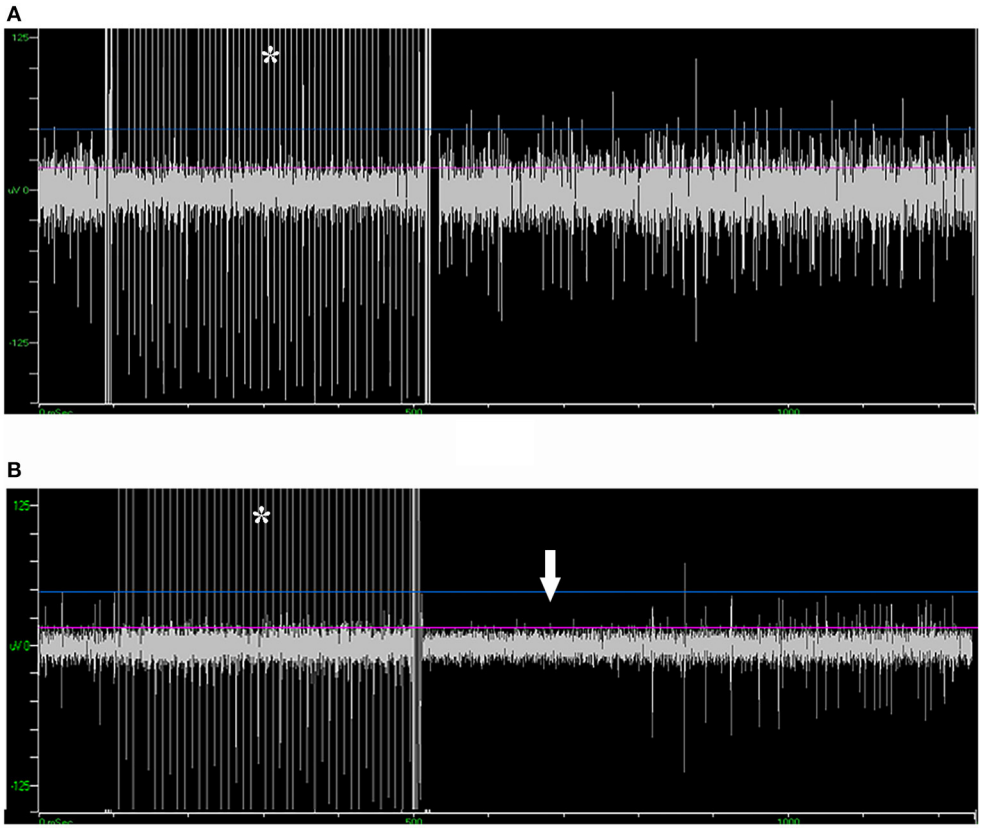

FIGURE 5 | Microstimulation-induced inhibition of neuronal activity in SNr but not in STN. **(A)** Microstimulation (asterisk) in STN failed to induce inhibition in neuronal activity. **(B)** Microstimulation induced long inhibition (arrow) in SNr. STN, subthalamic nucleus; SNr, substantia nigra.

those trajectories whose SSB was not identified (2.0 ± 0.9, $P = 0.005$, **Figure 7B**).

Microstimulation Contributes to Better Therapeutic Effectiveness

To assess the clinical values of microstimulation in terms of therapeutic benefits to the patients, we compared the alterations in UPDRS/UDRS scores assessed during the trial stimulation and before the surgery (ΔUPDRS/ΔUDRS) as well as the therapeutic windows between the tracks with and without microstimulation. The therapeutic windows were 2.27 ± 0.12 V in the tracks with microstimulation (Stim tracks) and 1.93 ± 0.13 V in the tracks without microstimulation (Non-Stim tracks, $P = 0.056$, **Figure 8A**). The ΔUPDRS/ΔUDRS scores were 15.13 ± 1.24 in the Stim tracks, which were significantly higher than those of the Non-Stim tracks (10.69 ± 1.14, $P = 0.010$, **Figure 8B**). Besides this, we also compared the ΔUPDRS/ΔUDRS scores and the therapeutic windows between the tracks in which the SSB was identified vs. the ones that were not. The therapeutic windows were 2.31 ± 0.11 V in the SSB-identified tracks (SSB tracks) and 1.85 ± 0.14 V in the SSB-unidentified tracks (Non-SSB tracks). The ΔUPDRS/ΔUDRS scores were 15.46 ± 1.23 in the SSB tracks and 9.78 ± 0.97 in Non-SSB tracks. Both the therapeutic windows and the ΔUPDRS/ΔUDRS scores were higher in the SSB tracks than in the Non-SSB tracks ($P = 0.014$ and 0.001, respectively, **Figures 8C,D**). These results show that microstimulation is promoting better therapeutic effectiveness.

DISCUSSION

A previous study has suggested the great potential of microstimulation in localizing the ventral border of STN (15). However, the study only tests on four patients, without evidence from imaging techniques and clinical assessments confirming the improvement on the lead placement and clinical effectiveness using this method. Our study is an extension of the previous study to evaluate the feasibility of microstimulation using more sophisticated methods and neurophysiological data from 41 patients. Our results showed that, in most trajectories with microstimulation (84.4%), inhibition of neural activity could be induced at the top part of the SNr but not at the bottom of the STN. Such difference in responses to the microstimulation of STN and SNr can be used as a tool to facilitate the localization of the STN exit and the SNr entrance (*i.e.*, the identification of SSB) during microelectrode recording, which helps to place the electrode tip inside or very close to the SSB, resulting in higher contact quantity inside the STN. Such placement of DBS leads is considered optimal for DBS surgery. In other words,

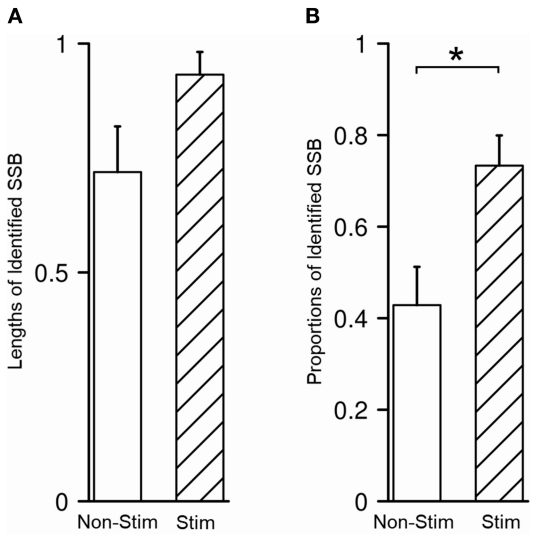

FIGURE 6 | Microstimulation promoted the identification of SSB. **(A)** There was no difference between the length of SSB in trajectories with and without microstimulation. **(B)** The proportion of identified SSB was significantly higher in trajectories with microstimulation than those without. SSB, boundary between subthalamic nucleus and substantia nigra. *$P < 0.05$.

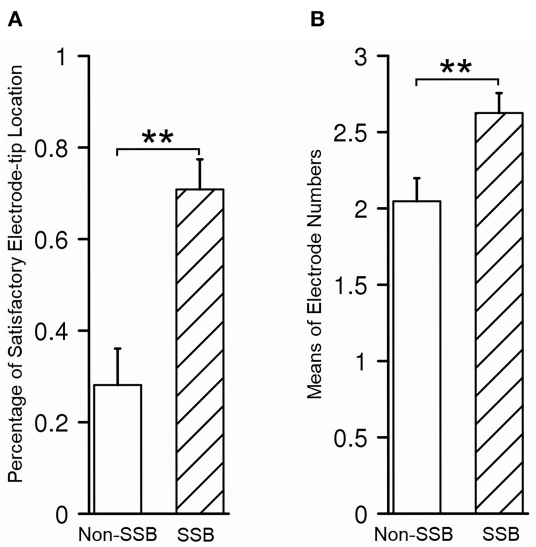

FIGURE 7 | Assessment of lead placement in trajectories with identified SSB and those without. **(A)** The percentage of satisfactory relative electrode tip location was higher in trajectories with identified SSB than those without. **(B)** The mean electrode number within STN was higher in trajectories with identified SSB than those without. SSB, boundary between subthalamic nucleus and substantia nigra. **$P < 0.001$.

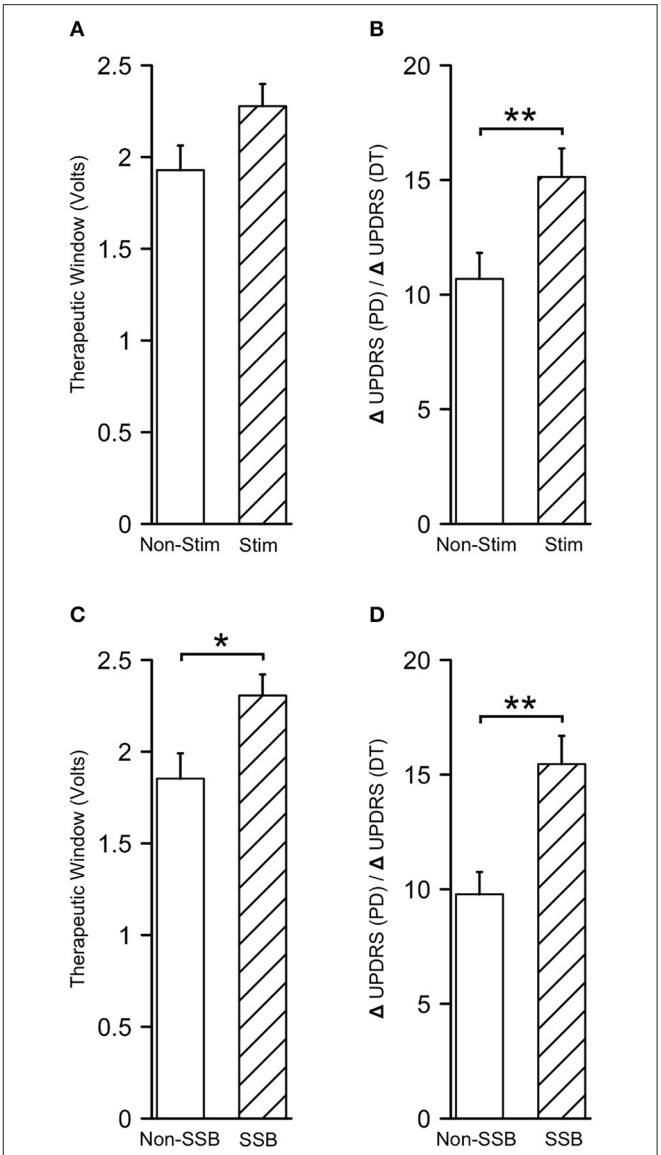

FIGURE 8 | Microstimulation contributes to better therapeutic effectiveness. **(A,B)** Therapeutic windows and differences in UPDRS/UDRS scores between the preoperative and intraoperative assessments (ΔUPDRS/ΔUDRS) in tracks with and without microstimulation. **(C,D)** Therapeutic windows and ΔUPDRS/ΔUDRS scores in the SSB and non-SSB tracks. SSB, boundary between subthalamic nucleus and substantia nigra. *$P < 0.05$; **$P < 0.001$.

our results demonstrated that microstimulation could be used to promote the identification of SSB and therefore contribute to better lead placement. This finding is supported by the wider therapeutic window and the greater decline in UPDRS/UDRS scores identified in tracks with microstimulation than those without. These results further indicate that microstimulation contributes to better therapeutic effectiveness.

Our results also showed some opposite scenarios, in which the microstimulation triggered inhibition in STN and failed to induce inhibition in SNr. Nevertheless, there were also a few units that acted differently to microstimulation in previous studies, whose percentage of outliers (1.4% for STN and 15.4% for SNr) was similar to ours (15, 22). Thus, our results are generally consistent with the previous findings (15). In the light of the close relationship between the SNr and the ventral border of the STN (see "INTRODUCTION"), it is possible that other factors

acted as confounds, including misinterpretation of the real microelectrode location, slight slide of the recording electrode, alteration in neuronal activity, tiny movement of the cables that transfer the signal, *etc*. Thus, it is difficult to determine whether these outliers reflected the real characteristics of these nuclei in response to microstimulation.

The location of DBS electrodes relative to the STN is important to the therapeutic effects of DBS (as is discussed in the "INTRODUCTION") (18). The key to the optimal placement of DBS electrodes is to cover the dorsolateral STN as much as possible (5, 21). Although the final placement of DBS leads is a clinical decision that depends on a myriad of factors, placing the electrode tip near the SSB is still recommended by most neurosurgeons to ensure better coverage of motor STN and fewer side effects (5, 11). During the surgery, it is often very difficult to determine where to stop in the STN because the signal near the ventral boundary of the STN is sometimes elusive (6, 11, 25). The gap between the STN and SNr can be very small that surgeons can misinterpret the SNr signal as the STN signal. In this case, microstimulation can be applied to test the different responses of these nuclei and contribute to the correct judgment on the real location of the microelectrode. The advantages of this method are as follows: (1) reliability: both our study and previous studies showed a high replicability of such phenomenon and a low percentage of outliers, and our results from the reconstruction of DBS leads, in turn, verified the judgment on the location of the SSB; (2) simplicity: this method is easy to apply, and the entire length of one trial of microstimulation takes no more than 10 s; and (3) safety: no abnormal scenario was induced or reported in our study. Therefore, we recommend that microstimulation can be conducted during routine microelectrode recording or only when the surgeons are doubtful of the microelectrode location.

Limitations

The study that we presented here is primarily limited by the selection of trajectories. We only picked tracks that electrophysiologically displayed a typical STN signal and radiologically traveled through a good portion of the STN (shown by reconstruction). Another limitation of our study lies in the reconstruction method that we employed. Lead DBS software projects the DBS leads to standardized brain and atlas after normalization. Although studies have verified the accuracy of Lead DBS (23, 26), a tiny discordance between the computed nuclei and the real brain may exist. Therefore, a future study with a better design is needed to investigate the efficacy of microstimulation for guiding lead implantation.

CONCLUSION

Our study tested the efficacy of a previous finding which has not been widely applied in DBS surgery: microstimulation can work as a tool to aid in targeting the ventral border of STN. Our results show that microstimulation can be used to promote the identification of the gap between the STN and SNr and thus can contribute to better lead placement.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethic Committee of Beijing Tiantan Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AY, JZha, and LS conceived and designed the study. LS, SF, TY, QZ, YD, HZ, HL, and FM performed the study and collected data. JZhe, HF, and ZX investigated the data and performed statistical analyses. LS, HF, JZhe, and QZ wrote the first draft. JZhe, AY, and JZha revised the paper. All authors met the requirements for authorship. All authors believe the manuscript represents honest work and approved the submission and publication of the final version of the manuscript.

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Subthalamic Peak Beta Ratio Is Asymmetric in Glucocerebrosidase Mutation Carriers With Parkinson's Disease: A Pilot Study

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Introduction: Up to 27% of individuals undergoing subthalamic nucleus deep brain stimulation (STN-DBS) have a genetic form of Parkinson's disease (PD). *Glucocerebrosidase* (*GBA*) mutation carriers, compared to sporadic PD, present with a more aggressive disease, less asymmetry, and fare worse on cognitive outcomes with STN-DBS. Evaluating STN intra-operative local field potentials provide the opportunity to assess and compare symmetry between *GBA* and non-*GBA* mutation carriers with PD; thus, providing insight into genotype and STN physiology, and eligibility for and programming of STN-DBS. The purpose of this pilot study was to test differences in left and right STN resting state beta power in non-*GBA* and *GBA* mutation carriers with PD.

Materials and Methods: STN (left and right) resting state local field potentials were recorded intraoperatively from 4 *GBA* and 5 non-*GBA* patients with PD while off medication. Peak beta power expressed as a ratio to total beta power (peak beta ratio) was compared between STN hemispheres and groups while co-varying for age, age of disease onset, and disease severity.

Results: Peak beta ratio was significantly different between the left and the right STN for the *GBA* group ($p < 0.01$) but not the non-*GBA* group ($p = 0.56$) after co-varying for age, age of disease onset, and disease severity.

Discussion: Peak beta ratio in *GBA* mutation carriers was more asymmetric compared with non-mutation carriers and this corresponded with the degree of clinical asymmetry as measured by rating scales. This finding suggests that *GBA* mutation carriers have a physiologic signature that is distinct from that found in sporadic PD.

Keywords: GBA mutation carriers, Parkinson's disease, subthalamic nucleus beta power, deep brain stimulation, local field potential (LFP)

INTRODUCTION

Activity from populations of neurons can be recorded in the form of local field potentials (LFPs) during deep brain stimulation (DBS) surgery for Parkinson's disease (PD) (1). The most used surgical target for PD, the subthalamic nucleus (STN), is characterized by pathologic LFP rhythms that oscillate in the low-frequency (LF) band (2–7 Hz), beta band (8–30 Hz), gamma band (60–90 Hz), and high-frequency band (>200 Hz) (2). Beta power has been a particular focus of study as it has been found to be a marker of motor impairment. In fact, the reduction in beta power after administration of levodopa is positively correlated with improvement of motor impairment (3). Similarly, continuous high frequency DBS results in a reduction in beta power and correlates with an improvement in motor function in PD (4–6).

Interestingly, relatively consistent pathologic resting state beta power characteristics have been defined for PD (1, 7) despite significant variation in PD phenotype. Though alterations in the rate and pattern of basal ganglia neurons may partly explain the phenotypic variation (8), the contribution of individual genotype to differences in beta power has not yet been explored. This is important because an increasing number of studies have demonstrated that genotype is an important predictor of DBS outcome (9–13). For instance, several studies have shown that *glucocerebrosidase* (*GBA)* mutation carriers fare worse with STN-DBS compared with non-mutation carriers from a cognitive standpoint, though they still maintain motor benefit (9–13). In contrast, *LRRK2 G2019S* mutation carriers fare the same as non-mutation carriers from a cognitive standpoint and have at least the same or even better motor outcome compared with sporadic PD patients (9–13). Very importantly, 22–27% of individuals undergoing STN-DBS have a genetic form of PD (13, 14), indicating that genetic variability could be particularly useful in understanding individual patient phenotype and DBS outcome. As LFP signals are now being used clinically in adaptive DBS systems, these signals, when combined with genotypic data, may provide important insights into genotype-phenotype relationships and the variability in DBS outcomes.

In this pilot study, we examined differences in beta power comparing *GBA* mutation carriers and non-mutation carriers with PD. We focused on *GBA* because mutation in the *GBA* gene is the most common genetic risk factor for PD and is a harbinger of aggressive cognitive and motor decline. Also, up to 17% of PD patients undergoing DBS are *GBA* mutation carriers (13, 14). In a prior study using motion analysis, our group demonstrated that *GBA* mutation carriers had more symmetric arm swing velocity compared with non-mutation carriers in the OFF state (15). Furthermore, *GBA* mutation carriers are less likely to have an asymmetric onset of PD compared with non-mutation carriers (16). Given these findings, we hypothesized that *GBA* mutation carriers would have more symmetric beta power compared with non-mutation carriers when LFPs were collected in the OFF state during STN-DBS surgery.

METHODS

Patients

The study was approved by the Rush University Medical Center Institutional Review Board. All participants provided written informed consent for study participation. Study participants were recruited based on a convenience sample from the Rush Movement Disorder clinic between July 2016 and August 2020. All patients with PD were offered the option to participate in the study after they were judged to be candidates for bilateral STN-DBS surgery by the movement disorders surgical team and decided to undergo bilateral surgery. As part of the inclusion criteria, participants had a confirmed diagnosis of PD according to the United Kingdom Parkinson Disease Society Brain Bank criteria (17), were responsive to dopaminergic medication, had significant motor fluctuations, presented with disabling dyskinesias and/or tremor, and lacked significant cognitive impairment and dementia as determined by formal neuropsychological testing.

All subjects completed a levodopa challenge as part of their candidacy assessment for DBS. The pre-operative OFF medication motor scores are reported as the Movement Disorders Society revision of the Unified Parkinson Disease Rating Scale (MDS-UPDRS Part III) (18). In subjects with only UPDRS Part III scores, scores were converted to MDS-UDPRS Part III scores (19). The sum of the bradykinesia and rigidity items with laterality was calculated for each side of the body using the relevant UPDRS (items 22–26) and MDS-UPDRS (items 3.3–3.8) items to determine the bradykinesia-rigidity score. We considered only bradykinesia and rigidity items and excluded tremor items as beta power has been shown to be related to clinical signs of bradykinesia and rigidity and not tremor (20–22). A simple difference between left and right scores were calculated (23). Positive scores indicated left-dominant PD, negative scores indicated right-dominant PD, and a score of 0 indicated symmetric PD. **Table 1** lists demographic and clinical data for the non-*GBA* and *GBA* groups.

Surgical Procedures

Participants were treated with standard clinical and surgical techniques to implant bilateral STN-DBS leads as described previously (24). Left and right STN-DBS leads were implanted during the same surgery. Participants underwent identical surgical procedures for target localization and lead implantation (i.e., stereotactic, awake, microelectrode localization, intra-operative CT, and with test stimulation to determine efficacy without adverse effects) (25, 26). Prior to the first surgery, participants underwent thin-cut high-resolution MRI brain imaging. This scan was used for direct targeting of the dorsolateral STN for DBS electrode placement, as well as co-registration with intra-operative CT to localize electrode position (26–28). Micro-electrode recording (MER) was used to assure the DBS electrode would be placed in the sensory-motor region of the STN. Confirmation that the DBS lead was in the same location as

TABLE 1 | Patient characteristics, MDS-UPDRS scores, and coordinates of lead location in the left and right STN.

	Non-*GBA* (*n* = 5)	*GBA* (*n* = 4)	*p*-value
Age (years)	60.0 (7.1)	54.0 (8.5)	0.29
Disease duration (years)	9.4 (4.2)	6.3 (2.9)	0.19
Sex	M, 4; F, 1	M, 3; F, 1	
Ethnicity (n)	2	3	
Caucasian, non-Hispanic	1	1	
Caucasian, Hispanic	2	0	
Asian	0	0	
Other			
MDS-UPDRS Part III (OFF medication)	51.8 (13.6)	47.3 (8.3)	1.0
MDS-UPDRS Part III (ON medication)	22.6 (5.3)	29.8 (10.5)	0.41
Bradykinesia asymmetry score	−0.6 (3.5)	7.0 (2.9)	0.01
Left STN			
X	−10.6 (1.4)	−9.7 (1.7)	0.56
Y	−4.8 (1.0)	−4.3 (0.7)	0.41
Z	−5.0 (0.8)	−4.8 (0.9)	1.0
Right STN			
X	10.5 (1.0)	9.2 (0.2)	0.06
Y	−3.7 (1.6)	−4.4 (0.4)	0.19
Z	−6.3 (1.0)	−5.4 (1.0)	0.19

Mean values (standard deviation) are shown; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; STN, subthalamic nucleus; GBA, Glucocerebrosidase; M, male; F, female.

the MER tract that offered the "best" recording was done via O-arm™ (Medtronic, Inc. Minnesota, USA) spins with the microelectrode in place and then with the DBS electrode in place. Once the leads were implanted, and before macro-stimulation testing, the LFP recording testing protocol was performed. Typically, leads were inserted, location verified, and LFPs were recorded for each side sequentially; thus, the duration between lead insertion and LFP recording was similar between the left and the right STN across participants.

Intraoperative LFP Recording

Data were acquired on an Alpha-Omega Neuro Omega system (Alpha-Omega, Nazareth, Israel). STN LFPs were recorded from all contacts from each lead in a referential electrode configuration. The reference, a needle placed on the scalp, was placed in the skin near the surgical opening. The output from the lead was connected to a custom-made cable that transmitted information from each contact in the lead to the Alpha-Omega Neuro Omega system. Depending on the type of lead (Medtronic 3389, Boston Scientific Vercise Cartesia model DB-2202-45 or Abbott-St. Jude Infinity model 6172) that was implanted, intraoperative LFP recording resulted in 4 to 8 channels of data. Each channel corresponded to data from a single contact on the DBS lead. The data were sampled at a rate of 1,375 Hz with a gain of 55,000. Data were stored on the Neuro Omega system. Prior to transfer for further analysis, the data were converted to the MATLAB format through an Alpha-Omega conversion routine and then imported into MATLAB. LFPs from the left and right STN were recorded during rest for 120 seconds. Participants were supine on the operating table; their arms were completely supported with their elbows extended and placed at their sides. Participants were asked to relax during data collection. After obtaining a stable baseline signal for 5 seconds (limiting insertional effects), LFPs were then recorded continuously for 120 seconds. The data were visually reviewed in real time to identify signal artifact or excessive noise. Notation was also made of any tremor activity. If the motor task was interrupted or inconsistent, signal acquisition was halted and restarted. If signal artifact or excessive noise was identified, the signal acquisition was halted and restarted.

LFP Analysis

All available channels of raw LFP data were analyzed by a rater (MJM) blinded to *GBA* status of the participants. The objective of the LFP analysis was to identify the contact with the highest beta power in the left and right STN. As beta power is known to be localized to the dorsolateral STN (29), the fundamental premise was that the contact with the highest beta power would be the most likely contact closest to the dorsolateral STN.

LFP data were processed using custom-made scripts and built-in functions of MATLAB, EEGLAB (30), and Fieldtrip (31). **Figures 1A–G** shows the LFP data processing pipeline. The raw LFP data was bipolar referenced (configuration for the 4-contact lead: 1–0, 2–1, 3–2; configuration for the 8-channel segmental lead: each segmental lead was referenced to the closest ring electrode) (32), band pass filtered (2 and 128 Hz), and line noise was filtered using a notch filter at 60 and 120 Hz. Then, the LFP data was divided into 5s epochs. Using EEGLAB, each 5s epoch was statistically analyzed to detect artifacts by identifying epochs with large outliers (greater than ± 500 μv), abnormal linear trends (a slope >50 μv), improbable data points using a joint probability function, abnormal distribution using kurtosis of activity, and abnormal spectra (30). Each epoch statistically deemed to contain artifacts were excluded from further analysis following visual confirmation. Epochs that had tremor artifact were excluded from the analysis. Our focus was to determine the spectral power of each 5s epoch. This was carried out in FieldTrip using the ft_freqanalysis function with a Hanning window (31). Parameters used for configuring ft_freqanalysis function can be found at this link: https://www.fieldtriptoolbox.org/reference/ft_freqanalysis. A Hanning taper was used as our frequencies of interest were less than 30Hz. Our frequencies of interest were beta frequencies, i.e., 12Hz to 30Hz in steps of 1Hz. Our analysis was restricted to the beta band as the beta band has been shown to be related to bradykinesia and rigidity (20–22). Power in the beta band for each 5s epoch was calculated and averaged for each contact. Next, robust Fisher's G statistic and its accompanying *p*-value were calculated to determine if the beta peaks associated with a given contact were statistically significantly greater than surrounding peaks (33). The G-statistic is a formal test that uses the false discovery approach to determine if a given peak in a time series is statistically significantly greater than the surrounding peaks (34). Only the contact with the largest beta peak was

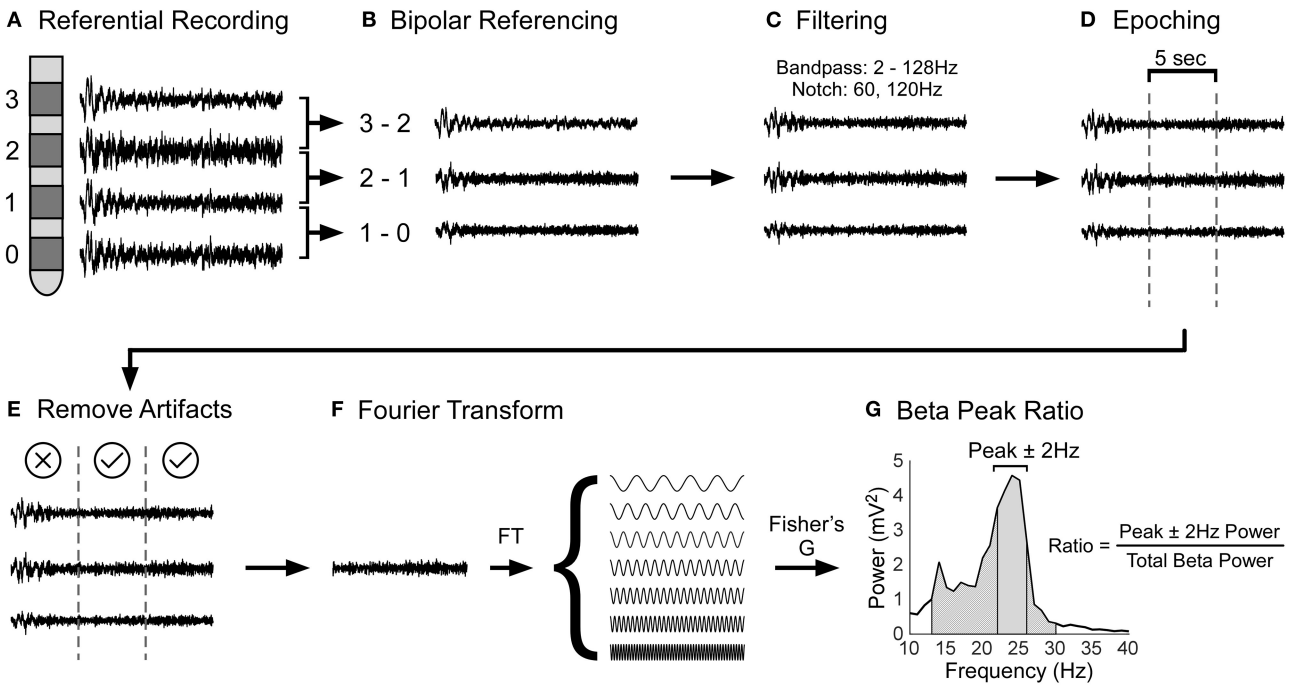

FIGURE 1 | Schematic of local field potential data processing pipeline. **(A)** During surgery, STN LFPs were recorded in a referential electrode configuration. **(B)** The raw LFP data was bipolar referenced and then **(C)** filtered using a band pass (2 and 128Hz) and notch filter (60 and 120Hz). **(D)** After, the LFP data was divided into 5s epochs and **(E)** epochs with artifacts were removed from analysis. **(F)** The LFP data were Fourier transformed to determine the power of each frequency. Power in the beta band was calculated by evaluating the area under the power spectral density, which is the square of the magnitude of Fourier Transform (not shown in the figure). **(G)** Finally, the beta peak ratio was calculated by dividing the power at the frequency with peak beta ± 2Hz (solid gray segment) by the total power of the beta band (diagonally lined segment).

used in subsequent analyses. For this contact, the ratio of the area under the frequency with peak beta ± 2 Hz, to the area of the entire beta band was calculated for each 5s epoch (see **Figure 1G**); thus, the peak beta area was normalized to the total beta area. Expressing peak beta power as a normalized value allowed us to make between subject comparisons. This peak beta ratio was calculated for the left and right STN for *GBA* and non-*GBA* participants and was used as the outcome in our statistical analysis.

Genetic Testing

Genetic testing categorized our participants into non-*GBA* and *GBA* carriers. Enrolled participants were screened for *GBA* mutation status. Prior to STN-DBS surgery, blood samples were sent to the University of Cincinnati Biobank for molecular testing and sequenced for all *GBA* mutations as previously described (35). Study staff and subjects were blinded to mutation status during LFP recording and analysis.

Statistical Analysis

The peak beta ratio was subject to a mixed-effects regression model. The fixed effects were Group (*GBA* and non-*GBA*), STN side (left and right), and the Group by STN side interaction. The random effect was participant. This random effect allowed for the distinction between the within-participant variance vs. the between-participant variance (i.e., it accounts for correlation within a participant), and we assumed an unstructured correlation structure. To ensure that between-group differences in age, age of onset, and disease severity (quantified by the OFF-medication MDS-UPDRS part III sub score) did not influence our results, we included these variables as covariates in our model. To test differences in left and right beta power in non-*GBA* and *GBA* mutation carriers, we performed planned pairwise comparisons (*t*-tests) on the differences of the mean least squares estimates co-varying for age, age of disease onset, and disease severity obtained from the mixed effects model. The following planned comparisons were performed: Left vs. Right STN for the non-*GBA* group, and Left vs. Right STN for the *GBA* group. All statistical tests used a two-sided 5% level of significance and *p*-values associated with pairwise comparisons were adjusted using the Bonferroni method. Normal theory methods and residual diagnostics were used to evaluate validity of assumptions. Between-group differences in demographic variables including age and disease duration, MDS-UPDRS part III sub scores, bradykinesia-rigidity asymmetry scores, and DBS lead locations were evaluated using appropriate parametric or non-parametric statistical methods. All statistical analyses were performed using SAS ® (version 9.4; SAS Institute, Cary, NC).

RESULTS

LFP data was obtained from 5 non-*GBA* (male, 4) and 4 *GBA* (male, 3) participants with PD. All *GBA* mutation carriers had the E326K risk variant. On average, the non-*GBA* relative to the *GBA* group: was 6 years older than the *GBA* group; had a 3.1 year longer disease duration; was 4.5 points higher on the off medication MDS-UPDRS part III sub score; was 7.2 points lower on the on medication MDS-UPDRS part III sub score; had less asymmetry and was 7 points lower on the bradykinesia-rigidity asymmetry score; was similar to the *GBA* group with respect to DBS lead locations. As can be seen in **Table 1**, only the bradykinesia-rigidity asymmetry score was significantly different between groups ($p = 0.01$). None of the of the other measures were statistically different between groups; however, despite the lack of statistical significance, the magnitude of difference in age (6 years), age of disease onset (3.1) and off medication MDS-UPDRS part III scores (4.5 points) may be clinically significant. Our statistical model included age, age of disease onset, and off medication MDS-UPDRS part III scores as covariates; thus, adjusting for differences between groups that may be clinically significant. The type of DBS lead and respective manufacturer are summarized in the **Supplementary Table 1**.

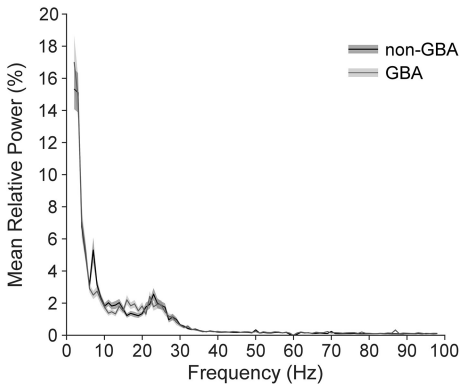

FIGURE 2 | Power spectrum averaged across all participants in the non-*GBA* and *GBA* groups while off medication, estimated using the contact pairs displaying the peak beta ratio. Power in each frequency is expressed as percentage of total power in the 2–98Hz range. Note that there were no distinct peaks above 30Hz.

We observed clear beta signal in all subjects. **Figure 2** illustrates the mean ± 1SE power spectrum from 2 to 98 Hz for the non-GBA and GBA groups for the contact pair displaying the maximum beta ratio. Power in each frequency was represented as a percentage of total power in the 2–98 Hz range. **Figure 2** shows a marked increase in the theta band (4–8 Hz) in the non-GBA group compared to the GBA group, distinct beta peaks in both the non-GBA and GBA groups, and a lack of distinct peaks beyond 30 Hz.

Figure 3A is a histogram illustrating the distribution of the frequency of beta peaks by participant in the non-GBA and GBA groups. As can be seen in **Figure 3A**, the beta peak frequencies are quite variable between the non-GBA and GBA groups, as well as between subjects within each group. **Figure 3B** is a histogram of peaks in the low beta (12–20Hz) and the high beta (20–30 Hz) bandwidth. There were no differences with respect to the peak beta frequencies between groups.

Planned pairwise comparisons revealed that peak beta ratio between the left and right STN was similar for the non-*GBA* group (estimated difference, 0.03; 95% confidence level, −0.03 to 0.08; $p = 0.56$; **Figure 4**) but was significantly different for the *GBA* group (estimated difference, 0.08; 95% confidence level, 0.02 to 0.13; $p < 0.01$; **Figure 4**). The degree of beta asymmetry corresponded with the degree of clinical asymmetry as measured by the bradykinesia-rigidity asymmetry score (**Table 1**).

Participant level data demonstrated that the number of 5s epochs that contributed to the participant mean peak beta ratios were similar between participants in the non-*GBA* (145 epochs) and *GBA* (149 epochs) groups (**Figure 5A**). One participant

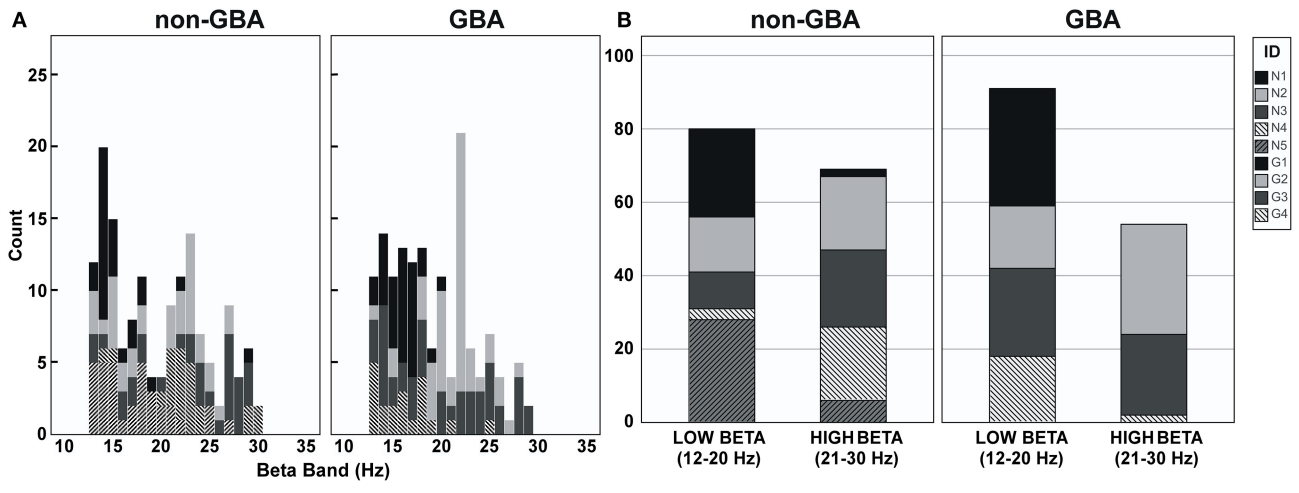

FIGURE 3 | (A) Histogram of peak frequencies in the beta band for participants in the non-GBA and GBA groups. **(B)** Histogram of peak frequencies in the low beta band (12–20Hz) and the high beta band (21–30Hz) for participant in the non-GBA and GBA groups.

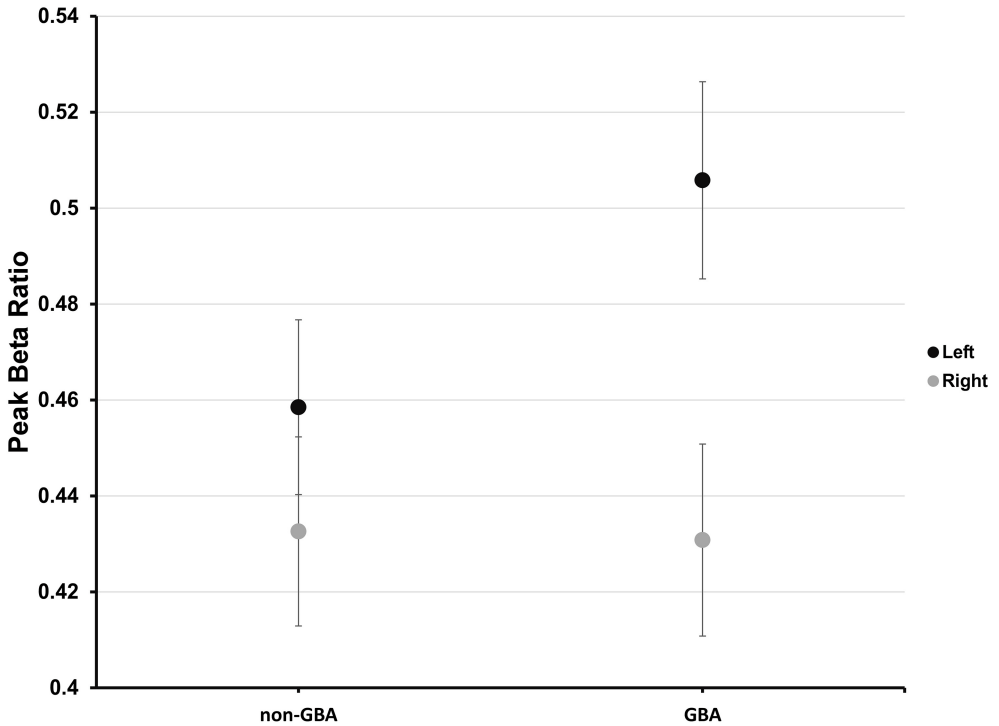

FIGURE 4 | Estimated mean peak beta ratio in the non-*GBA* and *GBA* groups for the left (black circles) and right (gray circles) STN after co-varying for age, age of onset of PD, and disease severity. The error bars reflect ±1 standard error.

in the non-GBA contributed only 6 epochs for the right STN, else the number of epochs were similar between groups. **Supplementary Table 2** lists the number of number of epochs used for each participant. A Mann-Whitney U test confirmed that there were no differences between groups ($p = 0.46$). In addition, as can be seen in **Figure 5A** there was considerable within-participant variability in the peak beak beta ratio (estimate, 0.014; Wald Z, 11.92; $p < 0.001$), but the between-participant variability was similar (0.0005, Wald Z, 1.13; $p = 0.13$). **Figure 5B** summarizes the data presented in **Figure 5A**.

DISCUSSION

In this LFP pilot study, the peak beta ratio in *GBA* mutation carriers with PD was more asymmetric compared with non-mutation carriers and this corresponded to the degree of clinical asymmetry as measured by the bradykinesia-rigidity asymmetry score. This finding demonstrates that *GBA* mutation carriers may have a physiologic signature that is distinct from that found in sporadic PD. We also observed a marked increase in theta band activity in the non-GBA group compared to the GBA group. We recognize that this may be an important distinguishing feature between non-GBA and GBA participants with PD and requires further research.

Our results are consistent with a study by McNeill et al. (2013) which demonstrated that *GBA* mutation carriers with PD had greater asymmetry of radio-ligand uptake on DATscan imaging compared with other genetic forms of PD (36). Penetrance of *GBA* is only 10% at 60 years of age and 19% by 80 years of age (37), indicating that mutations in the gene are not sufficient to induce neurodegeneration. Therefore, in *GBA* mutation carriers, conversion to PD may be due to the combination of asymmetric focal neurodegeneration (related to the abnormal GCase activity) that is then exacerbated by other factors (e.g., head trauma, environmental toxins, etc.). The rate of neurodegeneration is accelerated in *GBA* mutation carriers compared with sporadic PD (38), and thus it would be reasonable to expect LFP signal asymmetry in *GBA* mutation carriers as demonstrated in the present study. As mutations in the GCase enzyme result in accumulation of sphingolipids and subsequent alpha-synuclein accumulation (39), the process by which this translates to changes in beta is unknown.

The greater asymmetry found in *GBA* mutation carriers in this study is seemingly at odds with our prior study in which we found *GBA* mutation carriers with PD demonstrated more *symmetric* arm swing velocity compared with non-mutation carriers in the OFF state, while arm range of motion and stride length were not different between the two groups (15). This may be because sensor-based motion analysis provides more granular detail regarding measurements of motor function, deconstructing bradykinesia into variety of specific parameters such as arm swing velocity, arm range of motion, and stride length. In contrast, LFPs provide information about the physiologic state of the brain and the contralateral body at rest (as does DATscan), but only to the extent that the motor region of the STN is traversed

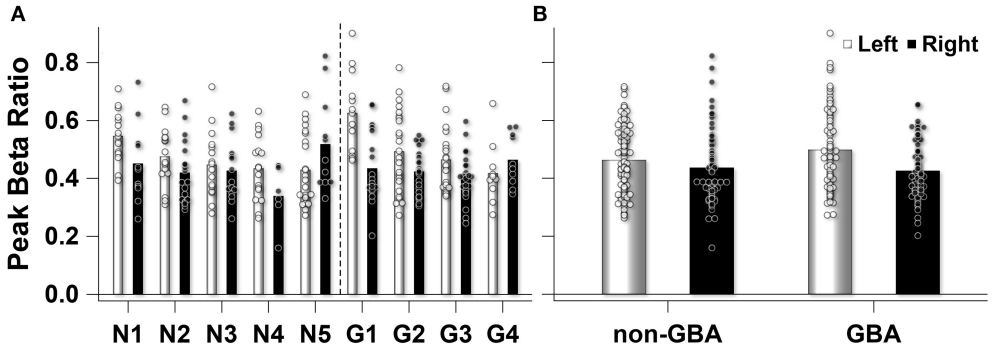

FIGURE 5 | (A) Observed peak beta ratio for each participant in the non-*GBA* (N) and *GBA* (G) group. The unfilled (left STN) and filled (right STN) bars show the mean peak beta ratio for each participant. The unfilled (left STN) and filled (right STN) circles represent the peak beta ratio for each 5s epoch that contributed to the mean for each participant. **(B)** The mean peak beta ratio for the non-*GBA* ($n = 5$) and *GBA* ($n = 4$) participants. Unfilled bars and circles represent left STN mean and individual 5s epochs that contributed to the mean, while the filled bars and circles represent the right STN.

by the lead. If the DBS electrode is in the homuncular region that comprises primarily the head and arm region of the STN, LFPs from these regions will be overrepresented compared to the lower extremity. Given the small size of the STN, typically on the order of 180 mm^3 (40), to our knowledge it is not possible to study the physiological correlate of one specific region of the body in pure isolation from neighboring body regions. Another possibility is that our finding is specific to our sample: the *GBA* group was simply more asymmetric than the non-*GBA* group; both with respect to beta power and bradykinesia-rigidity asymmetry scores. In addition, subjects in the gait study were walking and not at rest as in the present study, thereby limiting the utility of comparison of the two studies. Finally, we did not take into account the influence of specific phenotypes on changes to beta power, i.e. tremor dominant PD vs. postural instability gait disorder phenotypes. Godinho et al. (2021) found that supervised learning algorithms aimed at discriminating PD phenotypes based on STN-LFP band power features were most accurate when tremor dominant and postural instability gait disorder movement-induced desynchronization ranges were considered (41). Future studies can employ such algorithms and include genotype to improve phenotypic classification using physiologic signals.

The strengths of this study include a population of *GBA* mutation carriers with the same mutation, E326K, the length of LFP recording time, and consistency of results across participants. Limitations include the small sample size and lack of inclusion of subjects with mild or severe *GBA* mutations. With the recent FDA approval of the Medtronic Percept^{TM} PC (42), that can record LFPs using its BrainSense^{TM} technology, studies such as this will be able to be performed and reproduced in the clinic rather than the operating room, and additional differences, particularly related to cognition, can be examined in *GBA* mutation and non-mutation carriers. Furthermore, genetic testing for PD, especially pre-DBS, is not the current standard of care. There is increased interest in utilizing genetics to understand outcomes of interventions such as DBS (43). As the incorporation of genetic testing into the clinical setting becomes routine and as we gain access to LFPs outside of the operating room, studies such as this can be performed with more facility and larger samples sizes. Lastly, we acknowledge the clinical differences between the groups as a limitation. The non-GBA group was on average 6 years older, had 3 more years disease duration and this may result in less asymmetry. However, *GBA* carriers have faster motor progression as than their non-GBA counterparts (38) and may come to DBS earlier, so it is difficult to compare individuals with similar disease durations. In our sample, there was no correlation between disease duration and beta power. However, we cannot exclude that the non-GBA group could have presented with less asymmetry just because they had a longer disease duration. Furthermore, we used age, age of onset, and disease severity as covariates in our statistical model to adjust for these differences between groups.

The results of this study requires verification in a larger cohort, and future studies should determine if the asymmetry found in *GBA* mutation carriers correlates with mutation severity. Critically, given that that the electrophysiological characteristics of LFP-STN recordings are unknown for GBA carriers, future studies should conduct a broader electrophysiological analysis. This analysis should include a larger sample size such that it has sufficient power to identify group differences in the theta, alpha, and gamma bands, as well as differences in beta features such as beta burst duration, strength, and frequency. As LFP recordings are being used to develop long-term feedback control signals for adaptive DBS systems, genotype-phenotype studies such as this one may be useful in understanding pattern variations of LFP signals that can be used to refine or improve such systems.

DATA AVAILABILITY STATEMENT

The statistical databases supporting the conclusions of this article will be made available by the corresponding author, Fabian J. David, upon reasonable request. Due to the nature of this

research, participants of this study did not agree for their data to be shared publicly, so raw data is not available.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Rush University Medical Center Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Research project: JS and GP: conception. FD, MM, JS, SS, and GP: organization. FD, MM, JS, MP, PH, WN, MA, SS, LV, and GP: execution. Statistical analysis: FD: design and execution. MM, JS, LV, DC, and GP: review and critique. Manuscript: FD and GP: writing of the first draft. MM, JS, MP, PH, WN, MA, SS, LV, and DC: review and critique. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.723476/full#supplementary-material

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REVIEW
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Basal Ganglia Local Field Potentials as a Potential Biomarker for Sleep Disturbance in Parkinson's Disease

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Sleep disturbances, specifically decreases in total sleep time and sleep efficiency as well as increased sleep onset latency and wakefulness after sleep onset, are highly prevalent in patients with Parkinson's disease (PD). Impairment of sleep significantly and adversely impacts several comorbidities in this patient population, including cognition, mood, and quality of life. Sleep disturbances and other non-motor symptoms of PD have come to the fore as the effectiveness of advanced therapies such as deep brain stimulation (DBS) optimally manage the motor symptoms. Although some studies have suggested that DBS provides benefit for sleep disturbances in PD, the mechanisms by which this might occur, as well as the optimal stimulation parameters for treating sleep dysfunction, remain unknown. In patients treated with DBS, electrophysiologic recording from the stimulating electrode, in the form of local field potentials (LFPs), has led to the identification of several findings associated with both motor and non-motor symptoms including sleep. For example, beta frequency (13–30 Hz) oscillations are associated with worsened bradykinesia while awake and decrease during non-rapid eye movement sleep. LFP investigation of sleep has largely focused on the subthalamic nucleus (STN), though corresponding oscillatory activity has been found in the globus pallidus internus (GPi) and thalamus as well. LFPs are increasingly being recognized as a potential biomarker for sleep states in PD, which may allow for closed-loop optimization of DBS parameters to treat sleep disturbances in this population. In this review, we discuss the relationship between LFP oscillations in STN and the sleep architecture of PD patients, current trends in utilizing DBS to treat sleep disturbance, and future directions for research. In particular, we highlight the capability of novel technologies to capture and record LFP data *in vivo*, while patients continue therapeutic stimulation for motor symptoms. These technological advances may soon allow for real-time adaptive stimulation to treat sleep disturbances.

Keywords: Parkinson's disease, sleep, local field potential (LFP), deep brain stimulation (DBS), biomarker

INTRODUCTION

The cardinal motor features of Parkinson's disease (PD) include bradykinesia, rest tremor, and rigidity. Though non-motor features have been recognized since the original description of the disease by James Parkinson in 1817, only recently has the prevalence and impact of non-motor symptoms become the focus of intense study (1, 2). Disturbances of sleep are among the most common non-motor manifestations of PD. In a 2009 survey of more than one thousand PD patients across 55 clinical centers, ∼37% of patients reported experiencing insomnia, 21% reported excessive daytime sleepiness, 15% reported restless legs, and 30% reported rapid eye movement (REM) sleep behavior disorder (RBD) (3). In all, 64% of PD patients reported at least one symptom affecting sleep, which was second in frequency only to psychiatric symptoms (the most common being anxiety/nervousness, depression, and anhedonia, prevalence 67%). Sleep disorders commonly occur prior to the appearance of typical motor symptoms. The most well-known prodromal sleep disorder is RBD, which may develop years to decades prior to the onset of motor symptoms (4–6). The presence of RBD is one of the most specific predictors for developing a neurodegenerative disease, with a risk of over 90%. The risk for developing PD specifically, when RBD is present, may be as high as 65% (7–9).

Given that sleep contributes to the regulation of many physiological homeostatic processes, sleep disturbance has a significant impact on quality of life in PD (10–12), and places high strain on caregivers, even predicting earlier transfer to a nursing home (13–15). Thus, the ability to treat sleep disorders represents an opportunity to make substantial improvements in not only mood, cognition, and overall satisfaction, but also significantly alleviate caregiver burden and relieve financial strains associated with the need for nursing home care. Though numerous symptomatic therapies exist, the treatment of sleep disorders in PD is limited by a lack of adequately powered, randomized studies providing high quality evidence (16). The possibility of treating disorders of sleep with DBS is thus an appealing one. Although, DBS is primarily used to treat PD motor symptoms and reduce the need for dopaminergic medications, several studies have shown that DBS provides benefit for non-motor symptoms, including sleep disturbance (17, 18). However, the optimal DBS target and stimulation parameters to address sleep remain unknown. In recent years, recording of LFPs primarily from STN has identified unique spectral patterns in oscillatory activity between the awake, REM sleep, and non-REM (NREM) sleep states, thereby providing novel insights into sleep architecture and basal ganglia physiology in patients with PD. STN LFPs may therefore be suitable for use as a biomarker for sleep, allowing stimulation to be tailored to ameliorate sleep disturbance. This article will briefly discuss pathophysiology of sleep-wake disturbances in PD, review existing literature on subcortical electrophysiology in sleep, highlight the potential for novel DBS technologies to address sleep, and describe future directions for investigating the use of LFPs as a biomarker for treating sleep disturbance with DBS.

SLEEP DISTURBANCES IN PD

Sleep is classified into NREM and REM stages based on polysomnography (PSG), which is primarily comprised of electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG) recordings. NREM sleep is notable for slow, rolling eye movements, prominent parasympathetic tone, and rare dreaming (19, 20). NREM sleep is further divided into stages N1–N3. In N1, the lightest sleep stage, the normal waking posterior dominant alpha (8–12 Hz) rhythm is lost (21). N2 sleep is characterized by the emergence of both sleep spindles (brief oscillations of 12–14 Hz) and K-complexes (sharp high voltage biphasic waves lasting more than 0.5 s) (21). In N3 (slow-wave) sleep, delta (0.5–2 Hz) EEG waves make up at least 20% of any given sleep epoch (21). REM sleep is characterized by low-amplitude, mixed frequency, desynchronized EEG (similar to wakefulness with the eyes open), rapid eye movements, and suppressed chin EMG activity (21). Dreams typically occur during REM sleep (22).

Nearly all aspects of sleep are affected in PD, though disorders of sleep-wake transition/sleep architecture as well as parasomnias (i.e., atypical/unusual behaviors during sleep) affecting both REM and NREM sleep are more common (23–28). Understanding of these sleep disturbances has been largely driven by studies using formal PSG in case-control studies.

PSG studies of PD patients have demonstrated several alterations in sleep architecture, including increased sleep onset latency, reduced total sleep time, increased wakefulness after sleep onset (WASO), and decreased sleep efficiency (defined as the ratio of time asleep to time spent in bed) (29–33). Decreased sleep efficiency has been demonstrated in studies involving both treated and untreated PD patients (31, 34, 35). In investigating NREM sleep stages, studies have demonstrated a trend toward increased time spent in stage N1, an effect which seems to be most prominent in the early stages of PD (31, 35, 36). Alterations in the architecture of NREM sleep seem largely to be driven by changes during stages N2 and N3, both of which are reduced (37–39). It should be noted that these changes have not been universally reported, reflecting the likely heterogeneity of PD and resultant sleep disturbances, as well as methodological differences between studies (31, 35, 37, 40–42). However, a recent meta-analysis from 2020 did confirm a reduction in both N2 and N3 sleep in PD patients vs. control subjects (43). The reduction in N3 sleep, in particular, seems to be progressive in a manner that correlates with disease duration (30, 37).

Aberrant REM sleep is a consistent feature of PD. In the same recent meta-analysis mentioned above, the percentage of time spent in REM sleep and duration of contiguous REM epochs (i.e., REM density) were significantly reduced in PD patients compared to controls, while REM latency was increased (43). Decreased REM sleep has been found in *de novo*, untreated PD patients, and the duration of REM sleep seems to shorten with disease progression (30, 36). Furthermore, REM sleep is characteristically affected by RBD, a parasomnia characterized by abnormal behaviors, such as talking, laughing, shouting, gesturing, grabbing, flailing, punching, or kicking during REM sleep that are associated with dream content and enactment (44).

Estimates of the prevalence of RBD in PD range from ∼30 to 60% (45–47).

Electrophysiological alterations in sleep in PD occur across stages N2, N3, and REM. N2 sleep in PD seems primarily to be affected by a reduction in K-complexes and sleep spindle formation, a finding which has been replicated across several studies (29, 39, 48–50). A reduction in sleep spindle density has also been found in patients with idiopathic RBD (51). A single study, in contrast to these results, found no difference in the quantity of K-complexes or sleep spindles in PD patients compared to controls, though it should be noted that PD patients included in this study had lower Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores and lower levodopa doses, raising the possibility that reduction in K-complexes and sleep spindles is not a feature of early, mild disease (32). Slow wave activity (SWA), an EEG oscillatory pattern of 0.5 to 4.0 Hz that is a normal hallmark of stage N3 sleep, is reduced in PD (31, 43, 45, 52, 53). This reduction may become more severe with advancing PD (52). REM sleep in PD patients is marked by increased power in the high theta/alpha frequency range (7.8–10.5 Hz) (40, 54, 55). This alteration in REM physiology has been mostly observed in early, untreated patients or in those not taking dopaminergic medications, and was not seen in a study of patients on dopaminergic therapy, raising the possibility that antiparkinsonian medications may modulate REM sleep (56). Further study of this hypothesis is needed.

Further discussion of the spectrum of sleep disorders in PD can be found in recent reviews by Chahine et al. (16) and Zhang et al. (43).

SUBCORTICAL ELECTROPHYSIOLOGY AND RELEVANT PATHWAYS OF SLEEP—ANIMAL STUDIES

Our understanding of the electrophysiological activity of subcortical structures has been greatly informed by studies of normal animals as well as animal models of PD. These studies have provided significant insight into mechanisms of, and potential therapies for, sleep disturbance in PD.

Studies in rodents using single-neuronal as well as multi-unit activity (MUA) recordings have demonstrated a rhythmic bursting pattern in STN neurons during slow-wave sleep, while globus pallidus neurons exhibited a slowing in firing rate during slow wave sleep compared to both wakefulness and REM (57, 58). During slow-wave sleep, medium spiny neurons of the striatum display brisk firing resulting from rhythmic membrane potential fluctuations, unlike the irregular and disorganized firing seen during wakefulness (59).

Recent animal studies exploring the generation and maintenance of sleep at the single neuron and circuit levels have revealed a multi-nodal brain-wide network contributing to the sleep-wake transition. These studies posit that control of sleep requires the integration and coordination of both autonomic and somatomotor control networks, with distinct circuits, including the basal ganglia, contributing to this global brain state (60). Several regions of the basal ganglia, specifically within the indirect pathway [inhibition of gamma-aminobutyric acid (GABA)-ergic neurons of the GPe, leading to disinhibition of glutaminergic neurons of the STN and thus activation of GABAergic substantia nigra pars reticulata (SNr) neurons projecting to the thalamus], have been implicated in different stages of sleep. Both the nucleus accumbens and dorsal striatum have been shown to promote NREM sleep *via* activation of adenosine A_{2A} receptor (A_{2A}R)-expressing GABAergic neurons (61, 62). In particular, the A_{2A}R neurons of the dorsal striatum were found to innervate the globus pallidus externus (GPe) in a topographical pattern synapsing onto parvalbumin (PV)-expressing neurons, and ablation of these PV neurons abolished the NREM-promoting effect of A_{2A}R activation (62). In addition to these findings in GPe, glutamatergic neurons of STN projecting to the SNr, when activated *via* optogenetic manipulation, significantly prolong NREM states (63). Even within the zona incerta (ZI), which lies dorsal and posterior to the STN, LIM homeodomain factor (Lhx6)-expressing GABAergic neurons within the ventral ZI promote NREM sleep *via* selective activation, and decrease both NREM and REM sleep when selectively ablated (64). Finally, the substantia nigra, which is a basal ganglia output structure and a critical node within the indirect pathway, also contributes to sleep regulation: Optogenetic activation of glutamate decarboxylase 2 (Gad2) neurons within the medioventral region of SNr both terminates movement during wake periods and significantly enhances the initiation of sleep (65).

Mizrahi-Kliger et al. (66) studied the activity of single neurons in the basal ganglia in a pair of vervet monkeys. They found that the firing rate of basal ganglia neurons was significantly lower and more irregular (burst-like) during slow wave sleep than during REM and wakefulness. This was particularly true in GPi, GPe, and SNr. Basal ganglia neurons also exhibited slow oscillations in firing rate during slow wave sleep, similar to those observed in cortical neurons in both humans and non-human primates. LFP recordings in the basal ganglia demonstrate dramatically reduced slow oscillations compared with thalamocortical networks. Furthermore, unlike in the thalamus and cortex, basal ganglia LFPs were noted to be desynchronized between individual neurons. Proposed causes for this inter-neuronal desynchronization include the highly convergent nature of input to the basal ganglia, wherein a single GPi or GPe neuron may receive input from numerous striatal cells, each of which, in turn, is receiving input from numerous cortical cells (67). Thus, the basal ganglia are uniquely placed in brain-wide sleep physiology, by virtue of receiving slow oscillatory activity from vast cortical areas and, *via* dyssynchronous firing, capable of activating multiple disparate cortical areas at any one time.

In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model of parkinsonism, increased power in an LFP frequency band that encompassed alpha and low beta (10–17 Hz) activity during NREM was seen in GPe, GPi, and STN (68). This increase in alpha and low beta activity was associated with a decrease in the power of slow oscillatory firing of the basal ganglia. Epochs with higher average beta

power were associated with a decreased propensity for sleep and an increased frequency of awakenings. Furthermore, the authors demonstrated a temporal association between beta activity and sleep-wake cycles, in that falling asleep was associated with a gradual decrease in LFP beta activity across the basal ganglia, and beta oscillations became more prominent in the approach to awakenings. Thus, given the results of these studies, a potential mechanism for sleep disturbance in PD emerges, whereby synchronized beta oscillations from the basal ganglia are relayed to the cortex, disrupting cortical slow oscillations that are characteristic of NREM sleep (66, 68). Of course, non-human animal studies should not provide the sole basis for informing conclusions about human physiology. Although MPTP does produce an excellent model of parkinsonism, the disease course is more fulminant in the model—both in rapidity of onset and in severity—than in idiopathic PD. Additionally, sleep in PD is almost certainly affected by degeneration of several different brain nuclei and neurochemical pathways not targeted by MPTP, which is highly selective for dopaminergic neurons (69). Collectively, these shortcomings of the MPTP model may preclude a faithful recapitulation of the progressive nature of sleep dysfunction in patients with PD.

SUBCORTICAL ELECTROPHYSIOLOGY AND RELEVANT PATHWAYS OF SLEEP—HUMAN STUDIES

In PD patients, early studies using MUA demonstrated slow oscillations in the globus pallidus and caudate during slow wave sleep, similar to those identified in primates (70). These oscillations were similarly attenuated during wakefulness and REM sleep. In a study of PD patients with STN DBS, single-unit recordings demonstrated a decrease in firing rate during sleep, and that neuronal firing developed a grouped or bursting pattern (71).

More recently, electrophysiological studies have focused on LFP recordings rather than on single or multi-unit data (**Table 1**). This was largely driven by several important characterizations of LFPs, primarily in PD patients: First, LFP activity is strongly correlated with several PD disease states, in particular the OFF state, in which power in the beta band (typically 13–30 Hz) is prominent in both STN and GPi (76–80). Specifically, increased beta frequency band power is associated with worsened bradykinesia and rigidity, but not with tremor (79–81). After administration of dopaminergic medications, beta activity attenuates and other frequencies, for instance 4–10 and 60–90 Hz, become more prominent (76, 78, 79, 82, 83). Not all studies, however, have demonstrated the 60–90 Hz peak after administration of medication (84). There is also an association between specific LFP bands and specific PD symptoms. For instance, decreased power in the high beta range (20–30 Hz) and increased power at <10 Hz have been reported in PD patients with dyskinesia (85). Furthermore, LFPs are an appealing target of study as they reflect synchronous changes in large populations of neurons, are locally generated (rather than conducted from the cortex), and are suppressed by both behaviorally relevant stimuli and voluntary movement (81).

In the first study using LFPs to assess sleep, Urrestarazu et al. (72) recorded LFPs from STN in 10 PD patients undergoing DBS implantation. Recording was performed between 2 and 4 days after macroelectrode implantation. Notably, in five subjects, sleep recordings were acquired during nap periods in the early afternoon, and in the remaining five subjects, were acquired during nighttime sleep. For each subject, analysis was conducted on a total of 6 min accumulated from 18 artifact-free segments, each of 10-s duration and drawn from each sleep and awake period (i.e., 3 min acquired during periods of wakefulness and 3 min acquired during sleep). During NREM sleep, power in the beta frequency band was significantly reduced compared to OFF-state wakefulness. In five patients from whom REM sleep was recorded, beta activity, particularly at 20–30 Hz, again became more prominent and in fact occurred at a slightly higher power than in wakefulness (**Table 2**). Low beta (13–20 Hz) power was lower in REM compared to wakefulness. Four of the five patients additionally showed a peak at 10–15 Hz, which was not seen during other sleep stages nor during wakefulness. In three patients who exhibited REM sleep without atonia (RSWA), power in the beta band was higher during RSWA episodes compared with episodes of REM with atonia. No video assessment of movement was made, so it is unknown if these episodes of RSWA were associated with dream enactment behaviors suggestive of RBD.

Subsequent studies have demonstrated the feasibility of using LFPs to determine sleep stage. Thompson et al. (73) recorded LFPs from the STN of 10 patients 3 weeks after implantation of a DBS macroelectrode for a single, full night of sleep (∼9 h per subject), and compared these to formal PSG obtained concurrently. Polysomnography was scored according to the 2007 American Academy of Sleep Medicine (AASM) guidelines (86). These investigators found significant band-power differences in all NREM states compared with REM and wakefulness, in a manner that corroborates typical EEG findings. Delta (0–3 Hz), theta (3–7 Hz), and alpha (7–13 Hz) all increased in NREM sleep compared to REM, while beta and gamma (30–90 Hz) power decreased (**Figure 1**). In contrast to the findings of Urrestarazu et al., beta power during REM sleep was lower than in wakefulness. Importantly, there was significant between-subject variability in the relative power of each frequency band during each sleep stage, suggesting that an individualized analysis for each subject is likely necessary to accurately monitor and treat sleep dysfunction. To this end, the authors used a support vector machine (SVM) model to predict sleep stage based on LFP power spectra. SVM models accurately predicted sleep stage for the subject on which they were trained, but performed poorly for other subjects. This work was then improved by development of a feedforward artificial neural network (ANN) to predict sleep stage based on 30-s epochs of LFP data (**Figure 2**) (75). In a leave-one-group-out analysis, the ANN was able to predict sleep stage (awake, NREM, or REM, without breaking down NREM into component stages N1–3) with an overall accuracy of 91%, though accuracy was lower (77%) for REM sleep—likely a consequence

TABLE 1 | Summary of pertinent studies of LFPs in sleep in PD patients.

Study	Sample size, *n*	Age, mean (range)	PD duration, mean (range)	MDS-UPDRS part III*, mean (range)	Location	Timing (after DBS implantation)	Medications	Recording period analyzed	Major findings
Urrestarazu et al. (72)	10	62.2 (56–72)	12.3 (8–25)	34.4 (26–46)	Bilateral STN	2–4 days	Off (timing not specified)	3 min sleep + 3 min wakefulness (5 afternoon naps, 5 nocturnal sleep)	NREM: beta power reduced compared to OFF-period wakefulness
									REM: high beta (20–30 Hz) power slightly higher power than wakefulness; low beta (13–20 Hz) lower than wakefulness
									RSWA: beta power higher than REM with atonia
Thompson et al. (73)	10	58.4 (39–70)	UA	40.4 (15–62)	Unilateral STN	3 weeks	Off several hours	24-h recording; average 7.5 h nocturnal sleep	NREM: increased power in delta, theta, alpha range, decreased beta, and gamma power compared to wakefulness
									REM: beta power increased but lower than wakefulness
									Beta power increased over the course of the night
									Subject-specific models able to classify sleep stage based on LFP signature
Chen et al. (74)	12	54.8 (40–67)	10.2 (7–20)	UA	Bilateral STN	1 month	Off at least 8 h	4–6 h nocturnal sleep; 6 min wakefulness prior to sleep	NREM: increased power in delta, theta, alpha range, decreased beta, gamma power compared to wakefulness
									REM: beta, gamma power increased, similar to wakefulness
									Subject-specific models able to classify sleep stage based on LFP signature

**Before DBS, off medication.*

PD, Parkinson's disease; MDS-UPDRS, Movement Disorders Society-Unified Parkinson's Disease Rating Scale; STN, subthalamic nucleus; DBS, deep brain stimulation; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; RSWA, REM sleep without atonia; UA, unavailable; ANN, artificial neural network.

of diminished REM in these PD study subjects. This represents a significant improvement in performance over the SVM, in that the ANN was able to accurately stage sleep in subjects it had not previously encountered.

Chen et al. (74) studied 12 PD patients undergoing STN DBS. LFPs were recorded at 1 month after electrode implantation and compared to PSG, staged according to AASM guidelines. They again demonstrated that delta, theta, and alpha band power significantly increased from wakefulness to N2 and decreased in REM sleep. Beta and gamma power decreased from wakefulness to N2. In REM sleep, beta band power was similar to wakefulness. As with Thompson et al., there was significant between-subject variability in relative power across frequency bands during each sleep stage. Machine learning algorithms were then applied to classify sleep stage based on LFP power spectra. Subject-specific models performed significantly better than a study-wide model. Classification accuracy was over 90% for distinguishing wakefulness from N1, wakefulness from N2/N3, wakefulness from REM, N1 from N2/N3, N2/N3 from REM, and wakefulness from sleep overall. Performance was lower (73%) for distinguishing N1 from REM sleep. A predictive model achieved similar accuracies.

Several important limitations to these studies should be noted: sample sizes were small, relatively heterogenous populations were included, and control groups were lacking for comparison. Given that the studies cited above involved externalized DBS leads for recording, data collection was restricted to a single night, thus limiting our knowledge of the significance of between-night differences in individuals. Recordings were also acquired in a hospital or sleep laboratory setting, creating an unfamiliar environment that likely affected naturalistic sleep behavior. Experiments were carried out between 2 days and 1

TABLE 2 | Characteristic LFP signatures of sleep and wakefulness in PD.

State	LFP characteristics	Notes
Wakefulness—OFF state	↑ Beta frequency power	Beta frequency power more closely linked with bradykinesia, rigidity than tremor
Wakefulness—ON state	↓ Beta frequency power	Emergence of gamma frequency not consistent across studies
	↑ Theta, gamma frequency power	Dyskinesia may be associated with increased theta and decreased high beta (20–30 Hz) power
NREM sleep	↑ Delta, theta, and alpha frequency power	Significant between-patient variability in relative power across frequencies
	↓ Beta frequency power	Most studies do not differentiate between stage N1, N2, and N3 sleep
REM sleep	↑ Beta frequency power	Beta frequency power may be lower, similar to, or greater than in wakefulness
	↓ Delta, theta, and alpha frequency power	Beta power may be higher in periods of REM without atonia than in REM with atonia

NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep.
Canonical frequency bands are as follows: delta (0–3 Hz), theta (3–7 Hz), alpha (7–13 Hz), beta (13–30 Hz), and gamma (30–90 Hz). ↑, Increased; ↓, decreased.

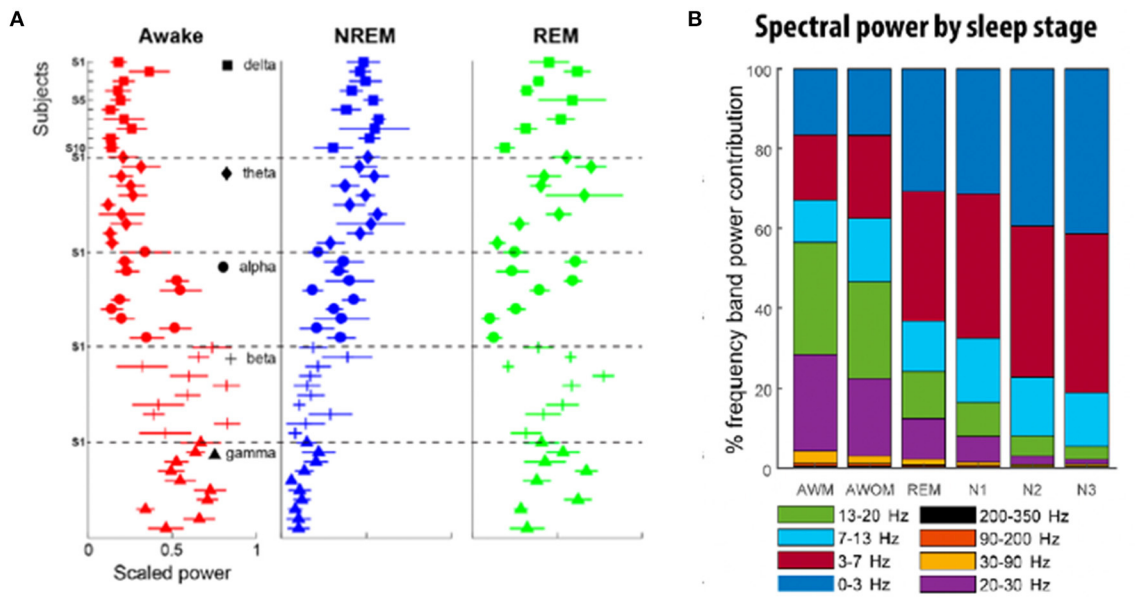

FIGURE 1 | (A) Relative frequency contribution of each spectral band to different sleep stages. There exist shared sleep-stage dependent spectral patterns across subjects, although with some notable across-subject variability. Each individual plot highlights the distribution of the power of a given frequency band to different stages of sleep for 10 different subjects. In the awake state (red), power is highest in the beta and gamma frequencies, while NREM sleep (blue) is dominated by lower frequencies (delta, theta, and alpha). REM sleep (green) exhibits the greatest variability in representation across the frequency spectra [adapted from (73)]. **(B)** Distribution of frequency band power contribution to sleep stage for a cohort of nine subjects. AWM, awake with movement; AWOM, awake without movement; REM, rapid eye movement; N1–3, non-rapid eye movement stages 1–3 [adapted from (75)].

month following DBS implantation, making it difficult to know with certainty whether microlesional effects remaining from surgery or other peri-procedural factors influenced the results. However, it has been shown that the correlation between beta oscillations and parkinsonian syndromes during wakefulness remains present months and even years post-operatively, making it at least plausible that the same holds true for sleep (87, 88).

Though these studies provide support for a relationship between basal ganglia LFPs and sleep disturbance, important questions remain unanswered. First, it is unclear how to reconcile the increase in beta activity during REM sleep with the observation that motor control might actually be improved during REM (89). This increase in beta activity during REM would be unexpected given the otherwise akinetic nature of beta activity and may suggest a yet-undiscovered relationship between basal ganglia oscillations and movement. An alternate explanation for this apparent paradox might stem from the hypothesis that movement during REM sleep (i.e., dream enactment behavior) may bypass extrapyramidal pathways entirely (89). Additionally, the variability in beta power observed both between studies and within individuals over the course of a single night requires further exploration. As mentioned above, while some studies have found beta power in REM sleep to be similar to or slightly lower than during wakefulness, others have actually reported increased beta power during REM (72, 73, 75). In individuals, there does seem to be a reliable increase in

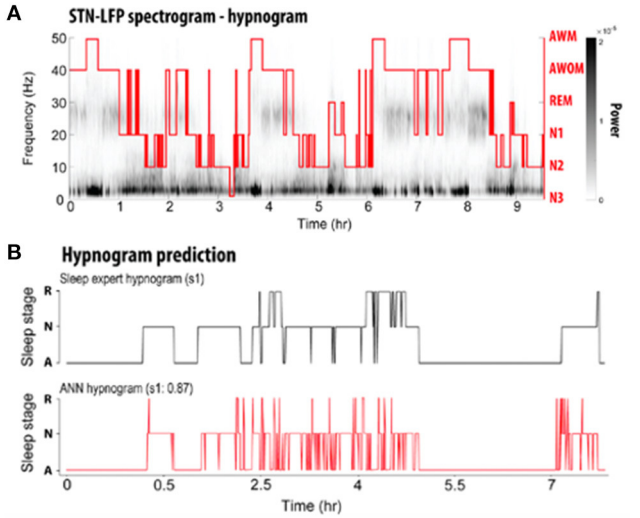

FIGURE 2 | (A) Representative spectrogram of a LFP recording acquired over the course of one full night's sleep from a DBS electrode implanted into the STN. A PSG-informed hypnogram assessed by a sleep expert is aligned with the LFP recordings (red line). AWM, awake with movement; AWOM, awake without movement; REM, rapid eye movement; N1–3, non-rapid eye movement stages 1–3. **(B)** Comparison of hypnogram assessed by a sleep expert (top; black) and ANN-predicted hypnogram (bottom; red) from a single patient. R, rapid eye movement; N, non-rapid eye movement; A, awake [adapted from (75)].

beta activity as the night goes on, across all sleep stages (73). Thompson et al. speculate that these findings might be explained by the wearing-off of dopaminergic medications from last dose before bedtime until first dose of the morning. There might also be a relationship with REM atonia, as the study by Urrestarazu et al. (72) found a difference in beta power between episodes of RSWA and times of normal REM atonia. This finding should be interpreted with caution, as not all studies have corroborated it, and other mechanistic explanations, such as interaction with subcortical pontogeniculo-occipital (PGO) waves, have been posited (20, 90). Finally, the significance of LFPs in other subcortical structures, particularly in relation to sleep, is largely unknown. LFPs recorded from the centromedian-parafascicular nucleus of the thalamus in PD patients show a prominent band of gamma activity in the ON-state that disappears in the OFF-state, but there is as yet no known correlation with arousal state (91). The GPi also displays beta frequency oscillations that modulate with volitional movement, though again studies of GPi LFPs in sleep are lacking (92, 93).

IMPACT OF CONVENTIONAL DBS ON SLEEP

The ability to record and stage sleep *via* STN LFPs raises the exciting possibility of using DBS to optimize treatment of not only the motor symptoms of PD during sleep (when patients are between medication doses), but also the disordered sleep itself. This possibility is bolstered by the observation that DBS, although not directly targeted nor programmed to improve sleep dysfunction, may confer some benefit on sleep in PD patients (94, 95). The evidence is most robust for STN DBS, where studies using subjective measures (validated sleep questionnaires) as well as objective measures (PSG or actigraphy) have demonstrated improvements in multiple sleep architecture outcomes including increased total sleep time and sleep efficiency, reduced wakefulness after sleep onset, and in some studies, an increase in REM sleep (18, 96–101). These improvements in subjective and objective measures seem to be an effect of stimulation, as studies examining sleep both on and off stimulation have demonstrated significant improvement in sleep when stimulation is on vs. off (17, 102). In addition to improvements in sleep architecture, STN DBS likely improves sleep *via* amelioration of nocturnal motor symptoms and may also improve symptoms of RLS, even when levodopa equivalent doses are reduced post-operatively (103–105). Current evidence does not suggest that STN DBS has any impact on RBD, though studies are limited (106). Evidence for the benefit of GPi DBS on sleep disturbance is sparse, though a few studies using subjective outcomes have suggested an improvement in sleep quality and daytime sleepiness with GPi DBS (107–109). A single study using objective sleep data in five PD patients with GPi DBS demonstrated a non-statistically significant increase sleep quality and efficiency, with decreased WASO, sleep onset latency, and REM latency (110). In a recent, double-blind, prospective, single-case report investigating the efficacy of GPe DBS for the treatment of insomnia, a PD patient with prolonged (7 years), severe insomnia, refractory to three hypnotic treatments, was implanted with one DBS lead in GPi and a second DBS lead in GPe. The patient exhibited improved sleep quality and decreased insomnia when GPe was selectively stimulated vs. co-stimulation of GPi and GPe (111). The study authors prospectively targeted GPe to ameliorate sleep disturbances based on prior animal studies that indicated activation of GPe resulted in increased REM and NREM duration (112, 113). Other targets have been suggested as possibly beneficial for sleep, particularly the pedunculopontine nucleus (PPN), given its role in sleep-wake modulation (114). In a series of five patients with both STN and PPN DBS, PPN stimulation improved sleep onset and maintenance insomnia compared to STN DBS. At 3 and 12 months, daytime sleepiness was improved by PPN DBS, but not by STN DBS (115). Further studies with larger numbers of patients are needed to accurately determine the efficacy of PPN DBS for sleep. Potential DBS targets for the modulation of sleep are highlighted in **Figure 3**. A recent review of these targets is provided by Sharma et al. (95).

UTILIZING LFPS FOR ADAPTIVE DBS TO TREAT SLEEP DISTURBANCE

Adaptive DBS (aDBS) refers to a system wherein stimulation parameters are modulated in response to an inferred state of pathophysiological activity (119). A current challenge for adaptive DBS is inferring the pathological state, which currently relies on either peripheral measures, for instance tremor

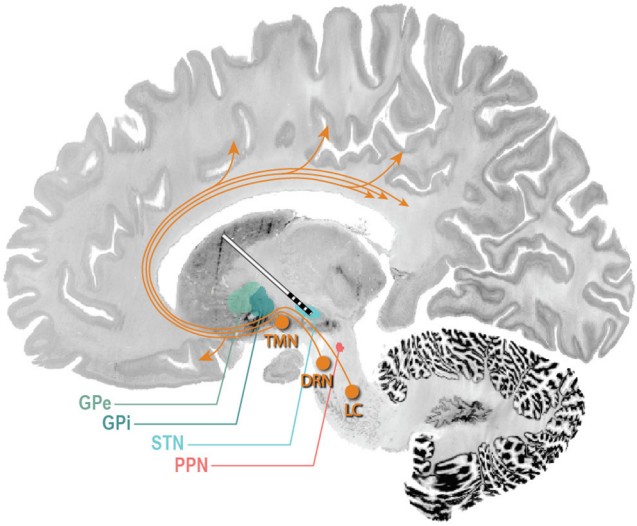

FIGURE 3 | Potential DBS targets for treatment of sleep dysfunction in PD. STN DBS may increase total sleep time and sleep efficiency, reduce wakefulness after sleep onset, and in some studies, increase REM duration. GPi DBS may improve sleep quality and daytime sleepiness. A single study in five PD patients with GPi DBS demonstrated a non-statistically significant increase sleep quality and efficiency, with decreased WASO, sleep onset latency, and REM latency. GPe DBS may improve insomnia and improve sleep efficiency. PPN DBS may improve sleep efficiency, REM duration, and daytime sleepiness, and decrease WASO. The ascending arousal system (orange arrows) sends projections from the brainstem and posterior hypothalamus throughout the forebrain (116). Neurons of the laterodorsal tegmental nuclei and PPN send cholinergic fibers to many forebrain targets, including the thalamus, which then regulate cortical activity. Aminergic nuclei diffusely project throughout much of the forebrain, regulating the activity of cortical and hypothalamic targets directly. These include neurons of the tuberomammillary nucleus containing histamine, neurons of the dorsal raphe nuclei containing 5-HT, and neurons of the locus coeruleus containing noradrenaline. TMN, tuberomammillary nucleus; DRN, dorsal raphe nucleus; LC, locus coeruleus (117, 118).

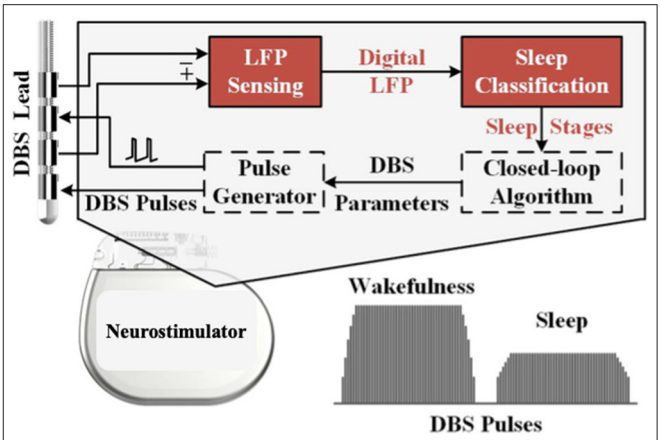

FIGURE 4 | Schematic illustration of an adaptive closed-loop DBS system used to treat sleep dysfunction. LFPs are detected by the DBS lead. With integrated classifiers, sleep stages are predicted, and closed-loop algorithms can adjust the DBS pulses. For example, stimulation amplitude may be decreased during certain sleep stages where beta frequency power is lower [modified from (74)].

amplitude in a limb, or direct recording of brain activity. aDBS is an active area of research as these proxy pathophysiological measures are either imprecise (peripheral measures) or lack evidence (i.e., direct recordings from the brain). aDBS has primarily been pursued in an effort to widen the therapeutic window for treating motor symptoms and also to reduce power consumption of the implanted pulse generator (IPG). However, given the ability to accurately record sleep-wake cycles with basal ganglia LFPs (overcoming the evidence challenge) and the plausibility of treating sleep with DBS, sleep disturbance may be an ideal target for aDBS. A schematic illustration is shown in **Figure 4**.

A few important factors must be considered in the effort to use LFPs as a biomarker for treating sleep with aDBS. First, for any biomarker to be useful in the long term, it must be durable, that is, present for the duration of the disease or as long as the aDBS system is to be used. Little is known about any change or diminution of LFPs over time, though a small number of studies have demonstrated that LFPs can reliably be detected through implanted DBS leads as far as 7 years after DBS implantation (88, 120). Further studies will be needed to verify these results and to ensure that LFPs remain present during both wakefulness and sleep.

Second, the biomarker should correlate with symptom severity. Though beta activity is reliably present during certain sleep stages, as well as in times of increased bradykinesia and rigidity during wakefulness, it remains unknown whether beta activity is causally related. In the case of motor symptoms there is evidence that the severity of bradykinesia and rigidity, though not the presence or severity of tremor, correlate with LFP power in the beta band (79, 121). Thus, although a causal link is not fully established, it can at least be reasoned that reducing beta LFP power *via* the delivery of stimulation will lead to symptom improvement. The same correlation between symptom severity and LFP power has not been established for sleep disturbance, though in a nonhuman primate MPTP model of PD, a correlation between insomnia severity and beta power has been demonstrated (68). If also present in humans, this correlation might help explain the significant variability in beta frequency power between subjects observed in studies thus far (73, 74). Establishing a correlation between LFP power and insomnia severity in humans would be greatly facilitated by recording several continuous nights of sleep in individuals, so that between-night differences in LFP signature and symptoms could be examined. The development and recent FDA approval of the Medtronic Percept^{TM} PC device now allows for the capturing and recording of LFPs simultaneously with the delivery of therapeutic stimulation for up to 60 days of stored data. This eliminates the need to obtain LFPs from an externalized DBS lead and will allow data to be collected in the home environment.

When considering aDBS for the treatment of sleep dysfunction, an optimal measure for efficacy must be determined. Should PSG studies be undertaken to examine changes in sleep

architecture? This would provide the most robust evidence of a benefit from aDBS, though it would also be the most time-consuming and expensive. Furthermore, a single night of recording may be insufficient, especially as the mechanism by which DBS exerts its therapeutic effect remains unknown, but may involve changes in synaptic plasticity and long-term anatomical reorganization (119, 122). Validated sleep questionnaires would be much easier to administer, although these do not provide direct information on changes in sleep architecture. Care must be taken to ensure that outcomes of interest, such as insomnia and daytime sleepiness, are differentiated from other sleep-related symptoms which may not as clearly respond to DBS, such as restless legs syndrome (RLS) and obstructive or central sleep apnea (95). Actigraphy or other wearable devices may represent a useful intermediary between PSG and questionnaires. These technologies provide an objective measure of movement which may correlate to actual sleep. They are less expensive than PSG and can be used home setting. They have also been validated in both healthy controls and PD patients, to record accurately several sleep parameters including total sleep time, sleep efficiency, WASO, and nocturnal motor activity (123–126).

Finally, other contributors to sleep disturbance may pose significant challenges in using DBS, either through adaptive or conventional stimulation, to treat sleep. While DBS may be able to suppress or alter pathological oscillations in the basal ganglia, degeneration in other brain areas not amenable to DBS may play a role in sleep disturbance. Synuclein pathology is more prevalent in brainstem and hypothalamic sleep/wake centers, including the locus coeruleus, raphe nuclei, paramammillary nuclei, and posterior hypothalamus, in PD patients with sleep disorders compared to those without, suggesting that these areas likely play a critical role in sleep dysfunction (127). A myriad of other comorbidities may also contribute to sleep fragmentation. These include depression, pain, nocturia, and RLS, all of which are found in higher frequency in PD patients compared to controls (16, 128). The influence of dopaminergic medications adds another layer of complexity to sleep disturbances in PD. As mentioned above, wearing off of medications during the night may contribute to higher beta power over the duration of nocturnal sleep. Other medications may contribute to daytime sleepiness, as with dopamine agonists, or may worsen insomnia, as in the case of the monoamine oxidase inhibitor selegiline (16, 129). The potential confounding effect of these treatments will need to be carefully considered in designing future studies, particularly as greater emphasis is placed on studying sleep in the home setting over several nights.

CONCLUSION

DBS is a highly effective therapy for the motor symptoms of PD. In recent years, the effect of DBS on non-motor PD symptoms has been investigated with increasing interest. Disorders of sleep are among the most prevalent non-motor symptoms of PD and come at a great cost to quality of life. The available evidence suggests that DBS does have a beneficial effect on sleep, specifically increased total sleep time and sleep efficiency, with reduced wakefulness after sleep onset. Subjective sleep measures are also improved by DBS. However, the optimal stimulation target and parameters to treat sleep, as well as the mechanisms by which DBS exerts its influence on sleep, remain largely unknown. Utilizing DBS to treat sleep disturbance will likely only be possible if a reliable biomarker for sleep exists. The most likely candidate biomarkers are LFPs. LFPs can reliably be recorded from the STN of PD patients, and multiple studies have proven the feasibility of using LFPs to determine sleep stage. Thus, LFPs would likely provide an excellent signal for an adaptive DBS system which targets sleep disturbance by varying stimulation in response to changes in sleep-wake state throughout the night. Additional research is needed to better define between-night differences in LFP signatures in individuals, establish a correlation between LFP power and symptom severity, and to develop and test aDBS systems aimed at treating sleep. If successful, these systems would likely have a profound impact on not only sleep, but also mood, cognition, and quality of life.

AUTHOR CONTRIBUTIONS

AB, DK, AA, and JT contributed to conception and design of the study. AB wrote the first draft of the manuscript. CK and MS provided key technical expertise and revisions. All authors contributed to manuscript revision, read, and approved the submitted version.

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Frequency-Specific Effects of Galvanic Vestibular Stimulation on Response-Time Performance in Parkinson's Disease

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Background: Galvanic vestibular stimulation (GVS) is being increasingly explored as a non-invasive brain stimulation technique to treat symptoms in Parkinson's disease (PD). To date, behavioral GVS effects in PD have been explored with only two stimulus types, direct current and random noise (RN). The interaction between GVS effects and anti-parkinsonian medication is unknown. In the present study, we designed multisine (ms) stimuli and investigated the effects of ms and RN GVS on motor response time. In comparison to the RN stimulus, the ms stimuli contained sinusoidal components only at a set of desired frequencies and the phases were optimized to improve participants' comfort. We hypothesized GVS motor effects were a function of stimulation frequency, and specifically, that band-limited ms-GVS would result in better motor performance than conventionally used broadband RN-GVS.

Materials and Methods: Eighteen PD patients (PDMOFF/PDMON: off-/on-levodopa medication) and 20 healthy controls (HC) performed a simple reaction time task while receiving sub-threshold GVS. Each participant underwent nine stimulation conditions: *off-stimulation*, RN (4–200 Hz), ms-θ (4–8 Hz), ms-α (8–13 Hz), ms-β (13–30 Hz), ms-γ (30–50 Hz), ms-h1 (50–100 Hz), ms-h2 (100–150 Hz), and ms-h3 (150–200 Hz).

Results: The ms-γ resulted in shorter response time (RPT) in both PDMOFF and HC groups compared with the RN. In addition, the RPT of the PDMOFF group decreased during the ms-β while the RPT of the HC group decreased during the ms-α, ms-h1, ms-h2, and ms-h3. There was considerable inter-subject variability in the optimum stimulus type, although the frequency range tended to fall within 8–100 Hz. Levodopa medication significantly reduced the baseline RPT of the PD patients. In contrast to the off-medication state, GVS did not significantly change RPT of the PD patients in the on-medication state.

Conclusions: Using band-limited ms-GVS, we demonstrated that the GVS frequency for the best RPT varied considerably across participants and was >30 Hz for half of the

PDMOFF patients. Moreover, dopaminergic medication was found to influence GVS effects in PD patients. Our results indicate the common "one-size-fits-all" RN approach is suboptimal for PD, and therefore personalized stimuli aiming to address this variability is warranted to improve GVS effects.

Keywords: Parkinson's disease, galvanic vestibular stimulation, stimulation frequency, response time, simple reaction time task

INTRODUCTION

Parkinson's disease (PD) is a progressive disorder marked by the degeneration of dopaminergic neurons in the substantia nigra projecting to the basal ganglia (BG). As these neurons degenerate, individuals with PD frequently experience the cardinal motor symptoms of slowness of movement, tremor, rigidity, and postural instability. The estimated prevalence and incidence are expected to grow as a result of aging populations (1).

Dopamine-based pharmacologic treatments such as levodopa remain the gold standard for symptomatic treatment of PD (2) and are robust and effective in improving motor function, particularly in the early stages of the disease. However, some symptoms such as gait and balance dysfunction may be poorly responsive to dopaminergic medication (3), and many people who have been treated with levodopa for prolonged periods may experience complications such as dyskinesias and motor fluctuations (2). Deep brain stimulation (DBS) is an effective treatment for advanced PD (4) but utilized in as few as 2% of the PD population (5) for reasons including the invasiveness of surgical intervention and associated potential complications (6), medical comorbidities that prevent surgery, lack of advanced medical care, relatively mild symptoms, and good response to medication. The exact mechanisms underlying DBS effects are not yet fully understood, but likely involve suppression of pathological neural oscillations [e.g., exaggerated beta oscillations (7, 8)] in the BG circuit (9).

Inspired by the success of DBS in alleviating PD symptoms, non-invasive brain stimulation (NIBS) is being increasingly explored. As with DBS, NIBS techniques can apply electric currents to the brain to modulate neural activity (10, 11) and affect downstream behaviors (12). NIBS can be safely and economically tested within a wide range of the PD population, from early to advanced disease stages. Although NIBS lacks the ability to directly target focal areas for maximum effectiveness of the stimulation compared with DBS, it does not rely on implantable hardware. Hardware that must be implanted has severe constraints on design as it must be small in size, strongly conserve battery power, and have strict temperature regulation. In contrast, NIBS is not affected by these limitations to the same degree and can utilize external (and potentially portable) stimulators. Thus, NIBS techniques can employ more complicated stimulus waveforms such as random noise (RN) and multisine signals that can be delivered to achieve different effects, as we show here, as compared to electrical pulses used in DBS.

Galvanic vestibular stimulation (GVS) is one type of NIBS technique that applies weak electric currents to the mastoid processes behind the ears to modulate the firing rates of the vestibular afferents. In human studies, GVS has been utilized primarily as a means to activate the vestibular system in order to study balance and head movement responses (13). A pioneering study to investigate GVS effects on PD patients was conducted in 2005 (14) by applying 24-h continuous noisy GVS to six idiopathic PD patients and one patient with akinesia. The stimulation improved short-range heart rate variability, speed of transitions between rest and activity in the trunk, and reaction time in a Go/NoGo task.

Since then, GVS is being increasingly investigated for the treatment of PD symptoms, motivated by anatomical and functional evidence supporting close connections between the vestibular nuclei, thalamus, and BG (15–19). Prior GVS studies in PD have reported improvement in autonomic system regulation, postural balance and gait, and motor task performance (**Supplementary Table 1**). Notably, six out of the nine (66.7%) GVS studies have used RN stimuli while the other studies (33.3%) used direct current (DC) stimuli. The predominance of DC stimuli is likely because it has been long-used in balance research to induce body sways using GVS (20). Similarly, a RN stimulus has been adopted as it was used in the original GVS study in PD (14) and has been supported by the *stochastic resonance theory* stating that the addition of an appropriate level of random noise can paradoxically enhance the response of the nervous system to a weak signal (21–23). Notably, the GVS frequencies used in these studies have been limited to <30 Hz as this reflects the frequency range of most physical movements, and therefore likely reflects the physiological range of endogenous vestibular activation (24). However, we do not know if RN is the most effective stimulus and if different stimulus frequencies significantly influence the motor effects.

Here, we assessed the motor performance of PD participants in a simple reaction time task using several band-limited multisine GVS stimuli. Specifically, we compared whether the multisine stimuli can result in better task performance compared to the more traditional RN stimulus. We next sought to answer the following questions: (1) is there a single band-limited stimulus that brings about the most robust and largest effects across individuals?; (2) does the most effective band-limited stimulus vary across individuals?; and (3) how much improvement in motor performance can be evoked by varying stimulation frequency within an individual? Increasing evidence demonstrates that the same transcranial electrical stimulation can induce substantial variability in individual responses (25–28) due to various factors including methodological differences in the study protocols and participants' physiological traits (e.g., age and sex) and brain states (e.g., emotional and mental states) (28, 29). Here, we posit that a data-driven approach—whereby

TABLE 1 | Demographic and clinical characteristics of the study participants.

	PD ($n = 18$)	HC ($n = 20$)
Age (years)	67.8 ± 7.3	68.7 ± 7.5
Gender (male/female)	9/9	10/10
Disease duration (years)	7.9 ± 4.4	–
UPDRS II	15.4 ± 8.2	–
UPDRS III	23.8 ± 9.7	–
- Bradykinesia [a]	9.3 ± 4.6	–
- Tremor [b]	8.0 ± 3.7	–
Hoehn and Yahr scale	1.3 (1–2)	–
Levodopa Equivalent Daily Dose (mg) (30)	731.3 ± 403.8	–

Mean ± Standard deviation (SD).
[a] *Sum of the scores in UPDRS III 3.4–3.8 sections.*
[b] *Sum of the scores in UPDRS III 3.15–3.18 sections.*

individual responses to different stimuli are assessed—may be a strategy to partly ameliorate these innate differences. Finally, for the first time, we aimed to address the question of whether GVS effects interact with levodopa medication by recruiting the same PD participants both off-/on-dopaminergic medication.

MATERIALS AND METHODS

Participants

A total number of 20 PD patients and 22 age-matched healthy controls (HC) took part in this study. The study protocol was approved by the Clinical Research Ethics Board at the University of British Columbia. All participants gave written, informed consent prior to participation. No participant had any reported vestibular or auditory disorder, and all were right-handed. The PD patients were classified as having mild-stage PD (Hoehn and Yahr stage 1–2) without atypical Parkinsonism or other neurological disorders. Two PD participants and one HC participant did not complete the entire study protocol (see 2.2 Study protocol) due to extraneous reasons such as occasional coughing and arriving late for the experiment. As the motor task data collected from these subjects were ultimately incomplete, we excluded them from the data analysis. One HC participant was also excluded from the data analysis because the subject did not hold a pressure-sensor bulb as instructed and data were not usable when we subsequently inspected the data. Notably, no subjects failed to complete the entire study protocol due to the intolerability of the GVS.

In total, 18 PD and 20 HC participants were included in the data analysis (**Table 1**). The Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III were assessed for the PD patients in the off-medication state prior to the experiment.

Study Protocol

In this present paper, we analyzed simple reaction time (SRT) task data collected as a part of a concurrent GVS-EEG study designed to investigate the effects of different GVS frequencies on: (1) cortical activity at rest; and (2) cortical activity and motor performance during the SRT task. In this section, we report the overall experimental procedure of the concurrent GVS-EEG study. The details of the SRT task are described in the next section.

The experiment consisted of 9 blocks with different GVS conditions that were 2 min apart to minimize any confounding post-stimulation effects. Each block included a 60-s rest condition, followed by the SRT task (**Figure 1A**). Prior to the experiment, each participant's cutaneous threshold to GVS was measured (see section GVS). Then, the participants were fitted with an EEG cap. They were instructed to comfortably sit in front of a computer screen and focus their gaze on a continuously displayed fixed target for 60 s until they saw a written instruction to press a key on the keyboard to start the motor task. Further instruction on how to perform the SRT task was given, followed by a practice run consisting of 10 trials, and then the experiment began.

The PD participants performed the experiment in two sessions on the same day, in the off-medication (PDMOFF) and on-medication (PDMON) states. They stopped taking their normal levodopa medication and any dopamine agonists at least 12 and 18 h prior to the experiment, respectively. After the first session, they took their regular dose of medication and rested for an hour before beginning the second session. The HC participants performed the experiment once. At the end of the experiment, all the participants were verbally asked whether they felt any particular sensation or experienced pain, vertigo, nausea, or heat sensation at the stimulating electrodes in order to confirm the absence of placebo and adverse effects (13, 31).

Simple Reaction Time Task

Participants were instructed to respond to a visual cue as fast as possible by squeezing a pressure-sensor bulb (**Figure 1B**). Each trial started with a hold phase in which a fixation cross was presented at the center for a randomized duration that ranged from 1,000 ms to 2,000 ms [$\mathcal{N}(1500,\ 500)$]. Then, a visual cue ("Go") appeared for 500 ms followed by a 1,000-ms white blank screen. The motor task in each stimulation block with the same stimulus consisted of 10 trials. A pressure-sensor bulb was used because it provides more descriptive behavior measures than a simple button-press and a prior study reported that PD patients demonstrate abnormal motor control while exerting pressure during a task of repeatedly squeezing a rubber bulb (32). The number of trials was selected such that the PD participants could still complete the entire study protocol without excessive tiredness (particularly during off-medication) while significant differences in task performance between conditions could still be detected.

The pressure was recorded at a sampling frequency of 250 Hz. For each trial, three temporal landmarks (t_1, t_2, and t_3) were defined in the pressure recording (**Figure 1B**). Response time (RPT) was defined as $t_3 - t_1$, which was divided into two subcomponents: (1) reaction time (RT) ($t_2 - t_1$; the time between the stimulus onset and movement onset); and (2) movement time (MT) ($t_3 - t_2$; the time required to execute the motor response), in order to further investigate whether GVS affects both RT and MT or only one of them exclusively. Mean RPT, RT, and MT across 10 trials in each block were computed for further statistical analyses.

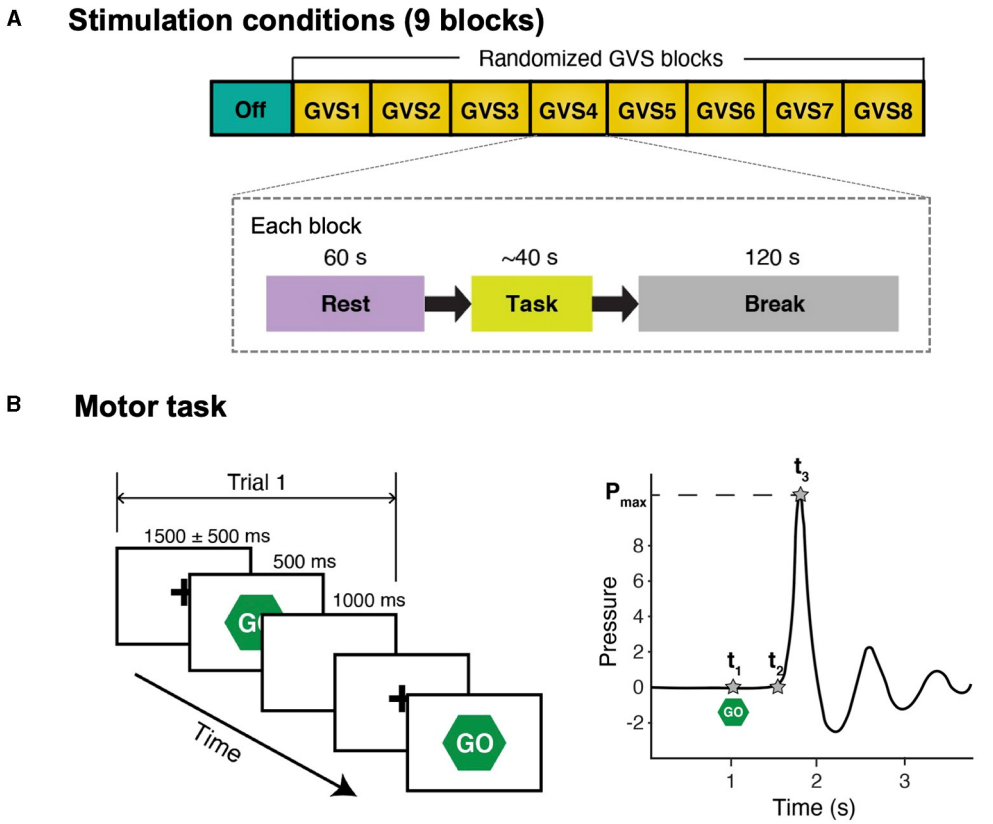

FIGURE 1 | Schematic diagram of study protocol and simple reaction time task. **(A)** There were 9 stimulation conditions (blocks) and the order of GVS blocks was randomized for each participant. In each block, participants were instructed to stare at a fixation cross on a computer screen for 60 s (Rest) and perform a simple reaction time task afterward. There was a 120-s break between the blocks to avoid potential carry-over effects (i.e., GVS was not delivered during break). **(B)** Left: participants were instructed to respond to a visual cue ("Go") as fast as possible by squeezing a pressure sensor bulb. There were 10 trials in each stimulation condition. For each trial, peak grip pressure (P_{max}), time of visual cue (t_1), time of movement onset (t_2), and time of peak pressure (t_3) were identified in the water pressure recording.

GVS

GVS was delivered in bilateral, bipolar fashion through pre-gelled Ag/AgCl electrodes (BIOPAC Systems Inc., USA) placed over the mastoid process behind each ear using a constant current stimulator DS5 (Digitimer, UK). We utilized systematic procedures previously used to determine individual cutaneous sensory threshold level (31, 33, 34). A noisy stimulus was delivered to the mastoid processes for 20 s at an imperceptible level, starting from a basal current level of 0.1 mA. The current intensity was then increased in 0.02 mA intervals until participants perceived a mild, local tingling sensation in the area of the stimulating electrodes for the duration of the stimulus. The current level was then decreased each time by one level until sensation was no longer reported and then increased by one step to confirm the threshold. In the experiment, GVS was applied at 90% of the determined threshold value to avoid the effects of placebo, general arousal, and/or voluntary selective attention.

In each stimulation block (**Figure 1A**), either random noise (RN; 4–200 Hz) or a band-limited multisine stimulus was delivered. A multisine stimulus was adopted as it has the advantages of reducing experiment time by testing multiple sinusoids at once and preserves the power spectrum over a frequency range of interest without any spectral leakage compared with random noise (35). A multisine signal $x(t)$ can be expressed as:

$$x(t) = A\sum_{k=1}^{N_k} \sin(\omega_k t + \phi_k)$$

where A is the amplitude, N_k is the number of sinusoidal components, ω_k and ϕ_k are the frequency and phase of each sinusoidal component k, respectively.

Seven multisine stimuli were designed in total. ms-θ, ms-α, ms-β, and ms-γ were designed to cover conventional EEG frequency bands, and ms-h1, ms-h2, and ms-h3 to cover high frequency ranges (**Table 2**). For each stimulus, the sinusoidal frequencies (ω_k) were uniformly distributed every 0.4 Hz (e.g., the ms-β consisted of sinusoids at 13.0, 13.4, …, 29.8 Hz). The phases (ϕ_k) of the sinusoids were chosen to minimize the crest

TABLE 2 | Frequency ranges of the GVS stimuli investigated in the study.

	RN	ms-θ	ms-α	ms-β	ms-γ	ms-h1	ms-h2	ms-h3
Frequency (Hz)	4–200	4–8	8–13	13–30	30–50	50–100	100–150	150–200

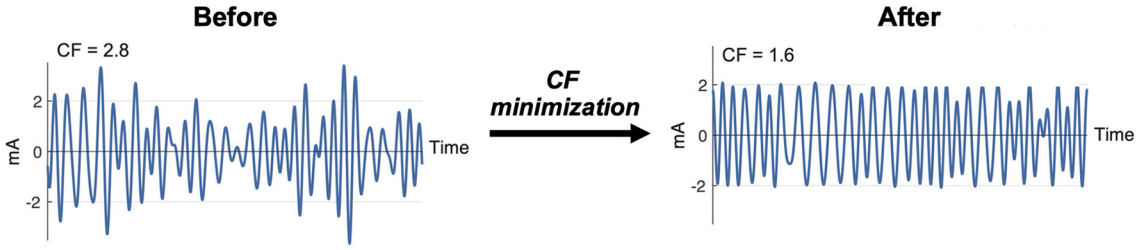

FIGURE 2 | Clipping algorithm to minimize crest factor (CF) of a multisine signal.

factor using a clipping algorithm (36) (**Figure 2**) to increase signal-to-noise ratios and improve participants' comfort (37, 38).

The active-GVS blocks were randomly ordered for each participant, and the *off-stimulation* block was conducted before any active-GVS block to enable a comparison of motor performance between the PD and HC groups without any carry-over stimulation effects. In this study, behavioral effects of GVS were investigated using only the active-GVS blocks that were completely randomized.

Statistical Procedures

GVS thresholds between groups were compared using the two-sample *t*-test, and correlations between GVS thresholds and age or clinical scores were tested using the Pearson correlation coefficient.

For each group, the RPTs during active-GVS blocks were compared using a one-way repeated measures analysis of variance (RM-ANOVA) with STIM (RN, ms-θ, ms-α, ms-β, ms-γ, ms-h1, ms-h2, and ms-h3) as a within-subject factor. To investigate the interaction effect of GVS and medication for PD participants, we additionally conducted an overall two-way RM-ANOVA with STIM and MED (on and off) as within-subject factors. Mauchly's test was used to assess the ANOVA assumption of sphericity, and the Greenhouse-Geisser correction was used if necessary to correct for non-sphericity. When a significant effect was found, *post-hoc* pairwise comparisons with the Bonferroni correction were conducted. If there was a stimulus that evoked a significantly different RPT compared with RN-GVS, the RT and MT were compared using a paired *t*-test.

All statistical analyses were performed using IBM SPSS (version 27). Significance was assigned to $P < 0.05$.

RESULTS

None of the participants reported any adverse effects nor awareness of any differences between stimulation conditions.

GVS Threshold

There was no significant difference between the PD and HC groups in GVS threshold level [PD: 0.50 ± 0.24 mA; HC: 0.46 ± 0.18 mA; $t_{(36)} = 0.56$, $P = 0.58$]. The thresholds of all participants were not significantly correlated with age ($r = 0.06$, $P = 0.73$), but there was a significant sex difference [males = 0.51 ± 0.21 mA; females = 0.35 ± 0.13 mA; $t_{(36)} = 2.89$, $P = 0.006$]. For PD participants, no significant correlations were found between their thresholds and clinical scores (disease duration: $r = -0.11$, $P = 0.69$; UPDRS III: $r = 0.22$, $P = 0.39$; bradykinesia: $r = 0.35$, $P = 0.16$; tremor: $r = -0.19$, $P = 0.44$).

Effects of GVS Frequencies on RPT

A one-way RM-ANOVA revealed a main effect of STIM for the PDMOFF [$F_{(7, 119)} = 4.38$, $P < 0.001$] and HC [$F_{(7, 133)} = 5.97$, $P < 0.001$] groups, but not for the PDMON group [$F_{(7, 119)} = 0.356$, $P = 0.93$] (**Figure 3A**). For the PDMOFF group, *post-hoc* tests found that RPT was significantly shorter during ms-β ($P = 0.008$) and ms-γ ($P = 0.026$) compared to RPT during RN, and the % change of RPT was −5.5 ± 4.8 and −5.4 ± 5.4%, respectively (**Figure 3B**). No significant change in RPT was observed for ms-θ ($P = 0.51$), ms-α ($P = 0.11$), ms-h1 ($P = 0.093$), ms-h2 ($P = 0.056$), and ms-h3 ($P = 1.0$). For the HC group, *post-hoc* tests revealed that, compared to RN, the RPT significantly decreased during ms-α ($P = 0.01$), ms-γ ($P = 0.001$), ms-h1 ($P = 0.012$), ms-h2 ($P = 0.008$), and ms-h3 ($P = 0.013$), but not during ms-θ ($P = 1.0$), and ms-β ($P = 0.24$) (**Figure 3A**).

We further investigated the nature of the significant RPT changes (**Table 3**). For the PDMOFF group, ms-β significantly decreased RT ($P = 0.0095$) but not MT ($P = 0.17$) whereas ms-γ decreased MT ($P = 0.013$) but not RT ($P = 0.076$). For the HC group, RT was decreased by ms-h1 ($P = 0.013$) and ms-h2 ($P = 0.048$). Overall, the results did not indicate that variation of GVS frequency evokes an exclusive change in RT or MT.

The two-way RM-ANOVA revealed a main effect of STIM [$F_{(7, 119)} = 2.78$, $P = 0.01$] and MED [$F_{(1, 17)} = 5.59$, $P = 0.03$]. Although PD participants tended to benefit from multisine stimuli more during off-medication state (**Figure 3B**), the STIM

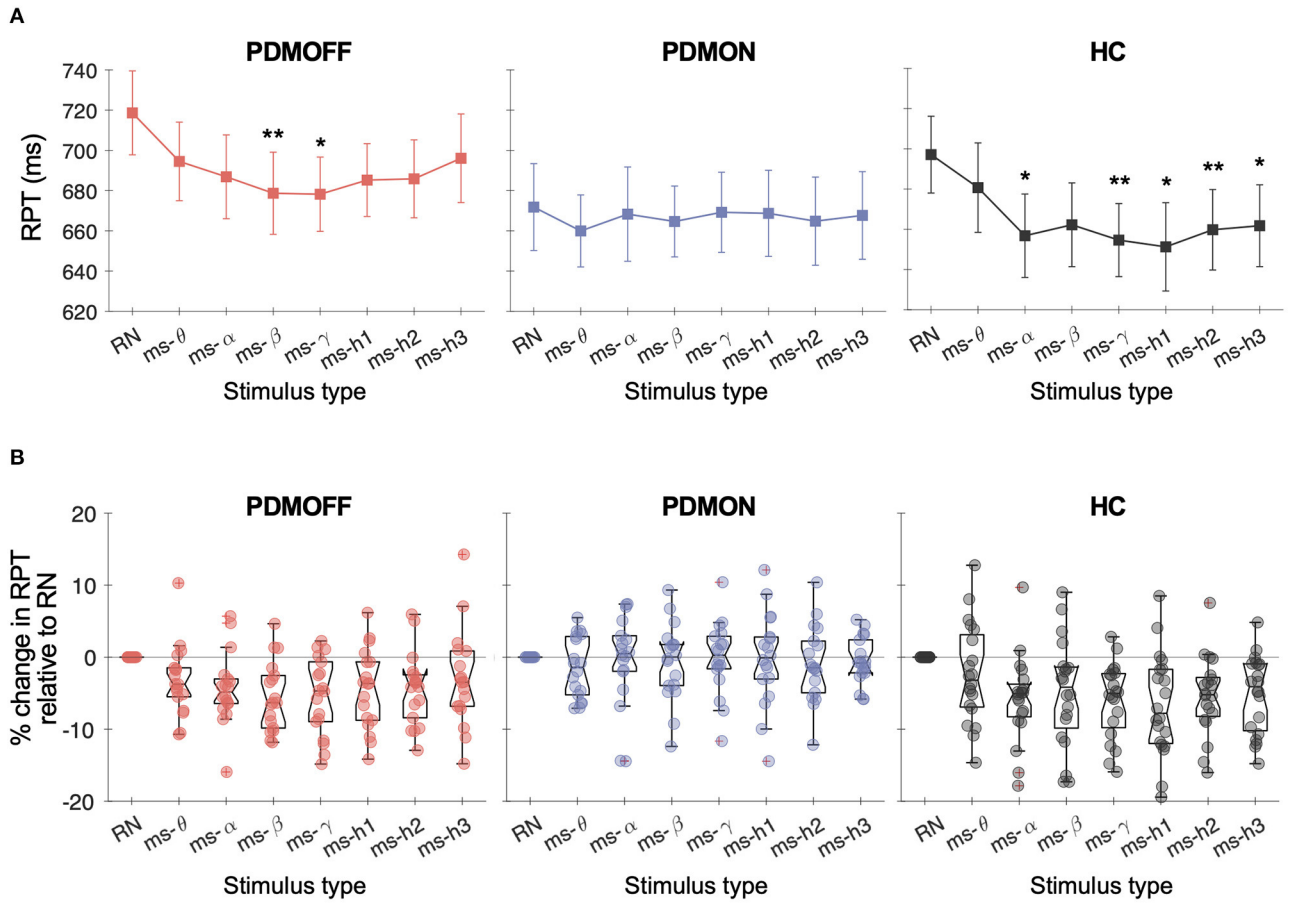

FIGURE 3 | (A) Response time (RPT) measured in different GVS conditions. Markers and vertical lines represent the group mean and standard error of the mean (SEM), respectively. *P* values from the *post-hoc* tests are indicated (*$P < 0.05$ and **$P < 0.01$ compared to RN). **(B)** % change in the RPT compared to RN-GVS. Each dot represents a participant.

TABLE 3 | *Post-hoc* comparisons of RT and MT measured during GVS.

	PDMOFF		HC	
Stimulus	**RT (ms)**	**MT (ms)**	**RT (ms)**	**MT (ms)**
RN	478.0 ± 16.1	240.8 ± 15.7	472.3 ± 9.9	225.0 ± 17.8
ms-θ	N/A	N/A	N/A	N/A
ms-α	N/A	N/A	452.9 ± 10.0 ($P = 0.09$)	204.0 ± 18.0 ($P = 0.069$)
ms-β	450.6 ± 13.2 ($P = 0.0095$)	228.1 ± 15.3 ($P = 0.17$)	N/A	N/A
ms-γ	456.6 ± 13.9 ($P = 0.076$)	221.6 ± 14.1 ($P = 0.013$)	449.1 ± 10.6 ($P = 0.065$)	205.9 ± 16.8 ($P = 0.097$)
ms-h1	N/A	N/A	445.7 ± 10.0 ($P = 0.013$)	205.7 ± 18.2 ($P = 0.065$)
ms-h2	N/A	N/A	450.4 ± 8.6 ($P = 0.048$)	209.3 ± 18.2 ($P = 0.20$)
ms-h3	N/A	N/A	454.0 ± 11.3 ($P = 0.14$)	207.8 ± 18.2 ($P = 0.15$)

Values are shown only for the RN and multisine stimuli that resulted in significant RPT change compared to RN.
P values from paired t-tests (multisine vs. RN) are shown. N/A, Not applicable.

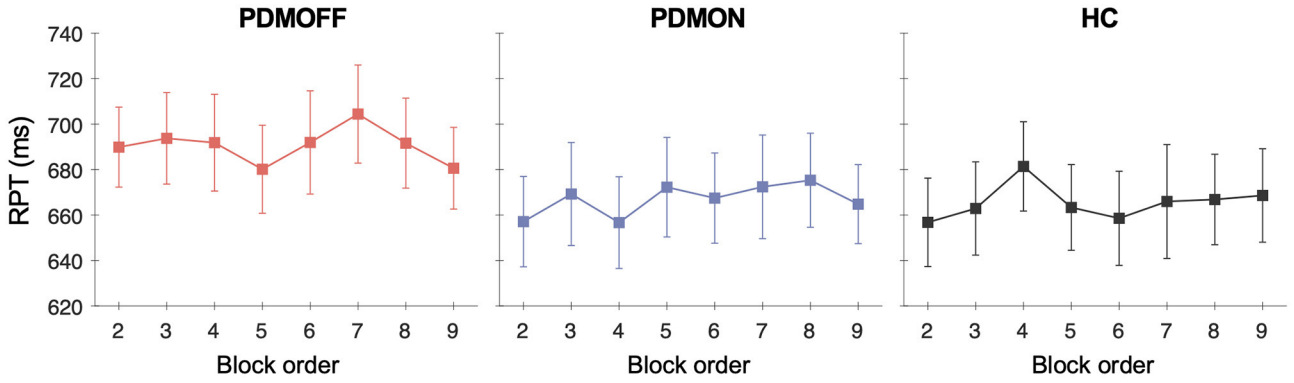

FIGURE 4 | Group mean and SEM of the RPTs that are temporally ordered as opposed to stimulus types. The x-axis represents the temporal order of the stimulation blocks. The first *off-stimulation* block (**Figure 1A**) is not shown.

× MED interaction effect did not reach the statistical significance [$F_{(7, 119)} = 2.03$, $P = 0.056$].

Effects of Time Order on RPT

To assess whether there was any spurious time-order effect on RPT, we re-arranged RPTs in chronological order for every participant and performed a one-way RM-ANOVA with TIME as a within-subject factor.

No effect of TIME was found for all three groups [PDMOFF: $F_{(7, 119)} = 1.31$, $P = 0.253$; PDMON: $F_{(3.8, 64.8)} = 1.38$, $P = 0.251$; HC: $F_{(7, 133)} = 1.14$, $P = 0.341$] (**Figure 4**).

Sensitivity of RPT on GVS Frequency

We investigated whether the degree of RPT variation induced by different stimuli differed between the PDMOFF, PDMON, and HC groups. To quantify this, for each participant, we computed the standard deviation (RPT_{SD}) and range (RPT_{range}; max–min) of RPTs across the eight stimulation blocks.

Group comparisons suggested that both RPT_{SD} and RPT_{range} were comparable between the PDMOFF and HC groups (**Table 4**). PDMON participants showed relatively smaller RPT_{SD} and RPT_{range} compared to the other two groups, but these differences did not reach statistical significance.

Intersubject Variability in Most and Least Effective Stimuli

Figure 5A shows the distributions of the most effective stimulus (GVS_{most}) that resulted in the shortest RPT for each participant. Interestingly, the distributions of the PDMOFF and HC groups appeared similar in that 77.8 and 90.0% of the participants, respectively, showed their best task performance during ms-α, ms-β, ms-γ, or ms-h1. By comparison, only 38.9% of the PDMON participants performed the best in these frequency ranges.

The contrast between the PDMON and the other two groups was also observed when we investigated the least effective stimulus (GVS_{least}) that resulted in the longest RPT (**Figure 5B**). RN and ms-θ were found to be the least effective stimuli for 55.5 and 90.0% of the PDMOFF and HC participants, respectively. On the other hand, only 16.7% of the PDMON participants showed their worst performance during RN and ms-θ.

Significance of the RPT Decrease by GVS_{most}

To assess whether the RPT evoked by GVS_{most} was significantly faster compared with the other stimuli, we computed its P value based on the empirical distribution of RPT estimated by a bootstrapping approach (**Figure 6A**). Note that as the RPT is computed as the mean over 10 randomly selected trials, it can still be shorter than the mean RPT during GVS_{most}. **Figure 6B** shows that 83.3, 66.7, and 85% of the PDMOFF, PDMON, and HC participants, respectively, exhibited significantly shorter RPT during GVS_{most} ($P < 0.05$) compared with the expected RPT during any GVS stimulus.

DISCUSSION

To our knowledge, this is the first study investigating SRT task performance of PD and HC participants while applying GVS across a wide range of frequencies. Overall, our results suggest that RPT can be improved by GVS in PD patients. However, as bradykinesia is a key feature in PD, we cannot disentangle whether or not the RPT improvements were a result of faster decision-making and/or faster movement. This will require examining the simultaneously acquired EEG and will be the topic of another report. We demonstrated that the motor improvement is significantly dependent on the GVS parameters used. Surprisingly, we found that RN-GVS, despite its popularity, did not actually evoke the best task performance in the PDMOFF and HC groups, with ms-γ (30–50 Hz) proving superior in reducing RPT (**Table 5**). The performance of the off-medicated PD participants during ms-β and ms-γ were comparable to the baseline performance when they were in the on-medication state. We found that the GVS frequency that resulted in the shortest RPT varied considerably across participants, suggesting that a one-size-fits-all stimulus will not be as effective as a personalized stimulus. For most of the PDMOFF and HC participants, the best GVS frequency varied in the range of 8–100 Hz. The worst

TABLE 4 | Comparisons of RPT variability (RPT_{SD} and RPT_{range}) across the eight GVS conditions.

	Mean ± SD			*P*		
	PDMOFF	**PDMON**	**HC**	**PDMOFF – PDMON**	**PDMOFF – HC**	**PDMON – HC**
RPT_{SD} (ms)	27.2 ± 9.9	23.2 ± 10.7	29.8 ± 11.2	0.15	0.45	0.074
RPT_{range} (ms)	82.2 ± 29.9	68.8 ± 31.4	89.6 ± 33.3	0.084	0.48	0.057

P values obtained from student t-tests are presented.

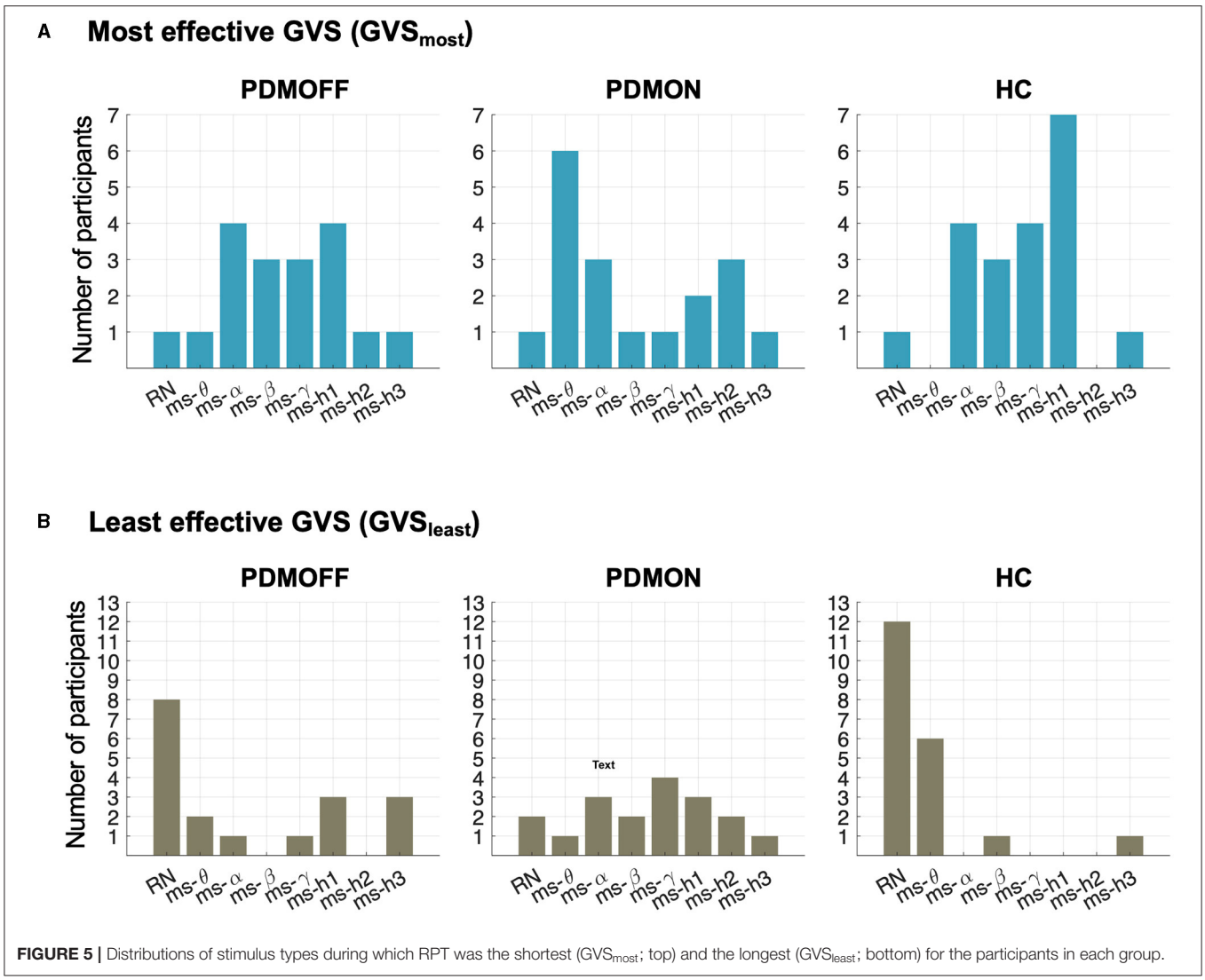

FIGURE 5 | Distributions of stimulus types during which RPT was the shortest (GVS_{most}; top) and the longest (GVS_{least}; bottom) for the participants in each group.

task performance was found during RN or ms-θ for more than half of the participants in these two groups. These results provide evidence that further work is required to tailor GVS parameters for maximum efficacy.

Whether or not RPT is actually delayed in PD has been controversial (39–41), partially due to methodological heterogeneity and different clinical characteristics of the participants (42). In this study, the difference in baseline RPT between the PDMOFF and HC groups did not reach statistical significance ($P = 0.068$; **Supplementary Table 2**). Instead, the most interesting finding was that responses to different GVS stimuli showed a similar trend between the two groups (**Figure 3**). This finding may suggest that there are some mechanisms underlying the GVS effects that are common between these groups.

In contrast, we found that the PDMON group showed relatively different responses to GVS. Normally, dopamine is active both phasically and tonically during motor performance. Levodopa has complex effects in PD, which may result in relative normalization of tonic dopamine firing, yet impairment of phasic

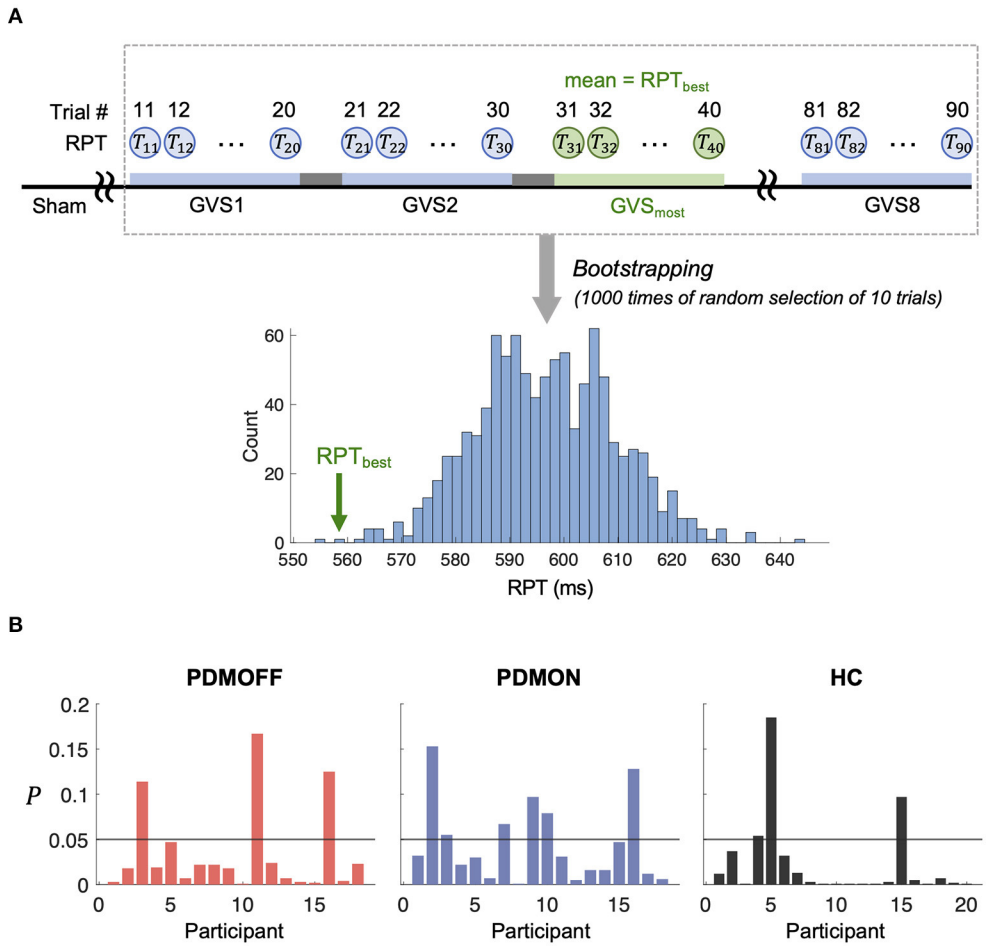

FIGURE 6 | (A) Schematic diagram showing a process to generate an empirical distribution of RPT for each participant. Each bootstrap sample randomly selects RPTs of 10 trials and the mean of the bootstrap samples is computed to generate the distribution. RPT_{best} represents the mean RPT during GVS_{most}. **(B)** *P* value of RPT_{best} computed based on **(A)** is shown for every participant.

firing (43). While phasic dopamine firing is normally associated with rewards in reinforcement learning paradigms, it may also be involved in internal representations of desired actions with actual sensory feedback during motor performance (44–46). Thus, many studies have suggested that movement-related phasic changes can be observed in nigrostriatal dopamine neuron firing (47–49), and that dorsal striatal phasic dopamine signaling is associated with specific kinematic features of movement (43). Complex effects of dopaminergic medication in PD have also been reported in fMRI studies (50–54) showing that levodopa medication does not simply restore brain connectivity aberrant in PD. Rather it induces functional connectivity changes distinctive from those identified to be different between PD patients and healthy controls (51, 54). Taken together, this is an important point to consider for future GVS studies, as prior studies (**Supplementary Table 1**) included only medicated PD patients, and the information on the dosage and timing of the medication was rarely reported.

Given the functional role of pathological beta oscillations in PD (55), the result of particular interest was that ms-β resulted in the largest decrease in RT among the tested stimuli in the PDMOFF group whereas it did not improve motor performance for the HC group. In this regard, there is some evidence to support the concept that beta-frequency stimulation may have clinical effectiveness in PD patients. In a transcranial alternating current stimulation (tACS) study conducted on 10 PD and 10 HC participants (56), 20-Hz stimulation at the primary motor cortex (M1) yielded a significant decrease in beta-band cortico-muscular coupling in PD patients but not in HC. A TMS study showed that 20–33 Hz stimulation at M1 elicited significant suppression of the motor evoked potential (MEP) in PD patients and the amount of suppression was correlated with their UPDRS III scores (57). It should be noted, however, that there have been only a handful of studies that utilized beta-frequency NIBS in PD patients, and it is difficult to determine from our results whether the ms-β effects observed in the PD participants were related to the pathological beta-band activity. Thus, further neuroimaging studies are strongly suggested to be carried out to validate our results and elucidate the mechanisms of action.

TABLE 5 | Summary of RPTs (unit: millisecond) measured during *off-stimulation* (baseline), RN-GVS, and multisine GVS for the PD and HC participants.

	PD ($n = 18$)	HC ($n = 20$)
Off-medication		
Baseline	748.5 ± 93.8	674.4 ± 107.5
GVS	RN: 718.7 ± 88.5 ms-β: 678.7 ± 86.6** ms-γ: 678.2 ± 78.3*	RN: 697.2 ± 85.4 ms-α: 656.8 ± 92.7* ms-γ: 654.6 ± 81.2** ms-h1: 651.3 ± 98.2* ms-h2: 659.8 ± 89.5** ms-h3: 661.8 ± 91.0*
On-medication		
Baseline	683.2 ± 92.4	N/A
GVS	RN: 671.82 ± 91.6	N/A

*For multisine GVS, only those that resulted in significant changes compared with RN-GVS are displayed (*P < 0.05 and **P < 0.01 compared with RN as in **Figure 3**). N/A, Not applicable.*

The frequency-dependent GVS effects we observed may be related to the overlap between the neural processes affecting RPT and neural pathways affected by external vestibular inputs. One of the main vestibular pathways is the direct ascending projection from the vestibular complex to the thalamus, primarily targeting the ventral anterior, ventral lateral, ventral posterior lateral, ventral posterior medial, intralaminar nuclei, and the geniculate bodies (58–60). Strong activations in these regions by vestibular stimulation (18, 59, 61–63) suggest a critical thalamic contribution to processing vestibular information (60, 63). The ventral parts of the thalamus are also closely connected with M1, premotor cortex, and BG (15, 58, 63, 64), modulating a range of aspects in motor control (15, 63, 65). Thus, we conjecture that GVS effects on RPT can be in part explained by vestibular inputs affecting the motor thalamus. This may also explain the mild GVS effects on the PDMON participants as the BG inputs to the motor thalamus would vary at different dopamine levels.

It is also possible that GVS affected the striatum, a region described as an integrative center for sensory information and involved in motor planning and execution. Although the largest inputs to the striatum are from the cortex, recent studies have elucidated the subcortical pathways critical for interpreting and responding to environmental stimuli (66, 67). Electrophysiological studies in animal models and neuroimaging studies in humans have shown that vestibular stimulation activates the head of the caudate nucleus and putamen (16–19, 62, 68, 69), likely through the parafascicular thalamic nucleus (PFN) (64, 70). In addition, it has been recently proposed that the striatal tail may play a role as a multisensory integration center (71), and thus it is possible that there are vestibular inputs to this region as well.

Our observations of different motor effects evoked by varying GVS frequency are consistent with many animal studies (72, 73). Surprisingly, canal and otolith afferents in macaque monkeys responded to GVS as a function of frequency such that the response gain (i.e., spikes/s/mA) increased more than twice when the stimulation frequency varied from 0.1 to 25 Hz (72). This seminal finding opposes the common idea that high-frequency GVS would result in *smaller* gains because the tissues between the electrode and vestibular afferents may act as a low-pass filter. Similarly, the firing rate of the PFN increases when the frequency of stimulation applied to the semicircular canal nerve is >100 Hz (73). Taken together, these findings could explain in part the efficacy of the frequency range we observed in most of the PDMOFF and HC participants.

There are several limitations in our study. Considering the study design and our primary objective to examine different types of GVS stimuli, we did not try to replicate previous findings demonstrating that GVS results in better motor performance compared to baseline performance seen during *off-stimulation*. Although we think the practice effect on the task performance is unlikely for a simple, over-learned motor task like ours, the possibility was not completely ruled out when *the baseline measurement* always preceded active-GVS. Similarly, our study was not designed to measure the after-effects of GVS. Post-stimulation behavior effects of GVS are largely unknown (13). Studies that examined GVS aftereffects stimulated participants for more than 30 min, and the results are conflicting (74–77). The issue of whether stimulation effects last after the cease of stimulation is not only limited to GVS but is one of the main controversial topics for transcranial electrical stimulation (78). As online stimulation effects differ depending on stimulation parameters (e.g., frequency, intensity, duration, target sites) and experimental tasks, the presence and duration of after-effects appear to be influenced by the stimulation parameters and tasks (79, 80). Although after-effects are infrequently reported, evidence from tES studies shows the presence of after-effects when stimulation was applied at >0.5 mA for longer than 10 min (78, 81–83). Given that we applied GVS for a short duration at a low current intensity with a 2-min inter-block off-stimulation break, we suggest that any effects carried over from previous stimulation were relatively mild compared to the online-stimulation effects. Validation of GVS after-effects and their relationships with stimulation parameters will be areas/topics of interest for future work. Note that, since GVS can utilize portable stimulators, reliance on much more subtle after-effects is not as important as other technologies that are not as easily portable (e.g., TMS). Finally, several studies support the notion that GVS effects are mostly spatially restricted to the vestibular organs. For instance, the auditory effects of GVS are rare (20) despite the proximity between the auditory and vestibular systems. GVS evokes circumscribed cortical activation of vestibular areas, and effects on the somatosensory cortex are only seen at specific frequencies (62). At higher intensities, the stimulation of the vestibular system can be self-reported by feelings of vertigo. A recent computational modeling study of the electric field generated by GVS (84) suggests that the bilateral and bipolar configuration, as used in our study, results in the most spatially-restricted current flow to the vestibular organs. However, some current may diffuse to the medulla, pons, and cerebellum. Although we note that both the electrodes (11 mm) and current intensity used here (0.43 ± 0.19 mA) were less than those used in the computational model (30 mm and 1 mA), we cannot completely discount that some of our results may be via modulation of extra-vestibular structures.

In conclusion, our findings provide key information necessary for the future development of GVS techniques to induce robust and effective therapeutic effects in PD. Future research is warranted to confirm similar behavioral effects of GVS applied at frequencies beyond the assumed physiological ranges and to establish potential mechanisms.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Clinical Research Ethics Board at the University of British Columbia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SL designed and conducted the study, including patient recruitment, data collection, and data analysis. MJM participated in the study design, data analysis, supervision, and funding acquisition. All authors have participated in manuscript writing and editing and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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ORIGINAL RESEARCH
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Galvanic Vestibular Stimulation Effects on EEG Biomarkers of Motor Vigor in Parkinson's Disease

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Background: Impaired motor vigor (MV) is a critical aspect of Parkinson's disease (PD) pathophysiology. While MV is predominantly encoded in the basal ganglia, deriving (cortical) EEG measures of MV may provide valuable targets for modulation via galvanic vestibular stimulation (GVS).

Objective: To find EEG features predictive of MV and examine the effects of high-frequency GVS.

Methods: Data were collected from 20 healthy control (HC) and 18 PD adults performing 30 trials total of a squeeze bulb task with sham or multi-sine (50–100 Hz "GVS1" or 100–150 Hz "GVS2") stimuli. For each trial, we determined the time to reach maximum force after a "Go" signal, defined MV as the inverse of this time, and used the EEG data 1-sec prior to this time for prediction. We utilized 53 standard EEG features, including relative spectral power, harmonic parameters, and amplitude and phase of bispectrum corresponding to standard EEG bands from each of 27 EEG channels. We then used LASSO regression to select a sparse set of features to predict MV. The regression weights were examined, and separate band-specific models were developed by including only band-specific features (Delta, Theta, Alpha-low, Alpha-high, Beta, Gamma). The correlation between MV prediction and measured MV was used to assess model performance.

Results: Models utilizing broadband EEG features were capable of accurately predicting MV (controls: 75%, PD: 81% of the variance). In controls, all EEG bands performed roughly equally in predicting MV, while in the PD group, the model using only beta band features did not predict MV well compared to other bands. Despite having minimal effects on the EEG feature values themselves, both GVS stimuli had significant effects on MV and profound effects on MV predictability via the EEG. With the GVS1 stimulus, beta-band activity in PD subjects became more closely associated with MV compared to the

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sham condition. With GVS2 stimulus, MV could no longer be accurately predicted from the EEG.

Conclusions: EEG features can be a proxy for MV. However, GVS stimuli have profound effects on the relationship between EEG and MV, possibly via direct vestibulo-basal ganglia connections not measurable by the EEG.

Keywords: EEG, biomarker, LASSO, motor vigor, GVS, Parkinson's disease

INTRODUCTION

The complex ways neural activity encodes motor actions and how this can be modulated is an area of active research. While traditionally, investigation of motor control has been through hypothesis-driven approaches, with the widespread availability and sheer volume of non-invasive brain data now available, data-driven techniques can be used to complement traditional methods. The expansion of non-invasive brain stimulation (NIBS) methods has also promoted work to link brain rhythms with behavioral measures (e.g., reaction time or motor vigor [MV]), as NIBS may induce behavioral changes primarily via modulation of oscillations, as opposed to, e.g., biochemical modulations induced via pharmacotherapy. NIBS at specific phases/amplitudes/frequencies (1) or customizing stimulus parameters based on the neuroimaging data to account for individual differences (2) may ultimately lead to different behavioral effects, which could be considered as potential treatments for neurodegenerative diseases such as Parkinson's disease.

Oscillatory coupling of neural activity between the motor cortex and the basal ganglia is normally required for the execution of voluntary movements (3). The basal ganglia have diverse functionalities, including action and suppression of potentially competing actions, control of the scale of movement and related cost functions, online correction of a motor error, and motor learning (4). The dopamine deficiency seen in Parkinson's disease profoundly affects basal ganglia function, resulting in beta-band hyper synchronization (5) and an increase in the signal-dependent noise (6). Altered oscillatory/behavioral relations in Parkinson's may also lead to functional deficiencies such as impaired MV, defined as the ability to execute component movements over a range of speeds, amplitudes, and frequencies (7). The decision to move vigorously "may be thought of as an economic decision in which one spends effort to acquire a reward" (8): if a movement is deemed rewarding, one will move with increased MV, moving with shorter latency (i.e., reaction time), and faster (i.e., shorter movement time). Previous findings suggest that the quality and components of voluntary movement (e.g., velocity, accuracy, energy consumption, end-point variability, etc.) are modulated by the action execution time if the time carries a cost (8, 9). Accomplishment of a timed task can impose an implicit reward and accordingly modulate MV. In particular, bradykinesia (slowness of movement), hypokinesia (decreases in the amplitude of movements), and akinesia (poverty of movement), all key motor features of PD, are postulated to be the result of impaired movement vigor (10–12). Dopaminergic striatal activity is likely involved in value-based behavioral activation and invigoration, and a recent model of dopaminergic function suggests the dorsolateral motor striatum estimates how worthwhile it is to expend effort for the energy costs of moving (13). Increasing dopamine makes it more likely that an animal will decide it is worth spending energy to move or to move faster. As such, abnormal computation of vigor costs may be the basis of PD bradykinesia (14–17).

While MV is predominantly encoded in the basal ganglia (4), deriving (cortical) EEG measures of MV may provide valuable targets for modulation via NIBS methods such as galvanic vestibular stimulation (GVS). However, trying to map a low dimensional feature such as the presence/absence of a NIBS stimulus to another low dimensional feature such as MV is likely unsuitable for machine learning (ML) models, as this would require an impractically large number of trials to capture all sources of variability. In contrast, having an intermediate, relatively high dimensional representation of the brain state, such as the EEG, will allow first deducing the oscillatory/behavior relationships. Later on, the effects of psychosocial factors and/or NIBS on brain oscillations can then be determined. The risk of such an approach is that GVS may modulate basal ganglia structures at least in part through vestibulo-basal ganglia connections (18)—something the EEG may not be able to capture. Previous studies have demonstrated complex effects of GVS stimuli on ongoing EEG rhythms (19), with regions affected being associated with multisensory processing, likely via broadly distributed thalamocortical fibers. Thus determining the full range of cortical and subcortical areas involved in vestibular functioning and assessing the complex effects of GVS is still an active area of research and will likely include advanced models (20).

An apparent constraint in the investigation of MV markers in EEG is the risk that movement affects the recordings (21, 22). While there have been some improvements in EEG recordings during movement (e.g., in ambulatory settings), movement related artifact remains a severe issue often requiring sophisticated *post-hoc* analyses to remove artifact [e.g., (23)]. Since we are looking at specific EEG features related to vigor, we wanted to minimize the minimum amount of data manipulation to reduce artifacts. The most straightforward motor movement that would not interrupt the EEG would likely be a button press. While this would allow for evaluation of reaction time, it would not allow us to assess vigor *per se*. Squeezing a bulb through a resistance, as performed in our experiment, was the best candidate to address discussed challenges because (1) it allowed for both reaction time and movement time to be assessed,

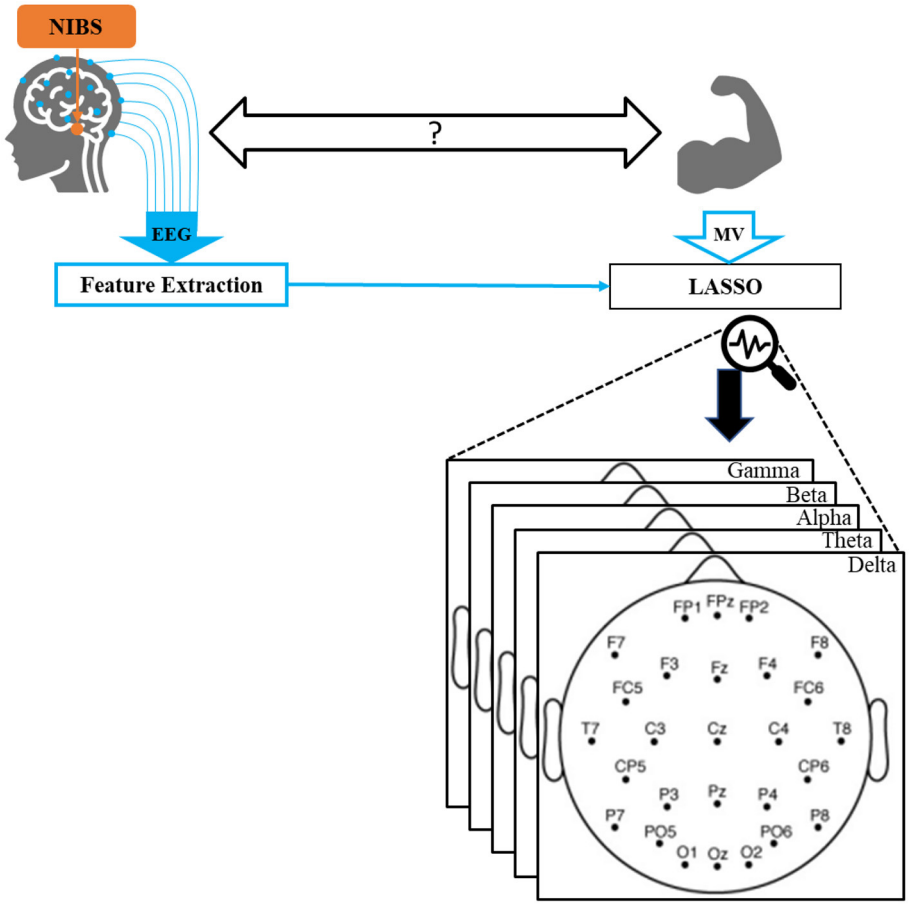

FIGURE 1 | Overall schematic of our proposed method. EEG and motor vigor data were collected while participants received non-invasive brain stimulation. A comprehensive set of standard features were extracted from EEG. Utilizing LASSO, MV was predicted by a subset of features, which were finally projected back into the EEG spectral and spatial space.

(2) it resulted in minimal head movement (and hence minimal EEG artifact), and (3) was not so effortful that PD subjects would remain fatigued after only a few trials.

In this study, we examine the relations between EEG features and MV and determine the effects of specific GVS stimuli on the EEG using LASSO regression models (24). By extracting a comprehensive set of features using LASSO models (**Figure 1**), we seek answers to the following questions: (a) What fraction of the MV variability can be deterministically estimated from the EEG before and during movement? (b) Which frequency sub-band(s) contribute most to accurate MV prediction? (c) Which EEG electrodes are important in terms of MV prediction? (d) What effects does GVS have on EEG/MV prediction?

METHODS

Participants and Study Protocol

The study protocol was approved by the Clinical Research Ethics Board at the University of British Columbia (UBC), and the recruitment was conducted at the Pacific Parkinson's Research Center (PPRC). All participants gave written, informed consent before participation.

We used the same EEG and behavioral used by Lee (25). In brief, data were collected from 20 healthy controls (9 males, 67.6 ± 8.9 years) and 18 PD participants (7 males, 67.3 ± 6.5 years). Demographic and clinical characteristics of both PD and healthy controls are provided in **Table 1**. The experimental paradigm included a simple motor task in different blocks with 10 trials. In each block, participants received either *sham* (i.e., no) GVS stimulation or brain stimulation with different waveforms. *Sham* stimulation was performed at the beginning, and the order of the blocks with stimulation was counterbalanced between subjects.

During the experiment, subjects performed a simple, overlearned task. Subjects were comfortably seated in front of a computer screen and instructed to focus their gaze on a continuously displayed, fixed target for 60 sec. Then, a written instruction was given to press a key on the keyboard to start the motor task. Subjects were then instructed to respond to a visual cue ("Go") as fast as possible by squeezing a rubber bulb. There were 10 trials each started with a 1,500 ms fixation screen

TABLE 1 | Demographic and clinical characteristics of the patients with Parkinson's disease (PD) and healthy controls (HC).

	PD	HC
Age (years), mean (sd)	68.2 (7.1)	68.6 (7.6)
Gender, n (male/female)	9/9	11/9
Disease duration (years), mean (sd)	7.4 (4.3)	-
UPDRS II, mean (sd)	14.8 (8.1)	-
UPDRS III, mean (sd)	23.3 (9.1)	-
Hoehn and yahr scale, mean (range)	1.3 (1-2)	-
Levodopa equivalent daily dose (mg), mean (sd)	635.9 (356.4)	-

UPDRS II: Motor aspects of the experience of daily living.
UPDRS III: Motor symptoms.

jittered 500 ms followed by a 500 ms Go screen and a 1,000 ms blank screen (see **Figure 2A**). We formed the same size epochs of EEG signals using the last 1,000 ms of each trial time-locked at the end to the peak time of each individual subject. We chose to include EEG signals of the reaction period (up to the peak time) because we were interested in the investigation of the dynamics of neuro-modulations from both before and after task execution, which is affecting the motor vigor. We used sham (no stimulation) condition trials to characterize the dynamics of neural activities correlated with motor vigor. In addition, we pooled two other multi sine stimuli (GVS1: 50–100 Hz; GVS2: 100–150 Hz) to investigate the influence of stimulations on neural level dynamics compared to the sham condition.

Data Collection

EEG data were recorded from 27 scalp electrodes with a sampling rate of 1 kHz using the Neuroscan SynAmp2 EEG acquisition system (Neuroscan, USA) and a standard electrode cap (64-channels Quik-Cap, Neuroscan, USA). EEG electrodes were positioned according to the international 10–20 placement standard. The reference electrode was between CPZ and CZ. The ground electrode was placed on the back of the head. The data were re-referenced to the common average. The electrodes were attached using Electro-Gel (Electrode-Cap International, USA), and impedances were kept below 15 kΩ.

Data Analyses

Preprocessing

We estimated MV as the inverse of the time to reach maximum force after a "Go" signal (26) (see **Figure 2B**). The EEG data were first bandpass filtered between 0.5 and 45 Hz using a zero-phase finite impulse response (FIR) filter. Furthermore, we removed the artifacts using a wavelet-based filter approach (see **Supplementary Material Section 1** for more information). We also performed data augmentation (27) and doubled the number of trials by downsampling by a factor of 2 to create two EEG epochs per each recorded MV. We clipped time points that were three standard deviations greater/smaller than the mean as outliers. Furthermore, after extracting 53 EEG features from each channel (see feature extraction section in the **Supplementary Material Section 2**), features and MVs are normalized within subjects using Z-Score scaling to bring their mean to 0 and standard deviation to 1 to minimize inter-subject variability.

Feature Extraction

We extracted 53 features per channel per trial, including relative spectral power, harmonic parameters, and amplitude and phase of bispectrum in frequency ranges corresponding to standard EEG channels, delta (0.5–4 hz), theta (4–8 hz), alpha-low (8–12 hz), alpha-high (12–16 hz), beta (16–32 hz), and gamma (32–45 hz). We chose this set of features to investigate and characterize the MV-related neural dynamics in the standard EEG spectral bands because standard EEG bands are well studied, and their cognitive functional correlates have been reported in the related studies. Technical details of the feature extraction section are provided in the **Supplementary Material**. We performed feature extraction in MATLAB, and source code is accessible online (see the code and data availability statement).

Data Modeling

Since the data was high dimensional (53 features per 27 channels, 1,431 independent variables), we used the LASSO (least absolute shrinkage and selection operator) method (24) to find which subset of independent variables (i.e., features) gave the best linear regression model to predict MV. Since we were less interested in capturing inter-subject variabilities but rather robust features affecting MV, we performed a bootstrapping technique in 40 separate iterations on a subset of trials randomly selected from all participants in each iteration. Specifically, at each iteration, 80% of randomly selected trials were fed into LASSO algorithm to find the best regression model to predict MV, and the remaining 20% trials were used to estimate the performance of the model in predicting MV. We defined performance as the correlation between the original MV and estimated MVs by the model. We chose the correlation over the mean square error (MSE) or the mean absolute error (MAE) and/or other alternatives to best explain the dynamics and variabilities of MV and prevent a flooring effect that might affect MSE (28). We then repeated the process using only features specific to a given band (e.g., delta) to fit new LASSO models, in addition to examining the LASSO-selected coefficients using all the features to infer the spatial location, weight, and direction of the frequency-specific features that best predicted MV.

To investigate whether there were differences in MV behavioral performance between HC and PD groups in different stimulus conditions, we conducted a 2 (Disease status: HC and PD) X 3 (Stimulus: Sham, GVS1, and GVS2) mixed ANOVA, with the stimulus type varied within participants. To compare if different band-limited features affected prediction performance, we conducted a 2 (Disease status: HC and PD) by 3 (Stimulus: Sham, GVS1, and GVS2) by 7 (Bands: Broadband, Delta, Theta, Alpha-low, Alpha-high, Beta, Gamma) mixed ANOVA on average Fisher z-transformed correlations between original and estimated MVs.

All LASSO model fits and performance estimations were performed in MATLAB, and statistical analyses on performance and beta values were done in R using ANOVA and t-test

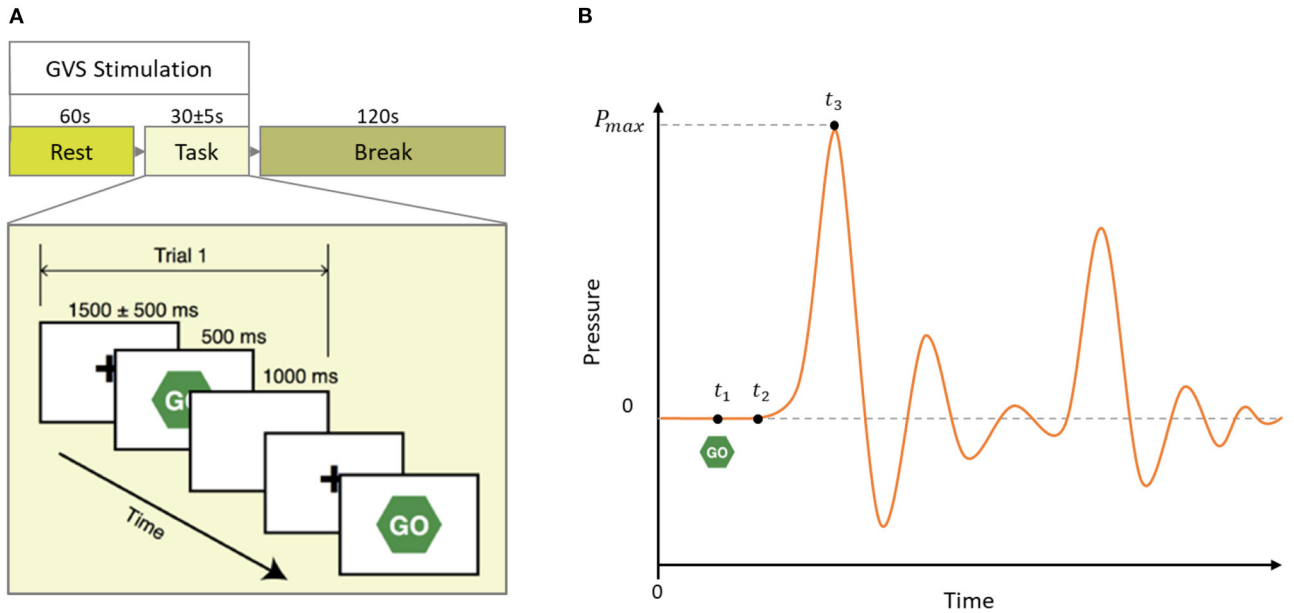

FIGURE 2 | (A) Schematic of a block of the experimental paradigm in which 60 s rest followed by 10 task trials and 120 s break time. In each block, GVS stimulation (Sham, GVS1: 50–100 Hz, and GVS2: 100–150 Hz) was delivered during the rest and task period. **(B)** Mock pressure signal of a squeezing bulb. GO screen appeared at t_1, the participant started to squeeze the bulb at t_2 and reached maximum pressure at t_3. Peak time is defined as $t_3 - t_1$.

comparisons. We used the Bonferroni correction to deal with multiple comparisons.

RESULTS

The mixed ANOVA results applied to the behavioral data showed a main effect of Stimulus type, $F_{(2,72)} = 49.22$, $p < 0.001$, $\eta_p{}^2 = 0.58$, such that the average MV in the *sham* condition was significantly lower (M = 14e-4, SD = 2e-4) than the average MV in both GVS1 (M = 15.5e-4, SD = 2e-4), $t(37) = 7.74$, $p < 0.001$, and GVS2 (M = 15.4e-4, SD = 2e-4), $t(37) = 7.64$, $p < 0.001$. There were no main effect or interaction effects with disease status ($ps > 0.138$).

MV Predictability Performance

Average correlations between original and estimated MVs over 40 runs of different LASSO models are depicted separately for healthy and PD groups under each stimulus type in **Figure 3** (see **Supplementary Table 1** for the numerical values of the mean and standard deviation).

We found a significant main effect of Stimulus type, $F_{(2,234)} = 103.34$, $p < 0.001$, $\eta_p{}^2 = 0.47$, such that average performance of predicting MV in the *sham* condition ($M = 0.54$, $SD = 0.12$) was significantly higher than that in GVS1($M = 0.26$, $SD = 0.11$), $t(39) = 9.56$, $p < 0.001$, which in turn was significantly higher than GVS2 ($M = 0.13$, $SD = 0.15$), $t(39) = 4.33$, $p < 0.001$. We also found a significant main effect of model band, $F_{(6,1404)} = 175.63$, $p < 0.001$, $\eta_p{}^2 = 0.43$, such that broadband features gave the best performance ($M = 0.98$, $SD = 0.35$) overall compared to each of the other band models ($ps < 0.042$) and the alpha-low ($M = 0.14$, $SD = 0.07$) band model gave the lowest performance compared to each of the other band models ($ps < 0.042$). Average performance of delta ($M = 0.23$, $SD = 0.09$), theta ($M = 0.21$, $SD = 0.09$), alpha-high ($M = 0.21$, $SD = 0.10$), beta ($M = 0.18$, $SD = 0.09$), and gamma ($M = 0.22$, $SD = 0.10$) band models were not significantly different ($ps > 0.061$). This result is further confirmed by a significant interaction between Stimulus type and band models, $F_{(12,1404)} = 7.71$, $p < 0.001$, $\eta_p{}^2 = 0.62$.

We also found a significant main effect of disease status, $F_{1,234} = 5.64$, $p = 0.018$, $\eta_p{}^2 = 0.02$, such that performance in PD population ($M = 0.28$, $SD = 0.08$) was significantly lower than healthy controls ($M = 0.34$, $SD = 0.13$), $t(61.51) = 2.37$, $p = 0.021$; which is confirmed by a significant interaction between disease status and band models, $F_{(6,1404)} = 14.98$, $p < 0.001$, $\eta_p{}^2 = 0.06$, which is further confirmed by a significant 3-way interaction between disease, stimulus type, and band models, $F_{(12,1404)} = 8.29$, $p < 0.001$, $\eta_p{}^2 = 0.07$. In each sham and GVS2 condition, broadband models were performed at the same level ($ps > 0.191$). However, broadband models significantly gave a lower performance on PD population compared to healthy in the GVS1 condition, $t(66.84) = 5.01$, $p < 0.001$. In the *sham* condition, only delta, alpha-low, and beta models had significantly different performance (lower) on PD population compared to healthy ones ($ps < 0.03$). In the GVS1 condition, delta and alpha-high models had significantly better performance in predicting MV in the healthy population ($ps < 0.002$), while theta, beta, and gamma models performed significantly better in PD population ($ps < 0.015$). Critically, under the effect of GVS1 beta and gamma models performed similarly to broadband models ($ps > 0.31$). In the GVS2 condition, beta models had

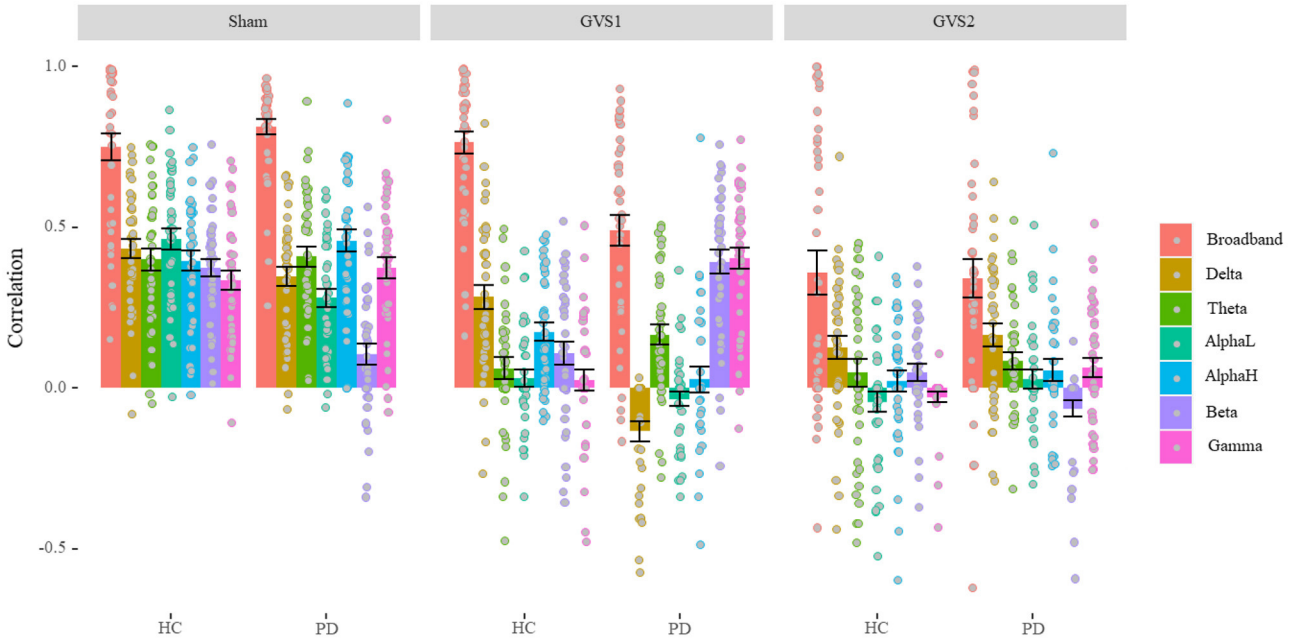

FIGURE 3 | LASSO correlation performance (Model Comparison). Under GVS stimuli, the overall performance of the models is dropped except for broadband in healthy controls (HC), and beta and gamma models in the PD population under models only under GVS1. In sham conditions, band models gave almost the same level of performance except for the beta model in the PD population that gave the lowest performance. PD, Parkinson's disease; HC, healthy controls. Sham: No stimulation, GVS1: 50–100 Hz; GVS2: 100–150 Hz.

significantly better performance on the healthy controls ($p = 0.004$), and gamma models performed significantly better in the PD population ($p = 0.013$). However, in the GVS2 condition, all bands had a significant performance drop, except the broadband and delta models.

To investigate the extent to which GVS1 and GVS2 affected individual feature values of the EEG in different ways and also compared to sham, we conducted a 2 (Health: HC, and PD) by 3 (Stimulus: Sham, GVS1, and GVS2) by 53 (EEG Features) mixed ANOVA. We found no main or interaction effect of stimulus ($ps > 0.079$).

Spectral and Spatial Characterization of MV Neuro-Markers

Figure 4 shows the regression coefficients (beta values) of the features averaged across channels in broadband models. The numerical values are listed in **Supplementary Table 2**. We conducted a one-sample *t*-test to determine whether beta-values were statistically different from zero. All beta values were significantly different from zero ($ps < 0.018$) except beta values for alpha-low of PD population in the GVS2 condition ($p = 0.100$). We conducted a 2 (Disease status: HC and PD) by 3 (Stimulus: Sham, GVS1, and GVS2) by 7 (Spectral bands: Broadband, Delta, Theta, Alpha-low, Alpha-high, Beta, Gamma) mixed ANOVA and found all main and interaction effects significant ($ps < 0.001$) specifically the three-way interaction between stimulus type, health, and spectral bands, $F_{(10, 1170)} = 52.44$, $p < 0.001$, $\eta_p^2 = 0.31$, suggesting that EEG neuro-markers contribute to MV in different extents based on health status and stimulus type. Nevertheless, ignoring the absolute value across different stimuli, in the HC population, delta always negatively correlated with MV, and theta, alpha-low, and beta correlated positively, while gamma contribution under sham and GVS2 was negative and under GVS1 was positive. The PD population was more variable across different stimulus types; however, gamma and beta always negatively correlated with MV, and theta correlated positively.

We further investigated the spatial distribution of spectral bands in the sham condition by averaging non-zero beta values of features across different runs within each channel. Each spectral band had non-zero values only in a limited number of channels (**Figure 5**). We observed that the main contribution of electrodes at each EEG spectral band in the HC population was as follows: delta (PO5, P8, Fz), theta (F7, Oz), alpha-low (T8, C3), alpha-high (FC5), beta (T7, CP5, P7), gamma (FP2); and in PD group are: delta (FC5, F7), theta (PO5, T8, O1), alpha-low (T7, F4), alpha-high (FP1, FC6, F4, F8, C4, O1), beta (F3, O2, F6), gamma (P8, PO6, P7, T7).

DISCUSSION

Using a comprehensive set of EEG features time-locked to reaching the maximum force, we could predict MV with an accuracy of around 75% in HC and around 81% in PD. These are comparable to the prediction based on features from deep brain

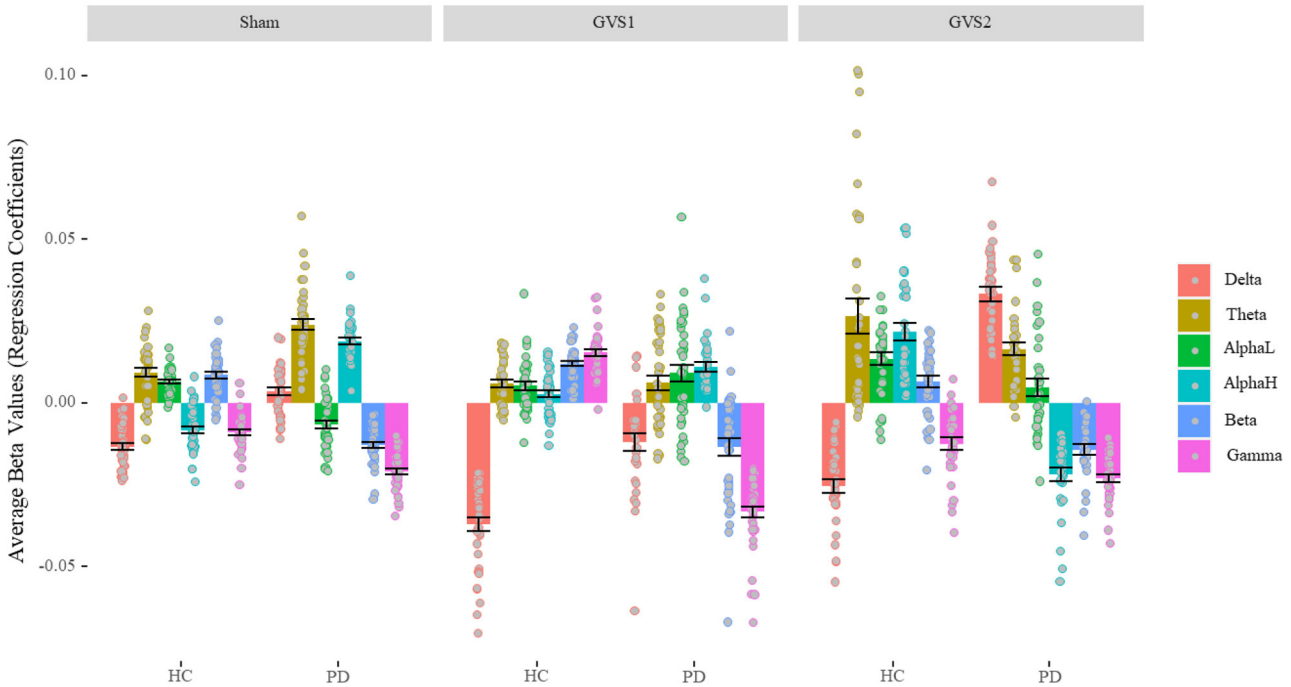

FIGURE 4 | Average Beta values of BB model (Characterizing EEG bands contribution). In the healthy control group, the delta band always negatively correlated with MV, and theta, alpha-low, and beta correlated positively. In the PD population, gamma and beta always negatively correlated with MV, and theta correlated positively. PD, Parkinson's disease; HC, healthy controls. Sham: No stimulation, GVS1: 50–100 Hz; GVS2: 100–150 Hz.

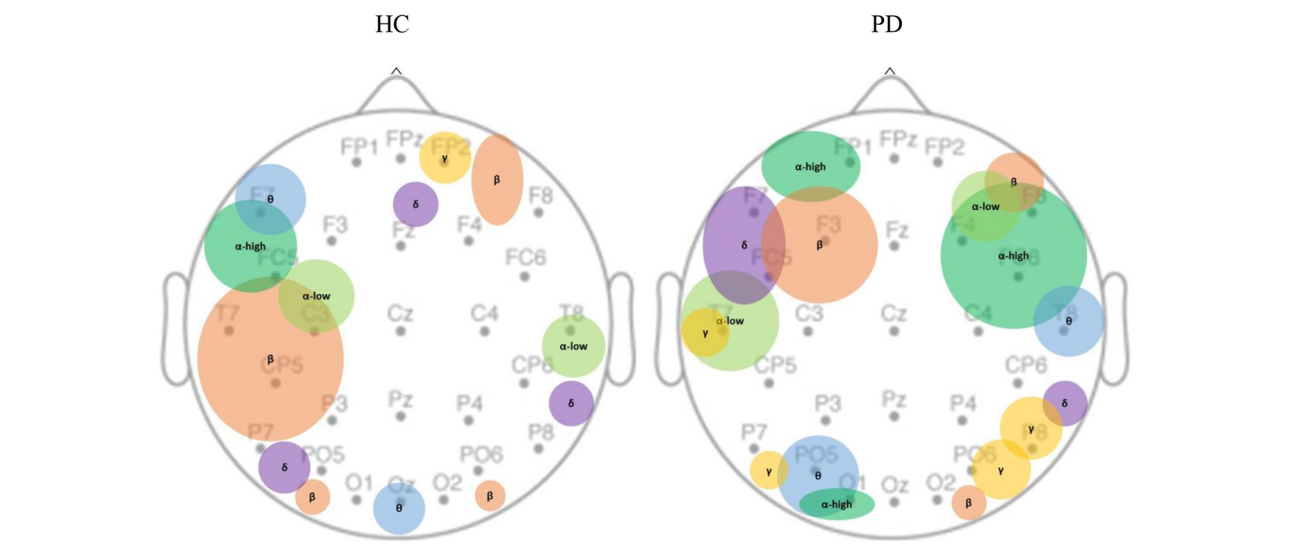

FIGURE 5 | Spatial distribution of EEG bands contributed to MV under the sham condition. MV was localized over the dominant hemisphere in healthy controls as opposed to bilateral localization in PD population. In healthy controls, theta, beta, and alpha-high are primarily concentrated in the left hemisphere; gamma is only found in the mid-frontal. In PD population, delta, beta, alpha-high, alpha-low are mostly observed in the frontal areas; theta, and gamma are mostly observed in temporal, parietal, and occipital areas. PD, Parkinson's disease; HC, healthy controls. δ: Delta band; θ: Theta band; α: Alpha band; β: Beta band; γ: Gamma band.

stimulation recordings (29), but the EEG may actually be superior to subthalamic local field potentials for movement decoding in PD (30). This suggests that, under normal conditions, cortically based EEG signals may provide sufficient information to create an MV biomarker. This is perhaps remarkable, as MV is typically assumed to be encoded in the basal ganglia, and monitoring

of basal ganglia activation would normally require technologies such as fMRI. The spatial distribution of the informative channels (**Figure 5**, left) suggests that in controls, the beta-band features were found over the central-parietal regions, possibly related to beta band event-related desynchronization normally seen during movement (31). In controls, important channels were localized over the dominant hemisphere but were more bilateral in PD subjects, possibly related to compensatory mechanisms (32), where bilateral activity is more likely to be seen.

It is perhaps unsurprising that models that included features from all EEG sub-bands demonstrated better performance predicting MV compared to models relying on sub-band features (**Figure 3**). What is remarkable is that both GVS stimuli did not change the feature values themselves yet still had profound effects on both the MV in the behavioral data and on the predictability of MV from the same EEG features (**Figure 3**). While it is possible that the EEG features we utilized did not capture any complex effects of GVS stimuli that still influenced MV, another possibility is that the GVS stimuli are affecting non-cortical sites (not measured by the EEG) that influence MV, such as connections between the vestibular system and the basal ganglia (18). Thus, we propose that vestibular-basal ganglia connections may be central in some of GVS's effects as opposed to GVS first activating cortical regions that then influence MV.

Recent work has started to explore the role of vestibular inputs on decision-making behavior. GVS affects risk-taking behavior in healthy controls as assessed by the Balloon Analog Risk Task (BART) (33). However, this was found with left-anodal and right-cathodal GVS as opposed to the alternating currents explored here. Caloric vestibular stimulation also modulates purchase decision making (34) and vestibular stimulation has been proposed more generally to probe cognitive processes that include decision making (35). While the basis of these reward-related cognitive vestibular effects has been suggested to be an overlap between emotional circuits and vestibular regions in the cortex such as the insular and orbitofrontal cortices (34), presumably this will involve subcortical structures as well: striatal neurons encode reward independent of sensory and motor aspects (36) More work is required to delineate the cortical and subcortical contributions of GVS-related modulation of reward behavior.

The different GVS stimuli had complex effects on EEG-based MV prediction (**Figure 2**). Both GVS stimuli frequencies were outside the EEG band frequencies, and any changes observed outside the stimulus frequency ranges are characteristic of a non-linear system (37). The GVS stimuli used were far outside the normal physiological ranges of vestibular stimulation as would occur with, e.g., head movement, supporting the role of data-driven models that we employed here. As expected, in most cases, band-specific EEG features were less capable of predicting MV than including the features seen in all bands, as less information is available to make the prediction. However, there were some notable exceptions: with GVS1 stimuli in the PD group, the beta band predictability actually increased compared to the sham condition (**Figure 3**). We speculate that in PD subjects receiving GVS1 stimuli, activity along direct vestibular-basal ganglia connections allowed for the basal ganglia to again be sensitive to cortical EEG beta rhythms. The GVS2 stimuli resulted in severe degradation of MV prediction via the EEG in both controls and PD subjects. This implies an overall insensitivity of the basal ganglia to motor cortical signals, although the same stimuli still resulted in behavioral improvements in MV.

Looking at the regression coefficients in the models using all of the features (**Figure 4**) provides insights into the relative contributions of different EEG bands in predicting MV. In contrast to the models that only trained on band-specific features (**Figure 3**), the regression coefficients in **Figure 4** are *relative* weights in the regression, so the weights of each EEG band can only be interpreted in the context of the other EEG bands. There are some surprises, namely that in PD subjects, both beta and gamma features were negatively correlated with MV, in the context of positive theta and high-alpha values. If beta is considered "anti-kinetic" and gamma-band activity is considered "pro-kinetic" (38), we would expect the gamma weights to be positive, not negative. This may, in part, be because the features we used included both phase and power. In controls, we found that theta, low-alpha, and beta features were associated with increasing MV, but delta, high-alpha, and gamma were associated with decreasing MV (**Figure 4**). In contrast, in PD subjects, theta and high-alpha were associated with increasing MV and beta and gamma (**Figure 4**). Although many studies have emphasized the critical role of altered beta band dynamics in PD during movement (39), gamma activity in the basal ganglia is also closely related to the coding of movement. Insufficient recruitment of fast gamma bursts during movement may underlie bradykinesia, and subthalamic gamma power correlates positively with maximal velocity (40). The above results suggest that examining specific bands for predicting MV in isolation may be misleading—individual bands must be considered in the context of other bands.

There are several limitations to our study. There are a limited number of trials which makes it hard to conduct a within-participants analysis. However, collecting a large number of trials in a motor task that require not just a simple button press, but squeezing against a resistance, can be particularly challenging in elderly and patient populations. Unlike conventional experiments that explore reward/motor behavior, in this experimental design, we had no explicit reward based on movement speed and/or accuracy. For this preliminary work, this was an explicit decision not to introduce extra confounds. We had too few trials to adequately dissociate complex aspects of decision-making processes in the EEG (i.e., monitoring reward, accuracy, and movement). Our goals were more modest here: we simply instructed people to "move as fast as they can" without additional (e.g., monetary) rewards. In addition, we only investigated standard EEG band-related features. However, defining a comprehensive set of features that can possibly capture the effects of GVS stimuli on dynamics of neural activity from EEG is not easy. Consequently, we suggest using data-driven methods like deep neural network models that can directly work with EEG signals and are not limited to hand-picked features.

Nevertheless, such methods require a large amount of data to be guaranteed to find the best GVS-related features in the raw EEG signals.

In summary, despite measuring predominately cortical activity, the EEG can predict MV in both Parkinson's and control subjects. However, care must be taken to use the EEG to guide the development of GVS stimuli, as GVS affects EEG/behavioral relationships likely through vestibulo-basal ganglia pathways not measurable by the EEG.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Clinical Research Ethics Board at the University of British Columbia (UBC). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MSM, AK, and MJM: conceptualization and writing-review and editing. MSM and AK: methodology, software, validation, formal analysis, visualization, and draft preparation. MJM: supervision and funding acquisition. SL: EEG/behavioral data collection. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.759149/full#supplementary-material

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Transcranial Magnetic Stimulation Alleviates Levodopa-Induced Dyskinesia in Parkinson's Disease and the Related Mechanisms: A Mini-Review

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After long-term use of levodopa, Parkinson's patients almost inevitably develop dyskinesia, a kind of drug side effect manifesting as uncontrollable choreic movements and dystonia, which could be crippling yet have limited therapeutic options. Transcranial magnetic stimulation is the most widely studied non-invasive neuromodulation technology to treat levodopa-induced dyskinesia. Many studies have shown that transcranial magnetic stimulation has beneficial effects on levodopa-induced dyskinesia and is patient-tolerable, barely with reported adverse effects. Changes in brain connectivity, neuroplasticity, neurotransmitter, neurorestoration, and blood flow modulation could play crucial roles in the efficacy of transcranial magnetic stimulation for levodopa-induced dyskinesia. The appearance of new modes and application for emerging targets are possible solutions for transcranial magnetic stimulation to achieve sustained efficacy. Since the sample size in all available studies is small, more randomized double-blind controlled studies are needed to elucidate the specific treatment mechanisms and optimize treatment parameters.

Keywords: transcranial magnetic stimulation, Parkinson's disease, dyskinesia, mechanism, treatment

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease characterized by the degeneration of substantia nigra dopaminergic neurons. Levodopa is the mainstay drug choice in the clinical management of PD. However, long-term levodopa supplements convert Parkinson's patients from akinetic state to hyperkinetic state, namely levodopa-induced dyskinesia (LID), with its severity ranging from mild and barely noticeable to severely disabled. After 4–6 years of levodopa administration, the occurrence rate of dyskinesia is 40%, while after 15 years, the occurrence rates can be up to 94% (1).

Modifying dopaminergic therapy to provide more continuous dopaminergic stimulation is helpful for the management of LID. Apart from dopaminergic drugs, amantadine is currently regarded as the most effective drug for LID treatment (2). Although the efficacy of amantadine has been proved to be long-lasting and remarkable, its use might induce/exacerbate

unacceptable hallucinations and also is contraindicated in patients with end-stage renal disease (3). Discontinuation of this drug is even associated with a significant risk of worsening dyskinesias (3). These undesirable effects limited the long-term use of amantadine. Several other chemicals targeting adenosine, adrenergic, glutamatergic, and serotonergic receptors have significantly decreased dyskinesias in animal models but not in parkinsonian patients (3). For patients refractory to medical management, neurosurgical approaches are also the procedure of choice. Among them, deep brain stimulation has been widely studied and recommended as one priority procedure for LID patients who need surgery. However, deep brain stimulation costs much, needs regular follow-up appointments over several years, and bears a danger of possible adverse effects after electrode placement (4). Surgical ablation of the globus pallidus has been reported to have remarkable efficacy in treating contralateral dyskinetic symptoms, while its efficacy is more petite than bilateral subthalamic nucleus deep brain stimulation in one case of a randomized controlled trial (4). A new minimally invasive approach using magnetic resonance-guided focused ultrasound to ablate globus pallidus has only been shown to improve dyskinesia in a case report (4).

In contrast, another non-invasive procedure, transcranial magnetic stimulation (TMS), has been applied to treat LID since 2005 (5) and has shown some benefits to a certain extent in several studies. TMS might be a promising neuromodulation skill to improve LID. The purpose of the present review is to discuss the main points of TMS in the management of LID and related mechanisms to allow for a better understanding of its potential uses.

AN OUTLINE FOR STUDIES CONCERNING TRANSCRANIAL MAGNETIC STIMULATION IN THE MANAGEMENT OF LID

Studies Utilizing Repetitive Transcranial Magnetic Stimulation

A pilot study subjected 8 PD patients with LID to 1 day of 15-min, low-frequency (1 Hz) rTMS (LF-rTMS) over the supplementary motor area (SMA) during apomorphine infusion (5). Mean (average of two raters) dyskinesia was significantly lower immediately and 15 min after the LF-rTMS sessions but not 30 min afterward (5). Brusa et al. conducted the same LF-rTMS on 10 PD patients with LID over SMA after levodopa intake (6). Unlike the pilot study, besides 15-min, single-day stimulation, this study also observed the effect of repeated, 5-day stimulation (6). This study found that mean (average of two raters) dyskinesia were significantly lower 15 and 30 min but not 45 and 60 min after the single-day and 5-day LF-rTMS sessions (6). Also, both single- and multiple-session LF-rTMS increased dyskinesia onset latency to the same degree comparing with sham control and no rTMS condition (6).

A later study conducted a 10-day LF-rTMS protocol over the primary motor cortex (MC) for 6 PD patients with LID after levodopa intake (7). Peak (during peak ON) and mean (average of early ON, peak ON, and late ON) dyskinesia were significantly lower for up to 1 day but not 2 weeks, whereas cortical excitability remained no change for all these time points (7). Although this study did not conduct sham control, we still could make some preliminary conclusions from it. Firstly, alterations of cortical excitability might not be the only mechanism involving the efficiency of LF-rTMS since cortical excitability did not correlate with the observed improvements in LID in this study. Secondly, more prolonged stimulation after-effects could be attained by extending stimulation days appropriately, such as 10 days rather than only 5 days. Positive relations between longer-lasting reduction of LID and longer sessions could be affirmed if further studies could apply longer-session LF-rTMS, such as a 3-week or even 4-week course.

A sham-controlled study later applied 4 consecutive days of LF-rTMS on 10 PD patients with LID during levodopa intake (8). In this study, a single session per day was increased from the previous 15 to 32 min (8). One-day reduction of LID severity was observed (8). However, it was a pity that this study did not record when the efficacy of LF-rTMS disappeared. Comparing with the outcome from Wagle-Shukla et al. (7) this finding suggests prolonged after-effects might also be obtained by increasing daily stimulation duration besides stimulation days (8). Also, this study firstly found that the major effect of LF-rTMS on LID improvement was on dystonia subscores (8).

Sayin et al. performed 10 consecutive days (30 min daily) of LF-rTMS over SMA on 17 PD patients with LID during levodopa intake (9). The study replicated 1 day of alleviation for LID, but the efficacy disappeared up to 120 min on the second day (9). Since this is a parallel sham controlled study, discrepancies of baseline dyskinesia severity between two groups might bring bias to outcomes (9). All aforementioned studies showed LF-rTMS had beneficial effects on LID improvement.

However, a later study showed adverse outcomes both after single-session and 5-day-multiple-session LF-rTMS (10). This was the first study to use two separate coils on bilateral MC; such an unexpected outcome might result from an offset of bilateral stimulation (10). It is speculated that a positive ipsilateral effect could be counterbalanced by a subsequent contralateral LF-rTMS session influencing more distant areas because previous studies have shown LF-rTMS ability to induce changes in areas distant from the stimulated area (11).

Lohse et al. firstly applied LF-rTMS over the pre-supplementary motor area (pre-SMA) on 17 PD patients with LID before levodopa intake (12). They found LF-rTMS utilization could help improve LID symptoms transiently (12).

Abbreviations: PD, Parkinson's disease; LID, levodopa-induced dyskinesia; TMS, transcranial magnetic stimulation; rTMS, repetitive TMS; HF-rTMS, high frequency rTMS; LF-rTMS, low frequency rTMS; TBS, theta burst stimulation; cTBS, continuous TBS; iTBS, intermittent TBS; MC, primary motor cortex; SMA, supplementary motor area; preSMA, pre-supplementary motor area; DLPFC, dorsolateral prefrontal cortex; IFC, inferior frontal cortex; SMA, supplementary motor area; SICI, short-interval intracortical inhibitions; LICI, long-latency intracortical inhibition; ICF, intracortical facilitation; SICF, short-interval intracortical facilitation; BDNF, brain-derived neurotrophic factor; GDNF, glial cell line-derived neurotrophic factor; LTP, long-term potentiation; MSO, maximum stimulator output; CFC, cross-frequency coupling; GABA, γ-Aminobutyric acid.

TABLE 1 | Overview of inhibitory TMS (LF rTMS/cTBS) for the treatment of LID in PD.

Sample target	Coil design	TMS administration	Degree and scale of dyskinesia	Findings	References
8	Bilateral 1 central coil	Single session (15 min* 1 day) of 1 Hz	Disabling	Improvement for	(5)
SMA	Sham controlled	LF-rTMS during apomorphine infusion	AIMS	15 min	
10	Bilateral 1 central coil	Single session (15 min* 1 day) of 1 Hz	Disabling	Improvement for	(6)
SMA	Sham controlled	LF-rTMS after levodopa intake	AIMS	30 min	
10	Bilateral 1 central coil	Multiple sessions (15 min* 5 days) of	Disabling	improvement for	
SMA	Sham controlled	1 Hz LF-rTMS after levodopa intake	AIMS	30 min	
6	Unilateral no coil type	Multiple sessions (15 min* 10 days)	Bothersome	Improvement for	(7)
MC	No sham	of 1 Hz LF-rTMS after levodopa intake	CAPSIT-PD	1 day	
10	Unilateral 1 central coil	Single session (40 s* 1 day) of cTBS	Disabling	Improvement for	(14)
Cerebellum	Sham controlled	After levodopa intake	CAPSIT-PD	45 min	
20	Bilateral 1 central coil	Multiple sessions (40 s* 10 days) of cTBS	Disabling	Improvement for	
Cerebellum	Sham controlled	After levodopa intake	CAPSIT-PD	4 weeks	
10	Unilateral no coil type	Multiple sessions (32 min* 4 days) of	Obvious	Improvement for	(8)
MC	Sham controlled	1 Hz LF-rTMS during levodopa intake	CDRS	1 day	
8	Bilateral 1 central coil	Multiple sessions (40 s* 5 days) of cTBS	Disabling	Improvement for	(15)
Cerebellum	Sham controlled	After levodopa intake	CAPSIT-PD	45 min	
17	Bilateral 1 central coil	Multiple sessions (30 min* 10 days) of	Disabling	Improvement for	(9)
SMA	Sham controlled	1 Hz LF-rTMS during levodopa intake	AIMS	1 day	
8	Unilateral no coil type	Single session (40 s* 1 day) of cTBS	Bothersome	Improvement for	(16)
IFC	Sham controlled	After levodopa intake	AIMS	30 min	
8	Unilateral no coil type	Single session (40 s* 1 day) of cTBS	Bothersome	No change	
MC	Sham controlled	After levodopa intake	AIMS		
9	Bilateral 2 separate coils	Single session (16 min* 1 day) of 1 Hz	Bothersome	No change	(10)
MC	Sham controlled	LF-rTMS during levodopa intake	AIMS,UPDRSIV,PDYS-26		
6	Bilateral 2 separate coils	Multiple sessions (16 min* 5 days) of 1 Hz	Bothersome	No change	
MC	Sham controlled	1 Hz LF-rTMS during levodopa intake	AIMS,UPDRSIV,PDYS-26		
10	1 central coil	Single session (40 s* 1 day) of cTBS	Disabling	Improvement for	(17)
IFC	Sham controlled	After levodopa intake	AIMS	No exact time	
11	1 central coil	Single session (40 s* 1 day) of cTBS	Bothersome	Improvement for	(18)
Cerebellum	Sham controlled	After levodopa intake	CAPSIT-PD	60 min	
17	1 central coil	Single session (30 min* 1 day) of 1 Hz	Obvious	Improvement for	(12)
preSMA	Sham controlled	LF-rTMS before levodopa intake	UDysRS	No exact time	
17	Unilateral 1 central coil	Single session (16 min* 1 day) of	No mention	No change	(13)
preSMA	Sham controlled	1 Hz LF-rTMS before levodopa intake	AIMS		

PD, Parkinson's disease; LF rTMS, low-frequency repetitive transcranial magnetic stimulation; cTBS, continuous theta-burst stimulation; LID, levodopa-induced dyskinesia; SMA, supplementary motor area; MC, motor cortex; IFC, Inferior Frontal Cortex; AIMS, Abnormal Involuntary Movement Scale; mAIMS, Modified Abnormal Involuntary Movement Scale; CAPSIT-PD, Core Assessment Program for Surgical Interventional Therapies; LF-ADLS, Lang-Fahn Activities of Daily Living Scale; CDRS, Clinical Dyskinesia Rating Scale; PDYS-26, dyskinesia scale; VAS, Visual Analog Scale; UPDRS, Unified PD Rating Scale; UDysRS, Unified Dyskinesia Rating Scale.

This was also the sole study regarding the relationship between stimulation intensity of LF-rTMS and its clinical impact on LID. Stimulation intensity is documented as the percentage of maximum stimulator output (MSO). With MSO of LF-rTMS increasing up to 60%, Lohse et al. found a significant linear correlation between stimulation intensity and individual prolongation of the time to onset of dyskinesia after levodopa intake (12). They also found a similar trend between MSO and individual reduction in dyskinesia severity, but it did not reach statistical significance (12). Recently, Flamez et al. conducted single-session LF-rTMS (16 min daily) over pre-SMA on 17 PD patients with LID before levodopa intake but failed to replicate the therapeutic effect on LID (13).

Overall, most of these studies validated the short-term beneficial effect of LF-rTMS, but long-term therapeutic effects still needed to be explored. Among these studies, no adverse

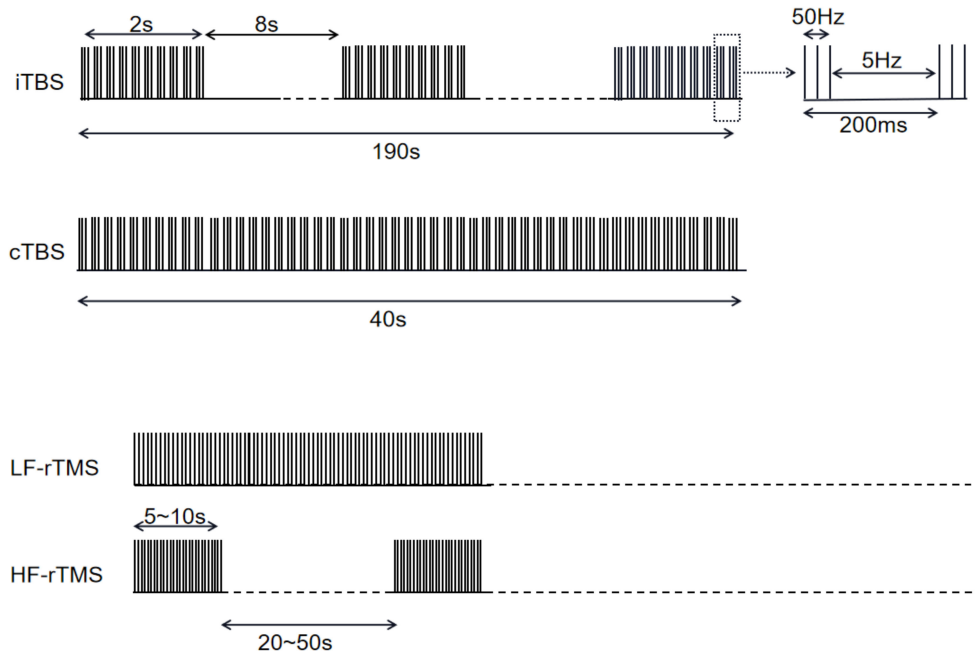

FIGURE 1 | Overview of stimulation modes in studies mentioned in **Tables 1**, **2**.

event was reported. Moreover, these beneficial effects are less likely to be induced by placebo effects. LF-rTMS seems to be a potential approach to treat LID. However, the conclusions from these studies are limited by the small sample sizes used. Also, differences in pharmacological status, dyskinesia assessment scales, and stimulation parameters (**Table 1**, **Figures 1**, **2**) can confound outcomes of these LF-rTMS studies. Thus, once a mode of LF-rTMS with definite, reproducible, and sustained improvement on LID is established, LF-rTMS might be one of the most valuable approaches to alleviate LID in clinical settings.

On the other hand, it was shown that all high frequency (5 and 10 Hz) rTMS (HF-rTMS) studies (**Table 2**, **Figure 1**) have no effect on LID.

Studies Utilizing Theta Burst Stimulation

Unlike rTMS, the protocol of TBS is comparatively more consistent among studies (**Table 1**, **Figures 1**, **2**). For all five studies utilizing continuous TBS (cTBS), cTBS consists of three-pulse bursts at 50 Hz repeated every 200 ms for 40 s (20) and was administered after levodopa intake.

In Koch's study, they firstly applied single-session cTBS on 10 PD patients with LID over the cerebellum, and a 45-min reduction was observed (14). In this study, a 10-day course of cTBS was further conducted and induced persistent clinical beneficial effects up to 4 weeks (14). However, a later study applied a 5-day course of cTBS on 8 PD patients with LID over the cerebellum only reduced LID up to 45 min (15).

A study applied single-session cTBS over the inferior frontal cortex (IFC) and MC on 8 PD patients with LID, respectively (16). Stimulation over the right IFC induced improvement of LID only up to 30 min, while stimulation over MC did not exhibit any change (16). Although efficacy duration was not mentioned, Ponza et al. also observed the beneficial effect of cTBS on LID symptoms after single-session stimulation over the right IFC (17). A recent study targeting cerebellum also displayed 60-min alleviation for LID after cTBS stimulation (18).

Among these cTBS studies, two have mentioned specific stimulation intensity. In Koch's and Cerasa's studies (14, 16), 46.2 $\pm$ 8.5% MSO applied over the right IFC and cerebellum alleviated LID symptoms, while the same stimulation intensity over MC failed to improve LID symptoms. Since Cerasa et al. did not conduct further study to see whether higher stimulation intensity over MC would change the result or not, it could be early to deny the role of stimulation intensity for cTBS efficacy.

Like LF-rTMS, the short-term benefits of cTBS have been corroborated in several studies and are patient-tolerable. Although a remarkably longer after effect of cTBS than of LF-rTMS was exhibited only in one study, such prolonged effect did not replicate in other studies.

When it comes to intermittent theta-burst stimulation (iTBS) mode applied on IFC or MC (**Table 2**, **Figure 1**), no change has occurred to LID symptoms at both regions.

AN OUTLINE FOR STIMULATION TARGETS IN TMS PROTOCOLS FROM THE STUDIES ABOVE

Brain Regions in Motor Basal Ganglia Loop

MC is a crucial brain region involving in the development of LID. Alterations of potentials recorded from MC shed light on

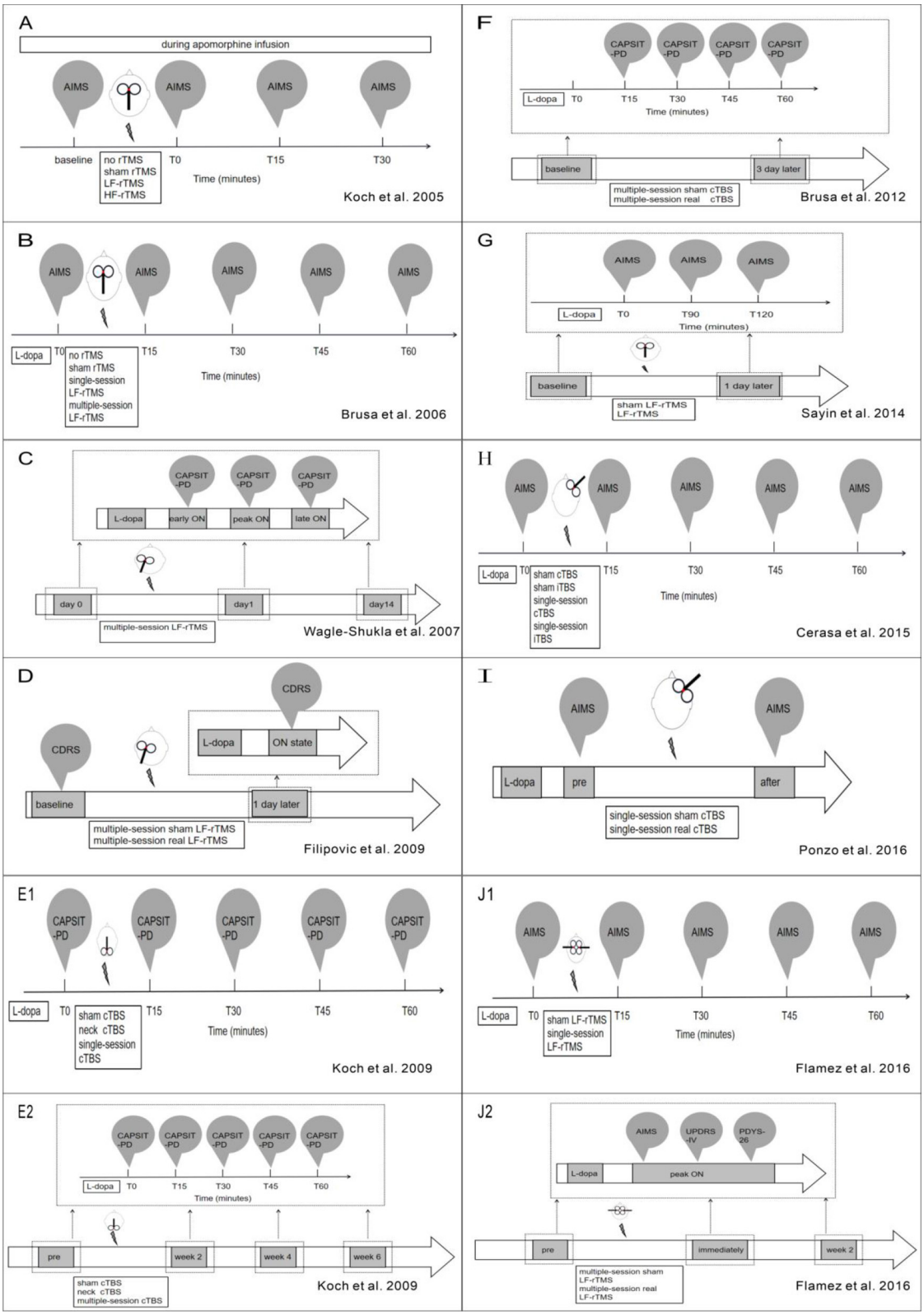

FIGURE 2 | *(continued)*

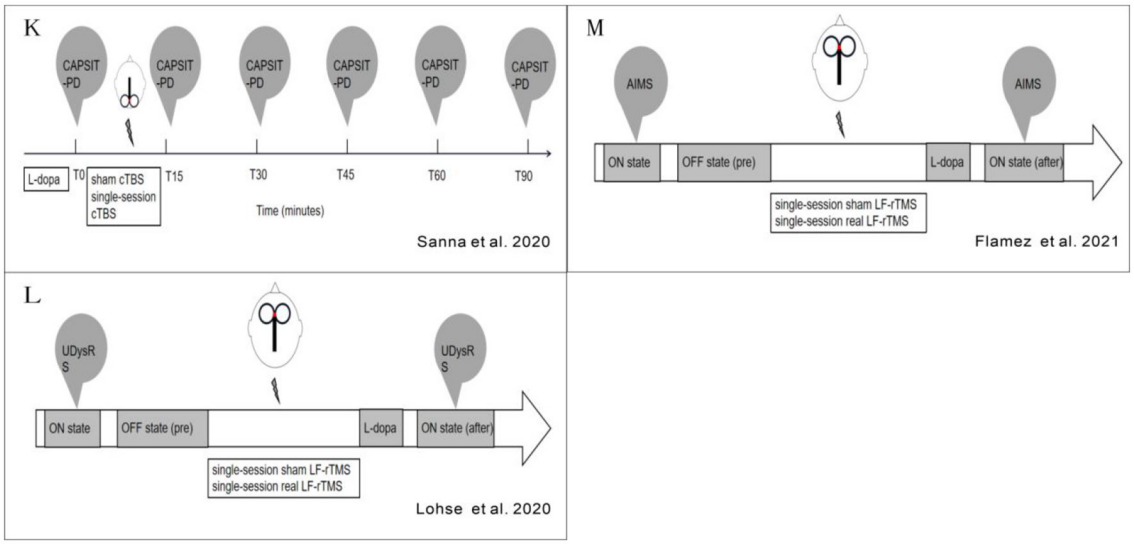

FIGURE 2 | (A–L) Refers to overview of stimulation workflow in studies mentioned in **Table 1**.

TABLE 2 | Overview of excitatory TMS (HF rTMS/iTBS) for the treatment of LID in PD.

Sample target	Coil design	TMS administration	Degree and scale of dyskinesia	Findings	References
8	Bilateral 1 central coil	Single session (15 min* 1 day) of 5 Hz	Disabling	No change	(5)
SMA	Sham controlled	HF-rTMS during apomorphine Infusion	AIMS		
4	Unilateral 1 central coil	Multiple sessions (no exact time* 5 days)	No mention	No change	(19)
DLPFC	Sham controlled	of 10 Hz HF-rTMS during levodopa intake	UPDRSIV		
4	Unilateral 1 central coil	Multiple sessions (no exact time* 5 days)	No mention	No change	
MC	Sham controlled	of 10 Hz HF-rTMS during levodopa intake	UPDRSIV		
8	Unilateral no coil type	Single session (40 s* 1 day) of iTBS	Bothersome	No change	(16)
IFC	Sham controlled	After levodopa intake	AIMS		
8	Unilateral no coil type	Single session (40 s* 1 day) of iTBS	Bothersome	No change	
MC	Cross-over sham controlled	After levodopa intake	AIMS		

PD, Parkinson's disease; HF rTMS, high-frequency repetitive transcranial magnetic stimulation; iTBS, intermittent TBS; LID, levodopa-induced dyskinesia; SMA, supplementary motor area; MC, motor cortex; DLPFC, left dorsolateral prefrontal cortex; AIMS, Abnormal Involuntary Movement Scale; UPDRS, Unified PD Rating Scale.

possible mechanisms underlying the benefits of LF-rTMS and cTBS for LID.

Short-interval intracortical inhibitions (SICI) and long-latency intracortical inhibition (LICI) reflect suppression of MC excitability (21, 22). In off therapy, SICI and LICI were decreased in PD patients with and without LID (23). Unlike PD patients without LID, administration of levodopa could not reverse decreased SICI and LICI in PD patients with LID (23). In off therapy, γ-Aminobutyric acid (GABAergic) agonist increased SICI in PD patients (24). Administration of GABAergic agonist could also alleviate LID (25). It is believed that SICI is likely to be mediated by GABA-A-ergic receptors (26) and LICI by GABA-B-ergic receptors (27, 28).

On the contrary, intracortical facilitation (ICF) and short-interval intracortical facilitation (SICF) reflect the facilitation of MC excitability (21, 29). Regardless of drug condition, ICF was found to decrease or remain normal in PD patients with LID (23, 30). Unlike ICF in dyskinetic patients, SICF kept increased in off and on the state (30). Such increase was positively correlated with the severity of LID (30). Increased SICF in LID patients could be alleviated by anti-glutamatergic drugs (30). Improvement of LID did not come with restoration of SICF (30), which suggests additional pathophysiological mechanisms might contribute to LID.

Findings of the two opposite types of potentials both indicated overexcitability of MC renders occurrence of LID. HF-rTMS (31) and iTBS (20) increases cortical excitability, whereas LF-rTMS (31, 32) and cTBS (20) decreases cortical excitability, which conforms to their opposite effects on LID symptoms. Apart from alterations of these potentials, dendritic spines in intratelencephalic-type corticostriatal neurons in MC became enlarged of rats with LID (33).

Although SMA did not show any structural modification in PD patients with LID (34), neuroimaging has linked overactive

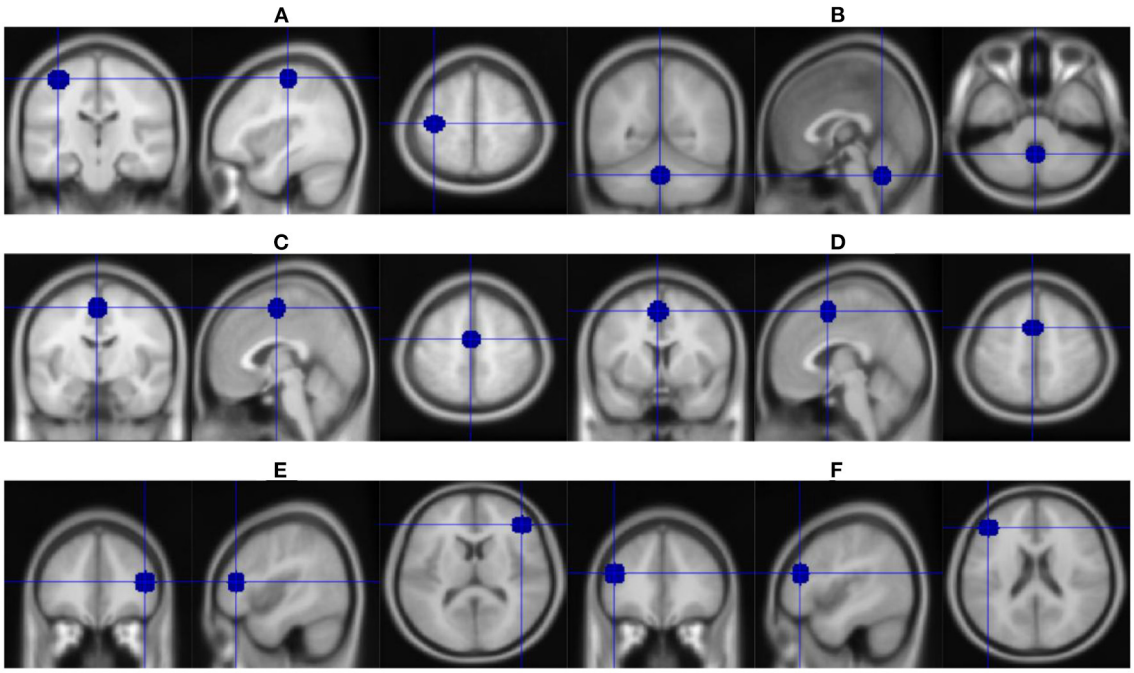

FIGURE 3 | Overview of stimulation brain regions in studies mentioned in **Tables 1**, **2**. **(A)** Left motor cortex. **(B)** Cerebellum. **(C)** Supplementary motor area. **(D)** Pre-supplementary motor area. **(E)** Right inferior frontal cortex. **(F)** Left dorsolateral prefrontal cortex.

SMA with the occurrence of LID (35, 36). Indeed, inhibitory LF-rTMS over SMA improved LID symptoms (5, 6, 9).

Brain Regions in Associative and Limbic Basal Ganglia Loop

Voxel based morphometry reveals increased gray matter volume of the bilateral IFC in dyskinetic patients (34). Right IFC engages in suppressing an already initiated manual response (37). One study further revealed dyskinetic PD patients have a weaker inhibitory interaction between the right IFC and contralateral MC (17). This finding conforms with beneficial effects of inhibitory cTBS over right IFC on LID (17). Another study revealed that connectivity of the right IFC with the left MC was decreased in patients with LID (16). Nevertheless, inhibitory cTBS over right IFC improved LID symptoms in this study as well (16). Authors speculated that the increased communication between the right IFC and the putamen observed in this study in patients with LID might interfere with the motor inhibition network (16).

Task-based functional magnetic resonance imaging revealed activation of pre-SMA after intake of levodopa in LID patients (38). The pre-SMA has been implicated in both the suppression and initiation of movements (39). This might partly explain the contradictory outcomes of two LF-rTMS studies over pre-SMA on LID (12, 13).

Activation of the dorsolateral prefrontal cortex (DLPFC) was also observed in PD patients with LID (40). However, it was bewildering that HF-rTMS Stimulation of the left DLPFC induced a significant MC depression (19). Moreover, such MC depression did not reach a significant reduction of LID symptoms (19).

Cerebellum

Increased metabolic activity in the dentate nucleus (15) and in the red nucleus (41) indicated cerebellar involvement in the development of LID. Further studies revealed cerebellar-cortical interaction in dyskinetic patients. After delivery of inhibitory cTBS over cerebellum, alleviated LID symptoms concurrently accompanied by enhancement of MC plasticity (42). Also resting-state functional connectivity was found to increase between cerebellum and left IFC: the greater the enhancement of cerebellar-IFC functional connectivity, the shorter was the latency of dyskinesia onset (43).

Since many circuits take part in the occurrence of LID, identification of the critical brain region (**Figure 3**) involved in all LID mechanisms as the stimulation target or combination of different regions might prolong treatment efficacy.

THE THERAPEUTIC MECHANISM OF TMS IN THE CLINICAL MANAGEMENT OF LID

Brain Connectivity

Electrophysiology and functional imaging are helpful to explore the role of brain connectivity in the occurrence of LID. Cross-frequency coupling (CFC) refers to a phenomenon that oscillations recorded by microelectrodes in various brain regions interact with each other (44). Such CFC is presented as a quantitative value to show inter-brain synchrony (44). It is

revealed that CFC between MC and dorsolateral striatum was decreased in LID rats (44). After delivery of HF-rTMS, hippocampus-prefrontal CFC in patients with major depression was enhanced (45). How LF-rTMS and cTBS alleviate LID symptoms by the change of CFC remains unknown.

Neuroplasticity

MC lacks long-term potentiation (LTP) -like synaptic plasticity when levodopa is not being administered (46). LTP can be reversed in non-dyskinesia patients by administering levodopa (46). In LID patients, this therapeutic option may fail to reverse LTP (46). Deficiency of depotentiation exists in PD patients with LID (47). Theta and gamma wave patterns recorded by electroencephalography were found to be potent inducers of neuroplasticity (48). HF-rTMS was found to induce theta wave, and cTBS was found to induce theta and gamma in physiological conditions (49), which shows the capability of TMS to change neuroplasticity. Nevertheless, how rTMS-evoked neuroplasticity reverses dysfunctional neuroplasticity (that refers to lack of depotentiation) in the occurrence of LID and shows beneficial improvement on LID remains unknown.

Neurotransmitter and Receptor Modulation

Imbalanced neurotransmitters are the major pathological mechanisms for LID. Studies have explored the roles of neurotransmitters and their receptors in TMS. Elevated GABA receptor levels have been found in postmortem samples of LID patients (50). The N-methyl-D-aspartate receptor antagonist, dextrorphan hydrochloride, has been shown to improve LID clinical outcomes (51). HF-rTMS increases the expression of amino acids (taurine, aspartate, and serine) and dopamine in the hypothalamic paraventricular nucleus and dorsal hippocampus, respectively, and decreases expression of arginine vasopressin in the hypothalamic paraventricular nucleus in healthy brains of rats and mice (52). LF-rTMS was, however, not capable of exhibiting any changes in neurotransmitters (53). Both LF-rTMS (54) and HF-rTMS (55) bring about an imbalance between glutamate and glutamine in healthy human brains. It has been shown that cTBS decreases vesicular glutamate transporters one and increases plasmatic glutamate transporters one in healthy rat brains (56). Upregulation of glutamate transporter and GABA transporter mRNAs have been reported in TMS-treated mice (57). Studies have confirmed the pivotal roles of glutamatergic and GABAergic neurotransmitters during TBS (58). More studies are needed to evaluate the role of neurotransmitters and receptors in LID patients during TMS therapy (59).

Neurorestoration

Administration of glial cell line-derived neurotrophic factor (GDNF) improved LID both in patients and marmosets (60, 61). GDNF-mediated neurorestoration was revealed to selectively induce sprouting of dopaminergic cells without affecting GABAergic or serotonergic cells (62). In 50-sample animal research, rTMS alleviated LID with remarkably increased GDNF (63). However, cTBS alleviate LID with decreased brain-derived neurotrophic factor (BDNF) levels (18). Over-expression of BDNF was found to induce striatal serotonin fiber sprouting and lead to LID in 6-OHDA-lesioned rats (64). These findings suggest TMS might alleviate LID by sparing dopaminergic innervation and promoting serotonergic denervation. It is intriguing to note that different BDNF genotypes have a variable response to cTBS treatment (18). Val66Val carriers exhibited improvement of LID symptoms with decreased BDNF level after receiving cTBS treatment, while the Val66Met group showed no change for LID symptoms and the amount of BDNF as well (18).

Blood Flow and Glucose Metabolism

Blood flow and glucose metabolism dissociation in subcortical regions, especially putamen, has been found implicated in the occurrence of LID (65, 66). Blood flow increased while glucose metabolism decreased in the putamen, be it in the medicated or unmedicated state (65, 66). Bilateral cerebellum cTBS alleviates LID by reducing [18F]-fluorodeoxyglucose positron emission tomography metabolism in bilateral cerebellar hemispheres and dentate nucleus (15). This study suggests that metabolic changes might mediate the efficacy of TMS (15). Till now, none studies have unraveled the relation of blood flow with TMS in the management of LID. Nevertheless, many studies indeed identified blood flow alteration after TMS in a wide range of brain regions and various diseases. Blood flow and glucose metabolism may imply some beneficial effects of TMS on LID.

PROSPECTS

To sum up, TMS has a neuromodulatory potential that might be successfully used in the clinical management of LID. However, more large randomized controlled studies of TMS application in LID are needed to understand better the underlying mechanisms, the efficacy evaluation, and optimization of stimulation protocols.

AUTHOR CONTRIBUTIONS

YW: writing—original draft preparation. X-bC: conceptualization. W-qZ, HZ, X-qZ, X-mY, CC, J-lW, and X-mY: resources. YX: writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

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Clinical Efficacy and Dosing of Vibrotactile Coordinated Reset Stimulation in Motor and Non-motor Symptoms of Parkinson's Disease: A Study Protocol

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Enhanced neuronal synchronization of the subthalamic nucleus (STN) is commonly found in PD patients and corresponds to decreased motor ability. Coordinated reset (CR) was developed to decouple synchronized states causing long lasting desynchronization of neural networks. Vibrotactile CR stimulation (vCR) was developed as non-invasive therapeutic that delivers gentle vibrations to the fingertips. A previous study has shown that vCR can desynchronize abnormal brain rhythms within the sensorimotor cortex of PD patients, corresponding to sustained motor relief after 3 months of daily treatment. To further develop vCR, we created a protocol that has two phases. Study 1, a double blinded randomized sham-controlled study, is designed to address motor and non-motor symptoms, sensorimotor integration, and potential calibration methods. Study 2 examines dosing effects of vCR using a remote study design. In Study 1, we will perform a 7-month double-blind sham-controlled study including 30 PD patients randomly placed into an active vCR or inactive (sham) vCR condition. Patients will receive stimulation for 4 h a day in 2-h blocks for 6 months followed by a 1-month pause in stimulation to assess long lasting effects. Our primary outcome measure is the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III off medication after 6 months of treatment. Secondary measures include a freezing of gait (FOG) questionnaire, objective motor evaluations, sensorimotor electroencephalography (EEG) results, a vibratory temporal discrimination task (VTDT), non-motor symptom evaluations/tests such as sleep, smell, speech, quality of life measurements and Levodopa Equivalent Daily Dose (LEDD). Patients will be evaluated at baseline, 3, 6, and 7 months. In the second, unblinded study phase (Study 2), all patients will be given the option to receive active vCR stimulation at a reduced dose for an additional 6 months remotely. The remote MDS-UPDRS part III off medication will be our primary outcome measure. Secondary measures include sleep,

quality of life, objective motor evaluations, FOG and LEDD. Patients will be evaluated in the same time periods as the first study. Results from this study will provide clinical efficacy of vCR and help validate our investigational vibrotactile device for the purpose of obtaining FDA clearance.

Clinical Trial Registration: ClinicalTrials.gov, identifier: NCT04877015.

Keywords: coordinated reset, vibrotactile stimulation, Parkinson's disease, study protocol, sensorimotor, non-motor symptoms, non-invasive stimulation

INTRODUCTION

More than 6.1 million people suffer from Parkinson's Disease (PD) worldwide (1), making it the most widespread neurodegenerative disorder second to Alzheimer's Disease (2). Dopamine precursors, such as levodopa, are used in medication to treat PD and are considered the gold standard in improving motor function (3). However, given that PD is a neurodegenerative disease resulting in patients' symptoms worsening over time, dopaminergic therapy can only go so far before patients increase their medication or no longer feel the same therapeutic benefit (3, 4). Furthermore, medications that increase dopaminergic transmission can have unwanted side effects, such as vomiting, hypotension, delusions, and dyskinesia (5). In addition, dopaminergic induced psychosis is often reported in PD patients, especially those in the advanced stages of the disease who experience cognitive impairment (6). In the later stages of PD, patients may undergo Deep Brain Stimulation (DBS), which has demonstrated to be more effective than medication alone (7). However, the invasiveness of the procedure and related potential surgical side effects (e.g., hemorrhage) (8) as well as side effects of the chronic stimulation, considered as DBS-induced movement disorders (9), make it less appealing to patients. For instance, different types of dyskinesias, blepharospasm, and apraxia of eyelid opening were observed with DBS delivered to the subthalamic nucleus (STN), whereas hypokinesia and freezing of gait were described with DBS of the globus pallidus internus (GPi) (9). Furthermore, DBS delivered to standard targets for PD, such as the STN or GPi, is less effective in treating gait, balance (10), and dysarthrophonia (11). Even in conjunction with medication, traditional high frequency DBS only provides temporary motor improvement, with symptoms returning almost immediately after cessation of stimulation (12). The development of non-invasive therapies that improve PD symptoms and potentially change pathological PD brain states in a way which slows, or reverses disease progression is much needed and essential in overcoming the limitations of the two most common types of PD treatments (13).

Abnormal neuronal synchrony of beta band is often found within the STN of PD patients (14), with decreases in this band correlating with improved motor capability (15). Based on this finding, we developed vibrotactile Coordinated Reset (vCR) which is a non-invasive treatment that delivers weak, non-painful random vibrations to the fingertips of patients (16). This type of therapy is based on extensive computational research done on the desynchronizing effects produced by CR (17–19). CR stimulation aims at disrupting neuronal synchronization by delivering phase resetting stimuli, typically periodically in time, separated by equidistant time differences given by T_s/N_s, where T_s is the duration of a stimulation cycle, and N_s is the number of active stimulation sites (20). Computationally, it was shown that CR-induced desynchronization may cause a reduction of the rate of neuronal coincidences, and in turn, a decrease of the strength of plastic synapses, ultimately shifting neural networks from stable, synchronized, strongly synaptically-connected states to stable desynchronized states with weak connectivity (18–21). For this, CR uses spike-timing-dependent plasticity (STDP), a fundamental learning mechanism that adapts the strength of synapses based on the relative timing of their pre- and postsynaptic spikes or bursts (22). Furthermore, in this study, we consider a vCR pattern with moderate stimulus time jitter. This is motivated by a previous computational study introducing spatial and temporal jitter (21). To this end, random reset (RR) stimulation was administered to a network of leaky integrate-and-fire (LIF) neurons with STDP and electrical model stimuli (21). It was shown that RR stimulation, characterized by adding spatial and temporal noise to the mechanism of CR stimulation, may lead to more robust long-term desynchronizing effects, that are less dependent on the detuning of the mean inter-stimulus interval in comparison with the dominant frequency of the abnormally synchronized neuronal rhythm (21).

In a previous study, monkeys injected with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) received brief, high frequency electrical pulse trains that were administered to the STN (CR-DBS) for 2 h on five consecutive days (23). Acute and sustained motor improvement lasting for several weeks was observed (23). This study was then performed with PD patients who received CR-DBS administered to the STN for 4 h a day for three consecutive days. Reduced beta band synchronization occurred, which correlated with a significant improvement of motor ability (24).

Similar findings have also been documented using vibration as a CR stimulus (17, 25). The first-in-human vCR study was conducted with five idiopathic PD patients, who received vCR stimulation for 4 h a day over three consecutive days (25). Patients exhibited improvements in gait and bradykinesia both during stimulation and after a 1-month pause in stimulation. Vibration by itself is known to increase motor responsiveness (26) and activation of the sensorimotor cortex (27) which corresponds to a decrease in cortical alpha and beta power (27, 28). In our most recent work, we further optimized vCR stimulation patterns and parameters which led to significant

improvements in motor ability in two PD studies (17). Study 1 consisted of a 3-month vCR intervention, in which patients received stimulation for 4 h a day. At baseline and after 3 months of vCR therapy, we examined motor changes in the Movement Disorders Society Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS) (29) and recorded electroencephalography (EEG) beta band activity while patents were at rest (17). After 3 months of daily vCR treatment, PD patients off medication and at rest exhibited a cortical decrease in high beta band (21–30 Hz) power in the sensorimotor cortex compared to baseline (17). Additionally, patients showed significant improvements on the MDS-UPDRS III while off medication both acutely (after 4 h of stimulation at day one) and cumulatively (after 3 months of daily vCR therapy) (17). Furthermore, by the 3rd month, patients were able to decrease their Parkinson's medication by an overall 7.82% (17). Study 2 examined the cumulative motor effects in a three-patient case study in which patients received daily vCR stimulation for 6+ months (17). MDS-UPDRS assessments were performed every 3 months while off medication. All patients showed a significant improvement in their motor ability (17). Additionally, of the three patients, one maintained their current medication regimen pre-study, while the other two reduced their medication (10.86 and 66%, respectively) by the end of the study (17). In one patient, we planned a 1-month pause in stimulation after 6 months of therapy. Results showed no considerable differences in motor ability. Additionally, we reduced this patient's daily vCR sessions (4 h) to 2 h three times a week after the 7-month follow-up. The patient continued to show significant motor improvements for the remainder of the study (3 additional months) (17).

Taken together, we believe that vCR has the potential to drastically improve motor abilities during and post treatment, decrease patient medication intake and potentially slow disease progression in a way that is non-invasive and presents little to no side effects. The current study protocol: *Vibrotactile coordinated reset: a non-invasive treatment for Parkinson's disease,* aims to understand the therapeutic benefits of vCR in a larger sample size, test against a dedicated sham pattern, study vCR effects on not only motor outcomes, but voice, speech, sleep and other non-motor symptoms, study vCRs long-lasting effects, and finally a vCR dosing regimen all within a 14-month clinical study protocol. Together, results from this study will demonstrate clinical efficacy of our vCR stimulation pattern and vibrotactile device for the purpose of acquiring Food and Drug administration (FDA) clearance.

METHODS AND ANALYSIS

Vibrotactile Coordinated Reset Therapy

Noisy vCR stimulation (see **Figure 1** for a schematic representation) was introduced by Pfeifer et al. (17). Vibratory stimuli are delivered at periodic times with a jitter that is uniformly distributed within the range of ±23.5% the inter-stimulus intervals. A vCR cycle comprises a sequence of four vibratory bursts delivered to each fingertip. The vCR sequence is randomly varied from one cycle to another. Three cycles with vCR stimulation ON are followed by two cycles with vCR turned OFF (3:2 ON–OFF CR). We apply bilateral noisy vCR in a mirrored manner, such that the right and left fingers two to five get coincidently activated, respectively. Vibration frequency is 250 Hz and duration of vibration bursts amounts to 100 ms. As in Pfeifer et al. (17) the CR frequency (f_{CR}), which is the CR sequence delivery rate, is 1.5 Hz. Accordingly, the length of a CR cycle is 667 ms. The duration of a single vCR session amounts to 2 h. To avoid patient unblinding, the parameters for the sham stimulation will be presented in our clinical results paper upon completion of this study.

Vibrotactile Device Description

The vibrotactile device is investigational and has not yet been cleared by the FDA for clinical use. The vibrotactile device is a mobile, battery-operated controller with wire-connected vibrotactile stimulators (tactors) fastened onto the fingertips of a custom glove (see **Figure 2**). The glove is fitted by trained clinical research coordinators during the baseline visit. Both sham and active vCR stimulation patterns were developed by the study's principal investigator and were tested together with Engineering Acoustic Incorporated (EAI). Stimulus patterns are loaded into the controller *via* secure digital (SD) cards. The controller is small enough to fit into a pocket or can be fastened to a belt (**Figure 2B**). The tactors (**Figures 2A,B**) are connected to a glove and are individually fastened to the fingertips *via* elastic Velcro bands. The tactors are connected to the controller (**Figure 2C**) and an Organic Light-Emitting Diode (OLED) screen displays information about battery status and the time left in the therapy session. The controller has a push button that can start, pause or turn off the device (**Figure 2D**). The controller logs patient therapy sessions and stores this information on the SD card. The research personnel uses the log information to verify that each patient is stimulating according to the stimulation protocol procedures. The controller has a charging port on its side (**Figure 2E**) and is charged with a micro-USB.

Patient Population

Patients will be screened and selected from the population of patients presenting with idiopathic PD who are routinely seen in the Stanford Neuroscience Clinic, referred from non-Stanford clinics or have found this study through clinicaltrials.gov. The principal investigator, designated movement disorders neurologist and research coordinators may introduce the study to potential candidates in-person at Stanford's Neuroscience Clinic. Additionally, clinical research coordinators may also contact potential candidates by phone or email after the referral. Patients allowed into the study will only be from the San Francisco Bay area.

Inclusion and Exclusion Criteria

Patients included in this trial will be between 45 and 85 years of age and have a diagnosis of idiopathic Parkinson's disease with Hoehn and Yahr Stages II–IV while on medication. Patients will need MDS-UPDRS III motor improvement ≥30% while on medication compared to while off medication and be on stabilized medication. Patients cannot have dopamine dysregulation syndrome or presence of other neurological

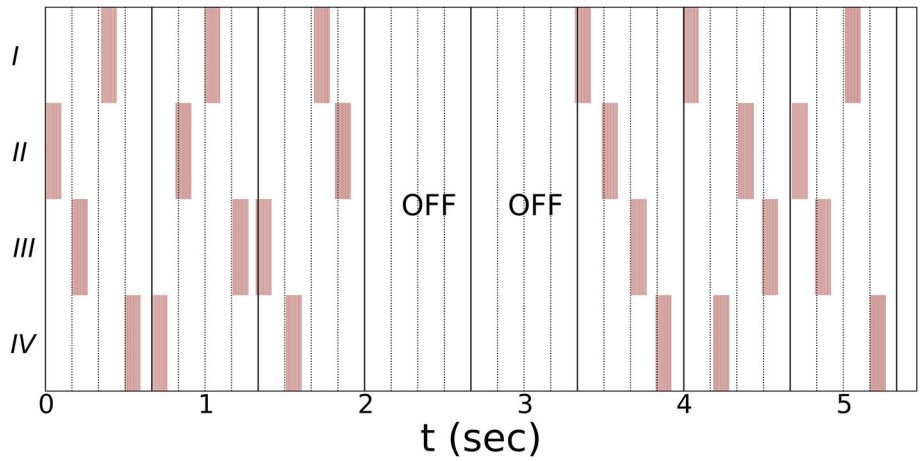

FIGURE 1 | Schematic illustration of the vCR stimulation using a three cycles ON: two cycles OFF pattern (17). Single vibratory bursts (highlighted by red bars) are delivered at periodic times subjected to a jitter that is uniformly distributed within the range of ±23.5% the inter-stimulus intervals. A vCR sequence comprises four subsequent vibratory bursts, delivered (on average) within one vCR cycle. Within one vCR sequence each fingertip (two through five) is activated exactly once. The CR frequency f_{CR}, i.e., the rate at which the CR sequences are delivered, is 1.5 Hz. Hence, the length of a CR cycle is 667 ms. Bilateral noisy vCR is administered in a mirrored manner to both hands, coincidently activating right and left fingers (two through five). Schematic shows the vCR pattern coincidently delivered to left and right hand. Vibration frequency is 250 Hz and duration of vibration bursts is 100 ms. The duration of a single vCR session is 2 h.

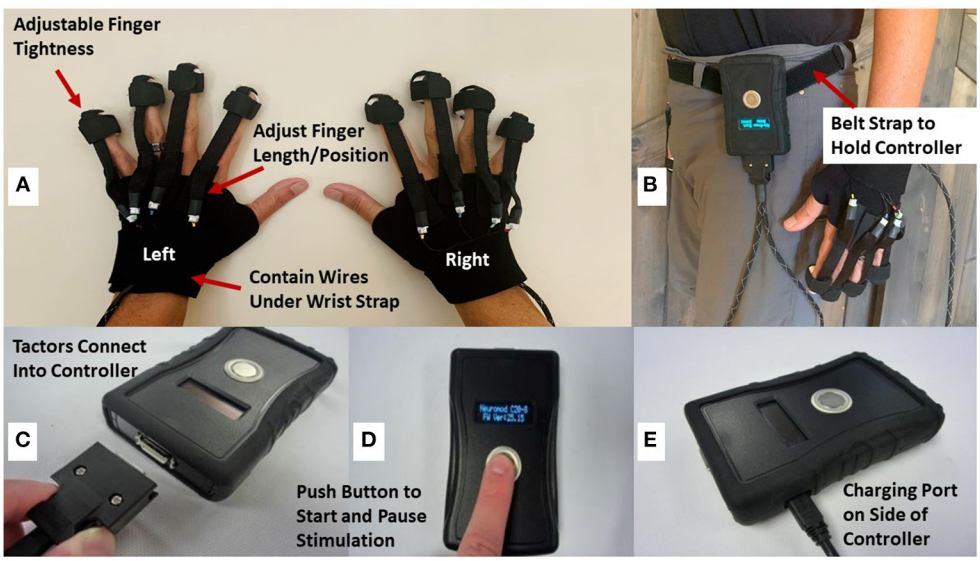

FIGURE 2 | Displays the vibrotactile wearable stimulator. **(A)** Displays the tactors and gloves that can be adjusted *via* Velcro straps for the finger pad or length of finger. **(B)** Depicts the controller being worn and fastened by a belt. **(C)** Displays the part of the controller in which the tactor ends plug into. **(D)** Displays the LCD screen which shows battery life and time remaining of stimulation. A push button turns on, pauses, and turns off the controller. **(E)** Displays the charging port of the controller which is charged with a micro-USB.

diseases such as major depression, dementia, attention deficit disorder, psychosis, or essential tremor. Patients cannot have a history of epilepsy, traumatic brain injury or brain surgery. Patients cannot have severe sensory abnormalities of the fingertips such as vibratory urticaria. Patients must clearly communicate with staff and speak English. Patients are excluded if they are currently on psychoactive or narcoleptic medications or are on medications that affect brain function or alter EEG recorded activity (i.e., anticonvulsants, ADHD, depression, or anxiety medication). Participation in this study requires that all patients do not participate in another drug, device, biologic, or intervention trial concurrently or within the preceding 30 days. Patients who are pregnant, breastfeeding, or trying to get pregnant during the duration of the study are excluded. Lastly, San Francisco Bay area residents may only be included in this study.

Pre-assessment Measures for Inclusion of Clinical Trial

Prior to on-site assessment measures, patients will receive a General Health Survey which includes questions regarding health history, inclusion/exclusion criteria and questions relating to dopamine dysregulation syndrome. If the patient is considered a good candidate, a trained staff neurologist, specialized in movement disorders, will verify idiopathic PD in potential patients at an on-site pre-study visit, four-eight weeks before the initial trial. Depending on the type(s) of Parkinson's medication the patient takes, he or she will be asked to withdraw from medication (12–48 h) prior to the in-person assessments. On-site, patients will be asked about their health history and a series of neurological and physical examinations will be performed by the study's movement disorders neurologist to rule out patients with physical or neurological problems unrelated to PD that may impact the study results. Verification of motor responsiveness to dopaminergic medication will be assessed using part III (motor evaluation) of the MDS-UPDRS. Patients will arrive off medication and perform the MDS-UPDRS III. Patients will then be prescribed Parcopa, a carbidopa-levodopa orally disintegrating, fast acting tablet that takes ∼1 h to take effect after which the MDS-UPDRS III will be performed again. Patients will then additionally perform the Mini Mental State Examination (MMSE) (30) and Scales for Outcomes in Parkinson's disease-Cognition (SCOPA-COG) (31) to rule out PD dementia. To exclude patients with severe vibratory sensory abnormalities, such as vibratory urticaria, patients will receive vibrations with high (0.35 mm) and low (0.03 mm) peak vibration amplitudes to each individual fingertip and be asked to verify which vibration type they received. Each patient's medication is then tracked for 1 month by the movement disorders neurologist to confirm that the patient's medication is stable.

Study Personnel and Their Roles

This study will include five movement disorders neurologists who are blinded during the first study. The first movement disorders specialist will serve as the *treating movement disorders neurologist* and perform physical and neurological examinations, evaluate and provide medical advice regarding patients' medication intake and serve as point of contact in the event of a serious or adverse event either unrelated or related to vCR for both the first and second study. The second movement disorders neurologist will serve as the studies' *main MDS-UPDRS movement disorders evaluator* who will perform assessments on patients throughout the first and second study. Three other movement disorders specialists will serve as the study's *video MDS-UPDRS III raters* for the first (main) study. The clinical research coordinators will oversee consent, objective motor measurements, video recordings, patient contact, vibrotactile glove administration, EEG recordings, voice recordings, and all self-report tests and questionnaires in both studies. Speech analysis will be performed by a voice disorders specialist and her trained team. An un-blinded statistical analyst, who is not associated with the study team and does not report to any member of the study team, will perform all statistical tests on outcome measures. All movement disorders specialists, speech analysis, and clinical research coordinators, will be blinded until completion of the first study.

Study 1 Design: Main Phase—Double Blind Sham-Controlled

We will perform a 7-month, double-blind, sham-controlled study including 30 PD patients randomly placed into either active vCR ($n = 15$) or a sham ($n = 15$) condition. All personnel and PD patients will be completely blinded to which stimulation pattern patients obtain. Parkinson's patients will receive vCR or sham stimulation for a total of 4 h a day (2 times 2 h a day with a break in between the 2-h sessions) at home for 6 months. To measure long-term effects, patients will pause stimulation for 1 month after the 6-month follow-up appointment.

Assessments: Study 1

The following outcome measures and their descriptions will be administered to patients. The *MDS-UPDRS parts IA*, *IB*, *II*, *III*, and *IV* (29). The MDS-UPDRS parts IA and IB concerns non-motor experiences of daily living, in which IA is assessed by the study's main MDS-UPDRS movement disorders evaluator and IB is self-reported. Part II is motor experiences of daily living and is self-reported. Part III is the in-person motor evaluation assessed by the study's main MDS-UPDRS movement disorders evaluator. In addition, part III will be video recorded and sent to the three blinded video MDS-UPDRS III raters. Patient recordings will be evaluated after each patient completes his or her 7-month visit. Video raters will additionally be blinded to the date of administration. Part IV incorporates patient details on motor complications with the study's main MDS-UPDRS movement disorders evaluators observations and judgements. The *PD Quality of Life Questionnaire-39* (*PDQ-39*) (32) is a self-report questionnaire that examines health related difficulties specific to PD in eight quality of life categories within the last month. The *Parkinson's disease sleep scale* (*PDSS-2*) (33) examines PD related sleep issues during the past week. The *University of Pennsylvania Smell Identification Test* (*UPSIT*) (34) is a smell test comprised of 40 odors, in which patients try to correctly identify the odorant presented. Patients will also take a tolerability and usability questionnaire regarding the vCR device. We will perform a *vibratory temporal discrimination task* (*VTDT*) that consists of two vibratory bursts, with one burst delivered to the index finger and one burst to the middle finger. Each burst will start randomly on either the index or middle finger. This procedure will be performed on the right and left hand separately. The patient is instructed to judge if he/she felt a delay between the two vibratory bursts. This task was designed as a possible calibration method for future vCR studies by serving as a sensitivity measure for vibratory temporal changes, in which reduced perceived vibratory time differences correspond to increased vibratory temporal discrimination. Patients will also undergo clinically established *speech and voice assessments.* Speech samples will be collected at a sampling rate of 44,100 Hz on a laptop using the Praat Speech Analysis program (Version 5.4, University of Amsterdam). To collect samples, a head-worn, unidirectional microphone will be placed over the participant's

ears and the microphone will be adjusted so that it is 6 cm from the participant's mouth. Specific samples will include sustained vowel phonations, sentence and paragraph length reading passages, and spontaneous speech. From these samples, speech and voice assessments will be conducted including measures of articulatory precision, speech intelligibility, speech rate, auditory-perceptual ratings of voice, and acoustic measures of vocal fundamental frequency, vocal intensity, and fundamental frequency and intensity variability. Additionally, the sentence intelligibility portion of the Assessment of Intelligibility in Dysarthric Speech (AIDS) (35) and patient self-assessment scales of Communicative Participation Item Bank (CPIB) (36) and the voice handicap index (VHI) (37) will be collected. For objective measures, patients will perform the *Kinesia ONE* motor evaluation, which uses a wearable accelerometer to assess motor activities similar to the MDS-UPDRS III and record their Parkinson's medication intake. The *Ambulatory Parkinson's Disease Monitoring* (*APDM*)'s Mobility Lab system will be used to measure objective gait disturbances. Lastly, the patient will also complete three different types of tasks during which *EEG* will be recorded. The first is a *sensorimotor EEG task,* in which patients receive a single vibratory stimulus to a random finger (excluding the thumb) on their non-dominant hand and are instructed with their dominant hand to push the response pad as fast as possible when they feel the vibratory burst. Each finger receives an equal number of vibratory pulses (50 per finger, equaling 200 trials) in a randomized order. Cortically, we expect to look at motor evoked potentials in response to cued vibration and their amplitude and latency changes throughout the course of treatment. Reaction time will also be documented. Additionally, we will record *vibration-only evoked potentials* in which we look at how two different types of vibratory pulses (high- and low-amplitude) affect different motor and sensory areas of the brain. The last task will be a recording done while the patient is at rest (*spontaneous EEG*). Patients will receive either active vCR or sham depending on the condition to which they were randomly assigned. For this task, we want to replicate our previous finding of decreased high beta band power (21–30 Hz) (17) for patients who received real vCR and quantify differences in activated brain areas in response to sham or active vCR. The MDS-UPDRS III off medication will be used as our primary outcome measure. All other measures are considered secondary.

Study 1: Visit Procedures

After inclusion into the study, the patients will be pseudo-randomly placed into a vibrotactile sham or real vibrotactile condition by staff personnel, not affiliated with the study. Patients will take the MDS-UPDRS parts IB, II, PDQ-39, PDSS, and the UPSIT online and at home on medication 1–2 weeks before every study visit. Patients will be asked to complete a usability and tolerability questionnaire about the vCR device after receiving therapy for 1 week following the start of the trial. Patients will then retake this questionnaire 1–2 weeks before all subsequent study visits.

Study visits will occur at baseline, 3, 6 months, and after a 1-month pause in stimulation at 7 months. Patients will arrive off medication and perform the following assessments in order. The participant's health history, physiological and neurological state will be examined upon arrival. Then, patients will perform the MDS-UPDRS III and will be video recorded. Electroencephalography recordings, the VTDT and speech assessments will be administered. Patients will then perform objective measurements including Kinesia ONE and the APDM. Parcopa is then given, and patients receive a 1-h break. The following assessments will be done on medication following the 1-h break. The MDS-UPDRS parts IA, III, IV, Kinesia ONE, and the APDM.

Study 1: At Home Therapy Procedures

During the first study visit, patients will be taught how to use, wear and adjust the vibrotactile device. Patients will then be sent home and asked to stimulate for a total of 4 h a day with a break in between each 2-h session (minimum 1-h break) for 6 months. At the end of the 6 months, patients will be asked to stop stimulation for 1 month. During the 7-month study, patients are asked to continue their prescribed medication as needed. If the patient would like to decrease his or her medication due to positive motor results throughout the study, the patient can reduce medication according to the advice of our study's treating movement disorders neurologist and the patient's personal movement disorders neurologist. While at home, patients will have their own Kinesia ONE system to log medication information and perform motor tasks while on medication 1–3 times every week to monitor movement ability. After the start of the study, patients will have a 1-month checkup with the study's treating movement disorders neurologist over the phone to check in on how the participant is doing. If the participant experiences any worsening of motor ability/or side effects that he/she believes is due to the vibrotactile device after the 1-month checkup, the patient can schedule a phone call with the study's treating movement disorders neurologist to discuss what the next steps will be. In the event the participant experiences an adverse event or a serious adverse event either related or unrelated to glove, he/she is required to schedule a call with the study's treating movement disorders neurologist for evaluation within 3 days of the event. For a detailed schematic of study 1 events see **Figure 3**.

Study 1: Statistical Analysis and Anticipated Results

A sample size of 30 was selected as a starting number of patients for the clinical trial. A priori analysis indicated that for a sample size of 30, we would need a large effect size ($f = 0.42$) in order to reach statistical significance ($p \leq 0.05$). In our previous study of six patients receiving vCR treatment for 3 months, using a paired samples t-test to compare MDS-UPDRS III scores pre- and post-treatment, the effect size was large ($d = 1.011$) (17). Based on this, our large f effect size of 0.42 may be reasonable. Nevertheless, an interim analysis will be performed by an un-blinded, experienced statistical research personnel, who is unaffiliated with the study team and does not report to any study team member, the principal investigator, nor any neurologist involved in the studies.

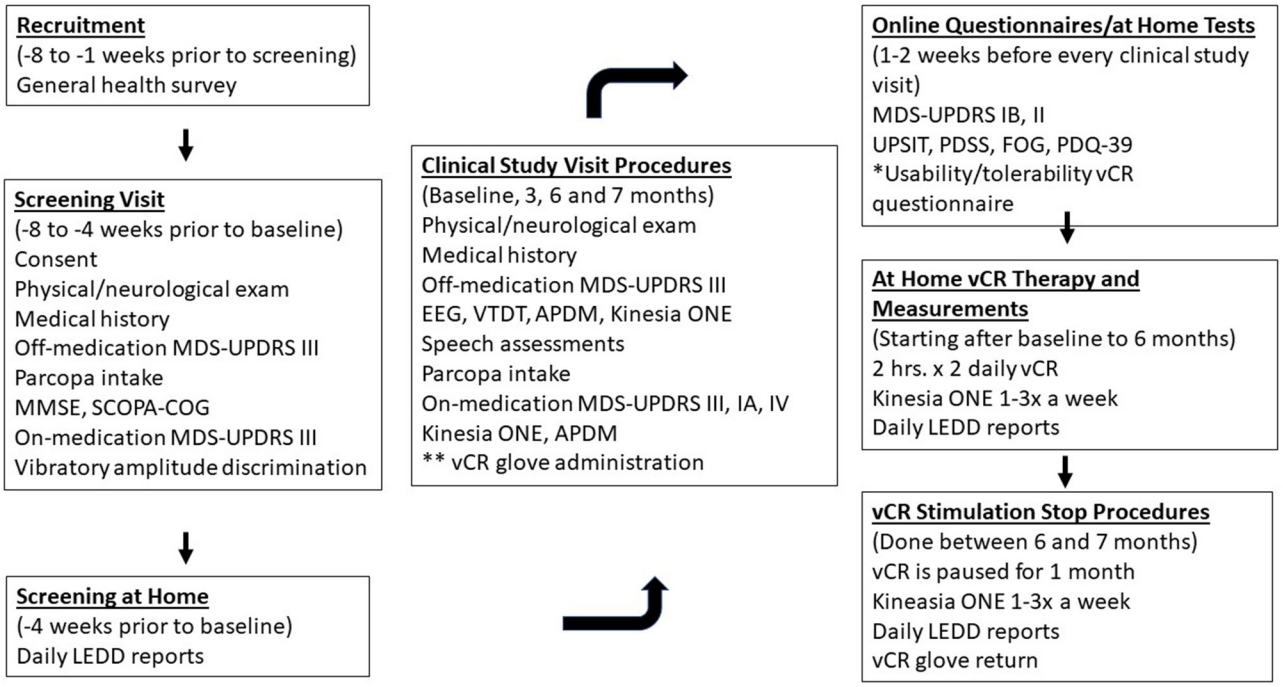

FIGURE 3 | Depicts study 1 procedures for the double-blind, sham-controlled vCR study. Patients will receive a General Health Survey which includes our inclusion/exclusion questionnaire and our dopamine dysregulation syndrome questionnaire developed for the purpose of our study *via* email 8–1 weeks prior to the screening visit. During the screening visit (8–4 weeks prior to baseline) patients will be consented and will arrive at Stanford off medication, to complete their physical/neurological examination and report their PD medical history. Patients will perform the MDS-UPDRS III off medication with the study's main movement disorders evaluator and then receive Parcopa (dopamine medication). Patients will then repeat the MDS-UPDRS III after 1 hour of taking medication. Patients will complete a vibratory intensity discrimination task to confirm that they do not have severe vibratory sensory abnormalities. The study's treating movement disorders neurologist will track patients for 4 weeks prior to their first clinical study visit (baseline) to confirm that their medication is stable. One to two weeks prior to every clinical study visit, patients will receive the following questionnaires/tests: MDS-UPDRS IB, II, UPSIT, PDSS, FOG, PDQ-39, and the usability/tolerability questionnaire of the vCR device. During the clinical study visits (baseline, 3, 6, and 7 months), patients will arrive to Stanford off medication and undergo the physical/ neurological examination, PD medical history, MDS-UPDRS III, EEG, VTDT, APDM, Kinesia ONE, and speech assessments. Patients are administered Parcopa and after 1 h perform the MDS-UPDRS III, IA, IV, Kinesia ONE, and APDM. After the 6-month visit, patients undergo a 1-month pause in stimulation to measure long term effects of vCR at the 7-month follow-up. During the entire length of the trial, patients will report their daily LEDD amount and starting from baseline will perform the Kinesia ONE motor evaluation at home one to three times a week for motor monitoring. *The Usability/Tolerability questionnaire is performed 1 week after the start of therapy and then 1-2 weeks before every study visit. **vCR glove administration occurs at baseline only.

This interim analysis will be performed when 16 patients have completed the 3-month mark, with eight belonging to the sham group and eight belonging to the vCR group. Results from the interim mixed factorial analysis of variance (ANOVA), will allow us to recalculate our desired sample size.

A 2 (sham vs. real vCR) by 4 (baseline, 3, 6, and 7 months) mixed factorial ANOVA will be done separately on the following measures: MDS-UPDRS I, II, III, IV, Levodopa equivalent daily dose (LEDD), EEG sensorimotor related evoked components, vCR resting EEG beta power response, vibratory temporal discrimination, speech assessments, UPSIT, PDSS, PDQ-39, FOG, and gait measurements obtained from the APDM Mobility Lab.

Statistically, for patients who received real vCR, we hope to see significant improvement in all measures by 6 months and expect to see no significant worsening when comparing assessments done after the pre-planned 1-month pause in stimulation at 7 months. In addition, we expect to see no significant improvements in the sham group patients.

Study 2 Design: Second Phase Remote Dosing Regime

At the 7-month appointment, the patient will be unblinded and given the option to continue or start real vCR stimulation for 6 additional months followed by a 1-month pause in stimulation. During the 7 additional months, patients will be remotely monitored and instructed to stimulate for six additional months as needed with parameters set to 2 h a day (maximum daily dose) to 2 h a day three times a week (minimum weekly dose). In addition, long-term effects will be measured after a 1-month pause in stimulation following the 6 additional treatment months.

Remote Study Procedures

If the patient chooses to remain in the study, the following procedures will take place remotely in the patient's home. After the 7-month follow-up in study 1, the patient will be reconsented sent home with the vibrotactile device equipped with active vCR. The patient will stimulate as needed and as instructed using

the parameters described above. Patients will take the online the PDQ-39, MDS-UPDRS parts IB and II, PDSS, FOG, and the usability and tolerability questionnaire of the vCR device. Patients previously in the sham condition will be given the usability and tolerability questionnaire 1 week after they start active vCR. Patients will complete all online questionnaires 1–2 weeks before every remote study visit. The patient will also continue to use the Kinesia ONE device one to three times a week so staff can monitor motor ability and report LEDD. The treating movement disorders neurologist will call patients after 1 month of stimulation to ask questions regarding the patients' treatment. At-home follow-up motor evaluations will take place at 10, 13, and 14 months *via* video meeting with the study's main MDS-UPDRS movement disorders evaluator. The study's treating movement disorders neurologist will additionally accompany the video call to check in on the patient. Depending on the type of medication, patients will go off medication (12–48 h) for these evaluations and perform the Kinesia ONE motor evaluation and the remote administration of the MDS-UPDRS IA, III, and IV (38). The remote MDS-UPDRS III will be our primary outcome measure, while all other measures are considered secondary. After 6 months of establishing a dosing regime, the patient will undergo a 1-month pause in stimulation and take his or her final online questionnaires and remote motor evaluation. The patient will mail his or her vCR device back to Stanford and will be thanked for his or her participation. For a detailed schematic of Study 2 events see **Figure 4**.

Statistical Analysis Study 2

The 15 patients receiving real vCR for 4 h a day in study 1 will be compared to the 15 patients who switch to real vCR in study 2 (previous sham patients). A 2 (4 h of daily vCR stimulation vs. decreased vCR stimulation) by 4 (baseline, 3, 6, and 7 months) mixed factorial ANOVA will be done individually on the MDS-UPDRS I, II, III, IV, with ratings for part III comprising of only remote tasks, LEDD, PDQ-39, FOG, PDSS, and Kinesia ONE ratings.

We hope to see no significant differences in evaluations taken from individuals receiving 4 h of stimulation and individuals receiving reduced vCR stimulation. This may suggest that between 2 h a day to 2 h three times a week of therapy is sufficient to drastically improve PD symptoms.

Medication Withdrawal Procedures

In both studies, depending on the type of medication and, hence, its half-life, patients will withdraw from their medication for a maximum of 48 h prior to their off-medication assessments. Specifically, extended-release drugs: Mirapex extended release, Requip extended release and Neupro patches will be stopped 48 h prior to evaluations. Regular Mirapex, regular Requip, Sinement sustained or extended release and Rytary are stopped 24 h prior to off evaluations. Sinement immediate release, Comtan, Stalevo, Amantadine, Azilect, Selegiline, and Artane are stopped 12 h prior to off-medication evaluations.

Adverse/Serious Events Reporting From the Vibrotactile Device

There are no formal statistics available on the vibrotactile stimulator's safety. Previous pre-clinical study patients have reported the glove as being tolerable with little to no side effects (17). There may be physical discomfort (e.g., pinching, numbing, skin indentations, etc.) associated with wearing the vibrotactile glove and study personnel will be vigilant for this unlikely possibility. In a previous study (17), patients reported a decrease in their medication over the course of vCR treatment. With this in mind, we hypothesize that PD patients with medication-induced dyskinesias might experience an increase of the medication-induced dyskinesias as vCR stimulation reduces the required medication dose, and as a result, patients may want to decrease their medication. If patients experience dyskinesia from the vibrotactile device, they are instructed to consult their neurologist about potential medication decreases and to not decrease their medication without consulting their doctor first. If patients and their neurologists decide to decrease their medication, patients are instructed to contact the study's treating movement disorders neurologist no later than 10 business days since medication changes. If in the event the patient experiences clinical worsening from the vibrotactile device, the patient is instructed to contact the study's treating movement disorders neurologist no later than 10 business days from the time of the event.

Standard Operating Procedures and Training

For all evaluations, standard operating procedures (SOPs) have been developed to ensure uniformity between all study personnel. All study personnel received training of all protocol practices and use of equipment for their protocol roles.

DISCUSSION

This paper describes the study procedures for the study *Vibrotactile coordinated reset: a non-invasive treatment for Parkinson's disease.* This study is comprised of two types of study protocols which include Study 1, main phase double-blind sham-controlled study, and Study 2, second phase, remote dosing regimen within the same study participants who all receive active vCR. In both studies, vCR therapeutic benefits are examined by implementing motor and non-motor evaluations.

Study 1

Testing vCR against a dedicated sham group will further assist in the true understanding of vCR's therapeutic motor benefits. A larger sample size may additionally aid in how vCR affects sub-motor types of PD, for example, tremor-dominant (TD), postural instability and gait difficulty dominant (PIGD-GD) and akinetic rigid types.

Non-motor related questionnaires and examinations such as sleep and smell have not yet been systematically studied in vCR experiments. Olfactory loss is commonly reported in PD patients, with some studies reporting $\geq$ 90% of patients

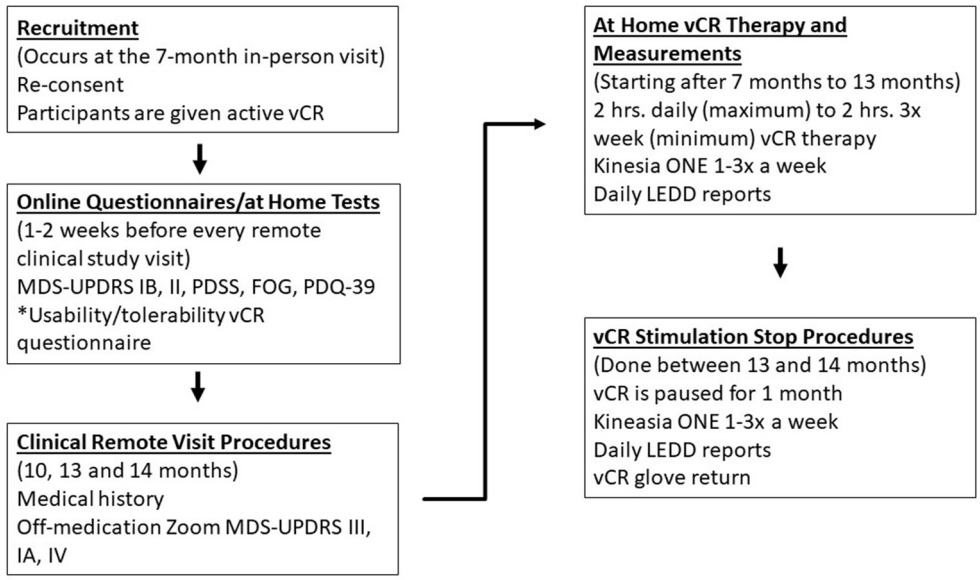

FIGURE 4 | Depicts study 2 remote procedures that detail vCR dosing techniques and clinical data obtained. At the 7-month in-person visit, patients will be reconsented and will be sent home with active vCR. Patients will be instructed to stimulate between 2 h a day (maximum) to 2 h three times a week (minimum) from months 7 to 13, report their LEDD amount and perform the Kinesia ONE motor assessment one to three times a week to monitor motor ability throughout the entire trial. One to two weeks before every remote study visit, patients take the following questionnaires: MDS-UPDRS IB, II, PDSS, FOG, PDQ-39, and the Usability/Tolerability vCR device questionnaire. Remote study visits occur at 10, 13 months, and after a 1 month (14th month) pause in stimulation to assess long-lasting effects. During these remote study visits, patients are off medication and the study's treating neurologist gathers medical history and the study's main movement disorders evaluator assesses the remote MDS-UPDRS III, IA, and IV. *The Usability/Tolerability questionnaire is performed 1 week after the start of therapy and then 1–2 weeks before every study visit.

with smell deficits (39, 40). The olfactory system is distinct, in that it has the unique capability to be activated by sniffing which by definition is a sensorimotor ability (41). Therefore, a therapy modulating sensorimotor areas of the brain (17) may have a positive impact on olfactory ability. Sleep disturbances are frequently reported in PD patients (42). Causes of sleep disturbances have been associated with nocturnal motor symptoms and dopaminergic medication (43). Given that vCR has positive benefits on the motor system and allows for a reduction of dopaminergic medications (17), we expect sleep to improve with vCR treatment. Speech and voice abnormalities are another area of interest simply because dopaminergic medication has been known to cause dysfluent speech (44–46) and traditional DBS can cause worsening of voice and speech (11). While the cause of voice and speech abnormalities is poorly understood, it is believed that improper integration of sensory and motor inputs due to dopamine loss within the striatum and basal ganglia can result in motor deficits that negatively affect subsystems related to speech motor control (47). Numerous studies have documented PD speech abnormalities related to sensorimotor deficits including errors in kinesthetic measurements (48), problems involving orofacial perception (49), and difficulties incorporating proprioceptive information during movement (50). Therefore, a therapy that targets the sensory and motor system and its interactions may have a positive benefit on speech and voice abnormalities in PD.

Using possible techniques such as the VTDT may aid in the understanding of vibratory sensory differences or abnormalities on a per patient basis which could help modify vCR patterns and parameters. Specifically, time as a dependent measure signifying the patient's vibratory temporal discrimination threshold may correlate to vCR effects. These measurements can then be used to modify vCR parameters on an individual basis so that patients receive the maximal benefit from vCR therapy. This could ultimately lead to a calibration-based personalized vCR therapy. Our VTDT is motivated by studies exploring somatosensory temporal discrimination in PD patients (51, 52). For instance, Conte et al. (51) used paired electrical stimuli delivered through surface skin electrodes. They found that somatosensory temporal discrimination threshold values were significantly greater in PD patients compared to in healthy subjects. In PD patients, dopamine reduced (i.e., partially restored) somatosensory temporal discrimination thresholds, whereas DBS delivered to the STN further degraded (i.e., increased) somatosensory temporal discrimination thresholds (51). In our pilot studies, we observed that in the course of the vCR therapy PD patients needed less dopaminergic medication (17). Accordingly, we hypothesize that vCR therapy may cause a cumulative and long-lasting reduction of somatosensory temporal discrimination thresholds assessed off medication.

In our VTDT, we deliver two vibratory bursts to the index and the middle finger. This is because the goal of vCR therapy is to

reduce abnormal synaptic connectivity. We hypothesize that due to vCR treatment, unwanted synaptic connectivity and, hence, abnormally strong interactions between index and middle finger decrease so that sensory input from index and middle finger can be processed in a separated and, thus, more efficient manner. Effective CR stimulation requires that the overlap of stimulated neuronal sub-populations should not attain higher levels (17, 23, 53). Hence, there might be an intricate relationship between the vibration amplitude used for vCR and treatment outcome. For instance, the stronger the abnormal synaptic connectivity between neighboring fingers, the smaller the vibration amplitude should be. However, particularly weak vCR may be less effective since the desired vibration phase-locked neuronal activity may occur in only smaller portions of the sensory thalamus and the sensorimotor cortex [see (16, 17)]. Hence, vCR stimulation might be more favorable if delivered at vibration amplitudes adapted to the VTDT results. Accordingly, during the course of vCR treatment the optimal vibration amplitude might need to adapt using VTDT results. However, this remains to be shown, e.g., in a first step by correlating VTDT and therapeutic outcome.

Patients with PD suffer from impairments in sensorimotor integration (48, 54–56). EEG recordings specifically investigating sensorimotor activity are important in understanding how the sensory system interacts with the motor system in PD. Vibration alone activates cortical motor areas of the brain (27), with desynchronization of the alpha and beta band corresponding to increased sensorimotor activity (27, 28). Faster (button press) times to a visual cue have been associated with desynchronization of sensorimotor rhythm (SMR) within the beta band, while increases of SMR are associated with longer reaction times (57). In our previous study, we found that after 3 months of vCR treatment, PD patients displayed a decrease in high beta band power over the sensorimotor cortex while patients were at rest (17). Based on this finding, we expect to find similar decreases in beta band power in response to a vibratory cue. In addition, reduction in reaction times accompanied by reduced beta power activity over the sensorimotor cortex during the course of vCR treatment could serve as a possible indicator of increased sensorimotor integration.

The readiness potential (RP) is an event related potential (ERP) slow wave that begins 1–2 s preceding voluntary movement (58). The RP contains early and late components, with the early component reflecting preparation of movement and the later component related to motor execution (58). The early RP is thought to be generated from the supplementary motor area (SMA) while the late readiness potential is associated with activation of the primary motor cortex (59). Dysfunction of the SMA (60, 61) and lower amplitudes of the RP have been found in PD patients (62–65). For this study, increases in RP amplitude prior to button press during the course of vCR treatment could serve as an indicator of improvements in motor ability and SMA function. In addition, Contingent Negative Variation (CNV) is a slow wave cortical potential that is related to attention, expectancy, and motor preparation (66, 67). It occurs when a participant is presented with a cued stimulus (i.e., vibration or sound) that requires a motor response (59, 67). Patients with PD exhibit reduced CNV amplitude (65, 68). Increases in CNV amplitude could serve as a measure of improved preparation and execution of a motor response in PD patients treated with vCR.

Study 2

Optimal therapeutic vCR outcome will require sufficient compliance. Accordingly, identifying a proper dosing regime is essential in providing patients with a reasonable number and duration of therapy sessions per week, such that these session times do not significantly interfere with their daily life. Motor and non-motor data of patients who received 4 h of daily active vCR stimulation for 6 months in study 1 will be compared to data from patients who received a lesser amount of vCR stimulation in study 2, which will further allow us to determine how much vCR stimulation is needed per week to produce maximal benefits. Our hope is that between 2 h of daily stimulation to 2 h daily three times a week will be sufficient to provide significant benefits that are equal to positive outcomes obtained from 4 h of stimulation a day. In our previous case study (17) we reduced one patient's daily 4-h dose of vCR therapy to 2 h three times a week. This patient had previously received 4 h of daily stimulation for 6 months. When the patient received a lower dose of vCR for 3 months, no substantial differences were found the patient's motor ability or medication intake. Specifically, the patient further improved as witnessed by his or her off-medication MDS-UPDRS part III score. Computationally, it was shown that long-term effects of CR stimulation do not only depend on stimulation duration. Rather, optimal dosing regimens with sufficient pausing in between CR epochs may cause long-lasting desynchronization even if CR stimulation is administered at particularly weak intensities rendering permanently delivered CR stimulation ineffective (69).

Summary and Outlook

Our study protocol comprises two study phases: *Study 1* is a double blinded randomized sham-controlled proof-of-concept study which corresponds to a phase IIA trial of the pharmaceutical trial categorization (70). The goal of this study is to demonstrate clinical efficacy of vCR compared to sham stimulation. To ensure therapeutic dosage, in study 1 we will apply two times 2 h of vCR or sham stimulation per day, respectively. However, in one patient of our case studies, in total 2 h vCR per day were sufficient to cause pronounced therapeutic effects (17), indicating that a daily dose of 4 h may not be necessary.

Study 2 aims to obtain knowledge of the therapeutic benefits of vCR stimulation at a reduced dosage regimen. To this end, sham patients from study 1 will be crossed over into active vCR for study 2, totaling 30 active patients for the dose finding study 2. All patients in study 2 will receive vCR at a dose ranging from 2 h a day (maximum daily dose) to 2 h a day three times a week (minimum weekly dose) for 6 months. Patients will select their actual weekly dose within this reduced dosage range depending on their individual needs, supposedly requiring less compliance and causing less interference with patients' day-to-day activities. Study 2 serves three purposes: (i) In the patients who received vCR in study 1, study 2 enables to collect data regarding safety,

tolerability, and efficacy on a longer time scale by delivering vCR for in total 12 months instead of 6. (ii) Comparing the effects obtained in vCR patients in study 1 with the effects observed in the sham patients from study 1 crossing over to low-dose vCR in study 2 provides a dose finding comparison between low-dose and high-dose 6-month vCR therapy, similar to a phase IIB trial in terms of the pharmaceutical trial categories (70). (iii) In addition, in both patient groups (i.e., vCR vs. sham patients from study 1) therapeutic effects obtained in study 2 will be separately correlated with the integral amount of self-administered dose.

Depending on the results of studies 1 and 2, additional dose finding studies might be envisioned to further optimize and potentially reduce the dosing pattern as well as to further optimize the stimulation pattern, e.g., by increasing the temporal jitter of stimulus onsets used for noisy vCR (17).

CONCLUSION

The aim of this study is to understand how vCR treatment affects a wide range of clinical symptoms associated with PD. We hypothesize that results obtained from this study will demonstrate clinical efficacy of our vCR therapy, procedure, and our investigational vibrotactile device for the purpose of acquiring FDA clearance.

ETHICS STATEMENT

The study *Vibrotactile Coordinated Reset: a non-invasive treatment for Parkinson's Disease* was reviewed and approved by Stanford's Institutional Review Board. Written consent will be obtained from all patients prior to the start of study 1 and 2. All research staff has taken a Good Clinical Practice Course online.

AUTHOR CONTRIBUTIONS

BM and PT: designed vibrotactile glove system. KP and PT: wrote manuscript. All authors contributed to the overall design of the study protocol and revised/approved manuscript.

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Transcranial Direct Current Stimulation on Parkinson's Disease: Systematic Review and Meta-Analysis

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Background: Clinical impact of transcranial direct current stimulation (tDCS) alone for Parkinson's disease (PD) is still a challenge. Thus, there is a need to synthesize available results, analyze methodologically and statistically, and provide evidence to guide tDCS in PD.

Objective: Investigate isolated tDCS effect in different brain areas and number of stimulated targets on PD motor symptoms.

Methods: A systematic review was carried out up to February 2021, in databases: Cochrane Library, EMBASE, PubMed/MEDLINE, Scopus, and Web of science. Full text articles evaluating effect of active tDCS (anodic or cathodic) vs. sham or control on motor symptoms of PD were included.

Results: Ten studies ($n = 236$) were included in meta-analysis and 25 studies ($n = 405$) in qualitative synthesis. The most frequently stimulated targets were dorsolateral prefrontal cortex and primary motor cortex. No significant effect was found among single targets on motor outcomes: Unified Parkinson's Disease Rating Scale (UPDRS) III – motor aspects (MD = −0.98%, 95% CI = −10.03 to 8.07, $p = 0.83$, $I^2 = 0\%$), UPDRS IV – dyskinesias (MD = −0.89%, CI 95% = −3.82 to 2.03, $p = 0.55$, $I^2 = 0\%$) and motor fluctuations (MD = −0.67%, CI 95% = −2.45 to 1.11, $p = 0.46$, $I^2 = 0\%$), timed up and go – gait (MD = 0.14%, CI 95% = −0.72 to 0.99, $p = 0.75$, $I^2 = 0\%$), Berg Balance Scale – balance (MD = 0.73%, CI 95% = −1.01 to 2.47, $p = 0.41$, $I^2 = 0\%$). There was no significant effect of single vs. multiple targets in: UPDRS III – motor aspects (MD = 2.05%, CI 95% = −1.96 to 6.06, $p = 0.32$, $I^2 = 0\%$) and gait (SMD = −0.05%, 95% CI = −0.28 to 0.17, $p = 0.64$, $I^2 = 0\%$). Simple univariate meta-regression analysis between treatment dosage

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and effect size revealed that number of sessions (estimate = −1.7, SE = 1.51, z-score = −1.18, $p = 0.2$, IC = −4.75 to 1.17) and cumulative time (estimate = −0.07, SE = 0.07, z-score = −0.99, $p = 0.31$, IC = −0.21 to 0.07) had no significant association.

Conclusion: There was no significant tDCS alone short-term effect on motor function, balance, gait, dyskinesias or motor fluctuations in Parkinson's disease, regardless of brain area or targets stimulated.

Keywords: transcranial direct current stimulation (tDCS), Parkinson's disease, neuromodulation, motor symptoms, meta-analysis

INTRODUCTION

Parkinson's disease (PD) is a chronic, multisystemic, neurodegenerative disorder with various mechanisms underlying its neuropathology (1). PD is standing out as a leading cause of disability-adjusted life year (DALY) globally (increasing 148% between 1990 and 2016), the most growing neurological disorder according to the Global Burden of Disease 2016 (2), and affecting 6.1 million people (3). As an aggravating factor, the forecast predicts that this number will double in the next generation (3).

Parkinson's disease is characterized by a triad of cardinal symptoms (bradykinesia, tremor, and rigidity). Bradykinesia or slowness of movement is the most characteristic motor symptom (4), covering many motor manifestations (5). Tremor initially appears unilateral and progresses to bilateral, worsening in stressful circumstances or cognitive tasks, and can be attenuated during sleep or movement (6). Rigidity causes constant or oscillating resistance to passive joint movement and can be increased by tasks demanding attention (7).

Among the current treatments available, drug administration is the most common option. However, a significant decrease in response to a drug occurs ∼5 years after initial treatment, worsening motor fluctuations, dyskinesia, dystonia, incoordination, and arthralgia (9). Neurosurgical procedures involving deep brain stimulation are another option, but this method presents high cost (9), surgical risk (8), and possibility of worsening of verbal fluency and axial motor symptoms (8, 9). Appropriate interventions present little or no adverse effects, improve functionality and well-being, and delay the progression of the disease (9). Thus, new therapeutic approaches are necessary to provide a better quality of life and to reduce the financial burden for society and health systems.

Transcranial direct current stimulation (tDCS) has gained prominence for being a non-invasive, safe, low-cost neuromodulatory modality, with minimal or no adverse effect (10, 11). Its mechanisms of action go far beyond the elementary reasoning that anodic (a-tDCS) and cathodic (c-tDCS) stimulation increases or decreases, respectively, somatic polarity, excitability, and neuronal plasticity (12). Considering the complex functioning of the brain, the neurophysiology underlying tDCS is much more heterogeneous. It can encompass the following: complex forms of plasticity, involving distinct presynaptic and postsynaptic mechanisms (long-term potentiation and depression), soma polarization, dendrites, and synaptic terminals, axonal growth, network effects (amplifications and oscillations), and functions of interneurons, endothelial cells, and glia (13). Given the pathophysiological complexity of PD and the variability of its symptoms, multiple brain regions can modulate motor recovery, and consequently, the methods of applying tDCS can be diverging.

Previous reviews investigated tDCS and associated therapies (14–19), but tDCS alone is still a challenge to determine its clinical effect on PD (15). Thus, this systematic review and meta-analysis investigated the use of tDCS on PD based on the PICOS model: population (P): adult patients with PD; intervention (I): tDCS alone in different brain areas and number of stimulated nominal targets; comparison (C): control condition, placebo or sham; outcomes (O): PD motor symptoms; types of studies (S): clinical trials randomized or not with crossover or parallel design and open-label studies.

Abbreviations: PD, Parkinson's disease; tDCS, transcranial direct current stimulation; a-tDCS, anodic transcranial direct current stimulation; c-tDCS, cathodic transcranial direct current stimulation; DALY, Disability-adjusted life year; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PEDro, Physiotherapy Evidence Database; UPDRS, Unified Parkinson's Disease Rating Scale; HY, Hoehn and Yahr; FOG, Freezing of gait; MD, Mean difference; SMD, Standardized mean difference; CI, Confidence interval; DLPFC, Dorsolateral prefrontal cortex; M1, Primary motor cortex; TUG, Timed up and go; BBS, Berg Balance Scale.

METHODS

Protocol and Registration

A systematic review with meta-analysis and meta-regression was performed according to the Cochrane group (20), including review mechanisms, inclusion or exclusion criteria, search and selection of articles, analysis of the methodological quality of included studies, data extraction, and meta-analysis of results. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adopted (21). The selection of studies was performed by two independent reviewers (PCAO and TABA) according to the previously structured eligibility criteria. Disagreements between reviewers were resolved by a third reviewer (DGSM). The current review protocol was registered in the International Prospective Register of Systematic Reviews – PROSPERO–(https://www.crd.york.ac.uk/prospero/) under the publicly available registry number CRD42020188010 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020188010).

Search Strategy

The following databases were used for this review's literature survey: Cochrane Library, EMBASE, PubMed/MEDLINE, Scopus, and Web of science, and considered the literature until February 2021. The terms MeSh and operators Booleans were as follows: "Parkinson's disease" OR "Parkinson's disease" AND "transcranial direct current stimulation" OR "tDCS" OR "transcranial electrical stimulation" OR "non-invasive brain stimulation" OR "neuromodulation." In addition, the reference lists of selected articles and literature reviews on the subject were checked to retrieve articles that were not covered by the database searches.

Eligibility Criteria

The search was carried out for full text articles, peer-reviewed, published in scientific journals without language restriction. However, only studies in English were found. To be included, studies should (a) include adults (over 18 years of age) with a clinical diagnosis guided by the Movement Disorder Society diagnostic criteria for PD (5), all types and levels of severity or by a clinical definition; (b) apply a-tDCS or c-tDCS; (c) report motor outcome data only from individuals with PD; (d) report data on motor outcomes only from the intervention with tDCS alone (for studies involving multiple interventions); (e) provide quantitative data for at least one of the outcome measures (in the manuscript or upon request); (f) have randomized and non-randomized clinical trials with parallel, crossover, or open-label design; and (g) have a sham or control condition. Studies involving research on animals, *in vitro* or computational models, were excluded. The agreement between reviewers for the screening of studies was analyzed using the Kappa (K) statistic, and the results revealed an "excellent" agreement ($K = 0.969$; $p < 0.0001$). The percentage of agreement between the reviewers was 99.9%, and the third reviewer's tie was 0.1%.

Study Quality Assessment

The evaluation of the internal validity and presentation of necessary statistical information of the studies was performed by two independent reviewers (PCAO and TABA), who used the classification scale of the Physiotherapy Evidence Database (PEDro) (22). The PEDro scale consists of 11 items that assess the followings: (1) eligibility criteria, (2) randomness of groups, (3) secret allocation, (4) homogeneity between groups, (5) blinding of participants, (6) blinding of therapists, (7) evaluator blinding, (8) key outcome in more than 85% of subjects, (9) intention-to-treat analysis, (10) statistical comparison between groups, and (11) precision measure and variability measures. The PEDro scale is one of the most used instruments in rehabilitation to assess the methodological quality of clinical trials (23, 24). Thus, it is a measure with sufficient validity to be used in systematic reviews of clinical trials and clinical practice guidelines (22). The classification of the PEDro score was as follows: scores from 0 to 4 = low quality; 4 to 5 = acceptable quality; 6 to 8 = good quality, and 9 to 10 = excellent quality (25).

The risk of bias was evaluated using the Cochrane risk of bias assessment (26), which assesses the followings: (a) random sequence generation, (b) allocation concealment, (c) blinding of participants and personnel, (d) blinding of outcome assessment, (e) incomplete outcome data, (f) selective reporting, and (g) other biases. Each item was classified as "low risk of bias" ("+"), "high risk of bias" ("–") or "uncertain risk of bias" ("?"). Disagreements were resolved by a third reviewer (DGSM).

Data Extraction

Data extraction included sample size (number of individuals involved), participant characteristics [age, gender, time since PD diagnosis, Unified Parkinson's Disease Rating Scale (UPDRS) at baseline, medication, most affected hemibody, stage Hoehn and Yahr (HY)], intervention protocol (number of sessions, location of electrodes, anodic or cathodic, intensity, density, and duration of stimulation), and outcome measures (gait, motor function, motor aspects of daily life, dyskinesia, motor fluctuations, bradykinesia, manual dexterity, upper limb function, balance, postural stability, and freezing of gait) from all included studies. Missing article data were requested by email, and those who did not respond after three attempts or did not provide data for any reason were excluded from the meta-analysis. Thus, we excluded 15 articles from the quantitative synthesis, 11 for lack of response (27–37) and 4 for not having or not providing the data (38–41).

Quantitative Analysis

Quantitative synthesis was performed by combining individual studies into meta-analyses. We performed analyses comparing the effect of tDCS alone on motor symptoms according to the nominal stimulated target and compared the effect on single or multiple targets. To estimate the effect, we used continuous post-intervention mean and standard deviation data. We calculated the mean difference (MD) or the standardized mean difference (SMD), if the studies assessed the same outcome using different scales, confidence interval (CI) of 95% for each comparison, weighted by the inverse variance method using an effects model random or fixed-effects model, when applicable. Heterogeneity was assessed using chi-square ($p < 0.1$ = statistically significant), I^2 ($I^2 > 75\%$ = significant) and visual inspection of forest plots. If considerable heterogeneity was identified (chi-square $p < 0.10$; $I^2 > 75\%$), only a qualitative synthesis would be presented. Review Manager v.5.3 software (Copenhagen: Nordic Cochrane Center) was used for all data analysis, except for the meta-regression, performed in Python. The univariate meta-regression model used a sensitivity analysis to investigate possible effect moderators related to treatment characteristics (number of sessions and cumulative time). One predictor variable was analyzed at a time, and values of $p < 0.05$ were considered significant.

RESULTS

Overview

This review comprises the range from 1984 to February 2021. The PRISMA flow diagram summarizes steps in the study identification procedures (**Figure 1**). The literature search identified 6,386 studies, and Mendeley software excluded 146 duplicates. No study was included based on verifying the reference lists of selected articles or literature reviews on the

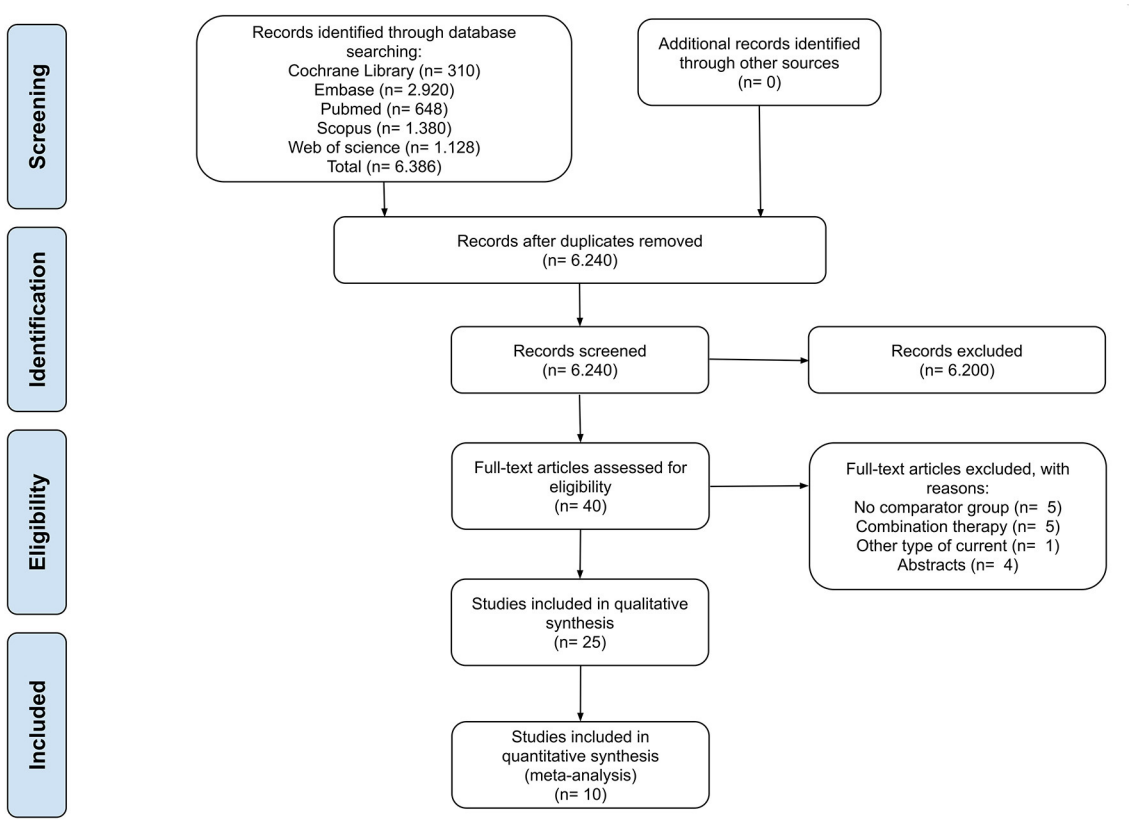

FIGURE 1 | PRISMA flowchart of included studies.

subject. Forty studies were eligible for full-text reading after evaluating titles and abstracts. The two most frequent causes of exclusion were an absence of a comparator and tDCS as a combined therapy. Another four studies were excluded after the analysis of abstracts. Studies that investigated non-motor outcomes after tDCS were also checked for the existence of motor outcomes for inclusion in the meta-analytic analysis. Finally, 25 studies involving 405 participants met our criteria and were included in the qualitative synthesis. Of those, 10 were included in the meta-analysis, covering a total of 236 participants.

Characteristics of Included Studies

Table 1 summarizes information of included studies, which investigated the effect of tDCS alone on the motor symptoms of PD. According to this table, 20 (80%) studies were randomized (27–29, 32, 34, 36–40, 42–51), four (16%) did not mention this information (31, 33, 35, 41) and one (4%) used pseudo-randomization (30). Twenty studies (80%) had a crossover design (28–37, 40, 41, 43, 44, 46–51) and five (20%) parallel (27, 38, 39, 42, 45). One (4%) study did not contain information about blinding (39), three (12%) trials had single-blind experiments (33, 44, 50), 20 (80%) double-blind experiments (27–32, 34, 36–38, 40–43, 45–51) and one (4%) double blind in only one of the experiments (35). Regarding the comparator group, 24 studies (96%) had a sham group (27–38, 40–51) and one (4%) had a control group, which did not undergo any type of therapy (39).

Characteristics of Participants

In total, 25 studies included 405 individuals with PD, and the mean sample size was 17.64 ± 7.40 (ranging from 7 to 26 participants), aged between 58 and 74 years. HY obtained a minimum score of 1.3 and a maximum of 2.8, indicating early to almost moderate stages of PD. The UPDRS II achieved a minimum score of 1.1 and a maximum of 11.6, a UPDRS III minimum of 13 and a maximum of 39.7, and a minimum of 16 and a maximum of 74.2 on UPDRS's total score. The duration of PD had a minimum of 4.3 and a maximum of 12.3 years whereas the dose of the medication had a minimum of 292.8 mg and a maximum of 1287.7 mg. Twenty-two (88%) studies performed the experiment in the ON state of the medication (27–35, 37–39, 41, 43–51), two (8%) in the OFF state (36, 40) and one (4%) in both states (42). Details of the participants of each study are shown in **Table 2**.

tDCS Protocols

Three (12%) studies stimulated multiple targets, and 22 studies (88%) stimulated single nominal target with dorsolateral prefrontal cortex (DLPFC) and primary motor cortex (M1) as the most common montages (**Figure 2**). In addition, most

TABLE 1 | Characteristics of the included studies.

References	Design	Outcome measures	Follow-up	N sessions	Nominal target	Target	tDCS Set-up	Results
Albuquerque et al. (27)	Parallel	PGT, AMT	NO	1	(+): cerebellum & (–): buccinator muscle	Single	2 mA, 25 min, ND	Motor performance (=) in hand and arm tasks
Benninger et al. (42)	Parallel	10MWT, Hand and arm movements (bradykinesia), UPDRS, SRTT	1 and 3 months	8	(+): PMC and MC & (–): Mastoids and (+): PFC & (–): Mastoids Sham: (+) and (–) 1 cm apart over the forehead, two additional electrodes inversely over the mastoids (not connected to the stimulator)	Multi	2 mA, 20 min, 0.021 mA/cm²	↓ in walking time (ON and OFF) until 1 month later in the ON group improvement in bradykinesia (ON and OFF) for more than 3 months (=) for UPDRS, SRTT
Beretta et al. (28)	Cross	UPDRS, Postural control assessment, EMG, fNIRS, MMSE	NO					EMG and CoP temporal parameters: (↓) recovery time x sham
Exp 1				1	(+): M1 hemisphere contralateral to the most affected body side & (–): over the contralateral supraorbital	Single	1 mA, 20 min, ND	
Exp 2				1	(+): M1 hemisphere contralateral to the most affected body side & (–): over the contralateral supraorbital	Single	2 mA, 20 min, ND	EMG and CoP temporal parameters: (↓) onset latency with 2 mA, (↓) recovery time x sham
Bueno et al. (43)	Cross	TUG, video gait analysis	NO	1	(+): L-DLPFC & (–): R-frontal areas	Single	2 mA, 20 min, 0.057 mA/cm²	(=) TUG and video gait analysis

(Continued)

TABLE 1 | Continued

References	Design	Outcome measures	Follow-up	N sessions	Nominal target	Target	tDCS Set-up	Results
Cosentino et al. (29)	Cross	FT, upper limb bradykinesia test, UPDRS III	NO	2	(+): M1 & (–): contralateral orbitofrontal cortex; (+): contralateral orbitofrontal cortex & (–): M1	Single	2 mA, 20 min, ND	a-tDCS in most affected M1: improvement in FT, (↓) in Upper Limb Bradykinesia test time in both hands, (↓) in UPDRS III c-tDCS in less affected M1: improvement in FT, (↓) in Upper Limb Bradykinesia test time in both hands c-tDCS in most affected M1: (↑) at the time of the upper limb bradykinesia test
Criminger et al. (44)	Cross	TUG	NO	1	(+): L-DLPFC & (–): R-DLPFC	Single	2 mA, 20 min, ND	(=) TUG
da Silva et al. (45)	Parallel	Gait kinematics analysis, UPDRS III	NO	1	(+): M1 and SMA & (–): over the supraorbital area ipsilateral to the most affected side	Multi	2 mA, 15 min, ND	(↓) in gait cadence
Dagan et al. (46)	Cross	TUG, FOG-provoking test	NO	2	(+): M1 motor leg-area & (–): ND; (+): L- DLPFC and M1 & (–): ND	Single & Multi	2 mA, 20 min, ND	a-tDCS in M1 + DLPFC: (↓) in FOG-Provoking Test and TUG
Doruk et al. (38)	Parallel	UPDRS III, sRT, 4-CRT, PPT, FT, WT, BU, SP	1 month	10	(+): L-DLPFC & (–): R-frontal areas; (+): R-DLPFC & (–): L-frontal areas	Single	2 mA, 20 min, ND	(=) motor function
Ferrucci et al. (47)	Cross	UPDRS III/IV	1 and 4 weeks	5	(+): M1 bilaterally & (–): R-deltoid muscle; (+): cerebellum & (–): R-shoulder	Single	2 mA, 20 min, ND	a-tDCS in M1 and cerebellum improved levodopa-induced dyskinesias

(Continued)

TABLE 1 | Continued

References	Design	Outcome measures	Follow-up	N sessions	Nominal target	Target	tDCS Set-up	Results
Fregni et al. (30)	Cross	UPDRS, sRT, PPT	NO	1	(+): M1 dominant hemisphere & (–): contralateral orbitofrontal cortex (+): contralateral orbitofrontal cortex & (–): M1 dominant hemisphere (+): DLPFC & (–): orbitofrontal cortex	Single	1 mA, 20 min, ND	a-tDCS in M1: improvement in UPDRS and sRT, (=) for PPT a-tDCS in DLPFC: significant main effect for UPDRS and sRT, (=) for PPT c-tDCS in M1: (=) for UPDRS, sRT and PPT
Kaski et al. (48)	Cross	6MWT, gait velocity, stride length, TUG, pull test	NO	1	(+): M1 (leg areas, 10–20% anterior to Cz) & (–): inion	Single	2 mA, 15 min, ND	(=) gait speed, stride length, TUG, 6MWT and pull test
Lattari et al. (49)	Cross	BBS, DGI, TUG	NO	1	(+): L-DLPFC & (–): R-frontal areas	Single	2 mA, 20 min, ND	a-tDCS improves balance and functional mobility x sham-tDCS
Lawrence et al. (39)	Parallel	UPDRS II	week 12	4	(+): L-DLPFC & (–): above the left eye	Single	1.5 mA, 20 min, ND	Isolated tDCS did not generate significant improvement in any motor test
Lu et al. (40)	Cross	UPDRS III, gait initiation on the force platform	NO	1	(+): SMA & (–): Fp	Single	1 mA, 10 min, 0.123 mA/cm²	a-tDCS did not improve self-start gait in PD and FOG
Manenti et al. (31)	Cross	TUG	NO	1	(+): L-DLPFC & (–): R-frontal areas; (+): R-DLPFC & (–): L-frontal areas	Single	2 mA, 7 min, 0.057 mA/cm²	(↓) Selective on TUG reaction times after a-tDCS on R-DLPFC and (=) L-DLPFC

(Continued)

TABLE 1 | Continued

References	Design	Outcome measures	Follow-up	N sessions	Nominal target	Target	tDCS Set-up	Results
Mishra and Thrasher (32)	Cross	GAITRite (velocity), phoneme verbal fluency task	15 and 30 min	1	(+): L-DLPFC & (–): R-frontal areas	Single	2 mA, 30 min, ND	a-tDCS x sham in the dual task: participants walked faster and generated a (↑) number of words/min, at 15 and 30 min after stimulation The cost of dual task associated with gait speed was significantly (↓) 15 min after Single task: (=) for gait and cognitive performance
Putzolu et al. (33)	Cross	GAITRite	NO	1	(+): L-DLPFC & (–): R-frontal areas	Single	1.5 mA, 20 min, ND	Improvement in gait performance during cognitive dual task in the FOG group
Putzolu et al. (34)	Cross	GAITRite	NO	1	(+): L-DLPFC (–): orbitofrontal cortex	Single	1.5 mA, 20 min, ND	Improved stride length, stride speed and double support time
Salimpour et al. (35)			NO					(↓) on signal-dependent noise in the most affected arm (↑) on patients' willingness to assign strength to the most affected arm and improvement of motor symptoms
Exp 1	Cross	Isometric task, UPDRS III	NO	1	(+): L-M1 & (–): R-M1	Single	1 mA, 25 min, 0.04 mA/cm²	-

(Continued)

TABLE 1 | Continued

References	Design	Outcome measures	Follow-up	N sessions	Nominal target	Target	tDCS Set-up	Results
Exp 2	Cross	Isometric task, UPDRS III	NO	1	(+): R-M1 & (–): L-M1	Single	2 mA, 25 min, 0.08 mA/cm²	(↓) in the subjective cost of force (↑) in the willingness to assign force to the affected side (↓) in noise laterality
Exp 3	Cross	Isometric task, UPDRS III	NO	2	(+): M1 contralateral to the affected side & (–): M1 contralateral to the affected side	Single	2 mA, ND, 0.08 mA/cm²	(↑) in the willingness to give strength to the affected side (↓) in the laterality index (↓) at UPDRS
Exp 4	Cross	Isometric task, UPDRS III, PDQ-39	NO	5	(+): M1 ipsilateral & (–): M1 contralateral to the affected side	Single	2 mA, ND, 0.08 mA/cm²	c-tDCS x sham: further improvements in the laterality index (↓) higher in the subjective cost of strength in the affected arm change in one-hand noise significant effect on UPDRS improvement in PDQ-39
Schoellmann et al. (36)	Cross	UPDRS III, EMG, EEG	30 min	1	(+): M1 & (–): R-frontal areas	Single	1 mA, 20 min, <0.1 mA/cm²	Clinical motor improvement of the UPDRS III subtotal (items 22–25) of the MSD lasting at least 30 min

(Continued)

TABLE 1 | Continued

References	Design	Outcome measures	Follow-up	N sessions	Nominal target	Target	tDCS Set-up	Results
Swank et al. (50)	Cross	TUG, PDQ-39, UPDRS	NO	1	(+): L-DLPFC & (–): R-DLPFC	Single	2 mA, 20 min, ND	(=) TUG or PDQ-39
Valentino et al. (37)	Cross	UPDRS III and total, SWS, FOG-Q, GFQ	2 days, 2 and 4 weeks	5	(+): M1 (leg area that starts walking) & (–): contralateral orbitofrontal cortex	Single	2 mA, 20 min, ND	Improved gait (↓) on the number and duration of FOG episodes (↓) in total UPDRS and III
Verheyden et al. (41)	Cross	STS, FR, SS180, TUG, 10MWT	NO	1	(+): M1 of the dominant hemisphere & (–): contralateral orbitofrontal cortex	Single	1 mA, 15 min, ND	(↓) of speed at 10MWT no immediate effects and, in fact, a possible decline in motor performance
Workman et al. (51)	Cross	25FWT, TUG, 6MWT, BBS, Posturography	NO	1	Unilateral (+): Hemisphere cerebellar more affected & (–): Contralateral upper arm Bilateral (+): Hemisphere cerebellar more affected & (–): hemisphere cerebellar contralateral	Single	2 mA, 20 min, 0.06 mA/cm² 4 mA, 20 min, 0.11 mA/cm²	4 mA bilateral: (↑) on the BBS

N, number; PGT, precision grip task; AMT, arm movement task; mA, milliamps; min, minutes; ND, not described; 10MWT, 10 m; UPDRS, Unified Parkinson's Disease Rating Scale; walk test; SRTT, serial reaction time task; PMC, premotor cortex; MC, motor cortex; PFC, prefrontal cortex; EMG, electromyography; fNIRS, functional near-infrared spectroscopy; MMSE, mini mental state examination; CoP, center of pressure; Exp, experiment; M1,primary motor cortex; TUG, timed up and go; L, left; DLPFC, dorsolateral prefrontal cortex; R, right; FT, finger tapping; a-tDCS, anodal transcranial direct current stimulation; c-tDCS, cathodal transcranial direct current stimulation; SMA, supplementary motor area; FOG, freezing of gait; sRT, simple reaction time; 4-CRT,4-choice reaction time; PPT, Purdue Pegboard test; WT, walking time; BU, buttoning-up; SP, supination–pronation; 6MWT, six-min walk test; BBS, Berg Balance Scale; DGI, Dynamic Gait Index; Fp, frontal polar; PD, Parkinson's disease; GAITRite, gait assessment system; PDQ-39, Parkinson's Disease Questionnaire 39 Items; EEG, electroencephalography; MSD, superior right member; SWS, stand–walk–sit; FOG-Q, Freezing of Gait Questionnaire; GFQ, Gait and Fall Questionnaire; STS, sit-to-stand; FR, functional reach; SS180, standing-start 180 degrees turning; 25FWT,25-foot walk test; Cross, crossover design; parallel, parallel design; Single, single target; Multi, multiple targets; (↑), increase; (↓), decrease; (=), equal.

TABLE 2 | Characteristics of participants.

References	Sample (W/M)	Age (years)	Hoehn and Yahr	Duration of disease (years)	UPDRS at baseline	Medication (mg)	Most affected hemibody (Right, Left, Bilateral)	ON/OFF phase
Albuquerque et al. (27)	22 (10 W/12 M)	71.3 ± 8.6	Active: 2.3 ± 0.65 Sham: 2.0 ± 0,63	ND	Active: 24.7 ± 5.7 Sham: 28.4 ± 12.1 (ND)	Active: 584.8 ± 516.2 Sham: 468.5 ± 193.7	20R/2L	ON
Benninger et al. (42)	25 (9 W/16 M)	63.9 ± 8.7	Active: 2.5 ± 0.1 Sham: 2.4 ± 0.2	Active: 10.6 ± 7.1 Sham: 9.1 ± 3.3	Active: 42.5 ± 10.8 Sham: 39.5 ± 12.8 (total) Active: 22.2 ± 8.7 Sham: 17.5 ± 8 (III)	Active: 1024.3 ± 541.5 mg Sham: 1287.7 ± 808.8 mg	ND	ON/OFF
Beretta et al. (28)	24 (10 W/14 M)	68.91 ± 8.47	ND	4.84 ± 3.11	36.00 ± 14.32 (III)	545.01 ± 288.59 mg	ND	ON
Bueno et al. (43)	20 (8 W/12 M)	64.45 ± 8.98	2.25 ± 0.63	7.80 ± 5.32	11.60 ± 4.00 (II) 22.35 ± 6.77 (III) 33.95 ± 9.44 (total)	ND	ND	ON
Cosentino et al. (29)	14 (6 W/8 M)	58 ± 12.1	ND	ND	ND	386.2 ± 233.5 mg	11R/3L	ON
Criminger et al. (44)	16 (4 W/12 M)	68.13 ± 9.76	2 ± ND	8.69 ± 9.76	40.31 ± 18.27 (total) 23.44 ± 9.73 (III)	ND	ND	ON
da Silva et al. (45)	17 (7 W/10 M)	Active: 66 ± 5 Sham: 66 ± 10	2.35 ± 0.29	Active: 6 ± 6 Sham: 5 ± 1	ND	ND	ND	ON
Dagan et al. (46)	20 (3 W/17 M)	68.8 ± 6.8	2.5 ± 0.6	9.0 ± 5.7	74.2 ± 23.3 (total) 39.7 ± 14.6 (III)	554.7 ± 401.1 mg	ND	ON
Doruk et al. (38)	18 (6 W/12 M)	61 ± 8	ND	ND	ND	ND	ND	ON
Ferrucci et al. (47)	9 (4 W/5 M)	74.33 ± 7.98	2.5 ± 0.35	10.77 ± 2.1	Active Cerebellar: 13 ± 4.9 Active M1: 13 ± 4.8 Sham: 13.3 ± 4.8 (III)	ND	ND	ON
Fregni et al. (30)	17 (6 W/11 M)	62.3 ± 1.6	2.4 ± 0.2	12.3 ± 1.6	37.4 ± 3.9 (III)	615.0 ± 63.1 mg	9R/8L	ON
Kaski et al. (48)	8 (ND)	ND	ND	ND	25.8 ± 5.74 (total)	ND	ND	ON
Lattari et al. (49)	17 (4 W/13 M)	69.18 ± 9.98	2.35 ± 1.06	7.06 ± 2.70	18.0 ± 8.96 (III)	748.29 ± 343.80 mg	ND	ON

(Continued)

TABLE 2 | Continued

References	Sample (W/M)	Age (years)	Hoehn and Yahr	Duration of disease (years)	UPDRS at baseline	Medication (mg)	Most affected hemibody (Right, Left, Bilateral)	ON/OFF phase
Lawrence et al. (39)	tDCS: 7 (5 W/2 M) control: 7 (4 W/3 M)	tDCS: 72 ± 6.45 control: 72.29 ± 6.21	ND	tDCS: 5.50 ± 5.66 control: 5.36 ± 4.14	tDCS: 1.27 ± 0.56 (II) control: 1.18 ± 0.69 (II)	tDCS: 573.29 ± 586.25 control: 292.88 ± 274.51	ND	ON
Lu et al. (40)	10 (3 W/7 M)	66.3 ± 9.9	2.7 ± 0.4	7.7 ± 4.0	39.2 ± 17.2 (III)	761.0 ± 362.2 mg	ND	OFF
Manenti et al. (31)	10 (4 W/6 M)	67.1 ± 7.2	1.3 ± 1.1	8.1 ± 3.5	13.3 ± 5.7 (III)	749.2 ± 445.5 mg	2R/8L	ON
Mishra and Thrasher (32)	20 (6 W/14 M)	67.8 ± 8.3	1.9 ± 0.9	4.8 ± 3.8	ND	ND	ND	ON
Putzolu et al. (33)	20: FOG+ (4 W/6 M) FOG- (5 W/5 M)	FOG+: 70.1 ± 3.84 FOG-: 72.8 ± 6.87	ND	FOG+: 9.3 ± 5.5 FOG-: 7.2 ± 5.2	FOG+: 20.1 ± 8.4 (III) FOG-: 22.9 ± 8.1 (III)	ND	ND	ON
Putzolu et al. (34)	21: FOG+ (4 W/6 M) FOG- (4 W/7 M)	FOG+: 69.20 ± 5.20 FOG-: 70.36 ± 6.23	FOG+: 2.05 ± 0.44 FOG-: 1.77 ± 0.52	FOG+: 8.00 ± 5.50 FOG-: 5.82 ± 5.29	FOG+: 39.30 ± 11.39 (total) FOG-: 36.27 ± 16.58 (total) FOG+: 18.60 ± 6.38 (III) FOG-: 20.45 ± 8.15 (III)	ND	ND	ON
Salimpour et al. (35)								ON
Exp 1	10 (4 W/6 M)	59.6 ± 6.68	1.75 ± 0.54	6.9 ± 4.6	15.7 ± 4.8 (III)	515 ± 274.92	10R/0L	
Exp 2	10 (2 W/8 M)	61.6 ± 10.76	1.75 ± 0.63	8.5 ± 5.8	18.6 ± 6.09 (III)	655 ± 434.90	10R/0L	
Exp 3	10 (4 W/6 M)	60.5 ± 9.16	1.85 ± 0.47	8.3 ± 4.13	24.6 ± 11.21 (III)	740 ± 500.99	8R/1L/1B	
Exp 4	8 (3W/5M)	59.37 ± 9.00	1.5 ± 0.46	6.87 ± 4.96	17.62 ± 4.47 (III)	712.5 ± 470.37	6R/2L	
Schoellmann et al. (36)	10 (4 W/6 M)	64.3 ± 11.4	ND	8.6 ± 4.1	ND	749.15 ± 423.99 mg	7R/3L	OFF
Swank et al. (50)	10 (2W/8M)	68.7 ± 10.2	2 ± ND	7.9 ± 7.1	37.0 ± 12.9 (total) 24.30 ± ND (III)	ND	ND	ON
Valentino et al. (37)	10 (5 W/5 M)	72.3 ± 3.6	2.8 ± 0.5	11 ± 4.9	32 ± 10.3 (III)	ND	4R/6L	ON
Verheyden et al. (41)	20 (ND)	71 ± 7	ND	9 ± 4	16 ± 5 (total)	ND	ND	ON
Workman et al. (51)	7 (2W/5M)	72.4 ± 6.4	1.9 ± 0.4	4.3 ± 2.5	32.6 ± 14.2 (III)	889.8 ± 497.7 mg	1R/6L	ON

W, women; M, men; UPDRS, Unified Parkinson's Disease Rating Scale; mg, milligrams; ND, not described; R, right; L, left; FOG, freezing of gait; Exp, experiment.

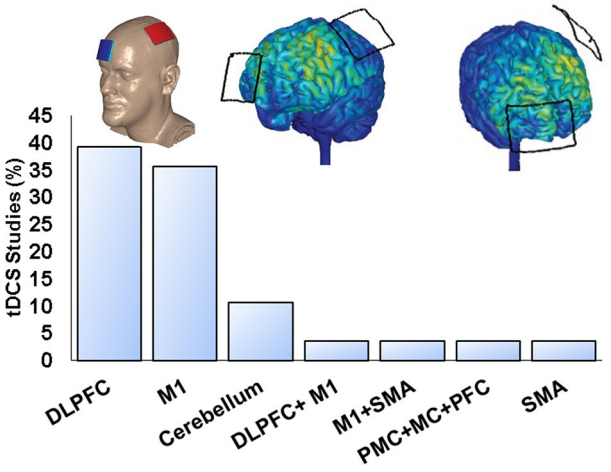

FIGURE 2 | Quantity of tDCS studies on PD using single nominal targets, and example of M1 anodal electrode on C3.

studies performed single tDCS session (66.7%), and others used 2 (11.1%), 4 (3.7%), 5 (11.1%), 8 (3.7%), and 10 sessions (3.7%). Twenty-two trials (88%) applied anodal tDCS (27, 28, 31–34, 36–51), whereas three (12%) performed anodal tDCS and cathodal tDCS (29, 30, 35). The minimum current intensity was 1 mA, the maximum was 4 mA, and the mean duration time of stimulation per session was 19.28 ± 4.47 min (minimum of 7 min and maximum of 30 min). Finally, 18 (72%) studies performed pre- and postintervention assessments (27–31, 33–35, 40, 41, 43–46, 48–51), whereas seven (28%) also performed follow-up evaluations (range from 15 min to 3 months) (32, 36–39, 42, 47).

Motor Outcome Result Measures

Gait was analyzed in 17 (68%) of those studies (31–34, 37, 38, 40–46, 48–51) and which was evaluated by the timed up and go (TUG) test, 10-m walk test, video analysis and pressure platform, six-min walk test, stand–walk–sit test, 25-foot walk test, and Dynamic Gait Index. Thirteen studies (52%) also investigated the effect of tDCS alone on UPDRS scores (28–30, 35–40, 42, 45, 47, 50), on bradykinesia, manual dexterity, and upper limb function (27, 29, 30, 35, 38, 42). Balance or postural stability was analyzed in five (20%) studies (28, 41, 48, 49, 51) and freezing of gait (FOG) in other three (12%) studies (37, 40, 47).

Quality of Included Studies

Internal validity and necessary statistical information were evaluated using the PEDro scale and obtained a mean score of 8.28 ± 1.24, which reveals a good methodological quality of the studies (25). Details of the scores for each study are shown in **Table 3**.

The results of risk of bias indicate a low or unclear risk for most studies except for allocation concealment that was considered high. Details of risk of bias of each study are shown in **Figure 3**.

Meta-Analysis Results

Single Nominal Targets on Motor Symptoms

UPDRS III–Motor Aspects

This analysis included one study (47) and two experiments divided by nominal target, namely M1 and cerebellum. A total of nine participants were involved and randomly assigned to one stimulation protocol at once. There was no significant effect of tDCS on motor aspects measured by the UPDRS III. Analyzing the combined effect of these areas (MD = −0.98%, 95% CI = −10.03 to 8.07, $p = 0.83$, $I^2 = 0\%$, without significant heterogeneity and fixed-effects model), there was no significant effect about isolated areas (**Figure 4A**).

UPDRS IV—Dyskinesias

One study (47) enrolled 09 participants and conducted two experiments in which nominal targets, M1 and cerebellum, were stimulated. There was no significant effect between tDCS and dyskinesias assessed by the UPDRS IV. Furthermore, analyzing the combined effect of these areas (MD = −0.89%, CI 95% = −3.82 to 2.03, $p = 0.55$, $I^2 = 0\%$, without significant heterogeneity and fixed-effects model), there was also no significant effect in the analysis of isolated areas (**Figure 4B**).

UPDRS IV—Motor Fluctuations

Two experiments divided by nominal targets included M1 (47) and cerebellum (47). A total of 09 participants were involved and randomly assigned to M1, cerebellum or sham stimulation. There was no significant effect of tDCS in relation to motor fluctuations, measured by the UPDRS IV. Analyzing the combined effect of these areas (MD = −0.67%, CI 95% = −2.45 to 1.11, $p = 0.46$, $I^2 = 0\%$, without significant heterogeneity and fixed-effects model), there was also no significant effect in the analysis of isolated areas (**Figure 4C**).

TUG—Gait

We analyzed 98 participants distributed in seven studies, grouped by areas of stimulation, namely DLPFC (43, 44, 49, 50), M1 (46, 48) and cerebellum (51). There was no significant effect of tDCS in relation to gait, measured by TUG. Analyzing the combined effect of these areas (MD = 0.14%, CI 95% = −0.72 to 0.99, $p = 0.75$, $I^2 = 0\%$, without significant heterogeneity and random effects model), there was also no significant effect in the analysis of isolated areas (**Figure 4D**).

Berg Balance Scale—Balance

We compared 24 participants and protocol stimulations distributed in two studies, divided according to the areas of DLPFC (49) and cerebellum (51). There was no significant effect of tDCS related to balance, measured by the BBS. Analyzing the combined effect of these areas (MD = 0.73%, CI 95% = −1.01 to 2.47, $p = 0.41$, $I^2 = 0\%$, without significant heterogeneity and random effects model), there was no significant effect in the analysis of isolated areas (**Figure 4E**).

TABLE 3 | PEDro scale.

	Total	Items										
		1	2	3	4	5	6	7	8	9	10	11
Albuquerque et al. (27)	8	1	0	0	1	0	1	1	1	1	1	1
Benninger et al. (42)	9	1	1	0	1	1	0	1	1	1	1	1
Beretta et al. (28)	9	1	1	0	1	1	0	1	1	1	1	1
Bueno et al. (43)	10	1	1	1	1	1	0	1	1	1	1	1
Cosentino et al. (29)	9	1	1	0	1	1	0	1	1	1	1	1
Criminger et al. (44)	8	1	1	0	1	1	0	0	1	1	1	1
da Silva et al. (45)	10	1	1	1	1	1	0	1	1	1	1	1
Dagan et al. (46)	9	1	1	0	1	1	0	1	1	1	1	1
Doruk et al. (38)	9	1	1	0	1	1	0	1	1	1	1	1
Ferrucci et al. (47)	9	1	1	0	1	1	0	1	1	1	1	1
Fregni et al. (30)	8	1	0	0	1	1	0	1	1	1	1	1
Kaski et al. (48)	8	1	1	0	0	1	0	1	1	1	1	1
Lattari et al. (49)	9	1	1	0	1	1	0	1	1	1	1	1
Lawrence et al. (39)	7	1	1	0	1	0	0	0	1	1	1	1
Lu et al. (40)	9	1	1	0	1	1	0	1	1	1	1	1
Manenti et al. (31)	8	1	0	0	1	1	0	1	1	1	1	1
Mishra and Thrasher (32)	8	0	1	0	1	1	0	1	1	1	1	1
Putzolu et al. (33)	6	0	1	0	1	1	0	0	0	1	1	1
Putzolu et al. (34)	9	1	1	0	1	1	0	1	1	1	1	1
Salimpour et al. (35)	4	0	0	0	0	1	0	0	0	1	1	1
Schoellmann et al. (36)	8	1	1	0	1	1	1	0	0	1	1	1
Swank et al. (50)	8	1	1	0	1	1	0	0	1	1	1	1
Valentino et al. (37)	9	1	1	0	1	1	0	1	1	1	1	1
Verheyden et al. (41)	8	1	0	0	1	1	0	1	1	1	1	1
Workman et al. (51)	8	0	1	0	1	1	0	1	1	1	1	1

Items: (1) eligibility criteria, (2) group randomness, (3) secret allocation, (4) homogeneity between groups, (5) blinding of participants, (6) blinding of therapists, (7) blinding of evaluators, (8) key result in more than 85% of individuals, (9) analysis of the intention to treat, (10) statistical comparison between groups, and (11) precision measure and variability measures.

Single and Multiple Nominal Targets on Motor Symptoms

UPDRS III—Motor Aspects

We analyzed three studies and four experiments, with 51 participants, grouped according to the number of stimulation areas: single target (47) and multiple targets (42, 45). There was no significant effect of tDCS in relation to the motor aspects assessed by the UPDRS III. Analyzing the combined effect of these areas (MD = 2.05%, CI 95% = −1.96 to 6.06, $p = 0.32$, $I^2 = 0\%$, no heterogeneity and random effects model), there was also no significant effect in the analysis of isolated areas (**Figure 5A**).

Gait

In this analysis, we included 10 studies, with 98 participants, grouped by the amount of stimulation areas: single target (43, 44, 46, 48–51) and multiple targets (42, 45, 46). The investigation did not show a significant effect of tDCS, regardless of the number of nominal targets stimulated, in relation to gait. Analyzing the combined effect of these areas (SMD = −0.05%, 95% CI = −0.28 to 0.17, $p = 0.64$, $I^2 = 0\%$, without significant heterogeneity and random effects model), there was also no significant effect in the analysis of isolated areas (**Figure 5B**).

Meta-Regression

Simple univariate meta-regression analysis was performed by a blinded investigator (ACRN) using Python "Pymare" library to investigate the association between effect size and treatment dosage considered as the number of sessions and cumulative time. Analysis revealed that the number of sessions was not significantly associated with effect size (estimate = −1.7, SE = 1.51, z-score = −1.18, $p = 0.2$, CI = −4.75 to 1.17). The analysis also revealed that cumulative time was also not significantly associated with effect size (estimate = −0.07, SE = 0.07, z-score = −0.99, $p = 0.31$, CI = −0.21 to 0.07).

DISCUSSION

This systematic review with meta-analysis and meta-regression includes 25 studies with 405 participants and investigated the effect of tDCS on the motor symptoms of PD. Our results demonstrated that there was no significant effect of tDCS on short-term motor symptoms of PD, regardless of brain area, number of stimulated nominal targets, or treatment dosage. The regions most covered by the included studies were DLPFC and M1.

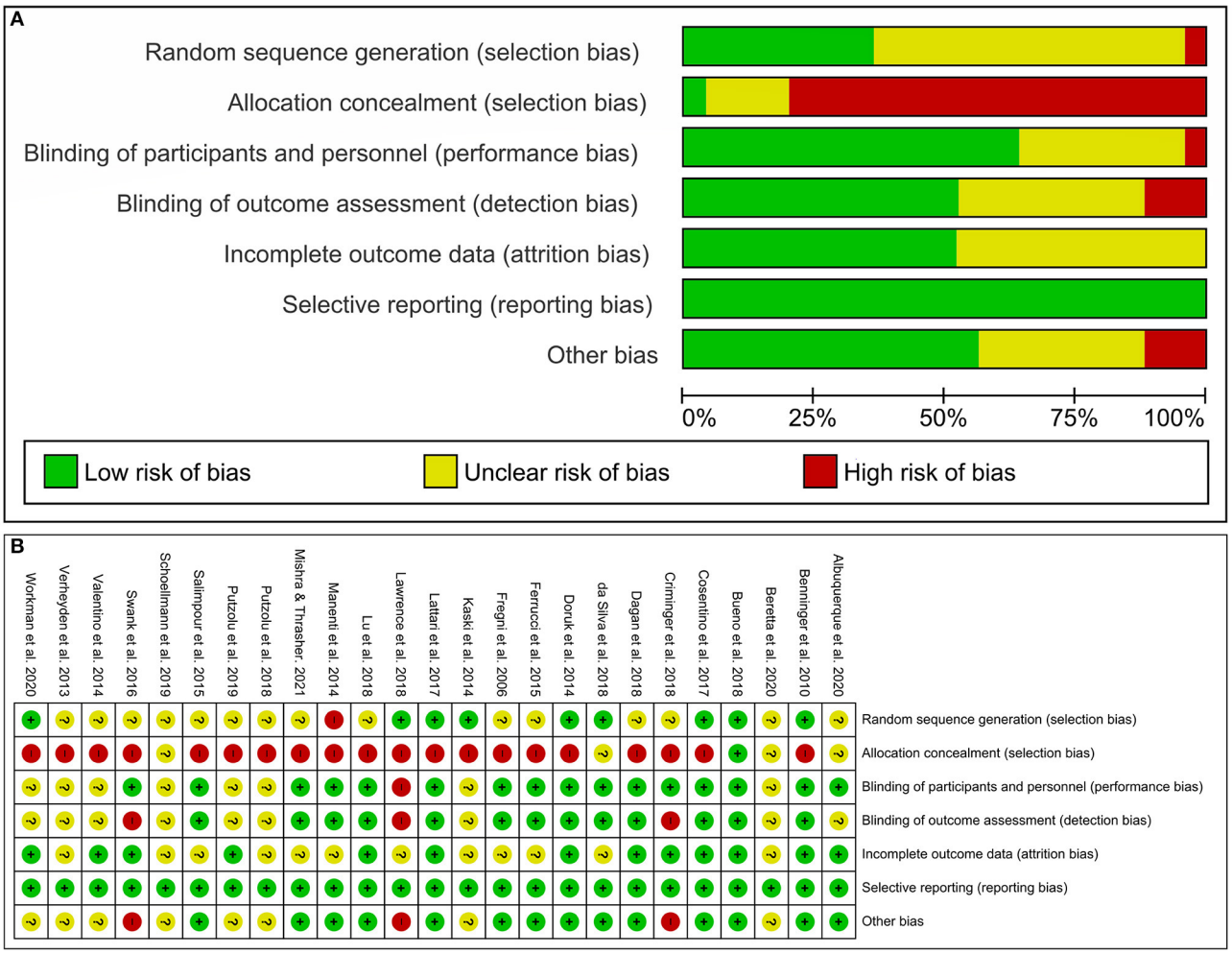

FIGURE 3 | Risk of bias graph **(A)** and risk of bias summary **(B)**.

The DLPFC is a brain region commonly studied in tDCS research to observe its effect on non-motor symptoms of PD, but it has also been widely investigated in motor symptoms. The justification includes several explanations: (a) the non-motor symptoms influence the motor symptoms because cognitive functions are needed to perform motor tasks and are partly modulated by the DLPFC (31). An example of this relationship is the execution of the gait, where the individual needs the ability to perform a dual task (43); (b) DLPFC appears to interfere with balance, through the attribution of the prefrontal cortex to spatial orientation (52) in addition to its activation during gait in several challenging conditions (53, 54). Thus, the hypothesis suggests that modulating DLPFC can improve visuospatial processing that improves the balance of individuals with PD (49). However, the literature shows divergent results related to the stimulation of this area to improve motor functions. Previous research (30, 38, 39, 43, 44, 50) found no significant effect of tDCS on DLPFC for motor function, simple reaction time, aspects of isolated and dual task gait, quality of life, or motor aspects of daily life. In contrast, other studies (31, 33, 34, 49) found a beneficial effect for walking alone and with dual task, FOG, functional mobility, or balance. Finally, responses in DLPFC can activate distinct networks of motor areas, such as M1, supplementary motor area, and premotor area, which exert direct control over motor aspects (55, 56). However, the possibility of cortical functioning through a matrix cannot be excluded, as in pain processing (12, 57).

In turn, the M1 area is also a widely investigated target for treatment of motor symptoms of PD, due to its primordial role in motor control and learning (58). In summary, the disturbance in the functioning of the basal ganglia causes cortical dysfunction and promotes the motor symptoms of PD. Thus, the hypothesis is that the modulation of cortical areas can drive changes in the cortical–subcortical pathway, positively influencing the basal ganglia, to correct such dysfunction and reduce symptoms (30). However, the literature about tDCS in M1 shows divergences. According to previous studies (29, 30, 35–37, 41, 47), tDCS in M1 showed a significant effect on hand motor performance, dyskinesia, gait, FOG, motor function, and simple reaction time,

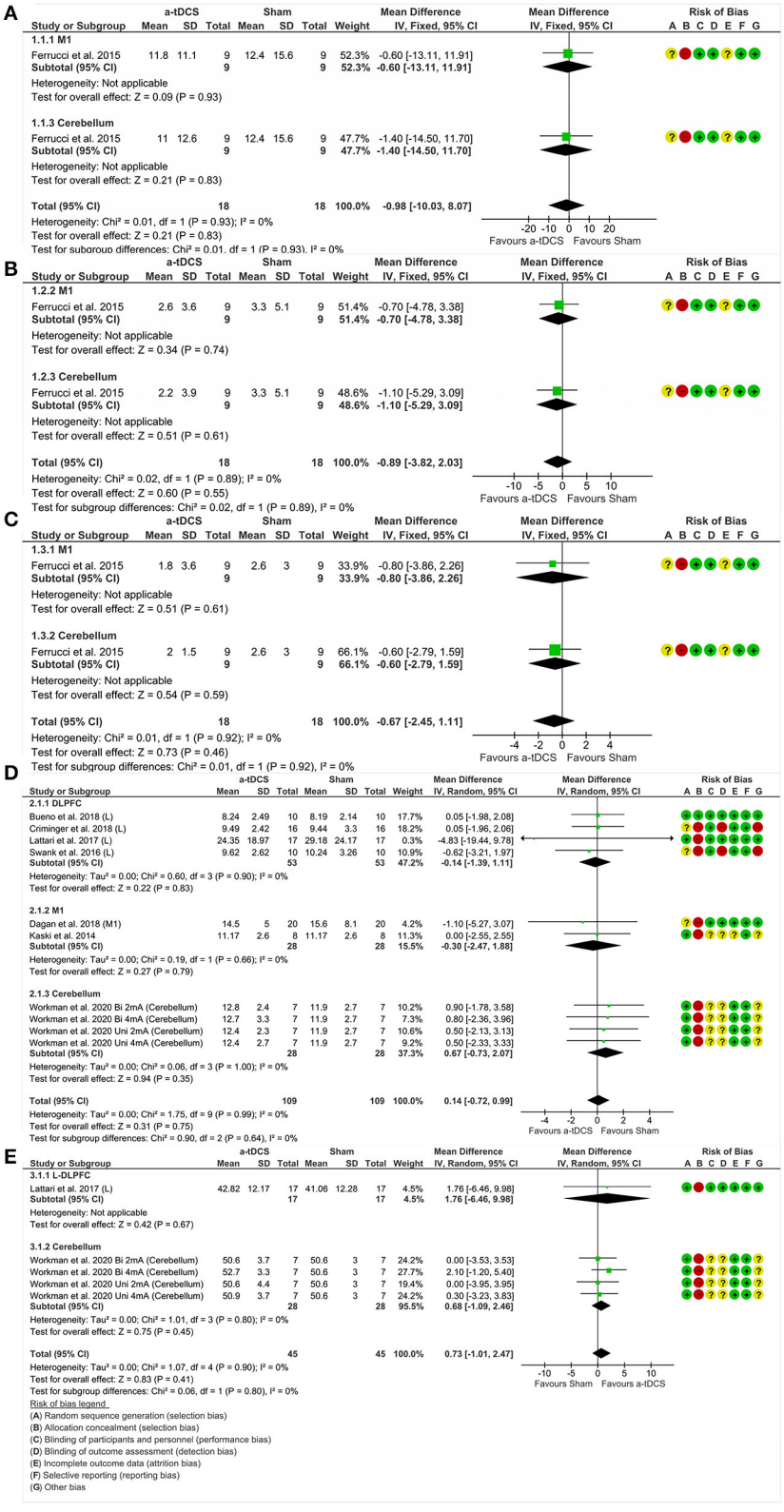

FIGURE 4 | Forest plot showing mean difference from the comparison between single targets in motor function—UPDRS III **(A)** and dyskinesias—UPDRS IV **(B)** and motor fluctuations—UPDRS IV **(C)** and the gait—TUG **(D)** and balance—BBS **(E)**. Risk of bias was deemed as "low risk of bias" ("+"), "high risk of bias" ("–"), or "unclear risk of bias" ("?").

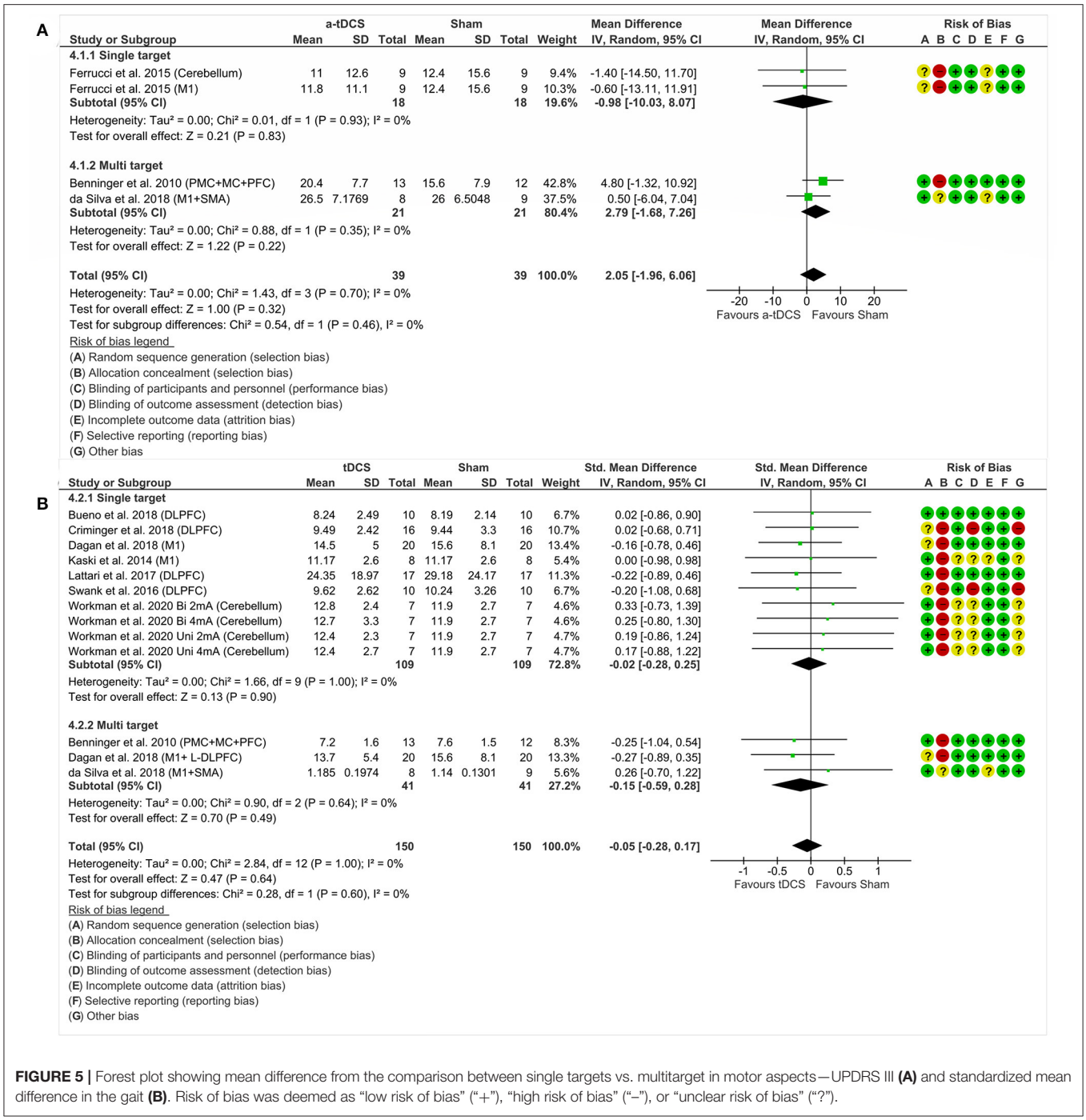

FIGURE 5 | Forest plot showing mean difference from the comparison between single targets vs. multitarget in motor aspects—UPDRS III **(A)** and standardized mean difference in the gait **(B)**. Risk of bias was deemed as "low risk of bias" ("+"), "high risk of bias" ("–"), or "unclear risk of bias" ("?").

respectively. However, other studies (46, 48) did not obtain a significant effect on gait and balance.

It is important to note that despite the inaccuracies in the clinical effect, there is evidence that tDCS stimulates both the target area and beyond (12). Neurophysiological mechanisms may include changes in neuronal excitability, plasticity, neuronal oscillations, and connectivity (12). Numerous studies using electroencephalography (59–62), functional magnetic resonance (57, 63–65), combination of transcranial magnetic stimulation with electroencephalography (66, 67), and functional near-infrared spectroscopy (68) have shown brain changes after tDCS in M1 with modulation of this neural network.

According to the meta-analysis, it is still not possible to determine the number of nominal targets to be stimulated in tDCS protocols to reduce motor symptoms in PD. Considering pathophysiological mechanisms, chronic evolution, multisystem repercussions, and varied symptoms, it is necessary to note

the importance of functional rehabilitation combined with additional approaches. The potential of tDCS at disease onset is also relevant as most motor treatment is provided in the early phase (during the 1st week and month) (69, 70). Here, we provide some evidences that tDCS can improve motor function in early-stage patients to some extent. In previous studies, early stimulation of tDCS reduced cadence (45), upper limb bradykinesia (29), FOG (46), and improved levodopa-induced dyskinesia (47).

There is little evidence regarding the mechanisms of action of tDCS in the pathophysiology of PD. However, our hypothesis is that multiple sessions of tDCS associated with rehabilitation training can activate brain regions by the task-related activity and, therefore, make them more sensitive to modulation by tDCS (13). Different hypotheses can explain our results: a) few studies involving PD, neuromodulation, and motor symptoms aimed to assess the isolated effect of tDCS. Furthermore, studies that proposed to investigate such aspects, an even smaller number presented essential numerical data for a meta-analytic evaluation; b) our meta-regression showed that the number and cumulative time of sessions were not associated with tDCS effect size, which may suggest insufficient corticospinal changes to increase motor performance and such insufficiency may be associated with other factors, including long interval of hours between applications and longer application time, which can inhibit overstimulation through neuronal counter-regulation, among others (71); (c) the sample size of the included trials may have been limited to provide an adequate effect size; and d) there is a lack of evidence on the non-motor aspects of PD, which may influence the effectiveness of tDCS on motor outcomes. Thus, it is likely that cognitive processing is supported by several brain regions and neural networks, which makes it challenging to identify specific nominal targets to stimulate. Furthermore, our results cannot be applicable to individuals in the OFF state of medication, as most studies (88%) performed their research only in the ON state.

This systematic review with meta-analysis and meta-regression aimed to fill the gaps in the literature related to the effect of tDCS on the motor symptoms of individuals with PD. Based on the evidence from previous meta-analyses, our study (a) provided a direct comparison between the effect sizes of studies that used motor and non-motor cortical targets, (b) compared the effects of single montages target vs. multitarget in motor function, (c) included a larger set of important studies (27, 28, 32, 34, 36, 40, 51) that bring relevant approaches to the field under investigation and that were published after previous reviews were carried out, and (d) analyzed the association of certain therapeutic variables with tDCS effect size. The recent evidence-based guidelines for neuromodulation target sites for the treatment of motor function in PD concludes that anodal tDCS over motor, premotor, and supplementary motor area is likely to be effective (level C), whereas on the prefrontal cortex, there is possibly no efficacy (level B) (15). Thus, considering the gaps that still exist in the literature and seeking clarification in future recommendations, further studies should include secret allocation, adequate blinding, homogeneous comparison group, sufficient sample size, application of tDCS in single and multiple brain regions, shorter interval of hours between sessions, and evaluation of the long-term effect on simple and complex motor tasks. Finally, future studies could go beyond the target area and investigate patterns of cortical activation at baseline and during treatment to infer possible predictors of response to therapy. A deeper look at the neurophysiological correlates in patients with PD is needed, particularly to provide neurophysiological evidence that cholinergic dysfunction may be an important and early contributor to motor and cognitive dysfunction in PD.

CONCLUSION

In summary, this systematic review with meta-analysis and meta-regression found no significant short-term effect of tDCS alone on motor function, balance, gait, dyskinesia, and motor fluctuations, regardless of brain area or number of stimulated nominal targets in patients with PD. We also found no relationship between the effect of tDCS alone and the number of sessions or cumulative treatment time.

DATA AVAILABILITY STATEMENT

The data supporting the conclusions of this review article will be made available by the corresponding author on request to qualified researcher.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PO and TA contributed with preliminary databases' searches, selection of studies, screening of research results and eligibility criteria, data extraction, risk of bias, quality assessment, data analysis, and manuscript writing. DM supervised the systematic review of studies, reviewed, and edited the manuscript. AR contributed to the meta-regression analysis. MB, SA, AO, HS, RP, and EM reviewed and edited the manuscript. All authors listed above have made a substantial, direct and intellectual contribution to this work, contributed to manuscript revision, read, and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be a potential conflict of interest.

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High-Frequency Repetitive Transcranial Magnetic Stimulation Over the Left Dorsolateral Prefrontal Cortex Shortly Alleviates Fatigue in Patients With Multiple System Atrophy: A Randomized Controlled Trial

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Background: Fatigue is a common symptom in patients with Multiple system atrophy (MSA), but effective treatments remain elusive. The present study aims to investigate whether high-frequency repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex (DLPFC) could relieve fatigue in patients with MSA.

Methods: This is a single-center, randomized and double-blind trial. Twenty-two patients with MSA and fatigue were randomly allocated to receive 10 sessions of either active ($N = 11$) or sham ($N = 11$) 10 Hz rTMS over the left DLPFC. The participants were assessed at baseline (T0), after the last session of treatment (T1), and at 2-week (T2), and 4-week (T3) follow-up timepoints. The primary outcomes were Fatigue Severity Scale-9 (FSS-9) scores, with Unified Multiple System Atrophy Rating Scale (UMSARS), 17-item Hamilton Depression Scale (HAMD-17), and Hamilton Anxiety Scale (HAMA) as secondary outcomes.

Results: Two-way repeated ANOVAs revealed significant group × time interactions for FSS-9 scores ($p < 0.001$), HAMD-17 scores ($p = 0.01$), HAMA scores ($p = 0.01$), and UMRSA part II ($p = 0.05$). *Post-hoc* analyses showed that compared to T0, the active group exhibited remarkable improvements in FSS-9 and UMRSA part II scores at T1 and T2, but not at T3, and also in HAMD-17 and HAMA scores at T1, T2, and T3. No significant improvement was found in the sham group.

Conclusion: High-frequency rTMS over the left DLPFC could provide short-term improvements for alleviating fatigue in patients with MSA, but the beneficial effects last no more than 4 weeks.

Keywords: transcranial magnetic stimulation, the left dorsolateral prefrontal cortex, multiple system atrophy, fatigue, effective

INTRODUCTION

Multiple system atrophy (MSA), an orphan, adult-onset, sporadic, progressive neurodegenerative disease, is characterized by Parkinsonian features, cerebellar ataxia, and autonomic failure in various combinations (1). Early and severe autonomic failure is a core feature of MSA, including fatigue (2). Studies have shown that fatigue, an independent non-motor symptom, is one of the most common and major problems for 38–61% MSA patients, which contributes greatly to reduced social participation and quality of life (3–5). Treatment of fatigue can be very challenging, as till now there is no widely accepted treatment protocol available, including pharmacological treatment, deep brain stimulation, and rehabilitation strategies (5, 6).

Repetitive transcranial magnetic stimulation (rTMS), a potent tool and non-invasive means of electrically stimulating neurons in the cerebral cortex, is able to modify neuronal activity of targeted cortical areas and has been widely applied to treat various neurological conditions (7). Several studies have shown that rTMS could alleviate the severity of motor disability in MSA patients (8–10). To our best knowledge, however, no study has so far specifically investigated the effects of rTMS on fatigue in patients with MSA. Previous studies have demonstrated that rTMS over the left dorsolateral prefrontal cortex (DLPFC) help improve fatigue symptom in some other neurological disorders, including fibromyalgia, myalgic encephalomyelitis, and multiple sclerosis (11–14). Moreover, high-frequency rTMS with an optimal frequency of 10 Hz applied to the DLPFC has been suggested as a potent treatment for fatigue with a Level A evidence (11–14). Here, in the present study, we aimed to investigate the effect of high-frequency rTMS over the left DLPFC on fatigue in patients with MSA. We hypothesized that high-frequency rTMS over the left DLPFC can alleviate fatigue in patients with MSA.

MATERIALS AND METHODS

Participants

Twenty-two MSA patients with fatigue were eligible for the study from the Movement Disorders Center of the Xuanwu Hospital of Capital Medical University in Beijing, China. Patients were diagnosed as possible or probable MSA according to the second consensus statement on the diagnosis of MSA (2). Inclusion criteria were: (a) 30–75 years old, (b) Presence of clinical fatigue: Fatigue Severity Scale-9 (FSS) $\geq$36, and (c) stable anti-Parkinsonian therapy for $\geq$4 weeks and constant medication regimens throughout the trial. Exclusion criteria included: (a) Mini-Mental State Examination scores (MMSE) $\leq$24, (b) presence of contraindications for rTMS. The study protocol was approved and supervised by the Xuanwu Hospital Ethics Committee; all patients had agreed and confirmed informed consent prior to the study. The present study was registered at the Clinical Trial Registration (http://www.clinicaltrials.gov, NCT 04313530).

Experimental Design

This study was a single-center, randomized, double-blind, and sham-controlled trial, in which the 22 participants were randomly assigned (with 1:1 ratio) with sealed envelopes into two groups to receive either 10-Hz rTMS ($N = 11$) or sham stimulation ($N = 11$) over the left DLPFC. Both the participants and researchers were blind to the randomization group, only the clinician responsible for the rTMS protocols was unmasked to the randomization sequence.

rTMS and Sham Protocols

Magnetic stimulation was applied using a 7-cm, handheld, figure-of-eight coil was connected to a biphasic magnetic stimulator (Magstim Rapid; TheMagstim Co. Ltd., UK). The treatment protocol was performed in a total of 10 sessions over two successive weeks, consisting of one session per day for five consecutive days followed by a 1-day interval. Intervention was given at approximately the same time of day for each participant. The rTMS parameters used in the present study were referred to several previous studies, which have reported beneficial effects of rTMS on fatigue (11–14). That is, each session consisted of 20 series of 2-s 10 Hz pulses followed by a 18 s interval, with an intensity of 100% resting motor threshold (RMT), which gave a total of 1,200 pulses per session. The RMT is defined as the minimum intensity to evoke a visible voluntary contraction of the target muscle, the thenar muscles of the right hand, in 50% of successive trials. The coil was oriented at a 45° angle to the midsagittal plane (15) and was fixed to an arm that could be adjusted in three dimensions. Sham stimulation protocol was same as the rTMS protocol, except the coil was oriented at a 90° angle to the midsagittal plane (15), which could produce similar sounds and sensations as active stimulation while not inducing currents within the brain. All the participants were arranged at different time to avoid them from discussing with each other which ensured blinding during the data collection process.

Clinical Assessments

The participants underwent clinical assessments at baseline (T0), and three follow-up timepoints, that is, immediately after the tenth treatment session (T1), 2 weeks (T2), and 4 weeks (T3) after T1. The primary outcome was the FSS score, a self-reported scale for assessing the fatigue severity over the last 2 weeks. The secondary outcomes were the part I and II of the Unified

Multiple System Atrophy Rating Scale (UMSARS), the Hamilton Depression Scale (HAMD), and the Hamilton Anxiety Scale (HAMA), which were used to assess motor performance and non-motor symptoms, respectively.

Side Effects

The safety of rTMS was assessed by monitoring the occurrence of adverse effects for all patients during the whole study process. These side effects were recorded at the T0, T1, T2, and T3 timepoints and were grouped into the following categories: (1) headache, (2) site discomfort, (3) nausea, (4) dizziness, and (5) others.

Statistical Analysis

All statistical analyses were performed using SPSS Version 26 (IBM, Chicago, IL, USA). Demographic data were presented as mean ± SD for continuous variables and ratios or percentages for categorical variable. Independent two samples *t*-test was used to compare continuous variables, and the χ^2-test was performed for the comparison of categorical variables. Two-way repeated ANOVA, with Group (rTMS/sham group) as between-subject factor and Time (T0, T1, T2, T3) as within-subject factor, was applied to estimate the effects of rTMS on the clinical outcomes. The threshold for the level of significance was set at $\alpha = 0.05$. In all cases, *P*-values < 0.05 was considered to defined as statistically significant result.

RESULTS

Participants

The demographic and clinical characteristics of the participants are presented in **Table 1**. The rTMS and sham group had similar baseline characteristics including age, gender, H-Y stage, levodopa-equivalent daily dose (LEDD), UMSARS scores, HAMA, HAMD, GDS, MMSE, and MoCA. The severity of fatigue was basically the same between the two groups.

Clinical Efficacy: Primary Outcome

As shown in **Table 2** and **Figure 1**, in the comparison of FSS score, there was a significant Group × Time interaction ($p < 0.01$), as well as significant Group ($p = 0.02$), and Time ($p < 0.001$) main effects. *Post-hoc* analyses showed that compared to T0, the rTMS group exhibited remarkable improvements in FSS-9 scores at T1 and T2, but not at T3. No significant improvement was found in the sham group.

Clinical Efficacy: Secondary Outcomes

Our analyses revealed significant Group × Time interactions for HAMA scores ($P = 0.01$), HAMD scores ($P = 0.01$), and UMSARS-II scores ($P = 0.05$), indicating that rTMS yielded improvements in these scores compared to sham stimulation. *Post-hoc* analyses showed that compared to T0, HAMA, and HAMD scores were significantly reduced in rTMS group at T1, T2, and T3; while the UMSARS-II scores were significantly improved at T1 and T2, but not at T3. We did not find any significant Group × Time interaction in the comparison of UMSARS-I scores.

TABLE 1 | Demographic and clinical features of participants.

Variables	rTMS group (*N* = 11)	Sham group (*N* = 11)	*P*
Gender (female/male)	6/5	6/5	1.00
Age (years)	58.64 ± 5.50	59.00 ± 6.02	0.73
Disease duration (years)	2.00 ± 1.00	1.91 ± 1.22	0.35
Subtypes (MSA-P/MSA-C)	6/5	4/7	1.00
H-Y stage	2.95 ± 1.19	2.86 ± 1.23	0.44
UMSARS I	18.45 ± 8.03	22.45 ± 6.76	0.99
UMSARS II	18.82 ± 9.31	20.27 ± 8.01	0.91
UMSARS IV	2.18 ± 1.25	2.72 ± 1.27	0.48
LEDD (mg/d)	295.45 ± 313.41	234.09 ± 295.80	0.37
MMSE	28.64 ± 1.86	27.64 ± 1.57	0.49
MoCA	23.82 ± 3.40	22.91 ± 3.75	0.69
FSS	51.36 ± 10.58	51.73 ± 8.92	0.28
HAMA	16.82 ± 10.83	14.27 ± 5.95	0.09
HAMD	15.27 ± 7.17	12.45 ± 5.24	0.25
GDS	17.09 ± 7.09	16.45 ± 6.31	0.53
ESS	7.72 ± 6.96	5.18 ± 3.49	0.23
RBDQ-HK	25.27 ± 13.30	23.18 ± 15.52	0.57
ADL	27.27 ± 11.74	33.18 ± 11.96	0.71

Continuous variables are represented by Means and standard deviations. ADL, activities of daily living; ESS, Epworth Sleepiness Scales; FSS, Fatigue Severity Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; H–Y stage, Hoehn and Yahr stage; LEDD, levodopa-equivalent daily dose; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MSA-C, Cerebellar subtype of Multiple system atrophy; MSA-P, Parkinsonism subtype of Multiple system atrophy; UMSARS I, Unified Multiple-System Atrophy Rating Scale Part I: historical; UMSARS S II, Unified Multiple-System Atrophy Rating Scale Part II: motor examination; UMSARS IV, Unified Multiple-System Atrophy Rating Scale Part IV: global disability scale; RBDQ-HK, Rapid-eye-movement Sleep Behavior Disorder Questionnaire HongKong.

Adverse Events

Few transient and minor adverse events were reported during the stimulation sessions only. Two patients in the rTMS group reported mild and transient headaches after the first session, which lasted around 10 min; while one patient in the sham group reported minor dizziness after the first stimulation.

DISCUSSION

In this randomized, double-blind, sham-controlled study, we demonstrated that high-frequency rTMS over the left DLPFC induced a short-lasting improvement in fatigue in patients with MSA. In addition, patients' motor symptoms, as well as depression and anxiety symptoms, were also shortly improved to a certain extent after the active rTMS. Though the beneficial effects lasted no more than 4 weeks, we suggest that the high-frequency rTMS over the left DLPFC could still be used as an available therapeutic protocol for alleviating fatigue in patients with MSA.

The beneficial effects of rTMS on fatigue have been previously reported in several neurological disorders, such as fibromyalgia, myalgic encephalomyelitis, and multiple sclerosis, as fatigue

TABLE 2 | Clinical efficiency of the rTMS and Sham group.

	rTMS group	Sham group		*DF*	*F*	*P*
FSS						
T0	51.36 ± 10.58	51.73 ± 8.92	Group	1	6.13	0.02
T1	32.00 ± 9.45	49.91 ± 9.85	Time	1	36.34	<0.001
T2	36.91 ± 7.27	50.82 ± 7.65	Group × time	1	21.53	<0.001
T3	51.91 ± 9.05	53.36 ± 7.46				
HAMA						
T0	16.82 ± 10.83	14.27 ± 5.95	Group	1	0.56	0.46
T1	9.36 ± 6.71	13.64 ± 4.93	Time	1.60	7.09	0.01
T2	11.46 ± 7.17	14.55 ± 5.17	Group × time	1.60	6.28	0.01
T3	11.64 ± 8.71	15.27 ± 5.24				
HAMD						
T0	15.27 ± 7.17	12.45 ± 5.24	Group	1	2.34	0.14
T1	7.64 ± 2.69	12.64 ± 4.27	Time	1.92	4.29	0.02
T2	10.27 ± 4.54	13.09 ± 3.89	Group × time	1.92	5.83	0.01
T3	9.91 ± 4.28	14.36 ± 4.39				
UMSARS-I						
T0	18.45 ± 8.03	22.45 ± 6.76	Group	1	2.22	0.15
T1	17.55±7.83	22.18 ± 8.32	Time	1.49	4.58	0.03
T2	18.00 ± 7.71	23.27 ± 7.55	Group × time	1.49	1.13	0.32
T3	18.73 ± 7.70	24.09 ± 7.52				
UMSARS-II						
T0	18.82 ± 9.32	20.27 ± 8.01	Group	1	0.59	0.45
T1	17.18 ± 8.55	20.73 ± 8.10	Time	1.84	10.48	<0.001
T2	18.36 ± 9.20	21.64 ± 8.10	Group × time	1.84	3.43	0.05
T3	19.45 ± 9.08	22.36 ± 8.43				

Continuous variables are represented by Means and standard deviations. FSS, Fatigue Severity Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; UMSARS I, Unified Multiple-System Atrophy Rating Scale Part I: historical; UMSARS S II, Unified Multiple-System Atrophy Rating Scale Part II: motor examination.

is a common symptom in these disorders and contributes substantially to decrements in quality of life and disability (15). A randomized-controlled trial provided evidence that 4 weeks of daily high-frequency (10 Hz) rTMS over the left DLPFC rTMS is able to improve fatigue in patients with fibromyalgia, and provided impetus that the utility rTMS may be an available approach for the relief of fatigue in related disorders (11). Another similar study investigating rTMS effect in patients with fibromyalgia revealed significant improvements in fatigue, depression, and quality of life in the rTMS treatment group when accepting daily high-frequency (10 Hz) rTMS to the left DLPFC over 3 weeks (12). Recently, Yang et al. (13) reported that rTMS over the left DLPFC improves fatigue in patients with myalgic encephalomyelitis and suggested that rTMS can be a novel therapeutic intervention for fatigue. None of the patients previously experienced serious side effects in these studies, which provide compelling evidence for the safety of rTMS treatment. These studies suggest that 10 Hz rTMS over the left DLPFC may be an effective and safe strategy to relieve fatigue in patients with chronic neurological disorders. In the present study, similarly, our findings also provided evidence for the beneficial effects of rTMS, indicating that high-frequency rTMS over the left DLPFC may be a safe and effective therapy for alleviating fatigue in patients with MSA.

It is well-known that the most common and widely used site for rTMS relieving depression is DLPFC (15–18). High-frequency rTMS over the left DLPFC has been suggested as Level A evidence (definite efficacy) for relieving depression, and as Level B evidence (probable efficacy) for improving Parkinson's disease related depression (19). Though fatigue and depression have some clinical features in common, fatigue is distinguishable from depression and indeed an independent entity from depression (20). Fatigue refers to subjective sensations of weariness, increasing sense of effort, mismatch between effort expended and actual performance, or exhaustion (20). However, fatigue and depression, both of which are common non-motor symptoms in patients with MSA, do have similar pathophysiological mechanisms, including serotonergic dysfunction in basal ganglia and limbic circuits, which contribute to dysfunction of prefrontal-basal ganglia loops and impaired integration of limbic input and motor functions (6). Although no evidence-based guidelines have been proposed on the therapeutic use of rTMS for fatigue yet (19), the left DLPFC has been chosen as the optimal stimulation target for fatigue treatment in several previous studies (11–13). Here, we used the same stimulation target and demonstrated similar favorable results. It has been generally suggested that rTMS can not only generate biological effects on the stimulation site per se, but also on other distant sites connected by the activated networks (21). High-frequency rTMS generates a remarkable change of blood-oxygen-level-dependent (BOLD) signal within large and distant areas of the cortex (22). Several studies have also

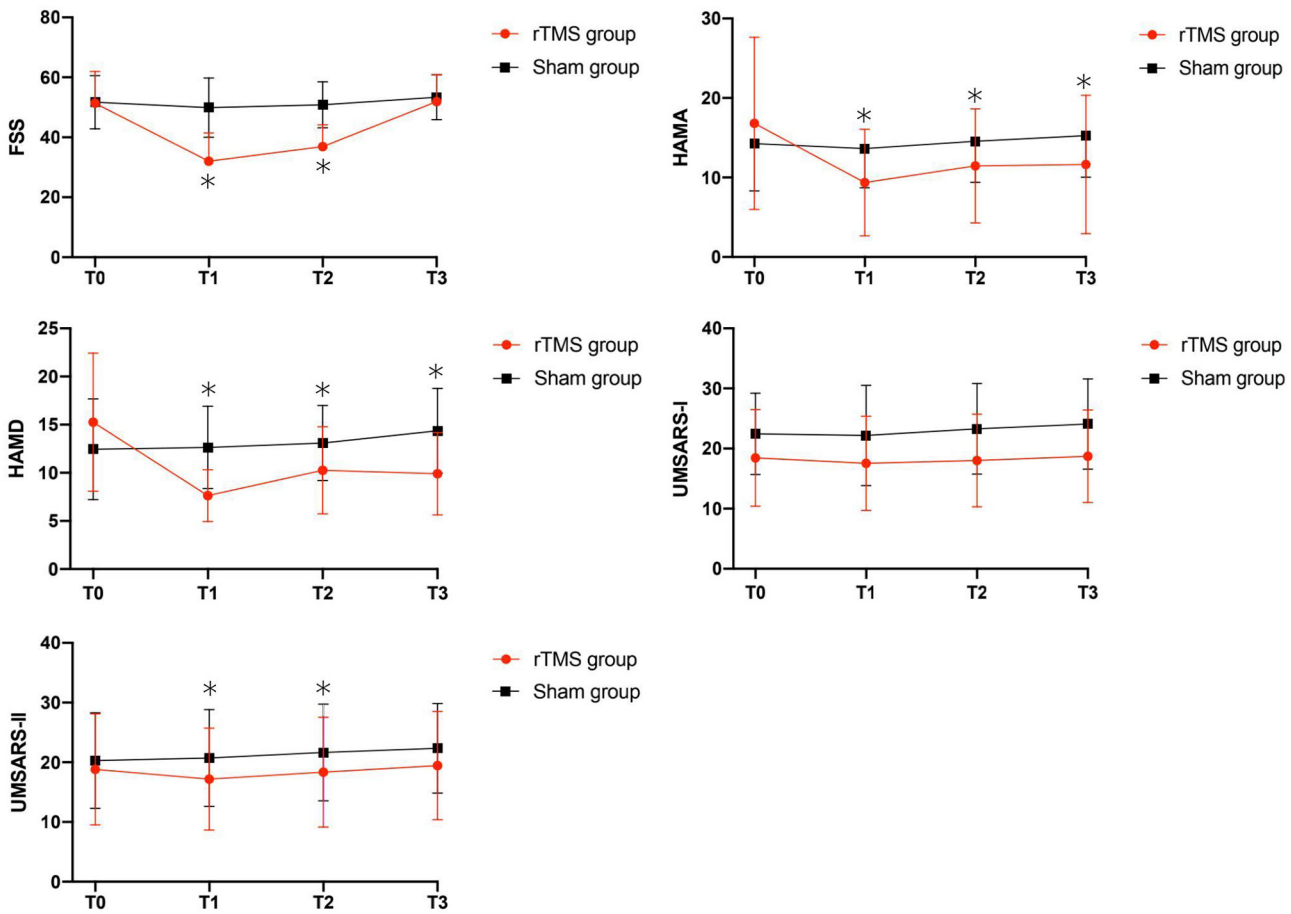

FIGURE 1 | Clinical score changes after the rTMS, including FSS, HAMA, HAMD, UMSARS-I and UMSARS-II scores. Red, rTMS group; black, sham group. **Post-hoc* analysis shows significant difference as compared to the baseline (T0) in the group.

proved that high-frequency rTMS of the DLPFC can increase dopamine release within basal ganglia (23, 24). Furthermore, the effects of high-frequency rTMS might be the result of not only a direct enhancement of motor cortex excitability (25), but also a decrease of inhibitory γ-aminobutyric acid (GABA) neurotransmission-mediated intracortical inhibition (26). Therefore, high-frequency rTMS over DLPFC is assumed to increase the cortex excitability and dopamine release and modulate cortical plastic, which may impart a beneficial effect on fatigue symptom.

In the present study, though we found that rTMS could improve fatigue in MSA patients, the beneficial effect lasted no more than 4 weeks. Differently, in another two randomized, placebo-controlled trials (11, 12), both studies showed long-term favorable rTMS effects on relieving fatigue in patients with fibromyalgia. Such discrepancy may be attributed to the different parameters used in our study, that is, with an intensity of 100% RMT (vs. 120% RMT in their studies), 1,200 pluses per session (vs. 3,000 pulses) and a total of 2 weeks duration (vs. 4 weeks). More importantly, MSA is characterized by a relentless worsening of motor and non-motor symptoms, with a more rapid progression at the onset (1); whereas fibromyalgia is a mild chronic disorder (11). This indicates that at the time of follow-up, patients may already experience aggravation of motor symptoms and non-motor symptoms, which may also contribute to the inconsistency.

In addition, our results showed that rTMS over left DLPFC could also improve depression and anxiety, as well as motor symptoms in patients with MSA. It is generally known that rTMS over the left DLPFC could improve depression, including Parkinson's disease-related depression (16–18). The improvements in MSA-related depression symptoms observed in our study are consistent with the results of many previous studies. Motor symptom scores were also statistically significant improvement between the two groups. As noted previously, the magnetic stimulus has distant actions, which means it not only activates local inter-neuronal circuits, but also those fibers projecting to distant structures. The distant actions of rTMS were initially demonstrated in some studies, which showed that rTMS over the DLPFC can modulated M1 excitability, even at a higher extent than direct M1 stimulation itself

(15, 17). It may provide evidence that motor symptoms were improved through rTMS stimulating over the DLPFC in our study.

Our study has several limitations. First, the study was conducted in a single center and the number of participants is relatively small. Second, as the diagnosis of early MSA is full of challenge, only patients with a clear diagnosis were enrolled in our study, indicating a relatively more sever disease. Future studies with a bigger sample size enrolling more MSA patients in the early stage are warranted to clarify the rTMS effect on fatigue in MSA patients.

CONCLUSIONS

In conclusion, our findings suggest that high-frequency rTMS over left DLPFC may ultimately serve as an add-on therapy for alleviating fatigue in MSA patients, though the beneficial effects last no more than 4 weeks. In the future, more optimistic rTMS protocols and techniques are needed to prolong the treatment effect in routine clinical practice.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Xuanwu Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PC, J-HM, and HS designed the study. JP carried out data collection, analyzed the data, and drafted the manuscript. PC and T-MM revised the manuscript. All authors have read and approved the final version for publication.

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Effect of Theta Burst Stimulation-Patterned rTMS on Motor and Nonmotor Dysfunction of Parkinson's Disease: A Systematic Review and Metaanalysis

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Background: Theta burst stimulation (TBS), a type of patterned repetitive transcranial magnetic stimulation (rTMS), has several advantages, such as short time of single treatment and low stimulation intensity compared with traditional rTMS. Since the efficacy of TBS on the symptoms of Parkinson's disease (PD) was inconsistent among different studies, we systematically searched these studies and quantitatively analyzed the therapeutic effect of TBS for patients with PD.

Methods: We followed the recommended PRISMA guidelines for systematic reviews. Studies from PubMed, EMBASE, CENTRAL, and ClinicalTrials.gov from January 1, 2005 of each database to September 30, 2021 were analyzed. We also manually retrieved studies of reference.

Results: Eight eligible studies with 189 participants (received real TBS and/or sham TBS) were included. This metaanalysis found that TBS did not significantly improve Unified Parkinson's Disease Rating Scale part III (UPDRS-III) score in the "on" medicine state (SMD = −0.06; 95% CI, −0.37 to 0.25; $p = 0.69$; $I^2 = 0\%$), while, it brought significant improvement of UPDRS-III scores in the "off" medicine state (SMD = −0.37; 95% CI, −0.65 to −0.09; $p < 0.01$; $I^2 = 19\%$). Subgroup analysis found that merely continuous TBS (cTBS) over the supplementary motor area (SMA) brought significant improvement of UPDRS-III score (SMD = −0.63; 95% CI, −1.02 to −0.25; $p < 0.01$). TBS had insignificant effectiveness for upper limb movement disorder both in the "on" and "off" medicine status (SMD = −0.07; 95% CI, −0.36 to 0.22; $p = 0.64$; $I^2 = 0\%$; SMD = −0.21; 95% CI, −0.57 to 0.15; $p = 0.26$; $I^2 = 0\%$; respectively). TBS significantly improved slowing of gait in the "off" medicine status (SMD = −0.37; 95% CI, −0.71 to −0.03; $p = 0.03$; $I^2 = 0\%$). Subgroup analysis suggested that only intermittent TBS (iTBS) over the primary motor cortex (M1) + dorsolateral prefrontal cortex (DLPFC) had significant difference (SMD = −0.57; 95% CI, −1.13 to −0.01; $p = 0.04$). Additionally, iTBS over the M1+ DLPFC had a short-term (within 2 weeks) therapeutic effect on PD depression (MD = −2.93; 95% CI, −5.52 to −0.33; $p = 0.03$).

Conclusion: Our study demonstrated that cTBS over the SMA could significantly improve the UPDRS-III score for PD patients in the "off," not in the "on," medicine state. TBS could not bring significant improvement of upper limb movement dysfunction. ITBS over the M1+DLPFC could significantly improve the slowing of gait in the "off" medicine status. Additionally, iTBS over the M1+DLPFC has a short-term (within 2 weeks) therapeutic effect on PD depression. Further RCTs of a large sample, and excellent design are needed to confirm our conclusions.

Keywords: Parkinson's disease, repetitive transcranial magnetic stimulation, theta burst stimulation, non-invasive brain stimulation, meta-analysis

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder. The prevalence of PD in industrialized countries is generally estimated at 0.3% of the entire population and ∼1% of people over 60 years of age (1). The classical motor symptoms of PD include bradykinesia, muscular rigidity, rest tremor, and postural and gait impairment. Nonmotor dysfunction, such as depression, and cognitive impairment are also frequently present (2). PD is associated with functional deficits in multiple brain areas, including basal ganglia nuclei, cerebellum, and cortical areas (3).

Transcranial magnetic stimulation (TMS) is a non-invasive and painless method to stimulate the human brain (4). Repetitive TMS (rTMS) refers to the application of trains of regularly repeating TMS pulses. Repeated applications of it can produce even long-term effects that last for weeks to months (4–6). In addition to the local stimulatory effect on the cortical area, rTMS can also induce a distant effect on other cortical and subcortical brain regions, probably *via* the cortico-basal, ganglia–thalamocortical motor circuit (7, 8). The previous work showed that high-frequency (HF) rTMS targeting bilateral primary motor cortex (M1) regions could improve the motor performance in patients with PD (9–14), and HF rTMS of left dorsolateral prefrontal cortex (DLPFC) had an antidepressant effect on patients with PD (13, 15, 16). Relevant evidence-based guidelines also gave recommendations on the therapeutic effect of rTMS in motor symptoms and depression in patients with PD (17).

Theta burst stimulation (TBS), a variation of rTMS, may facilitate induction of plasticity mechanisms (18), which affords a short stimulation duration, low stimulation pulse intensity, and a possibility to improve rTMS efficiency (19). When TBS is delivered continuously (cTBS), it decreases cortical excitability, whereas intermittent TBS (iTBS) increases cortical excitability (20). Since TBS may have fewer adverse effects, such as seizures, impairment of hearing and cognition function (21), and shorter time of single intervention (within several minutes) compared with traditional rTMS, in recent years, an increasing number of studies have begun to explore the therapeutic effect of TBS on the motor and nonmotor symptoms in patients with PD (22–35). Nevertheless, there are inconsistencies of conclusion among these studies. Besides, the latest evidence-based guidelines did not include recommendations on the therapeutic effect of TBS in patients with PD (17), which brought dilemma to clinical practice. This systematic review and metaanalysis examined the studies on the therapeutic effect and tolerability of TBS for motor and nonmotor dysfunction in patients with PD.

METHODS

Study Design

Our meta-analysis is according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (36).

Study Search and Selection

We systematically retrieved relevant literature published in PubMed, EMBASE, and CENTRAL, and ClinicalTrials.gov from January 1, 2005 to September 30, 2021. Database searches were limited to articles published in English. Besides, we also manually retrieved studies of reference. The search terms we used to query the databases were as follows: ("Parkinson Disease" or "Parkinson's Disease" or "Parkinsonism") and ("theta-burst stimulation" or "TBS" or "repetitive transcranial magnetic stimulation" or "rTMS" or "non-invasive stimulation)". Studies were included if they met the "PICOS" as follows: population [patients with a diagnosis of idiopathic PD according to the UK PD Brain Bank criteria, (37)], intervention (received true patterned rTMS: TBS), comparators (sham TBS), outcome measure (clinical evaluation of motor and nonmotor symptoms), and study design (clinical trial). Studies were excluded if: (1) they were clear from the article title or abstract that did not meet the inclusion criteria, (2) they did not have data available (mean ± SD/SE) for effect size estimation or lacked sufficient reporting detail, such as conference abstract or presentation review articles, editorials, and other nonclinical trials.

Two investigators (BC and TZ) independently screened the titles and abstracts of the literature and decided whether the article should be further retrieved according to the inclusion and exclusion criteria. Those that could not be excluded were retrieved, and the full text was reviewed by the two reviewers (WZ and LS). For articles that may be included, if reported data were insufficient for data analysis, we contacted the corresponding author by email to request access to additional data. Any disagreements were resolved by discussion with a third reviewer (SZ).

Data Extraction

The following information was extracted by two reviewers (BC and TZ) independently, from included studies: first author, year of publication, study design, patients' age, sample size, PD duration, gender distribution, Hoehn and Yahr scale, timepoints of assessment, neuropsychological symptom assessment scale, TBS protocols, and study quality.

Quality Assessment

The quality assessments were performed with the PEDro scale (38), which is based on the Delphi List criteria (39) and is considered valid and reliable (38, 40). The PEDro scale assesses the methodological quality of a study based on important criteria, such as concealed allocation, intention-to-treat analysis, and the adequacy of follow-up. These characteristics make the PEDro scale a useful tool for assessing the quality of physical therapy and rehabilitation trials. The PEDro scale consisted of 11 items. One item on the PEDro scale (eligibility criteria) is related to external validity and is generally not used to calculate the method score (41, 42). Therefore, a score of 0–10 was allocated to each study (9–10: excellent; 6–8: good; 4–5: fair; and ≤3: poor) (43). Additionally, publication bias on included studies was assessed by the funnel plot and bias tests. If the plot is symmetrical or $p > 0.05$ from bias tests, it should be deemed not publication bias.

Data Synthesis and Statistical Analysis

The RevMan5.3 and Stata16 software were used to combine the data when at least two studies reported similar clinical outcomes. For quantitative synthesis, the effect size was calculated based on the mean prepost change in the treatment group minus the mean prepost change in the comparison group, divided by the pooled pretest standard deviation (44). If the unit of measurement was consistent across trials, the results were presented as the weighted mean difference (MD) with 95% confidence intervals (CIs) or else replaced by the standard mean difference (SMD). Data from the standard error of the mean (SEM) were converted to the standard deviation (SD) using sample size in the formula $SD = SEM \times \sqrt{N}$ (45). We used the random-effects model and fixed-effects model to calculate the pooled SMD and generated forest plots to display the single study and pooled-effect size. The Chi-square test and I^2 statistic were used to assess heterogeneity among studies. Heterogeneity was considered significant if the p-value of the χ^2 test was < 0.1 or $I^2 > 50\%$ (46–48). If there was no significant heterogeneity, the fixed-effects model was used to pool data across the included studies; otherwise, the random-effects model was used (49, 50).

RESULTS

Search Results

Our search strategy to query limited databases retrieved 1,360 studies, while, many of these were identified as duplicates. After screening the titles and abstracts, 375 records were excluded as they did not meet the inclusion criteria ("PICOS") in our work, and we determined 59 articles for full-text reading. Finally, eight studies were included in our metaanalysis (23–25, 28–30, 32, 34). The literature selection is presented in **Figure 1**.

Study Characteristics

Eight eligible studies included for metaanalysis had 189 participants (received real TBS and/or sham TBS).

Four studies (24, 25, 30, 32) were parallel-controlled and four studies (23, 28, 29, 34) were crossover-controlled. Five studies gave single-session (23, 25, 28, 29, 34) and three studies gave multiple sessions (total of six to 42 sessions) (24, 30, 32). Four studies evaluated the immediate effects after TBS using clinical symptom assessment scales (23, 25, 28, 29, 34), and three studies conducted a follow-up of clinical effects range from 1 week to 1 month after TBS intervention (24, 30, 32). Two studies assessed the therapeutic effects of TBS only in the "on" anti-Parkinsonism medicine state (29, 51). While, two studies evaluated only in the "off" medicine status (under the anti-Parkinsonism medicine withdrawal status for at least 12 hours) (23, 34). Besides, four studies assessed the therapeutic effects of TBS both in the "on" and "off" medicine state (24, 25, 28, 32). The characteristics of the included studies are summarized in **Table 1**, and the TBS intervention parameters are summarized in **Table 2**.

Quality Assessment

The PEDro scores of the included studies ranged from 6 to 9, with mean scores of 7. Two studies were of excellent quality (24, 32) and five studies were of good quality. No studies (23, 25, 28–30, 34) were assessed as fair quality or poor quality. A detailed evaluation of the methodological quality of included studies for metaanalysis is provided in **Table 3**. Egger's test by Stata16 showed no significant publication bias for all clinical symptoms of quantitative analysis.

Effects of TBS on UPDRS-III Score

Six included studies provided the date of Unified Parkinson's Disease Rating Scale part III (UPDRS-III) score in the "on" and/or "off" medicine status (23, 24, 28, 30, 32, 34). The results showed that there was an insignificant difference in UPDRS-III score between the real TBS and the sham TBS in the "on" medicine state (SMD = −0.06; 95% CI, −0.37 to 0.25; $P = 0.69$; $I^2 = 0\%$. **Figure 2A**). Subgroup analysis based on different types of TBS (iTBS/cTBS) over the related brain targets (iTBS/cTBS-brain targets) showed insignificant differences among groups [iTBS- M1+DLPFC, SMD = −0.07; 95% CI, −0.41 to 0.26; $p = 0.68$, vs. cTBS-supplementary motor area (SMA), SMD = −0.01; 95% CI, −0.78 to 076; $p = 0.98$, **Figure 2A**]. Contrarily, there was a significant difference of UPDRS-III score between real TBS and sham TBS in the "off" medicine condition (SMD = −0.37; 95% CI, −0.65 to −0.09; $p < 0.01$; $I^2 = 19\%$, **Figure 2B**). Further subgroup analyses based on iTBS/cTBS-brain targets showed that merely cTBS-SMA brought significant improvement of UPDRS-III score (SMD = −0.63; 95% CI, −1.02 to −0.25; $p < 0.01$).

Effects of TBS on Upper Limb Movement

Five studies reported changes in symptom scale score concerning upper limb motor dysfunction in "on" and/or "off" medicine status (23–25, 28–30). UPDRS-III bradykinesia of sequential hand and arm movement time items; UPDRS-III finger tapping, hand movement, and arm rigidity items; and Purdue Pegboard test (PPT) were involved totally. Results showed that there was

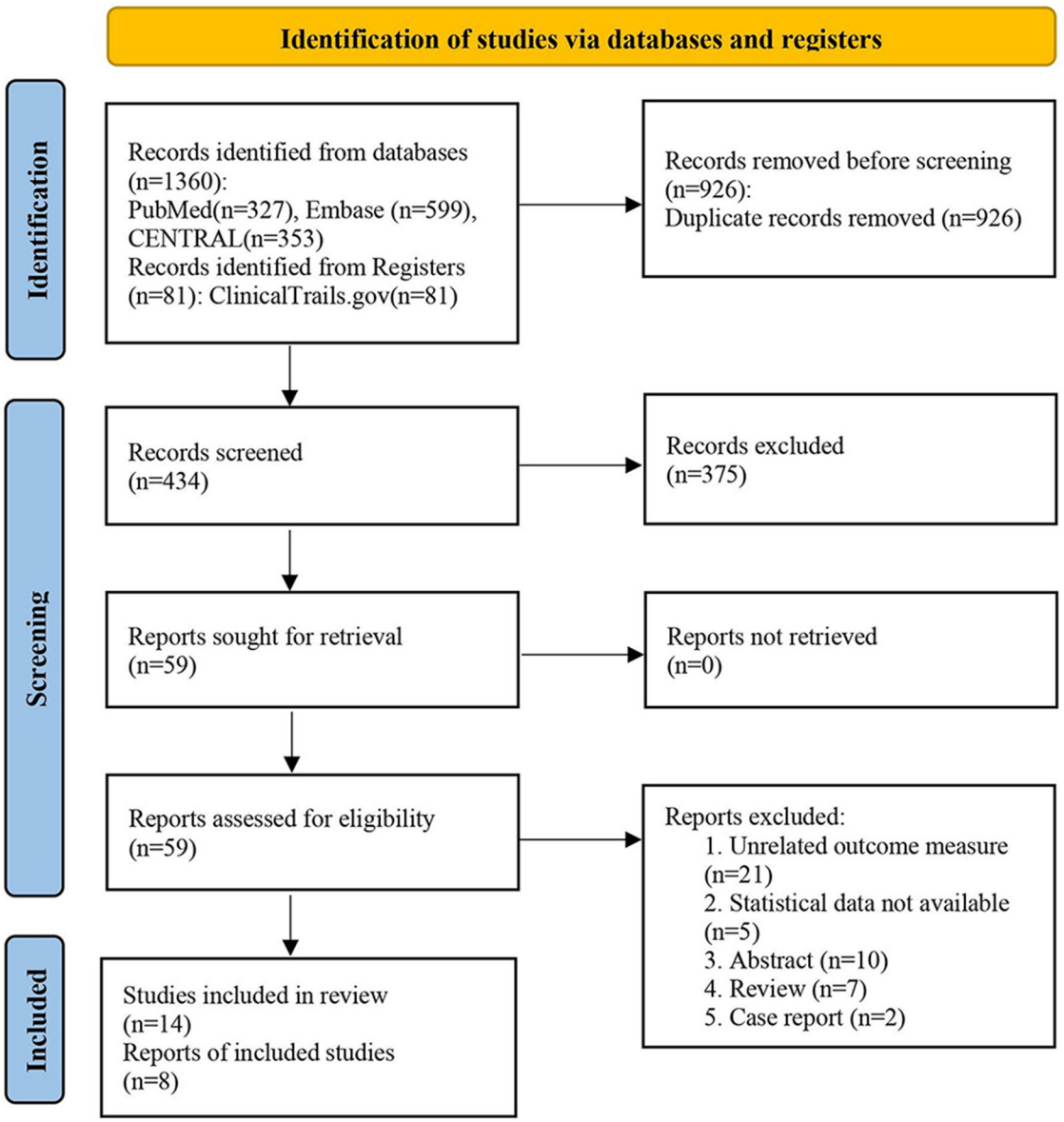

FIGURE 1 | PRISMA search strategy flow diagram of the studies selection process.

an insignificant difference in the upper limb motor disorder scores between real TBS and sham TBS in the "on" medicine status (SMD = −0.07; 95% CI, −0.36 to 0.22; $p = 0.64$; $I^2 = 0\%$, **Figure 3A**). Subgroup analysis based on iTBS/cTBS-brain targets showed insignificant differences among groups [iTBS-M1+DLPFC, SMD = −0.26; 95% CI, −0.72 to 0.20; $P = 0.26$, vs. cTBS-SMA, SMD = 0.01; 95% CI, −0.53 to 0.56, $P = 0.96$, vs. iTBS- dorsal premotor cortex (PMd), SMD = 0.29; 95% CI, −0.43 to 1.01, $p = 0.43$, vs. cTBS-PMd, SMD = −0.10; 95% CI, −0.81 to 0.62; $P = 0.79$. **Figure 3A**]. Similarly, there was no significant difference in the "off" medicine status (SMD = −0.21; 95% CI, −0.57 to 0.15; $P = 0.26$; $I^2 = 0\%$, **Figure 3B**). Subgroup analysis based on iTBS/cTBS-brain targets shown insignificant differences among groups (iTBS-M1+DLPFC, SMD = −0.36; 95% CI, −0.91 to 0.19; $P = 0.20$, vs. cTBS-M1, SMD = 0.13; 95% CI, −0.85 to 1.11; $P = 0.80$, vs. cTBS- SMA, SMD = −0.16; 95% CI, −0.70 to 0.39; $P = 0.57$. **Figure 3B**).

Effects of TBS on Gait Disorders

Two included studies reported the data of assessing the therapeutic effect on slowing of gait (including the time to walk 10 meters and 20 meters) (24, 32). The meta-analysis shown a significant difference of gait disorder in real TBS relative to sham TBS in the "off" medicine status (SMD = −0.37; 95%

TABLE 1 | Characteristics of included studies.

Study	Design	Age, y	Sample Size	PD duration, y	Sex (M/F)	HandY stage	Assessment time (pre-TBS, post-TBS)	Outcome measures (Clinical assessment)
Benninger et al. (24)	Parallel	E:62.1 ± 6.9 C:65.6 ± 9.0	E:13 C:13	E:10.8 ± 7.1 C:6.5 ± 3.4	E:7/6 C:11/2	E:2.6 ± 0.2[a] 3.0 ± 0.4[b] C:2.5 ± 0.1[a] 2.9 ± 0.2[b]	Baseline, 1th day, 1th month	Primary: Gait and bradykinesia by measuring UPDRS sub-items Secondary: UPDRS total, UPDRS-III, UPDRS-II, UPDRS- freezing, FAB, BDI, mental health, physical health, SRTT
Bologna et al. (27)	Crossover	61.9 ± 6.0	13	5.3 ± 4.46	9/4	NA	Baseline, 5th, 45th minute	MDS UPDRS-III items 3.17 (resting tremor amplitude)
Brugger et al. (34)	Crossover	64.30 (52.8–68.3) [c]	12	12.5 (10.5–15.0)[c]	10/2	2.0 (2.0–2.8) [c]	Baseline, immediately	UPDRS-III
Degardin et al. (25)	Parallel	E1:61.5 ± 8.5[a] 61.3 ± 9.6[b] E2:60.6 ± 11.8 C: 61.5 ± 9.9[a]	E1:11 E2:10 C:11	E1:6.8 ± 2.7[a] 6.2 ± 2.5[b] E2:1.8 ± 1 C: 8.2 ± 5.2[a]	E1:4/7[a] 3/5[b] E2:8/2 C:7/4	E1:2 ± 0.63[a] 2 ± 0.75[b] E2:1.3 ± 0.48 C:2.2 ± 0.63[a]	Baseline, immediately	UPDRS-III (finger tapping, hand movement and arm rigidity items from 0 to 4)
Eggers et al. (23)	Crossover	68.5 ± 5	8	4 ± 3	6/2	1.97 ± 0.58	Baseline, immediately	UPDRS-III (items 18–31, maximum: 108 points), PPT
Eggers et al. (28)	Crossover	E:60.8 ± 7.8[a] 64.7 ± 5.0[b]	E:13[a] 13[b]	E:7.1 ± 4.7[a] 5.8 ± 4.3[b]	6/7[a] 9/4[b]	1.7 ± 0.8[a] 1.8 ± 0.8[b]	Baseline, immediately	UPDRS-III (items 18–31, maximum: 108 points), PPT
He et al. (35)	Parallel	E:70.0 ± 6.3 C:74.8 ± 6.9	E:20 C:15	E:2.7 ± 1.5 C:2.5 ± 1.1	E:13/7 C:10/5	E:2.7 ± 1.1 C:2.5 ± 1.0	Baseline, immediately, 3rd month	RBANS, MoCA
Hill et al. (31)	Crossover	71.07 ± 5.11	14	4.86 ± 4.85	10/4	NA	Baseline, 5th, 30th min	BCST, N-Back tasks
Ji et al. (32)	Parallel	E: 61.7 ± 1.57 C: 60.2 ± 1.97	E:22 C:20	E: 4.3 ± 0.52 C: 5.3 ± 0.83	E:14/8 C:14/6	E:1.6 ± 0.12 C:1.7 ± 0.11	Baseline, 1st, 2nd week	Primary: UPDRS-III (2 weeks) Secondary: UPDRS-III (1 week), NMSS, timed up-and-go, 20-m walking
Koch et al. (22)	Parallel	64.7 ± 6.9	E:10 C:10	10.4 ± 4.3	NA	NA	Baseline, 2nd, 4th week	Global CAPSIT dyskinesia scale scores, UPDRS-III
Lang et al. (33)	Parallel	E: 68.43 ± 8.4 C:68.76 ± 8.3	E: 21 C: 20	E:5.95 ± 4.8 C:4.8 ± 4.0	E:14/7 C:13/7	NA	Baseline, 1th day, 1th month	Primary: Neuropsychological Tests battery according to five cognitive domains[d] Secondary: UPDRS-III, BDI-II, BAI
Trung et al. (30)	Parallel	E:71.3 ± 7.3 C:67.3 ± 5.2	E:14 C:14	E:10.39 ± 6.7 C:6.25 ± 3.0	E:8/6 C:11/3	1 to 3	Baseline,1st, 10th, 30th day	Primary: Neuropsychological Test battery according to cognitive domains[e] Secondary: SETS, BDI, BAI, AES, PDQ-39, UPDRS-III, MoCA
Vanbellingen et al. (29)	Crossover	66 ± 8.10	15	8.24 ± 4.64	11/4	2 ± 0.58	Baseline, immediately	CRT, Mod-MDS-UPDRS III, Jamar, proprioception (specific distal finger)
Zamir et al. (26)	Parallel	E:64.7 ± 10.3 C:63.1 ± 8.8	E:12 C:10	7.3 ± 3.2	E:7/5 C:4/6	NA	Baseline, Immediately	UPDRS-III

AES, Apathy Evaluation Scale; BAI, Beck Anxiety Inventory; BCST, the Berg's Card Sorting Test; BDI, Beck Depression Inventory; C, control group; CAPSIT, Core Assessment Program for Surgical Interventional Therapies; CRT, Coin rotation task; E, experimental group; FAB, Frontal Assessment Battery; HandY, Hoehn and Yahr scale; MDS, Movement Disorder Society; MoCA, Montreal Cognitive Assessment; NA, not available; NMSS, Non-Motor Syndrome Scale; PD, Parkinson's Disease; PDQ-39, Parkinson Daily Questionnaire-39; PPT, Purdue Pegboard Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SETS, Stanford Expectations of Treatment Scale; SRTT, Serial Reaction Time Task; TBS, theta-burst stimulation; UPDRS, Unified Parkinson's Disease Rating Scale (part II, activities of daily living; part III, motor examination; freezing, UPDRS II, item 14, freezing when walking); VAS, visual analog scales.

[a] *"on" anti-Parkinsonism medicine.*

[b] *"off" anti-Parkinsonism medicine.*

[c] *data are reported as medians (interquartile range).*

[d] *including Stroop Color and Word Test, Brixton Spatial Anticipation, Hayling Sentence Completion Section Methods, Trail Making Test (B), Clock Drawing Test (Command), Trail Making Test (A), Wechsler Memory Scale -IV Symbol Span, Wechsler Adult Intelligence Scale -IV Digit Span (Forward), Boston Naming Test, Semantic Fluency (Animals/Actions), Benton Judgement of Line Orientation, Rey Complex Figure Copy Test copy trial, Hopkins Verbal Learning Test (Retention/Discrimination Index), Wechsler Memory Scale -IV Logical Memory, Rey Complex Figure Copy Test delayed recall trial.*

[e] *including Trail Making Test Part A, Digit span test (forward, backward), Digit symbol test, Stroop test (color scale, naming scale), Brixton, Montreal Evaluation of Communication protocol test (orthographic verbal fluency), Trail Making Test Part B, Stroop test (inhibition scale), Boston Naming, Montreal Evaluation of Communication protocol test (semantic verbal fluency, without constraint verbal fluency), Rey-Osterrieth test (immediate recall), Rey Auditory Verbal Learning Test (RAVLT 1,2,3,4,5,1 to 5, Interference, RAVLT 6, Delay, Recognition), Hooper Visual Organization Test, Rey-Osterrieth test (figure copy), alternating with Taylor test (figure copy), Clock-drawing subtest of the Montreal Cognitive Assessment Scale.*

TABLE 2 | Study characteristics of TBS protocols included in the meta-analysis.

Study	Treatment protocol	Frequency	Intensity	Coil-type	Brain target	Continuous/ discontinuous days	Session(s)/ duration	Pulses/ Session
Benninger et al. (24)	iTBS	50Hz	80%AMT	C	DLPFC+M1 (bilateral)	Continuous (4 days)	8/2weeks	600
Brugger et al. (34)	iTBS	50Hz	100%AMT	F8	SMC (bilateral)	_	Single-session	600
Degardin et al. (25)	iTBS	50Hz	80%AMT	F8	M1	_	Single-session	600
Eggers et al. (23)	cTBS	50Hz	80%AMT	F8	M1	_	Single-session	600
Eggers et al. (28)	cTBS	50Hz	90%AMT	F8	SMA	_	Single-session	600
Ji et al. (32)	cTBS	50Hz	80%RMT	F8	SMA (left)	Continuous (14 days)	42/14days	600
Trung et al. (30)	iTBS	50Hz	80%AMT	F8	DLPFC (left)	Discontinuous	6/1week (within)	600
Vanbellingen et al. (29)	iTBS cTBS	30Hz	80%RMT	F8	PMd	_	Single-session	801
		30Hz	80%RMT	F8	PMd	_	Single-session	801

AMT, active motor threshold; C, circular; cTBS, continuous theta burst stimulation; DLPFC, dorsolateral prefrontal cortex; F8, figure of 8; iTBS, intermittent theta-burst stimulation; M1, primary motor cortex; PMd, dorsal pre-motor cortex; RMT, resting motor threshold; SMA, supplementary motor area; SMC, supplementary motor cortex.

TABLE 3 | Quality assessment of the studies included in the meta-analysis.

Study	1	2	3	4	5	6	7	8	9	10	11	Total score
Benninger et al. (24)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Brugger et al. (34)	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	7
Degardin et al. (25)	Y	N	N	Y	Y	N	Y	N	Y	Y	Y	6
Eggers et al. (23)	Y	Y	N	Y	Y	N	N	N	Y	Y	Y	6
Eggers et al. (28)	Y	Y	N	Y	Y	N	N	N	Y	Y	Y	6
Ji et al. (32)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Trung et al. (30)	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	7
Vanbellingen et al. (29)	Y	N	N	Y	Y	N	Y	N	Y	Y	Y	6
Mean												7

*1, Eligibility criteria and source of participants; 2, Random allocation; 3, Concealed allocation; 4, Baseline comparability; 5, Participant blinding; 6, Therapist blinding; 7, Assessor blinding; 8, Adequate follow-up; 9, Intention-to-treat analysis; 10, Between group comparison; 11, Point estimates and variability; * Item 1 dose not contribute to the total score.*

CI, −0.71 to −0.03; $P = 0.03$; $I^2 = 0\%$, **Figure 4**). Subgroup analysis based on iTBS/cTBS-brain targets suggested that there was significant difference between groups (iTBS-M1+DLPFC, SMD = −0.57; 95% CI, −1.13 to −0.01; $P = 0.04$, vs. cTBS-SMA, SMD = −0.25; 95% CI, −0.68 to 0.18; $p = 0.25$, **Figure 4**).

Effects of TBS on Depression

Two included studies reported the date of antidepressant effect by assessing beck depression inventory (BDI) scores (24, 30). The metaanalysis showed no significant difference in BDI scores for real TBS relative to sham TBS (MD = −2.03; 95% CI, −4.08 to 0.01; $p = 0.05$; $I^2 = 17\%$, **Figure 5**). Subgroup analysis based on different follow-up time showed that there was a significant difference between groups (within 2 weeks, MD = −2.93; 95% CI, −5.52 to −0.33; $p = 0.03$, vs. more than 2 weeks, MD = −0.55; 95% CI, −3.89 to 2.79; $p = 0.75$, **Figure 5**).

Effects of TBS on Cognitive Impairment and Dementia

Four included studies explored the therapeutic effect of TBS on cognitive dysfunction in patients with PD by evaluating the scores of cognitive domain scales (30, 31, 33, 35), and the results among these studies were inconsistent. We failed to synthesize data of cognitive disorders because we can only get details of the data (mean ± SD/SE) from one of the mentioned articles.

Safety/Adverse Events

Of the 14 studies included in this review, three studies (26, 30, 34) did not mention whether there were adverse events. Eleven studies (22–25, 27–29, 31–33, 35) reported that there were no serious adverse events, and one of the studies (33) reported uncomfortable sensation over local and adjacent areas of stimulation site during iTBS application, which was resolved by reducing the stimulation intensity (3–5%).

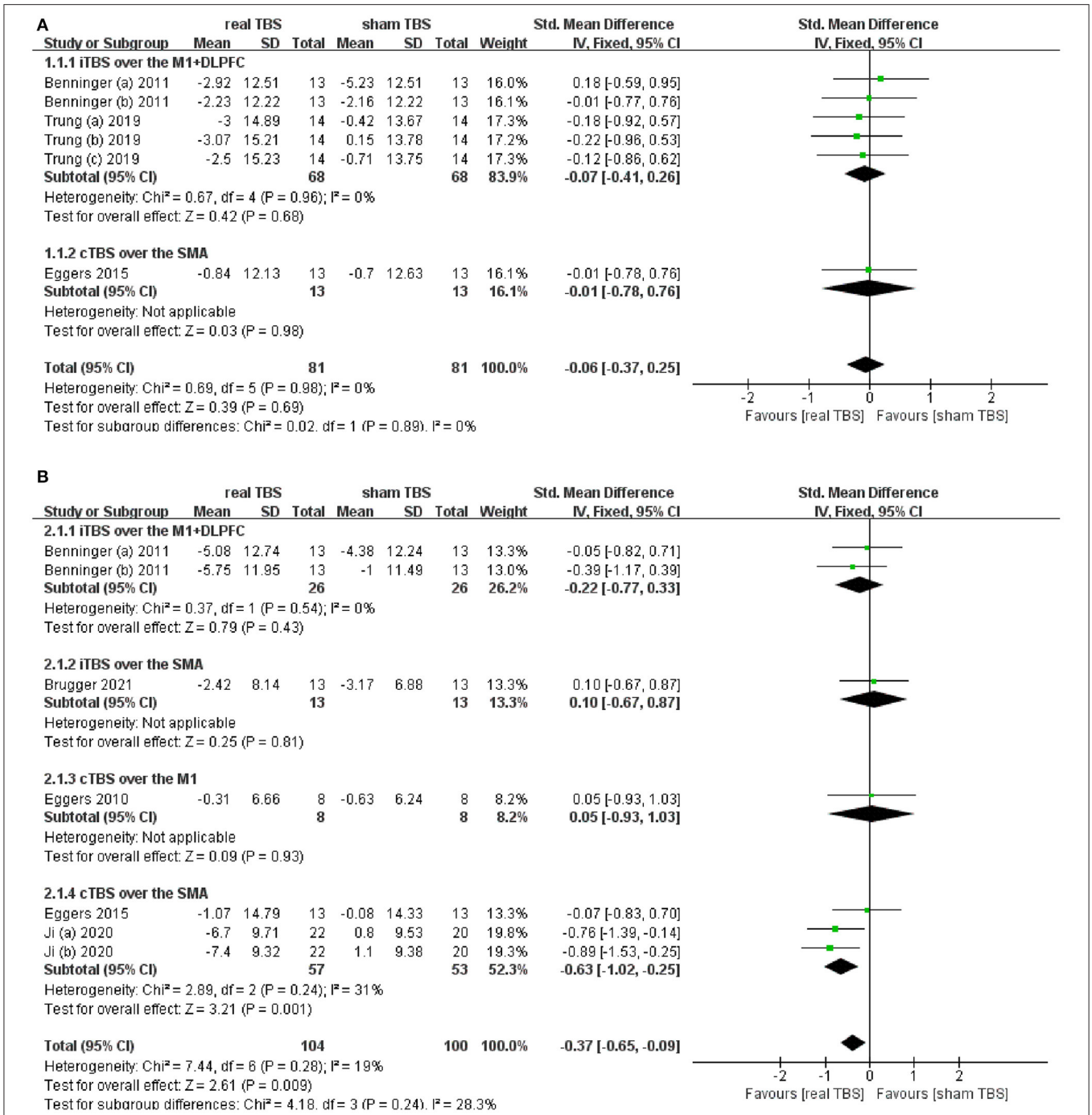

FIGURE 2 | (A) Forest plot and metaanalysis of UPDRS-III score between real TBS and sham TBS in the "on" medicine state: subgroup analysis based on iTBS/cTBS-brain targets. **(B)** Forest plot and metaanalysis of UPDRS-III score between real TBS and sham TBS in the "off" medicine state: subgroup analysis based on iTBS/cTBS-brain targets.

DISCUSSION

To the best of our knowledge, this is the first metaanalysis to evaluate the therapeutic effect of TBS, patterned rTMS, on motor and nonmotor symptoms in patients with PD. This study provides evidence to demonstrate that iTBS-M1+DLPFC or cTBS-SMA did not significantly decrease the UPDRS-III score in the "on" medicine state, while, cTBS-SMA, not iTBS-M1+DLPFC, iTBS-SMA, and cTBS-M1, could significantly improve the UPDRS-III score of these patients in the "off" medicine state. TBS had insignificant efficacy for upper limb

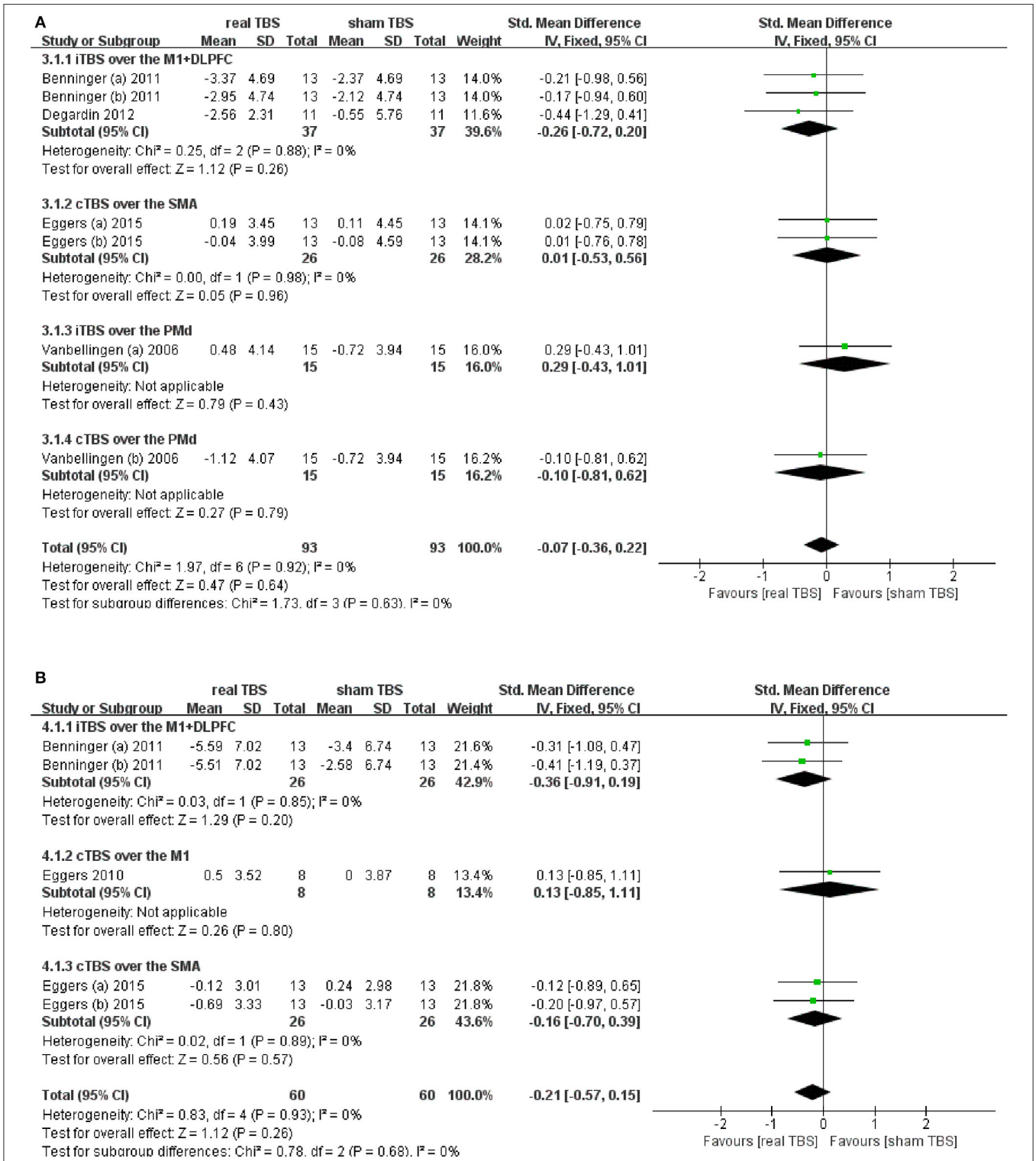

FIGURE 3 | (A) Forest plot and metaanalysis of upper limb movement between real TBS and sham TBS in the "on" medicine state: subgroup analysis based on iTBS/cTBS-brain targets. **(B)** Forest plot and metaanalysis of upper limb movement between real TBS and sham TBS in the "off" medicine state: subgroup analysis based on iTBS/cTBS-brain targets.

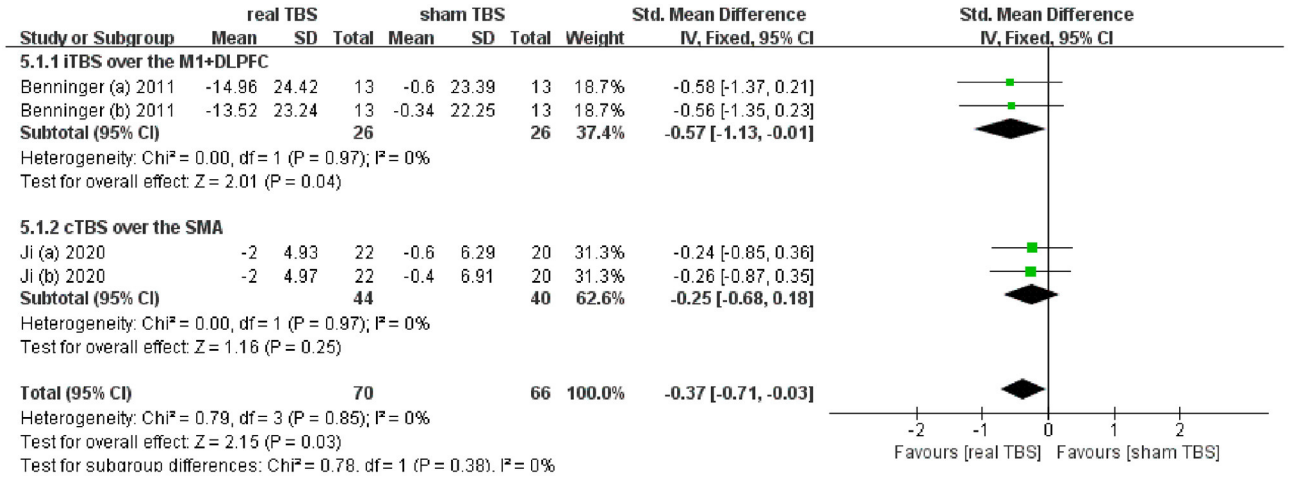

FIGURE 4 | Forest plot and metaanalysis of gait disorder between real TBS and sham TBS in the "off" medicine state: subgroup analysis based on iTBS/cTBS-brain targets.

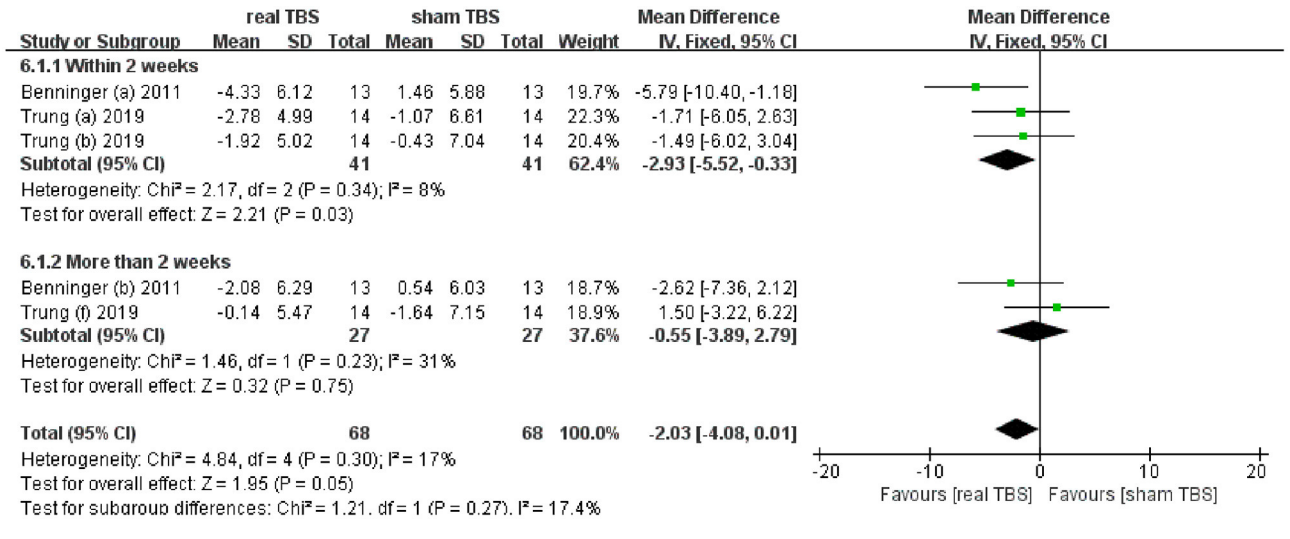

FIGURE 5 | Forest plot and metaanalysis of depression between real TBS and sham TBS: subgroup analysis based on different follow-up times.

movement disorder both in the "on" medicine state (iTBS-M1+DLPFC, cTBS-SMA, cTBS-PMd, and iTBS-PMd), and in the "off" medicine state (iTBS-M1+DLPFC, cTBS-M1, and cTBS-SMA). ITBS-M1+DLPFC, not cTBS-SMA, significantly improved slowing of gait in PD patients in the "off" medicine status. Additionally, iTBS -M1+DLPFC had a short-term (within 2 weeks) significant antidepressant effect on patients with PD.

The UPDRS-III is a reliable and valid scale for the assessment of motor performance for patients with PD, which also correlates with disease severity and quality of daily life (52). Our results demonstrated that TBS did not significantly improve the UPDRS-III score in the "on" medicine state. While there was a significant therapeutic effect in the withdrawal medicine state. Considering that different types of TBS (iTBS/cTBS) over the related brain targets may produce a significant difference of therapeutic effect, we performed subgroup analysis based on iTBS/cTBS-brain targets in both the "on" and "off" medicine status, which found that iTBS- M1+DLPFC or cTBS-SMA did not significantly improve UPDRS-III score in the "on" medicine state. It is unexpected that facilitatory iTBS over the M1 did not improve total motor performance (17). **Due to the limitation of the sample size in our study, the therapeutic effect of iTBS on the overall motor disorder in PD patients may be underestimated (type II error).** Conversely, cTBS-SMA significantly improved the UPDRS-III score in the "off" medicine state. For two included studies, Ji et al. gave cTBS-SMA for consecutive 14 days, a total of 42 sessions, and the results showed that cTBS over the SMA had a significant improvement of UPDRS-III score with follow-up for 2 weeks (32), **where change of UPDRS-III score reached a**

level that reflects a significant clinical improvement (53, 54), while in Eggers et al. work, single-session iTBS over the SMA did not significantly improve UPDRS-III score (28). Insufficient stimulation sessions may be an important reason. In our study, cTBS over the SMA improved the UPDRS-III score, which is consistent with previous studies that the improvement of motor symptoms was related to inhibiting the excitability of SMA (55–57). In terms of that cTBS-SMA significantly improved UPDRS-III in "off," not in the "on," medicine status, a possible mechanism is that dopamine has been suggested to have negative effects on the plasticity of the motor cortex in patients with PD (58). Most of the included studies in this meta-analysis defined "off" medicine state as anti-Parkinsonism medicine withdrawal status for at least 12 h, without considering the type of drug. It is necessary to select the scientific withdrawal time based on the different half-life of drugs and consider the equivalent dose of levodopa for confirming the difference of iTBS/cTBS over the corresponding brain targets in the "on" and "off" medicine state.

Upper limb motor dysfunction in patients with PD included a decrease concerning the speed and amplitude of movement, reaching and grasping deficits, and reduction of hand dexterity. Despite various upper limb dysfunctions that occur in PD, few studies reported treatment interventions for enhancing upper limb function (59). Our metaanalysis showed that TBS did not significantly improve the upper limb motor scores both in the "on" and "off" medicine state. Further analysis based on iTBS/cTBS-brain targets also found an insignificant difference among subgroups. PPT was chosen to explore upper limb movement and hand flexibility in two studies (23, 28), which has been demonstrated to correlate with disease severity, hand dexterity, and limitation of activity in patients with PD (60). Other studies selected the subitems of UPDRS-III concerning upper limb motor function (24, 25, 29). It is worth noting that Eggers et al. performed single-session cTBS over the SMA, and there was a significant difference in UPDRS-III score in the "off" medicine state (post-cTBS vs. pre-cTBS, $p = 0.024$), while did not have any significant effect in the "on" medicine status (28). As mentioned earlier, the possible mechanism may be the negative effect of dopaminergic drugs on the plasticity of the motor cortex. It is necessary to explore the efficacy of TBS on upper limb motor disorder in patients with PD by optimizing brain target and giving cumulative multiple-session TBS in the future.

For patients with PD, gait disorders and recurrent falls are common and cause disability in an advanced stage. Previous metaanalyses concluded modest efficacy of HF rTMS on motor performance in PD (61, 62). Controlled rTMS studies demonstrated positive effects on gait (63–65), suggesting more powerful stimulation protocols, such as TBS, could enhance efficacy (66, 67). Our results showed that TBS significantly improved the slowing of gait in PD in the "off" medicine state. Subgroup analysis based on iTBS/cTBS-brain targets found that iTBS-M1+DLPFC, not cTBS- SMA, had a significant therapeutic effect. Our results merely come from two studies (24, 32), and there was the limitation of a small sample size. In this metaanalysis, we failed to make a synthesis analysis for the date of freezing of gait (FOG). For PD patients, FOG is a refractory motor dysfunction resulting in an increased risk of falls. Two studies explored the efficacy of TBS on FOG by the gait parameter analysis (34, 68). The first study found that single-session iTBS- left premotor cortex did not improve FOG under normal medicine. The second study suggested that iTBS- SMA overall brought relative deterioration of gait, mainly in the time domain. The therapeutic effect of TBS on gait disorder in patients with PD needs to be further explored, and combined symptom scale of gaits and the gait parameter analysis are expected to be more effective for assessing improvement of gaits.

Depression is common in patients with PD, and it could even appear before the onset of motor symptoms. Previous studies regarding traditional rTMS found that HF rTMS over the DLPFC significantly improved PD depression, and the related guidelines also give recommendations for rTMS to intervene depression of patients with PD (13, 15–17). Our work found that iTBS-M1+DLPFC did not significantly improve the BDI score. However, subgroup analysis based on follow-up time found that it could bring short-term (within 2 weeks) therapeutic effect. For included two studies, Benninger et al. gave eight sessions of iTBS (within 2 weeks) over the M1+DLPFC (24), and Trung et al. performed six sessions of iTBS (within 1 week) over the left DLPFC (30). Whether more sessions and further optimized intervention targets can bring longer antidepressant effects requires further research.

Cognitive impairment and dementia are frequent in patients with PD (69). A growing number of researches support the view that cognitive decline in PD is mediated by degeneration and dysfunction of neural networks (70). Recent work assessing the efficacy of TBS in PD with mild cognitive impairment (PD-MCI) has shown mixed results. Hill et al. demonstrated that single-session iTBS-left DLPFC did not significantly improve working memory and executive function (31). Studies from Trung et al. and Lang et al. found that iTBS-left DLPFC had an insignificant effect on cognitive domain z-scores across time when comparing real with sham stimulation and correcting for multiple comparisons across cognitive domains (both received a total of six sessions iTBS within a week). However, the real iTBS group demonstrated a trend in the improvement of cognitive domain scores with 1-month follow-up compared with sham iTBS (30, 33). He and colleagues suggested that iTBS-left DLPFC for 10 consecutive weekdays brought significant improvement of repeatable battery for the assessment of neuropsychological status (RBANS) and Montreal cognitive assessment (MoCA) scores with a 3-month follow-up (p <0.001 for both) (35). Considering that multiple-session iTBS over left DLPFC had a positive impact on cognitive scores, future research is promising.

It is worth mentioning that Bentley et al. explored the neurophysiology changes of DLPFC after iTBS on different deep brain stimulation (DBS) targets, subthalamic nucleus (STN), or globus pallidus interna (GPi) in seven patients with PD and found that GPi stimulation results in significantly greater theta power vs. STN stimulation (71). It is the first study that suggested TBS can be safely transmitted to human subcortical by DBS. A recent RCT demonstrated that TBS on DBS HF (200 Hz) and low-frequency (50 Hz) TBS with adapted stimulation amplitude were effective in the reduction of PD motor symptoms (akinesia, tremor, and rigidity) in 17 patients with PD (72), and had no serious adverse events.

Limitations and Future Directions

Our study has several limitations. Firstly, the total number of included participants was small, as mentioned above; hence interpreting results should be cautiously done. Secondly, interpretation of changes for behavioral assessment should be associated with reaching a level that reflects a significant clinical improvement. Third, several uncontrolled variables, such as disease stage, side of onset, age, and sex, exist that could confound the results and must be acknowledged. Lastly, we did not definite the optimal iTBS/cTBS-brain targets and parameters of TBS that could bring significant therapeutic effect due to the limitation of the data in these included studies. A further study combining TBS with different neuroimaging techniques may better discover the potential pathophysiological mechanisms of clinical benefit and optimize TBS treatment protocols. Compared with the figure of eight coils mainly used in our included studies, the double-cone coil has the advantage of a stronger magnetic field with higher penetration depth, which is worthy of further study. Additionally, future research should try to establish a more precise relationship between the TBS effect and PD patients' clinical and demographic characteristics, such as anti-Parkinsonism medicine regimen, stage of disease, side of onset, symptom subtype (e.g., specific cognitive domain impairment), age, and gender, for finding the optimal stimulation protocols for individualized TBS treatment. Lastly, multicenter, large sample research is necessary for the future to evaluate the application prospect of TBS on invasive brain stimulation for expanding the therapeutic window and enhancing clinical benefits in PD.

CONCLUSION

Our study demonstrated that cTBS-SMA could significantly improve the UPDRS-III score for patients with PD in the "off," not in the "on," medicine state, whereas TBS could not bring significant benefits to upper limb movement. ITBS-M1+DLPFC could significantly improve the slowing of gait in the "off" medicine status. Additionally, iTBS- M1+DLPFC has a short-term (within 2 weeks) therapeutic effect on PD depression. Since the limitations, such as small sample size and heterogeneity of assessment scale among included studies, further researches of a large sample, comprehensive evaluation, and multi-center excellent-designed RCTs are needed to confirm our research conclusions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

SZ developed the review concept. BC and TZ performed the data collection, analysis, and interpretation under the supervision of SZ and WZ. LS, YS, and WX contributed reagents, materials, and analysis. BC wrote the manuscript. All authors approved the final version of the manuscript for submission.

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Effects of Unilateral Stimulation in Parkinson's Disease: A Randomized Double-Blind Crossover Trial

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Introduction: Previous studies have shown that subthalamic nucleus (STN) and unilateral globus pallidus interna (GPi) are similarly effective in the deep brain stimulation (DBS) treatment of motor symptoms. However, the counterintuitively more common clinical application of STN DBS makes us hypothesize that STN is superior to GPi in the treatment of motor symptoms.

Methods: In this prospective, double-blind, randomized crossover study, idiopathic PD patients treated with combined unilateral STN and contralateral GPi DBS (STN in one brain hemisphere and GPi in the other) for 2 to 3 years were enrolled. The MDS UPDRS-III total score and subscale scores for axial and bilateral limb symptoms were assessed preoperatively and at 2- to 3-year follow-up in four randomized, double-blinded conditions: (1) Med–STN+GPi–, (2) Med–STN–GPi+, (3) Med+STN+GPi–, and (4) Med+STN–GPi+.

Results: Eight patients had completed 30 trials of assessment. Compared with the preoperative Med– state, in the Med–STN+GPi– condition, the cardinal symptoms in both sides of the body were all improved. In the Med–STN–GPi+ condition, symptoms of the GPi-stim limb were improved, while only tremor was improved on the ipsilateral side, although all axial symptoms showed aggravation. Compared with the preoperative Med+ state, in the Med+STN+GPi– state, cardinal symptoms were improved on both sides, except that tremor was worsened on the STN-stim side. In the Med+STN–GPi+ state, the overall motor symptoms were aggravated compared with the preoperative Med+ state. Most axial symptoms worsened at acute unilateral STN or GPi DBS onset, compared to both preoperative Med– and Med+ states. No side effects associated with this study were seen.

Conclusions: Improvement in motor symptoms was greater in all sub-scores favoring STN. The effects of STN+ were seen on both sides of the body, while GPi+ mainly acted on the contralateral side.

Keywords: deep brain stimulation (DBS), Parkinson's disease, globus pallidus interna, subthalamic nucleus, personalized treatment

INTRODUCTION

Deep brain stimulation (DBS) is a well-established surgical intervention for patients with advanced Parkinson's disease (PD), especially those with medication-resistant motor symptoms, motor fluctuations, or levodopa-induced dyskinesia (1, 2). However, choosing a suitable stimulation target to maximize clinical outcomes while minimizing side effects remains a challenge.

The subthalamic nucleus (STN) and globus pallidus interna (GPi) are the two main targets in large randomized controlled trials in which patients with comparable clinical and demographic characteristics are randomized to receive either GPi DBS or STN DBS. Studies have demonstrated similar effects for both targets on motor symptom improvement (3). Unfortunately, for highly heterogeneous diseases, such as PD, these randomized controlled trials, designed to be conducted among different patients yielded inconsistent results, even when sufficient numbers of patients were included.

Most studies have investigated the differences between STN and GPi DBS either unilaterally or bilaterally in different patients and presented evidence for similar effectiveness of STN and GPi on motor symptoms (4). However, significantly more STN DBS were performed clinically, which made us wonder whether STN is more trusted than GPi with respect to its treatment effect. Therefore, we hypothesized that STN is superior to GPi in the treatment of motor symptoms.

In this study, we aimed to elucidate the nuances between STN and GPi DBS in PD patients. We conducted an intra-patient comparison by investigating the acute turning-on effects of unilateral STN stimulation vs. unilateral GPi stimulation on motor symptoms within each patient who had received a treatment comprising combined unilateral STN and contralateral GPi DBS. The asymmetrically targeted DBS treatment was first applied in our previous study to address the assumption of different therapeutic effects with unilateral STN and contralateral GPi DBS. Our previous research (5) showed that at the 1-year follow-up, this approach represented an effective and well-tolerated DBS treatment option for selected patients with advanced PD, incurring no significant increase in side effects.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

This study was conducted under the supervision of the ethical committee in Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. All patient's consent was collected according to the Declaration of Helsinki. This study is registered on clinicaltrial.gov (clinicaltrial.gov NCT04255719).

Abbreviations: DBS, deep brain stimulation; GPi, globus pallidus interna; MDS UPDRS-III, Movement Disorder Society-Unified Parkinson Disease Rating Scale part III; LEDD, levodopa equivalent daily dose; PD, Parkinson's disease; STN, subthalamic nucleus; "+", med/stimulation on; "−", med/stimulation off.

Trial Design

This was a prospective double-blind randomized crossover study designed to compare the acute effect of unilateral STN and GPi stimulation on motor symptoms in several patients with PD. Participants with advanced PD who had previously undergone combined unilateral STN and contralateral GPi DBS were screened based on the inclusion and exclusion criteria. Following recruitment, participants were comprehensively evaluated under four randomized, double-blind conditions: (1) Med–STN+GPi–, (2) Med–STN–GPi+, (3) Med+STN+GPi–, and (4) Med+STN–GPi+. The symbol + means on, while – means off. The **intervention** section explains the details of these conditions. All participants and trained assessors were blinded to the conditions, and patients were randomly assessed over the course of two continuous days (**Figure 1**).

Patients

Participants were recruited from the Department of Functional Neurosurgery at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai, China). A total of 10 patients with PD underwent combined unilateral STN and contralateral GPi DBS from September 2017 to September 2018. Following recruitment in April 2020 and screening, eight patients who had received the surgery for 2 to 3 years were included in this study. **Supplementary Material 1** explains the surgical procedure. The inclusion criteria were: (1) diagnosis of idiopathic PD; (2) age between 55 and 75 years, both male and female; (3) treatment with combined unilateral STN and contralateral GPi DBS for 2 to 3 years with optimal parameters for 3 months; and (4) a Hoehn-Yahr (H-Y) stage of less than 4 in the medication-off state. The exclusion criteria were: (1) history of serious psychosis; (2) history of intractable epilepsy (i.e., seizures); (3) diagnosis of severe cardiac, liver or kidney diseases, or other serious health conditions; (4) dementia (A Mini-Mental State Examination score of < 24), inability to comprehend the experimental protocol or voluntarily provide informed consent; (5) lack of cooperation; (6) poorly controlled depression or anxiety. The patients in this study overlapped partly with those in our previous study published in 2020; (5) those were patients 3, 7 and 8. Additionally, according to the asymmetry index, patients were divided into a symmetric group (asymmetry index < 0.15, both Med– and Med+ conditions before surgery) and an asymmetric group (asymmetry index ≥ 0.15, either Med– or Med+ conditions before surgery), and the corresponding subgroup analysis was performed. The asymmetry index was a left-extremity to right-extremity ratio in the MDS UPDRS-III, which was calculated using the formula (left extremity – right extremity) / (left extremity + right extremity) (6, 7). A team of experienced multidisciplinary DBS specialists made the clinical decision regarding the specific DBS target to be used in each patient. That was, unilateral STN DBS was applied to treat the more severe side since we hypothesized that STN is more effective than GPi. We highlighted three cases here. Patient 4 underwent DBS surgery because of the adverse effect of postural hypotension after taking the medication. Patient 7 had opposite asymmetry indices in the Med+ and Med– states, so STN was applied to the left hemisphere due to higher severity of the right limb in

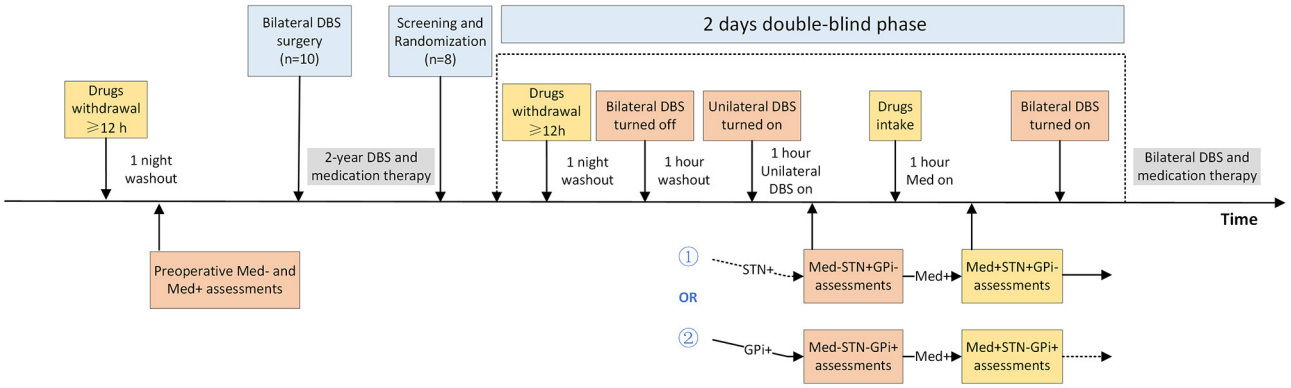

FIGURE 1 | Randomized, double-blind, crossover design of the study. This study involved two time periods, before and 2 to 3 years after surgery. Some patients (n = 10) were assessed for motor symptoms in Med– and Med+ states preoperatively and underwent asymmetric target (unilateral STN, contralateral GPi) DBS treatment. After parameter optimization, the patients were treated with medication and bilateral DBS. We recruited and screened patients 2 to 3 years after surgery (n = 8) and randomized them into two groups. One group of patients was evaluated first in the STN+GPi– state and then the next day in the STN–GPi+ state; the other group was the opposite, STN–GPi+ then STN+GPi–. Patients stopped intaking antiparkinsonian drugs the night before the assessment, ensuring that they were off medication for more than 12 h. Bilateral DBS was turned off and washed out for 1 h before assessment. Afterwards, the unilateral DBS was turned on and motor symptoms were assessed in the Med– condition. Following the Med– condition assessment, the patient took the medication and was assessed 1 h later in the Med+ condition. After completion of the first day's assessment, the patient's bilateral DBS was turned on, although medication withdrawal continued for more than 12 h. Assessment of the contralateral DBS on state was performed on the second day. Patients were blinded for all assessment procedures and resumed prior bilateral DBS and medication treatment after the four-state assessments. DBS, deep brain stimulation; GPi, globus pallidus interna; STN, subthalamic nucleus.

the Med– state (3). Patient 3 had the same scores on bilateral limbs in the Med+ and Med– states, and we applied unilateral STN DBS to the left hemisphere because there is evidence of a left-hemispheric dominance for appendicular movements and a right-hemispheric dominance for axial motor control (8, 9).

Interventions

Unilateral DBS of STN

Bilateral stimulation was turned off for an hour (10), and unilateral STN DBS was turned on afterwards. Participants were asked to complete a comprehensive set of assessments under unilateral STN stimulation in the Med– state. Participants were further required to complete the second set of assessments in the Med+ state 1 h after taking regular medications,.

Unilateral DBS of GPi

Unilateral GPi DBS was delivered after bilateral stimulation was turned off for an hour. The study protocol was identical to that used in the unilateral STN DBS intervention but was performed on a different day. After all these assessments, bilateral DBS will be turned on again and returned to normal treatment status.

Concomitant Interventions

Participants were asked to stop taking antiparkinsonian drugs for 12 h to stay in the Med– state until they completed the first set of assessments. Regular medication was taken 1 h before the second set of assessments to maintain a Med+ state. All processes were repeated for the contralateral target on the next day.

Randomization and Blinding

The testing sequence of the treatment conditions was randomly assigned in a counterbalanced manner on the scheduled days. The order of the DBS conditions was determined by the clinician who randomly picked up one of the eight folded sheets with different conditions written on them (half of the first day GPi; half of the first day STN) but was not allowed to participate in any rating or evaluation. Throughout the study, all participants, raters, and statisticians were blinded to treatment conditions. A movement disorder specialist was responsible for programming. In addition, motor symptom evaluation in this experiment was performed by an experimenter who was blinded to the study protocol and did not participate in data analysis or interpretation. Two raters who were blinded to the conditions conducted the video assessments independently, after which the average rating scores were calculated. For subscores with large deviancy, the final scores were determined after re-evaluation.

Trial Outcomes

Acute turning-on effects of unilateral STN stimulation vs. unilateral GPi stimulation on motor symptoms in each patient were compared as the primary outcome. Motor symptoms were defined by the MDS UPDRS-III scores which ranged from 0 to 132, with higher scores indicating more severe motor symptoms (11). To gain insight into the specific effects of each target, we classified the MDS UPDRS-III subscales into three categories: (1) axial signs, as measured by scores on speech, facial expression, arising from a chair, posture, gait, freezing of gait, and posture stability; scores could range from 0 (no axial signs) to 28 (severe axial signs); (2) STN-stimulated contralateral limb symptoms; and (3) GPi-stimulated contralateral limb symptoms. Limb symptom severity was measured using the subscale scores of the corresponding limb on rigidity, finger

TABLE 1 | Demographic and clinical characteristics of each patient.

Patients	Sex	Age at surgery (yrs)	Disease duration at surgery (yrs)	LEDD at surgery (mg)	Asymmetry index* Med–, Med+	Group	Target	Follow-up Period (months)
Patient 1	Male	74	7	700	0.09	Symmetric group	R-GPi	32
					0.03		L-STN	
Patient 2	Female	61	26	525	0.00	Symmetric group	R-STN	23
					0.00		L-GPi	
Patient 3	Female	69	9	500	0.04	Symmetric group	R-GPi	31
					0.02		L-STN	
Patient 4	Male	64	8	150	0.10	Symmetric group	R-GPi	32
					0.14		L-STN	
Patient 5	Male	73	4	425	−0.21	Asymmetric group	R-STN	29
					−0.10		L-GPi	
Patient 6	Female	58	4	787.5	−0.67	Asymmetric group	R-STN	32
					−0.50		L-GPi	
Patient 7	Male	72	18	1,050	0.15	Asymmetric group	R-GPi	32
					−0.20		L-STN	
Patient 8	Male	58	5	798.25	0.29	Asymmetric group	R-GPi	36
					0.38		L-STN	

*LEDD, levodopa equivalent daily dose; R-GPi, right unilateral stimulation of the globus pallidus interna; L-STN, left unilateral stimulation of the subthalamic nucleus; R-STN, right unilateral stimulation of the subthalamic nucleus; L-GPi, left unilateral stimulation of the globus pallidus interna. Asymmetric group, patients with asymmetry index ≥ 0.15 at either Med– or Med+ conditions before surgery; Symmetric group, patients with asymmetry index < 0.15 at both Med– and Med+ conditions before surgery. Mean age at surgery, 66.1 ± 6.3 yrs; mean disease duration at surgery, 10.1 ± 7.3 yrs; mean LEDD at surgery, 617.0 ± 276.0 mg. *The asymmetry index was calculated as the absolute difference between the total of the items for each side divided by the sum of the items for both sides [(left extremity – right extremity)/ (left extremity + right extremity)]. A higher asymmetry index indicated higher asymmetry in symptom severity or symptom types.*

tapping, hand movements, hand pronation supination, toe-tapping, leg agility, posture tremor, kinetic tremor, and resting tremor amplitude; scores could range from 0 (no limb symptoms) to 52 (severe limb symptoms). The Berg Balance Scale (BBS) was also compared as a second outcome at the 2- to 3-year follow-up. The patient's daily dose of antiparkinsonian medication was converted into a levodopa equivalent daily dose (LEDD).

Data Analysis

There were two types of comparisons conducted in this study. The first was the comparison between unilateral STN+ and GPi+ within the same patient group in Med– and Med+ conditions, and the second was the comparison between asymmetric and symmetric groups for the different patient groups in the same condition. Before the comparisons, the Shapiro-Wilk test was used to test the normality of data in each group, yielding the W statistic and *P*-value reflecting the evaluation criteria of distribution. For normally distributed data, a parametric test of the Student's *t*-test was used to assess the difference between groups. For the non-normally distributed data, the non-parametric Wilcoxon test was applied to compare the differences. The first comparison mentioned was based on the paired Student's *t*-test and Wilcoxon signed-rank test. The second comparison was based on the independent Student's *t*-test and Wilcoxon rank-sum test. All three tests mentioned were two-tailed tests with a P-value < 0.05 reflective of statistical significance. Bonferroni correction was applied for adjustment of multiple testing. Statistical calculations and techniques were performed using R-4.0.2.

Data Availability

Original data is available upon reasonable request.

RESULTS

Patients

Eight patients completed 30 trials of assessment at 2 to 3 years after DBS operation, of which 16 met the Med–STN+GPi–/ Med–STN–GPi+ conditions and 14 met the Med+STN+GPi–/ Med+STN–GPi+ conditions. The main demographics and clinical characteristics of the patients are presented in **Table 1**. All the actual postoperative lead locations were in accordance with the preoperative plan. The stereotactic coordinates and programming parameters of each patient are shown in **Supplementary Table 1**.

Acute Effects of Unilateral STN+/Med– vs. GPi+/Med–

We first analyzed the difference in treatment outcomes between unilateral STN+ and GPi+ in the Med– state compared to the preoperative Med– state. The mean total MDS UPDRS-III score was reduced by 26% in STN+/Med– but showed almost no change in GPi+/Med–. STN+ improved motor symptoms on both sides of the body, while GPi+ mainly on the GPi-stim side. Axial symptoms worsened in both STN+/Med– and GPi+/Med– states, but the deterioration was more pronounced

TABLE 2 | Motor symptoms in Med–STN+GPi– and Med–STN–GPi+ conditions before and 2 to 3 years after surgery ($n = 8$).

		Baseline Med–[a]	Follow-up Med–		Percentage of change		Adjusted *P*-value		
			STN+GPi–[b]	STN–GPi+	STN+GPi–	STN–GPi+	STNa	Gpi a	b
Total UPDRS-III		54.12 ± 24.7	40.25 ± 16.54	53 ± 17.76[b]	−25.6%	−2.1%	0.3498	1	0.0279
Tremor		10.38 ± 7.31	4.75 ± 4.68	7 ± 5.45	−54.2%	−32.6%	0.2346	0.621	1
Rigidity		11.75 ± 4.43	8.5 ± 3.78	12.12 ± 4.05[b]	−27.7%	3.1%	0.5202	1	0.0936
Bradykinesia		21.38 ± 8.68	13.75 ± 7.61[a]	18.62 ± 9.24[b]	−35.7%	−12.9%	0.0234	1	0.0459
STN-stim limb	Tremor	5 ± 2.93	1.88 ± 1.89[a]	3.5 ± 2.93	−62.4%	−30.0%	0.1215	0.6099	0.7629
	Rigidity	5.12 ± 1.81	2.5 ± 1.77[a]	5.12 ± 2.3[b]	−51.2%	0	0.0753	1	0.0753
	Bradykinesia	11.75 ± 3.37	6.38 ± 3.62[a]	11.38 ± 5.37[b]	−45.7%	−3.1%	0.0018	1	0.0141
GPi-stim limb	Tremor	2.88 ± 2.8	2 ± 2.14	2 ± 1.85	−30.6%	−30.6%	1	0.9051	1
	Rigidity	4.38 ± 1.69	3.38 ± 1.92	3.75 ± 1.67	−22.8%	−14.4%	0.7572	1	1
	Bradykinesia	9.62 ± 5.42	7.38 ± 4.47	7.25 ± 4.59	−23.3%	−24.6%	0.4929	0.5775	1
Axial signs	Total axial score	10.62 ± 7.25	13.25 ± 5.31	15.25 ± 5.12[b]	24.8%	43.6%	0.513	0.2421	0.1239
	Speech	1.12 ± 1.13	1.38 ± 0.74	1.75 ± 0.89	23.2%	56.3%	1	0.6558	0.4467
	Facial expression	1.88 ± 1.13	2.12 ± 0.35	2 ± 0.93	12.8%	6.4%	1	1	1
	Arising from chair	1.25 ± 1.49	0.88 ± 0.99	1.38 ± 1.19	−29.6%	10.4%	1	1	0.2157
	Gait	1.62 ± 1.19	1.62 ± 0.52	1.75 ± 0.46	0.0%	8.0%	1	1	1
	Freezing of gait	0 ± 0	0.62 ± 0.74	0.75 ± 0.89	∞	∞	0.267	0.2841	1
	Postural stability	1.25 ± 1.49	2.25 ± 1.75	2.38 ± 1.06[a]	80.0%	90.4%	0.267	0.1383	1
	Posture	2 ± 1.07	2.12 ± 0.83	2.5 ± 1.07[a]	6.0%	25.0%	1	0.0993	0.2388
	Global spontaneity of movement	1.5 ± 0.93	2.25 ± 0.89	2.75 ± 0.71[a]	50.0%	83.3%	0.2841	0.0048	0.6093
H-Y		2.38 ± 1.19	2.62 ± 1.06	2.88 ± 0.83	10.1%	21.0%	1	0.9912	1
Berg		NA	41.25 ± 9.29	37.38 ± 12.5	\	\			

Med–, without medication; GPi, globus pallidus interna; STN, the subthalamic nucleus; STN+GPi–, unilateral STN stimulation turning on with contralateral GPi turning off; STN–GPi+, unilateral GPi stimulation turning on with contralateral STN turning off; UPDRS-III, MDS Unified Parkinson Disease Rating Scale part III; H-Y, Hoehn-Yahr stage; Berg, Berg Balance Scare. The formula of percentage of change was (postoperative score–preoperative score)/preoperative score.

[a], [b], the letter a indicates a significant difference ($P < 0.05$) between 2 time points (baseline and follow-up), and b indicates a significant difference ($P < 0.05$) between STN+GPi– and STN–GPi+ (paired Student's t-test or Wilcoxon signed-rank test with Bonferroni correction). Values are presented as mean ± SD.

in the GPi+/Med– state, especially with differences in symptoms of postural stability, posture, and global spontaneity of movement (**Table 2**).

Acute Effects of Unilateral STN+/Med+ vs. GPi+/Med+

We then compared the therapeutic effects of STN+/Med+ and GPi+/Med+ after antiparkinsonian medicines were administered. The mean total MDS UPDRS-III score was almost identical to that in the preoperative Med+ condition in the STN+/Med+ state, while there was a worsening in the GPi+/Med+ state. Symptoms dramatically improved on both sides of the body in the STN+/Med+ state, except for the tremor symptoms on the STN-stim side, which showed worsening instead. The improvement of the limbs in the GPi+/Med+ state was more expressive on tremor and rigidity on the GPi-stim side. Similar to that in the Med- state, compared to the preoperative Med+ state, axial symptoms were aggravated in both STN+/Med+ and GPi+/Med+ states (**Table 3**).

Comparison of Unilateral STN vs. GPi DBS on Balance Function (BBS)

We directly compared unilateral STN vs. GPi stimulation on BBS scores in the Med– and Med+ states. In the Med–STN+GPi– condition, the mean score of BBS was 41.25, while it was 37.38 in the Med–STN–GPi+ condition. In the Med+ state, the mean score was 44.43 in the STN+ condition, and 43.14 in the GPi+ conditions (**Tables 1**, **2**).

Comparison of Patient Groups With Symmetric and Asymmetric Symptoms

In the preoperative Med– and Med+ states, the symmetric group had more severe motor symptoms compared to the asymmetric group. In contrast, in all four postoperative assessment states, the symmetric group showed better improvement in overall motor symptoms for both unilateral STN+ and GPi+ states. In addition, the treatment outcomes on both body sides of the symmetric group outperformed those of the asymmetric group (**Supplementary Tables 2, 3**).

Effects of Asymmetric Target DBS on Medication (LEDD)

We also compared medication consumptions before and at the 2- to 3-year follow-up. Compared to the preoperative period, a significant decrease of medication intake was observed at the 2- to 3-year follow-up (26.6%). Six patients had reduced drug use, while two had a slight increase in medication intake (**Supplementary Table 4**).

TABLE 3 | Motor symptoms in Med+STN+GPi– and Med+STN–GPi+ conditions before and 2 to 3 years after surgery ($n = 7$).

		Baseline Med+[a]	Follow-up Med+		Percentage of change		Adjusted *P*-value		
			STN+GPi–[b]	STN–GPi+	STN+GPi–	STN–GPi+	STNa	GPi a	b
Total UPDRS-III		36.57 ± 21.82	35.29 ± 14.42	43.14 ± 15.49[b]	−3.5%	18.0%	1	0.8655	0.0936
Tremor		4.71 ± 4.11	5.14 ± 3.58	5.43 ± 3.78	9.1%	15.3%	1	1	1
Rigidity		10.29 ± 5.65	7.43 ± 4.58	10.57 ± 3.95[b]	−27.8%	2.7%	1	1	0.1272
Bradykinesia		13.43 ± 11.27	10.29 ± 7.99	14.43 ± 9.83	−23.4%	7.4%	1	1	0.1932
STN-stim limb	Tremor	1.57 ± 1.51	2.14 ± 1.35	2.43 ± 1.9	36.3%	54.8%	0.6924	1	1
	Rigidity	4.43 ± 2.15	2.57 ± 1.9	4.43 ± 1.72[b]	−42.0%	0.0%	0.5571	1	0.0321
	Bradykinesia	7.29 ± 5.71	5.14 ± 3.58	8.14 ± 4.6[b]	−29.5%	11.7%	1	1	0.0084
GPi-stim limb	Tremor	2 ± 1.29	1.71 ± 1.8	1.57 ± 1.81	−14.5%	−21.5%	1	1	1
	Rigidity	3.86 ± 2.41	2.71 ± 2.21	3.14 ± 1.57	−29.8%	−18.7%	1	1	1
	Bradykinesia	6.14 ± 5.81	5.14 ± 5.15	6.29 ± 5.71	−16.3%	2.4%	1	1	1
Axial signs	Total axial score	8.14 ± 5.9	12.43 ± 4.58[a]	12.71 ± 4.42[a]	52.7%	56.1%	0.0954	0.0558	1
	Speech	0.43 ± 0.53	1.14 ± 0.38[a]	1.29 ± 0.49[a]	165.1%	200.0%	0.0699	0.1431	1
	Facial expression	1.57 ± 0.79	2 ± 0.58	2.14 ± 0.38	27.4%	36.3%	1	1	1
	Arising from chair	1 ± 1	0.71 ± 0.49	0.71 ± 0.49	−29.0%	−29.0%	1	1	1
	Gait	1.29 ± 1.25	1.57 ± 0.79	1.43 ± 0.53	21.7%	10.9%	0.8895	1	1
	Freezing of gait	0 ± 0	0.71 ± 0.76[a]	0.43 ± 0.79	∞	∞	0.0888	1	1
	Postural stability	1.14 ± 1.68	2 ± 1.63[a]	2.14 ± 1.21[a]	75.4%	87.7%	0.6939	0.195	1
	Posture	1.86 ± 1.07	2.14 ± 1.21	2.29 ± 0.95	15.1%	23.1%	1	0.4467	1
	Global spontaneity of movement	0.86 ± 1.07	2.14 ± 0.9[a]	2.29 ± 0.95[a]	148.8%	166.3%	0.1179	0.0915	1
H-Y		2.43 ± 1.27	2.43 ± 0.98	2.57 ± 0.98	0.0%	5.8%	1	1	1
Berg		NA	44.43 ± 7.74	43.14 ± 8.71	\	\			

Med+, with medication on; GPi, globus pallidus interna; STN, the subthalamic nucleus; STN+GPi–, unilateral STN stimulation turning on with contralateral GPi turning off; STN–GPi+, unilateral GPi stimulation turning on with contralateral STN turning off; UPDRS-III, MDS Unified Parkinson Disease Rating Scale part III; H-Y, Hoehn-Yahr stage; Berg, Berg Balance Scare. The formula of percentage of change was (postoperative score–preoperative score) /preoperative score. [a], [b], the letter a indicates significant difference ($P < 0.05$) between 2 time points (baseline and follow-up), and b indicates a significant difference ($P < 0.05$) between STN+GPi– and STN–GPi+ (paired Student's t-test or Wilcoxon signed-rank test with Bonferroni correction). Values are presented as mean ± SD.

Side Effects

After surgery, some patients experienced transient localized tingling and numbness that got resolved after parameter adjustment. This study focused on the acute effects of unilateral STN and unilateral GPi DBS on motor function in individual PD. When the DBS was turned off either bilaterally or unilaterally, or drug intake was stopped overnight, some patients experienced uncomfortable exacerbations of motor symptoms, including intense tremors, rigidity, and exacerbations of axial symptoms. However, these exacerbations served as observations in this study, which were not recorded as adverse side effects. Moreover, all patients resumed bilateral DBS and medication administration at the end of the trial, and these exacerbations disappeared subsequently. No significant worsening other than motor symptoms was noted after DBS was turned off. No other side effects were observed throughout the study.

DISCUSSION

In this study, we found that unilateral STN stimulation had a better effect than did unilateral GPi stimulation on improving most cardinal motor symptoms and axial symptoms in both Med– and Med+ states. STN stimulation acted on both sides of the body, whereas GPi stimulation mainly affected the contralateral side. The effects on balance function of STN+ and GPi+ were not significantly different between the Med+ and Med– conditions.

We also found that the improvement in motor symptoms in the Med– state before and after surgery was greater than that in the Med+ state before and after surgery, which was consistent with previous studies (12, 13). Most relevantly, our results suggest that STN is more advantageous than GPi in the treatment in all cardinal symptoms, which conflicts with the previous reports indicating that the two have similar effects (14–19). This may be because we compare the effects of two targets within one patient, reducing bias caused by differences before different cohorts.

Additionally, we found that STN had a effect on both body sides. In contrast, GPi had a treatment effect mainly on the GPi-stim side, while the effects on the STN-stim side were subtle. Previous studies have reported the phenomenon of "dominant STN," whereby, in some patients, unilateral STN stimulation improved motor symptoms in ipsilateral side, comparable to the effects of bilateral STN stimulation (20–25). However, no similar reportsof dominant GPi have been documented before, although there is a study claiming that the improvement in ipsilateral motor scores from unilateral STN- and GPi-DBS does not differ (26).

Our study also revealed an advantage of STN stimulation in axial symptoms. Previous studies on the therapeutic effects of DBS on axial symptoms have inconsistent results. In general, STN DBS might provide greater alleviation of axial symptoms than GPi DBS; rather, GPi DBS might be associated with a milder long-term decline with regard to these symptoms (3, 27). However, at the 2- to 3-year follow-up, our study indicated less worsening of STN on axial symptoms compared to GPi, which was partly consistent with the findings of previous studies. However, at the same time, the worsening of axial symptoms in both unilateral STN and GPi on conditions may imply that the deterioration mainly come from the disease progression itself. Balance has often been related to postural stability in previous studies (27). In our study, there was little difference in the balance function between STN and GPi stimulation.

Combined unilateral STN and contralateral GPi DBS was originally designed for patients with asymmetric symptoms (5). However, in the subgroup analysis of this study, we found that under unilateral DBS stimulation, patients with symmetric symptoms showed better treatment effects than those with asymmetric symptoms. This may be because the preoperative symptoms in patients in the symmetric group were worse than those in the asymmetric group, leaving more room for improvement. But this may indicate that asymmetric targets can be used equally well in the treatment of patients with symmetric symptoms.

The present results are in line with our previous findings (5) that medication reduction can be achieved by this approach, which may be particularly relevant to target selection for patients who have a pressing need for medication reduction and suffer from contralateral dyskinesia, mood disorders, or worsening cognition.

This study has some limitations. The presence of a biased patient sample and confounding variables cannot be excluded because the study involved a small number of patients. The small sample size implies that the statistical power was sufficient to detect relatively large clinical effects but was insufficient to distinguish between small and subtle effects. Furthermore, we did not conduct studies on STN–GPi– conditions because patients were unable to cooperate with the evaluation due to the sudden worsening of symptoms, which made us obtain the corresponding results indirectly. Nevertheless, this study adopted a new method to compare between different targets within the same patient, namely the "N-of-1" design, which can reduce the interference of PD heterogeneity among different patients. In the future, the synergy of asymmetric targets needs to be assessed in greater depth. Furthermore, the influence of different targets on cognition and neuropsychology can also be researched using the methods described in this article.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee in Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CZ, DL, and LW designed and conceptualized the study. ZZ, LW, LX, PH, and YP organized and executed the process of the study. WS, ZC, and YL designed and implemented the data analysis. ZZ and KR reviewed the data. ZZ wrote the manuscript. ZL and XX reviewed and performed the language revision. BS, CZ, and DL reviewed and critiqued the manuscript. All authors have approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.812455/full#supplementary-material

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BRIEF RESEARCH REPORT
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Shuffling Improves the Acute and Carryover Effect of Subthalamic Coordinated Reset Deep Brain Stimulation

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Coordinated reset deep brain stimulation (CR DBS) in the subthalamic nucleus (STN) has been demonstrated effective for the treatment of the motor signs associated with Parkinson's disease (PD). A critical CR parameter is an order in which stimulation is delivered across contacts. The relative effect of alternating vs. not alternating this order, i.e., shuffling vs. non-shuffling, however, has not been evaluated *in vivo*. The objective of this study is to compare the effect of shuffled vs. non-shuffled STN CR DBS on Parkinsonian motor signs. Two Parkinsonian non-human primates were implanted with a DBS lead in the STN. The effects of STN CR DBS with and without shuffling were compared with the traditional isochronal DBS (tDBS) using a within-subject design. For each stimulation setting, DBS was delivered for 2 or 4 h/day for 5 consecutive days. The severity of PD was assessed using a modified clinical rating scale immediately before, during, and 1 h after DBS, as well as on days following the discontinuation of the 5 days of daily stimulation, i.e., carryover effect. Shuffled STN CR DBS produced greater acute and carryover improvements on Parkinsonian motor signs compared with non-shuffled CR. Moreover, this difference was more pronounced when more effective stimulation intensity and burst frequency settings were used. tDBS showed limited carryover effects. Given the significant effect of shuffling on the effectiveness of CR DBS, it will be critical for future studies to further define the relative role of different CR parameters for the clinical implementation of this novel stimulation paradigm.

Keywords: Parkinson's disease, deep brain stimulation, subthalamic nucleus, coordinated reset, non-human primates

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INTRODUCTION

High frequency isochronal "traditional" deep brain stimulation (tDBS) is an established treatment for the motor signs associated with Parkinson's disease (PD). Its effectiveness, however, can be limited due to side effects resulting from unwanted current spread into adjacent fiber pathways, such as the internal capsule or non-motor regions of the targeted structure (1–3). The concept of coordinated reset (CR) stimulation arose from computational modeling studies that suggested that low amplitude periodic stimulation of synchronized neuronal populations can induce a long-lasting desynchronizing effect (4, 5). CR DBS alternates stimulation across multiple contacts of the

DBS lead and is hypothesized to induce a desynchronizing effect at lower current intensities than that required with tDBS (6, 7). CR DBS has been shown in both preclinical and clinical studies to produce acute motor improvement similar to tDBS with the added benefit that motor improvement would persist for hours, days, or weeks following discontinuation of stimulation, i.e., carryover effect (8–10). It may reduce the incidence of side effects by minimizing the current spread.

Coordinated reset stimulation was originally designed to deliver stimulation at multiple locations within the target structure by stimulating through individual contacts of a DBS lead using a repeated sequence of contacts (**Figure 1A**, top), i.e., non-shuffled pattern (4, 11–13). It was hypothesized that the effectiveness of this non-shuffled pattern results from activating neuronal subpopulations in a phase-shifted manner leading to a desynchronizing effect (14). In subsequent computational studies, however, a pseudorandomized sequence of contacts was used (**Figure 1A**, bottom), i.e., shuffled pattern, and this sequence was found to more effectively desynchronize neuronal populations than the non-shuffled CR (5). Although shuffled CR patterns have been used in recent studies (8–10, 15–17), the relative effect of these two approaches has not been investigated *in vivo*. In this study, we present a case series of two Parkinsonian non-human primates (NHPs) where we explored the relative effect of shuffled vs. non-shuffled subthalamic nucleus (STN) CR DBS using a within-subject design. We hypothesized that shuffled STN CR DBS would produce a greater acute effect as well as a longer carryover effect on motor improvement when compared with the non-shuffled CR DBS. Our findings provide preliminary evidence supporting this hypothesis and support the concept that shuffling the pattern of contact stimulation is an important feature of CR stimulation.

MATERIALS AND METHODS

Animal care complied with the Guide for the Care and Use of Laboratory Animals and all procedures were approved by the Institutional Animal Care and Use Committee.

Animals and Motor Assessment

The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) NHP model of PD was used in this study. Two adult female rhesus monkeys (NHP J, 10 kg; NHP B, 8 kg) were implanted with a DBS lead in the STN using an approach similar to that was described in previous studies (9, 18). Briefly, a cephalic chamber was placed on the skull oriented to target the STN in each animal. Microelectrode recording and stimulation techniques (19) were used to map the sensorimotor region and borders of the STN, following which an 8-contact DBS lead (NuMed Inc., TX, USA, 0.63 mm diameter, 0.5 mm contact height, and 0.5 mm space between contacts) was implanted. A version of the Unified Parkinson's Disease Rating Scale modified for NHPs (mUPDRS) (9, 20, 21) was used to assess the severity of parkinsonism on the side contralateral to the site of DBS implantation in each animal and changes in motor signs under different conditions of stimulation. The mUPDRS consists of scores for rigidity, akinesia, bradykinesia, and tremor for the upper and lower limbs, and food retrieval on a 0–3 scale (0 = unimpaired, 3 = severe); maximum total score = 27. The animals were rendered moderately Parkinsonian (mUPDRS: 10–17) using the neurotoxin MPTP. The mUPDRS scores for each animal were 11.3 ± 0.7 (mean ± SD, $n = 22$) in NHP J and 10.4 ± 0.4 ($n = 22$) in NHP B (**Figure 1B**). Both NHPs demonstrated akinesia, rigidity, and bradykinesia, while tremor was minimal and intermittently observed in both animals. Following completion of the study, NHP J was euthanized, and histology was performed. The 40 μm coronal sections were imaged and visualized in Avizo (FEI) with the sagittal view extracted to show the DBS lead location (**Figure 1C**, left). For NHP B, a post-implant CT was merged with the pre-operative MRI to verify the location of lead (**Figure 1C**, right). The schematic of the lead was created from an image of the lead that was overlapped with either the histologic lesion induced by the lead (**Figure 1C**, left) or the CT reconstruction (**Figure 1C**, right). This was used to demonstrate the location of the lead and individual contacts within the subcortical target.

Experiment Protocol

Prior to DBS testing in each animal, the mUPDRS assessment was performed 10 times over 2 weeks in NHP J and 14 times across 4 weeks in NHP B, to establish the baseline severity of motor signs for the study. Within each evaluation session (**Figure 1D**), CR DBS was delivered with an implantable pulse generator (IPG) (Precision Spectra, Boston Scientific, MA, USA, constant current) for 4 (NHP J) or 2 (NHP B) h daily for 5 consecutive days. This intermittent delivery pattern (2–4 h of stimulation per day) was determined based on previous modeling (22) and *in vivo* studies (8–10). The daily stimulation duration was set as 4 h originally for both NHPs based on our previous study (9), but reduced to 2 h for NHP B as the mUPDRS plateaued within 2 h of stimulation in this animal. mUPDRS scores were obtained daily on stimulation days pre, every 30 min during, and at 60 min post-DBS, and once every afternoon for at least 5 days following the end of 5 stimulation days. A new evaluation session (**Figure 1D**) was not initiated until the mUPDRS score returned to baseline. tDBS was delivered with a different IPG (Soletra, Medtronic, Ireland, constant voltage) for NHP J as the Boston Scientific IPG used for CR DBS was not available at the time, the experiments were initially performed. For NHP B, tDBS was delivered with the Boston Scientific IPG. tDBS was evaluated using the same schedule as with CR DBS, with the exception that the mUPDRS scores obtained during stimulation were collected every hour (1st, 2nd, and 3rd h in NHP J; 1st and 2nd h in NHP B) rather than every 30 min. Following 5 days of tDBS, mUPDRS scores were obtained for only 2 days for NHP J and were not further assessed for NHP B as the mUPDRS returned to baseline within minutes following discontinuation of tDBS in both animals.

Abbreviations: mUPDRS, modified Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; CR, Coordinated reset; DBS, deep brain stimulation; tDBS, traditional deep brain stimulation; STN, subthalamic nucleus; GPe/i, external/internal segment of globus pallidus; SN, substantia nigra; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; IPG, implantable pulse generator.

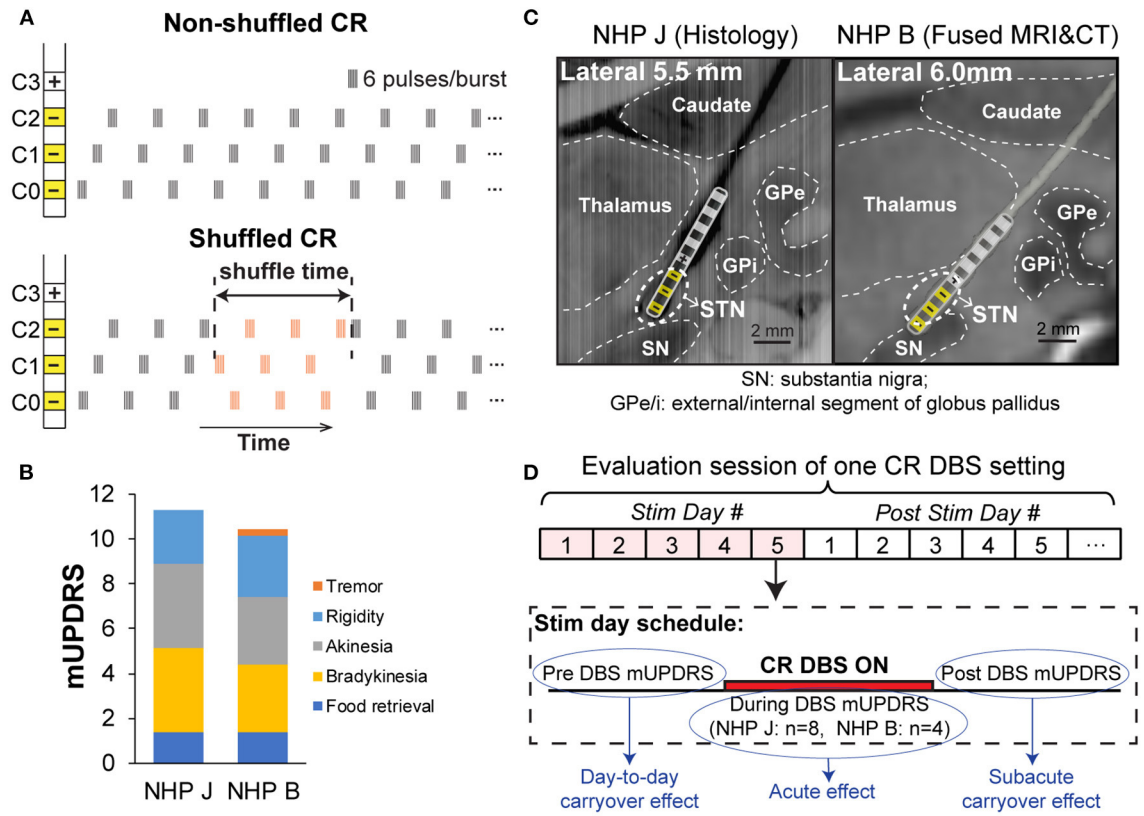

FIGURE 1 | (A) Non-shuffled and shuffled coordinated reset deep brain stimulation (CR DBS) patterns. Top: Non-shuffled CR DBS repeats the order of delivering bursts to different contacts, i.e., same contact sequence, throughout the stimulation time. Bottom: Shuffled CR pseudo-randomly changes the contact sequence at a certain frequency. **(B)** Mean total and subscores of modified Unified Parkinson's Disease Rating Scale (mUPDRS) for two Parkinsonian monkeys. **(C)** Deep brain stimulation (DBS) lead locations. Left: Sagittal view of the DBS lead track reconstructed from histology in NHP J (C0-C7 from bottom to top contact); Right: Fused MRI/CT images showing the DBS lead location. The lead schematic was overlaid in each figure and the stimulation contacts for CR DBS are indicated (yellow). **(D)** The experiment timeline demonstrates the evaluation schedule of CR DBS, and the mUPDRS scores used to assess the acute, subacute carryover, and day-to-day carryover effects.

Therapeutic stimulation parameters for tDBS were determined using a standard monopolar review (1). tDBS was delivered through C0–/C2+ at 2.1 V in NHP J, and C1–/C2+ at 0.32 mA in NHP B, with a pulse width of 120 μs and frequency of 130 Hz. For CR DBS, the four contacts within the STN region (C0/C1/C2–, C3+) were selected based on the lead location combined with results from the monopolar review in both NHPs. CR stimulation parameters were selected based on previous studies (8, 9), referred to as the "default" setting, including 0.1 mA intensity, 120 μs pulse width, 6 pulses/burst, 150 Hz intra-burst rate, and 21 Hz burst frequency. Shuffling (**Figure 1A**) was performed manually every 30 min in NHP J as the device was not capable of shuffling automatically at the time of the experiment. For NHP B, the function of automatic shuffling was incorporated into the Boston Scientific IPG and shuffling was performed automatically with a shuffling interval of 10 s. In NHP B, additional shuffled CR DBS sessions were performed to explore the impact of different current intensities and burst frequencies on the therapeutic effect. A stimulation intensity (0.16 mA) and burst frequency (27 Hz) that induced greater acute motor benefits and longer carryover effect relative to the default setting (0.1 mA, 21 Hz) was identified in this animal. Both shuffled and non-shuffled sessions were performed using these settings to further compare the effect of each on motor signs.

Data Analysis

All the mUPDRS scores obtained during DBS (acute scores) were converted into the percentage improvement relative to the baseline score: percentage improvement in mUPDRS = 100*(baseline score – acute score)/baseline score. The baseline score was defined as the median of the baseline mUPDRS scores obtained prior to DBS testing (10 scores for NHP J and 14 scores for NHP B). The daily acute effect of CR DBS was determined by the median percentage improvement in the mUPDRS scores obtained during daily CR DBS (**Figure 1D**, $n = 8$ for NHP J and $n = 4$ for NHP B each day). The acute effect of tDBS was determined by the median percentage improvement in the mUPDRS scores obtained during tDBS across the 5 stimulation days ($n = 15$ for NHP J and $n = 10$ for NHP B), due to the limited number of scores obtained each day and a similar level of effect across days. The acute effect of tDBS and daily acute effect of

CR DBS were compared with the baseline using the Steels test with control = baseline following a Wilcoxon test [χ^2 (DoF,N)]. Similarly, the daily acute effect of CR DBS was compared with the acute effect of tDBS using the Steels test with control = tDBS. The daily acute effects of shuffled and non-shuffled CR DBS were also compared with each other using the Wilcoxon test. Statistical analyses were performed in JMP (SAS Institute Inc., NC, USA), and alpha was corrected for 26 comparisons using the Bonferroni method. Detailed results of the statistical analysis are shown in **Supplementary Table 1**. The sub-acute carryover effect was determined by the percentage improvement in the mUPDRS score obtained 60 min post-DBS (1 score per stimulation day), relative to the pre DBS score on stimulation day 1. The day-to-day carryover effect was determined by calculating the percentage improvement in the pre DBS mUPDRS scores on stimulation days 2–5 and each day following discontinuation of the 5 days of CR DBS (1 score per day), relative to the pre DBS score on stimulation day 1.

RESULTS

Non-Human Primate J

Daily acute effects: except for a few days, both shuffled and non-shuffled CR DBS produced significant acute motor improvement. The degree of improvement during shuffled CR was greater than non-shuffled CR except for stimulation day 1 (**Figure 2A**). Shuffled CR DBS produced acute improvement comparable with that produced by tDBS except for stimulation day 1, while the non-shuffled CR produced significantly less acute benefit than tDBS on stimulation days 3, 4, and 5.

Carryover effects: the sub-acute carryover effect gradually improved over days in the shuffled CR DBS condition, achieving up to 21% improvement in the mUPDRS during stimulation days 3–5, while non-shuffled CR DBS fluctuated in the range of −12–4% change in the mUPDRS (**Figure 2B**). The day-to-day carryover benefits of shuffled CR DBS increased over days and reached 17.5% of improvement by stimulation day 5, carrying over for 1 day after 5 stimulation days. Non-shuffled CR DBS, however, produced a gradual worsening of motor signs over the 5 stimulation days that continued until the 3rd day after 5 stimulation days (**Figure 2C**). No carryover effect was observed with tDBS. The subacute and day-to-day carryover changes in mUPDRS associated with tDBS fluctuated in the range of −11.7–6.2%.

Non-Human Primate B

Daily acute effects: with the default stimulation intensity and burst frequency, there was only a modest difference in acute improvement between the shuffled and non-shuffled CR conditions (**Figure 3A**). Shuffled CR produced acute effects at the same level of tDBS in 4 out of 5 stimulation days, but the acute improvement induced by non-shuffled CR was similar to tDBS for only 2 out of the 5 days (**Figure 3A**). With the more effective stimulation intensity (0.16 mA) and burst frequency (27 Hz), however, the impact of shuffling on acute improvement was more pronounced. Shuffled CR produced greater acute improvement than non-shuffled CR in 4 out of 5 days (**Figure 3D**). The difference between the two stimulation conditions gradually increased over stimulation days and on the last day of stimulation, shuffled CR DBS produced acute motor benefits over two times that of non-shuffled CR DBS. Less variation in the daily mUPDRS scores was observed with the more effective stimulation intensity and burst frequency with both shuffled and non-shuffled CR DBS. Notably, shuffled CR DBS with the more effective setting produced the same acute effect as tDBS on the first 4 stimulation days and greater improvement on day 5 while the acute effect of non-shuffled CR produced less improvement than tDBS on most stimulation days (**Figure 3D**).

Carryover effects: greater sub-acute carryover benefits were observed with shuffled CR DBS than non-shuffled CR DBS on all stimulation days. This finding was consistent between CR using the default and more effective settings of stimulation intensity and burst frequency (**Figures 3B,E**). Different from the accumulating effects we observed with shuffled CR DBS in NHP J, the sub-acute benefits with CR DBS in NHP B were already achieved on stimulation day 1. Benefits with shuffled CR DBS fluctuated around 30% improvement, while those with non-shuffled CR fluctuated around 20% improvement in days 1–4 decreasing to ∼10% on day 5. The tDBS did not induce any sub-acute carryover benefits and the percentage of change in mUPDRS obtained 60 min after DBS on stimulation days fluctuated in the range of 0.7–10%.

With the default CR setting, shuffled CR for NHP B induced greater motor improvement and a longer day-to-day carryover effect than non-shuffled CR. Slightly over 33% of maximum day-to-day carryover motor improvement was achieved with shuffled CR compared with 21% of maximum improvement with non-shuffled CR (**Figure 3C**). Using 10% improvement as a threshold for carryover benefits, following the 5 days of daily stimulation shuffled CR induced 6 additional days of carryover benefit while non-shuffled CR only induced 2 days of carryover benefit. The difference between the effects of shuffled and non-shuffled CR DBS in NHP B became more pronounced once the more effective CR setting was used. With this setting, shuffled CR DBS produced day-to-day carryover motor improvement that peaked around 36% and persisted above 10% for 11 days after the 5 days of daily stimulation, while non-shuffled CR DBS produced day-to-day carryover improvement that peaked around 16% and only persisted for 4 days (**Figure 3F**). No day-to-day carryover effect was observed with tDBS indicated by the percentage of change in daily morning mUPDRS scores fluctuating in the range of −1.1–4.4%.

DISCUSSION

This study illustrates the dependence of CR DBS efficacy on defining the effective set of CR stimulation parameters for acute, sub-acute, and day-to-day carryover effects on motor signs. Our results provide preliminary evidence supporting our hypothesis that shuffled CR DBS produces greater therapeutic effects than non-shuffled CR DBS. In addition, the results provide further support for the beneficial effect of STN CR DBS. With

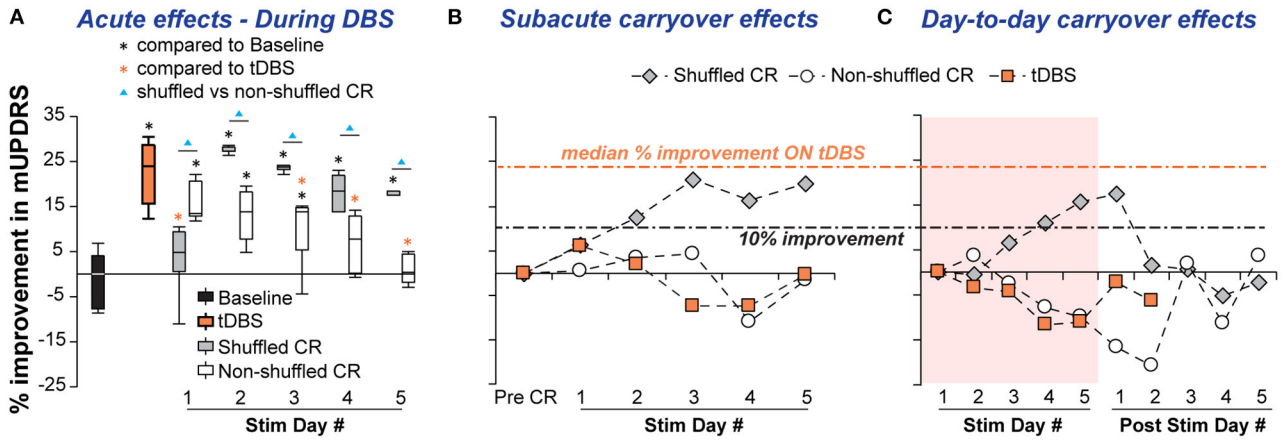

FIGURE 2 | Acute and carryover improvements in mUPDRS acquired by shuffled and non-shuffled CR DBS in NHP J. **(A)** Acute improvements were compared with the baseline using the Steel's test with control = Baseline (*$p < 0.05$) following a Wilcoxon test. Daily acute improvements of CR DBS were also compared to traditional DBS (tDBS) using the Steel's test with control = tDBS (*$p < 0.05$). Within each stimulation day, the shuffled and non-shuffled CR DBS were compared using the Wilcoxon test (▲$p < 0.05$). **(B)** Subacute carryover effects of CR DBS indicated by the percentage improvement in the post-DBS mUPDRS. **(C)** Day-to-day carryover effects of CR DBS indicated by the percentage improvement in the daily morning mUPDRS on stimulation and post-stimulation days.

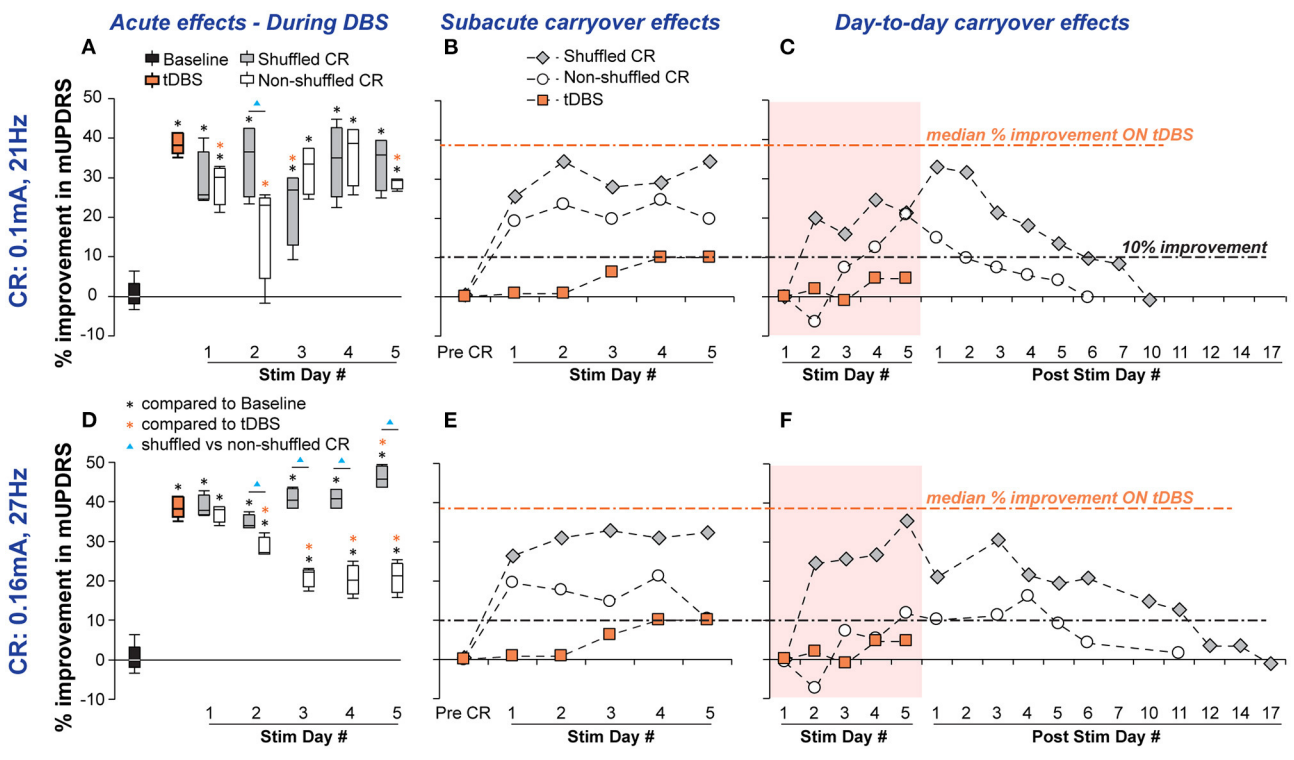

FIGURE 3 | Acute and carryover improvements in mUPDRS acquired by shuffled and non-shuffled CR DBS in NHP B in two conditions: (i) CR DBS with a default stimulation intensity of 0.1 mA and burst frequency at 21 Hz (Top row) and (ii) CR DBS with the more effective stimulation intensity of 0.16 mA and burst frequency at 27 Hz (Bottom row). **(A,D)** Acute motor benefits across stimulation days measured by the percentage of improvement in mUPDRS compared with the baseline between shuffled and non-shuffled CR DBS were compared in each condition. Statistical comparisons were performed using the same method for NHP J (*, ▲$p <$ 0.05). **(B,E)** Subacute carryover effects of CR DBS indicated by the percentage of improvement in the post-DBS mUPDRS. **(C,F)** Day-to-day carryover effects of CR DBS indicated by the percentage of improvement in the daily morning mUPDRS on stimulation and post-stimulation days.

the appropriate parameter setting, CR DBS produced acute therapeutic effects that were comparable with those produced by tDBS, while using only half the stimulation intensity (NHP B). Carryover benefits observed with shuffled CR DBS might allow further reduction in the stimulation time of CR DBS. Being able to reduce both the stimulation intensity and amount of time

required for stimulation are advantageous in that they are likely to be associated with a lower probability of side effects and energy consumption, requiring fewer battery replacement and/or less frequent recharging for rechargeable systems improving the quality of life for patients with PD who have undergone DBS.

Importance of Exploration in CR Parameter Space in the NHP Model of PD

Coordinated reset deep brain stimulation has a vast parameter space and some of these parameters have been found in modeling studies to have a significant impact on its effect, such as stimulation intensity (15), burst frequency (15), pausing between stimulation (11, 22), and shuffling (5). Systematic evaluation of these parameters is critical for the development and clinical implementation of CR DBS. As the evaluation of each CR setting is time consuming (days/weeks), evaluating all the critical parameters, while challenging in patients with PD, is achievable in the NHP model of PD (23). During this study, the significantly greater acute and carryover motor improvement observed in NHP J provided preliminary evidence of the important role of shuffling in CR. These results encouraged and supported the further development of the investigational IPG (Boston Scientific) to incorporate automatic shuffling in the CR pattern. Additional experiments in NHP B utilizing this new capability of automatic shuffling further demonstrated the importance of shuffling in CR DBS, providing greater acute motor improvement and longer carryover benefits. This study demonstrated the impact of shuffling stimulation patterns and the importance of identifying the role of individual variables to define the optimal setting for CR DBS.

Potential Mechanistic Differences Underlying the Effect of Shuffled and Non-Shuffled CR DBS

Modeling studies have hypothesized that a non-shuffled CR stimulation pattern activates neuronal subpopulations in a phase-shifted manner resulting in a desynchronizing effect that underlies its therapeutic effect (14). Models incorporating spike-time-dependent plasticity (STDP), however, have indicated that prolonged non-shuffled CR stimulation may induce synchronization within each neuronal subpopulation compromising the desynchronizing effect (5, 17). Instead of the abnormal synchronization related to PD, this synchronization can be induced by repeating the same stimulation sequence thus stimulating each neuronal subpopulation at a fixed frequency. The phase-shifting effect on neuronal subpopulations might underlie the acute therapeutic effects of CR DBS similar to that of tDBS observed with non-shuffled CR during the first 1 or 2 days of stimulation (**Figures 2A**, **3D**). With prolonged stimulation, however, the desynchronizing effect might be compromised as neuronal subpopulations become synchronized again as a result of using the same stimulation sequence. Such a phenomenon could also explain the stepwise worsening of motor signs we observed across stimulation days of non-shuffled CR in NHP J that carried over for 2 days. To provide additional evidence to either refute or support these theories, additional studies investigating the effect of different CR parameter combinations on behavior and corresponding changes in neuronal activity in the basal ganglia thalamocortical circuit will be necessary.

Limitations and Future Directions

Although significant differences between the shuffled and non-shuffled CR DBS were observed in both NHPs, there are several limitations to this study. Additional exploration in the CR stimulation intensities and burst frequencies in NHP B, were not performed in NHP J. This was due in part to the amount of time required to study each CR DBS setting but mostly to the different device capabilities and their availability. Different shuffle times and duration of stimulation were used in each animal due to the different capabilities of the device that was available at the time of experiments and different daily stimulation durations required to achieve a stable therapeutic effect. Although we were able to compare the effect of shuffled and non-shuffled CR DBS on motor signs within each subject, the difference in shuffle time, daily stimulation duration, and other parameters could have contributed to the differences in CR effects on each animal. It will be important in future studies to perform systematic evaluations of CR DBS using different combinations of critical parameters across multiple subjects. Our sample size was limited and assessments were not blinded. In spite of these limitations, the results provide important data setting the stage for future studies to confirm and expand upon these findings using quantitative, objective measures. Although stimulation related side effects were not observed in this study, with either tDBS or CR DBS, future long-term preclinical and/or clinical studies will be needed to compare the incidence of side effects related to these two DBS approaches. The results of this study, if supported with future studies, will have a direct translational impact on future DBS programming approaches as the capability of delivering CR patterns can be incorporated into current and future DBS systems.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Institutional Animal Care and Use Committee.

AUTHOR CONTRIBUTIONS

JW, JV, and GM conceived and designed the experiments. HB contributed to the study design. SK and HB designed and developed the study-specific IPG firmware and software. JW, SF, LJ, SN, and JZ contributed to animal training and instrumentation. JW, SF, and SN acquired and analyzed the data. JW, LJ, and JV were involved in drafting the article. All authors have reviewed the article and approved the final version for submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.716046/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Neurology

SYSTEMATIC REVIEW
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The Effects of Non-Invasive Brain Stimulation on Quantitative EEG in Patients With Parkinson's Disease: A Systematic Scoping Review

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Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor symptoms, aside from alterations in the electroencephalogram (EEG) already registered. Non-invasive brain stimulation (NIBS) techniques have been suggested as an alternative rehabilitative therapy, but the neurophysiological changes associated with these techniques are still unclear. We aimed to identify the nature and extent of research evidence on the effects of NIBS techniques in the cortical activity measured by EEG in patients with PD. A systematic scoping review was configured by gathering evidence on the following bases: PubMed (MEDLINE), PsycINFO, ScienceDirect, Web of Science, and cumulative index to nursing & allied health (CINAHL). We included clinical trials with patients with PD treated with NIBS and evaluated by EEG pre-intervention and post-intervention. We used the criteria of Downs and Black to evaluate the quality of the studies. Repetitive transcranial magnetic stimulation (TMS), transcranial electrical stimulation (tES), electrical vestibular stimulation, and binaural beats (BBs) are non-invasive stimulation techniques used to treat cognitive and motor impairment in PD. This systematic scoping review found that the current evidence suggests that NIBS could change quantitative EEG in patients with PD. However, considering that the quality of the studies varied from poor to excellent, the low number of studies, variability in NIBS intervention, and quantitative EEG measures, we are not yet able to use the EEG outcomes to predict the cognitive and motor treatment response after brain stimulation. Based on our findings, we recommend additional research efforts to validate EEG as a biomarker in non-invasive brain stimulation trials in PD.

Keywords: electroencephalography, transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (TMS), transcranial alternating current stimulation (tACS), non-invasive brain stimulation (NIBS), Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder caused by the degeneration of the dopaminergic neurons of the substance nigra pars compacta and involvement of other neural circuits, resulting in motor and non-motor symptoms (1, 2). Although medicinal therapy and deep brain stimulation (DBS) can be chosen as the treatments for these patients, non-invasive brain stimulation (NIBS) techniques have been suggested as an alternative therapy with related rehabilitative effects (3–6).

The most used NIBS techniques for motor and cognitive rehabilitation are transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES), which include transcranial direct stimulation (tDCS) and transcranial alternating current stimulation (tACS) (7). Despite the benefits associated with the use of NIBS in the treatment of patients with PD, such as the improvement of motor (3, 5, 8) and non-motor (9–11), the neurophysiological changes associated with these techniques are still unclear. In this regard, the electroencephalogram (EEG) is a tool of interest due to the possibility of identifying the changes in bioelectrical brain activity, which presents as a potential neurophysiological biomarker and prognosis for clinical management of PD (12, 13).

Studies with EEG in patients with PD have shown an excessive coherence of the beta frequency related to the motor symptoms (14, 15), while other studies showed low dominant frequencies or increased spectral power of lower frequencies bands, which are related to cognitive impairment (12, 16). NIBS can modify the cerebral oscillations and their associated functions, such as increased synchronization of the frequency bands of the EEG (17), decrease the spectral power of low or high frequencies (18, 19), suggesting a possible link between beta and gamma frequencies with the anti-kinetic and prokinetic effects, respectively (20). Finally, a review concluded that the modulation of beta frequency may be a consolidated marker of the success of NIBS in PD, however, it presented only preliminary results from TMS and tACS (21).

Nonetheless, despite studies that have investigated the effects of NIBS intervention on EEG oscillations, the variety of NIBS techniques and protocols and the different conditions in which the EEG was measured may lead to confusion in interpretation and future directions. Therefore, we conducted a systematic scoping review aiming to identify the nature and extent of research evidence on the effects of NIBS on the cortical activity measured by the EEG in patients with PD. Beyond presenting a summary of the body of available evidence, we will highlight existing gaps in the literature and discuss the possible paths for conducting future studies.

METHODS

The current study consisted of a systematic scoping review (22, 23), conducted and reported according to the guidelines of the *Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR)* (24). The review process was performed using the Rayyan platform (25), developed by the Qatar Computing Research Institute. The protocol of the revision was registered in the Open Science Framework (https://osf.io/2zvs3/).

TABLE 1 | Search strategy for PsycINFO database.

("Parkinson disease" OR "Parkinson's disease") AND (electroencephalography OR EEG) AND ("transcranial direct current stimulation" OR tDCS OR "binaural beats" OR "galvanic vestibular stimulation" OR tACS OR "transcranial magnetic stimulation" OR "non-invasive brain stimulation").

EEG, electroencephalogram; tDCS, transcranial direct current stimulation; tACS, transcranial alternating current stimulation.

The search strategy was configured by gathering evidence, without language restriction, from inception until April 2020, on the following basis: PubMed (MEDLINE), PsycINFO, ScienceDirect, Web of Science, and cumulative index to nursing & allied health (CINAHL). The following search terms, with the Boolean operators AND/OR, were used: "Parkinson disease"; "Parkinson's disease; "electroencephalography"; "electroencephalogram"; "EEG"; "transcranial direct current stimulation"; "tDCS"; "transcranial magnetic stimulation"; "TMS"; "non-invasive brain stimulation"; "NIBS"; "transcranial electrical stimulation"; "binaural beats (BBs)"; "galvanic vestibular stimulation (GVS)"; "transcranial alternating current stimulation"; and "tACS." The strategy was adjusted for each database following the example of PsycINFO (**Table 1**).

The inclusion criteria for the selection of studies were as follows: (1) enroll participants diagnosed with idiopathic PD; (2) perform any type of NIBS as the intervention; (3) present quantitative EEG as the pre-intervention and post-intervention outcome measures; and (4) to be a clinical trial. Case studies, simulations studies, conference abstracts, studies that used the NIBS for diagnoses purposes or used the EEG only for safety reasons (i.e., identification of epileptic waveforms) were excluded.

After removing the duplicates, two independent reviewers screened the results of the searches based on the titles and abstracts and applied the eligibility criteria. Next, the two reviewers evaluated the full texts of the selected publications and independently extracted the following data: author, year of publication, study design, sample size, type of NIBS and its protocol details, EEG acquisition and analysis, and main findings, and inserted the data in a customized table. A search for relevant articles was performed in the reference list of selected articles of the full text. Conflicts were resolved by consensus or by a third reviewer, if necessary. The reviewers involved in the search, screening, and data extraction were previously trained.

Although a quality assessment is not a mandatory stage of the scoping review, previous studies suggest that this is a necessary component in this type of review (26, 27). Since this study reviewed the evidence on the possible neurophysiological effects of a promising treatment for patients with PD, we decided to include the quality assessment of the included studies. We used the modified version of the tool proposed by Donws and Black (28), and with the final score, we classified the studies as "excellent" (24–28 points), "good" (19–23 points), "regular" (14–18 points), or "bad" (<14 points) (29).

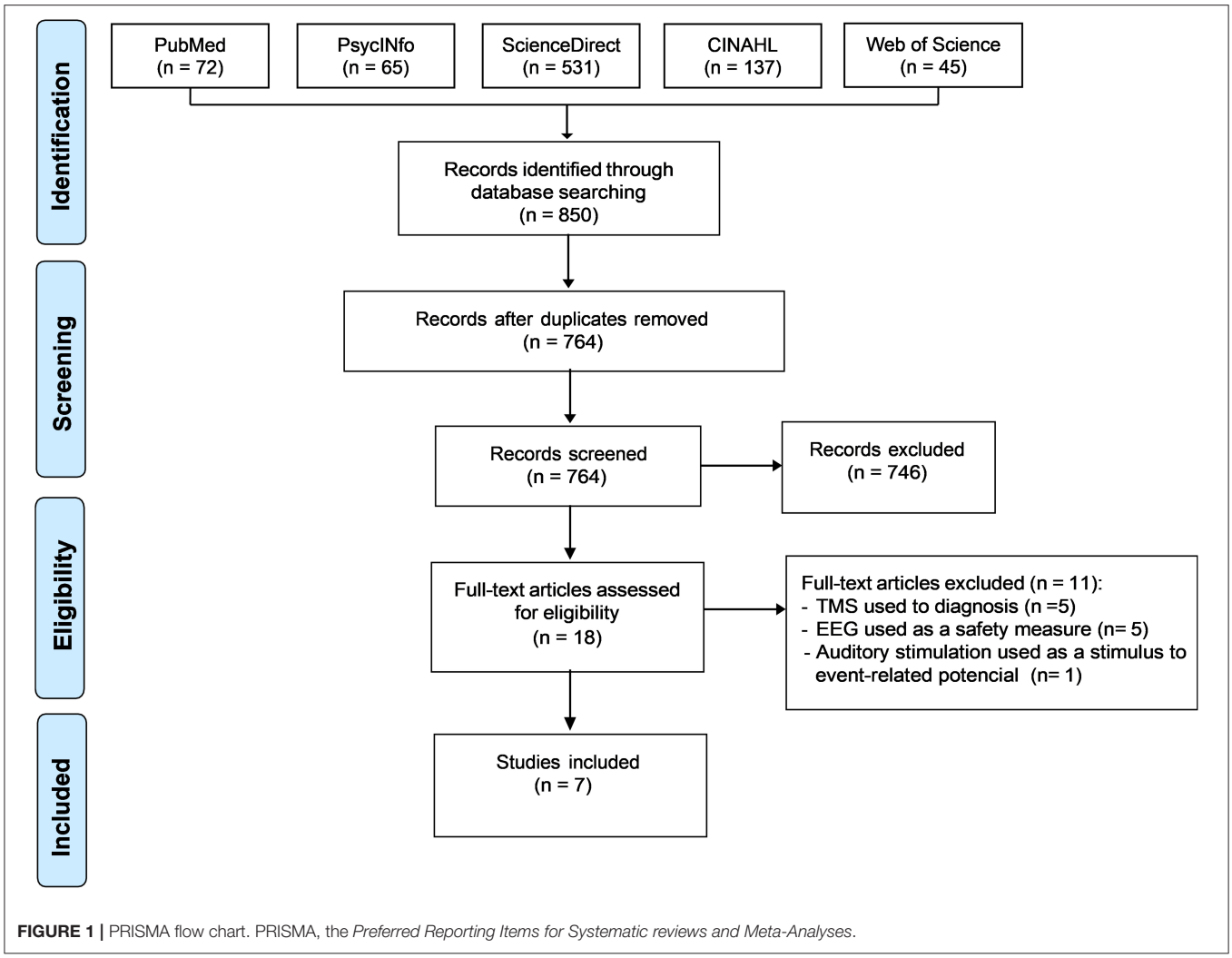

FIGURE 1 | PRISMA flow chart. PRISMA, the *Preferred Reporting Items for Systematic reviews and Meta-Analyses*.

RESULTS

After duplicate removal and screening, seven out of the initial 850 studies were included. The entire search and selection process is pictured in **Figure 1**. The studies were categorized per NIBS techniques used: TMS (30, 31), tES (32, 33), and other forms of NIBS (34–36).

The main results regarding the effects of NIBS on quantitative EEG and motor and non-motor outcomes in patients with PD are summarized in **Figure 2**.

Trials Using Repetitive TMS

Tanaka et al. (30) found increased theta frequency in the upper right temporal gyrus and decreased lower-alpha frequency (8.5–10 Hz) and lower-beta frequency (12.5–18 Hz) in the frontal gyrus after low-frequency (0.2 Hz) rTMS over the frontal cortex (**Table 2**). These changes in EEG activity were followed by decreased depressive symptoms, improved motor activity (i.e., 20-m walk test and finger tapping), and improved Unified Parkinson's Disease Rating Scale (UPDRS) (30). While Marchesi et al. (31) compared the effects of high-frequency (5 Hz) rTMS to a multidisciplinary intensive rehabilitation treatment (MIRT) on the EEG oscillations of patients with PD during a motor task. They found that despite both techniques improved learning of a rotation task, but only MIRT and not rTMS changed mean beta modulation in the opposite sensorimotor area to the movements, but both interventions improved the retention of new motor abilities.

Trials Using tES

The studies that used tES were randomized, blinded, placebo-controlled, and included clinical evaluations of PD. However, the EEG was evaluated during the different status of the parkinsonian medication action, at rest, and during a motor task (**Table 3**).

Del Felice et al. (32) evaluated the effect of tACS and transcranial random noise stimulation (tRNS), which was used as an active sham, for 2 weeks each in patients with PD. The frequency of stimulation was individualized so that those with excessive beta frequency received theta-tACS (4 Hz) and those with excessive theta received beta-tACS (30 Hz), compared to healthy controls (32). The theta-tACS group

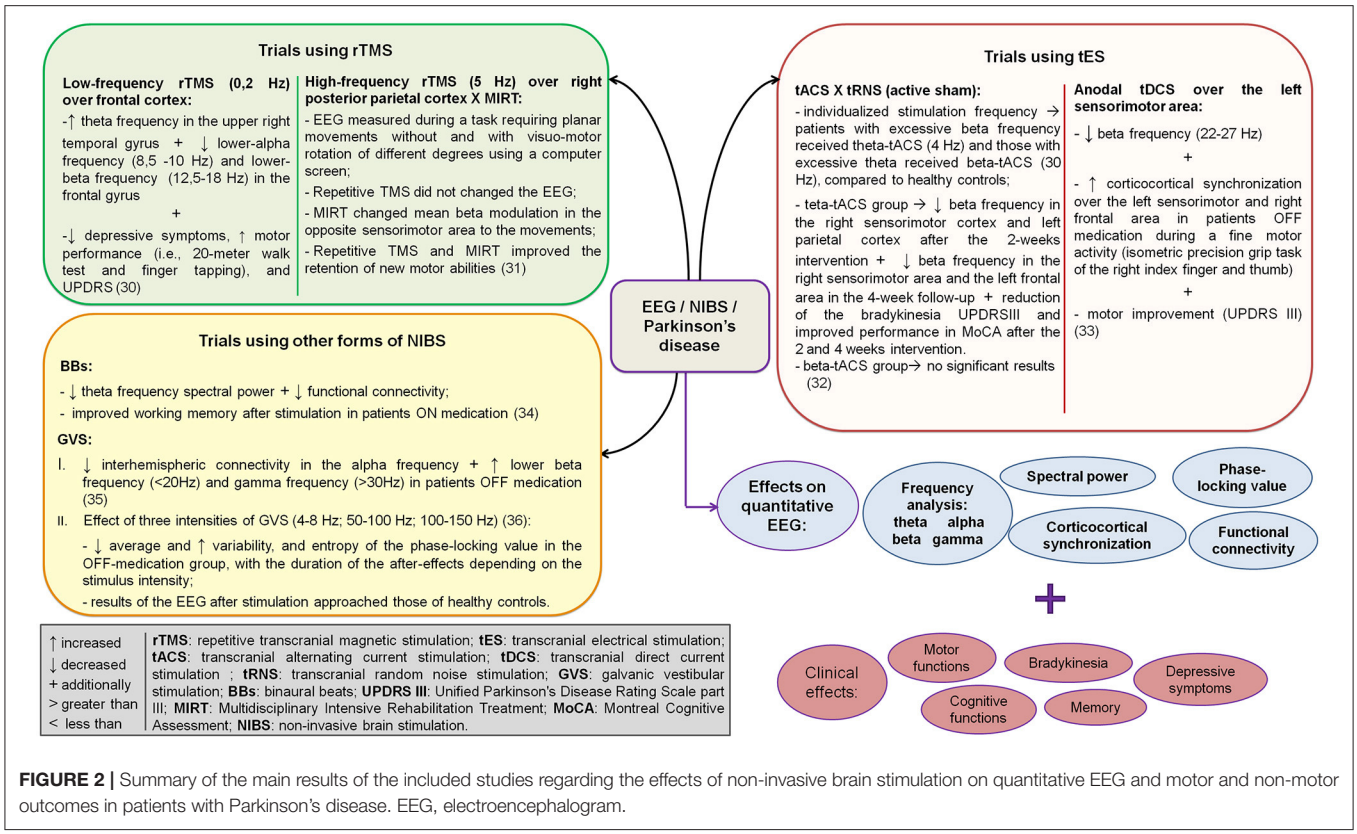

FIGURE 2 | Summary of the main results of the included studies regarding the effects of non-invasive brain stimulation on quantitative EEG and motor and non-motor outcomes in patients with Parkinson's disease. EEG, electroencephalogram.

TABLE 2 | Characterization of studies that used transcranial magnetic stimulation in Parkinson's disease.

References	Design: randomization/ blinding/ sham	Sample number (age range in years); sex distribution; stage (disease duration)	Stimulation protocol		EEG		Other outcomes
			Type of stimulation; parameters used	Number of sessions	ON or OFF medication	Number of channels; condition of assessment; data analysis	
Tanaka et al. (30)	No/No/No	7 (66.3); 5 males; HY>2 (NR)	rTMS (0.2 Hz, over frontal areas, 20 times per day, intensity of 1,5 T)	5	ON	20; eyes-closed resting before and after the stimulation; frequency analysis and LORETA	Motor activity with finger tapping and 20-m walking; UPDRS; actigraphy
Marchesi et al. (31)	Yes/No/Yes	29 (60); 23 males; HY 2–3 (8 ± 4 years) + 19 healthy controls (59); 10 males	rTMS (5 Hz, over right posterior parietal cortex)	2 (1 rTMS + 1 sham)	ON	256 (rTMS and control group) and 68 (MIRT group); recorded during motor task; analysis of frequencies calculated in the range of 15–30 Hz (oscillations beta)	Reaction time; amplitude of peak velocity; movement time and extention; directional error; learning and retention

HY, Hoehn and Yahr Scale; rTMS, repetitive transcranial magnetic stimulation; LORETA, Low-Resolution Electromagnetic Tomography; UPDRS, Unified Parkinson's Disease Rating Scale; MIRT, Multidisciplinary Intensive Rehabilitation Treatment; NR, Not reported.

presented decreased beta frequency in the right sensorimotor cortex and left parietal cortex after the 2-week intervention and a persistent reduction in the right sensorimotor area and the left frontal area in the 4-week follow-up. The theta-tACS group also improved bradykinesia and performance in the Montreal Cognitive Assessment (MoCA). However, beta-tACS did not yield significant results (32). On the other hand, Schoellman et al. (33) found decreased beta frequency (22–27 Hz) and increased corticocortical synchronization over the left sensorimotor and right frontal area on OFF medication during a fine motor activity after anodal tDCS over the left sensorimotor area. These changes in EEG were accompanied by motor improvement (i.e., UPDRS III) (33).

TABLE 3 | Characteristics of studies with transcranial electric stimulation in Parkinson's disease.

References	Design: randomization/ blinding/ sham	Sample number (age range in years); sex distribution; stage (disease duration)	Stimulation protocol		EEG		Other outcomes
			Type of stimulation; parameters used	Number of sessions	ON or OFF medication	Number of channels; condition of assessment; data analysis	
Del Felice et al. (32)	Yes/Yes/Yes	15 (69); 9 males; HY 1–2 (6.3 ± 4.8 years)	tACS; 4Hz (theta-tACS group) or 30 Hz (beta-tACS group); electrodes over the scalp area in which the power spectral difference was detected and over the ipsilateral mastoid; 1–2 mA, 30 min. -Active sham condition: tRNS alternate current with random amplitude and frequency (1–2 mA; 0–100 Hz), over the same sites of tACS	10 tACS + 10 active sham	ON	32; 10 min of open-eyes resting state, before, immediately after stimulation and at 4-weeks follow-up; analysis of power spectral density and the relative power. -EEG data from 21 healthy controls (45,14 years; 9 males) were used to choose the location and frequency of stimulation	UPDRS III; GDI; frontal-executive functions, memory, and mood
Schoellmann et al. (33)	Yes/Yes/Yes	10 (64.3); 7 males; HY: NR (8.6 ± 4.1 years) + 11 healthy controls (58.6); 6 males	tDCS; over the left sensorimotor (C3, anode) and right frontal areas (Fp2, cathode); 1 mA, 20 min -Sham condition: tDCS with 1 mA discontinued after 40s	2 (1 tDCS + 1 sham)	OFF	25; recorded at rest (3 min.) and during a performance of an isometric motor precision task (3 min.), before, directly after and 30 min after stimulation; analysis of the frequency-domain spectrum (power) and corticocortical connectivity.	UPDRS III (sum of items 22–25, right hand); fine motor assessment

HY, Hoehn and Yahr Scale; NR, Not reported; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; tRNS, transcranial random noise stimulation; UPDRS, Unified Parkinson's Disease Rating Scale; GDI, Gait Dynamic Index.

Trials Using Other Forms of NIBS

Studies that involved the use of other NIBS were characterized for the use of sham stimulation, similar age, and time of diagnosis of PD between participants. However, although the EEG was evaluated at rest, the studies differed in the condition of eyes open or closed and ON or OFF medication (**Table 4**).

Lee et al. (35) found decreased interhemispheric connectivity in the alpha frequency and an increased lower beta (<20 Hz) and gamma (>30 Hz) in PD patients OFF medication after GVS. Lee et al. (36) assessed the effect of three intensities of electrical vestibular stimulation (4–8, 50–100, and 100–150 Hz) and reported decreased average phase locking, increased variability, and entropy of the phase-locking value in the OFF-medication group, with the duration of the after-effects depending on the stimulus intensity. Interestingly, the results of the EEG after stimulation approached those of healthy controls. Finally, Gálvez et al. (34) showed decreased spectral power of the theta frequency, decreased functional connectivity, and improved working memory after a BB compared with the controlled sound in PD patients ON medication.

Quality Assessment

A single study was classified as presenting excellent methodological quality (32), three as good (33, 34, 36); two as fair (31, 35), and one as poor (30) according to the Downs and Black criteria (**Table 5**). In general, the studies attended the criteria regarding the reporting section, however, the main factors of confusion in the groups were not listed (30, 35) or were partially listed, and none of the studies mentioned the possible adverse effects of the stimulation. Besides, one of the studies did not present the exact values of probability in the results (30). Some studies did not attend the criteria related to external validity, because few of them reported the location and population of the participants recruited, which does not allow interpretation of the representativeness of the sample (32, 34, 36). Moreover, some studies did not include blinding of participants and personnel (30, 31, 35, 36). Concerning confusion bias/selection, the three studies with the best scores were randomized clinical trials and double-blinded that considered the distribution of factors of confusion in their analysis (32–34). Only one study demonstrated enough power to detect a clinically important effect through power calculations (32).

DISCUSSION

The summary of current evidence suggests that NIBS techniques may change EEG activity, which was associated with improvement in PD symptoms. This scoping review revealed two important findings: (1) there is limited evidence regarding the effects of NIBS on quantitative EEG in patients with PD and (2) the quality of the studies was poor/fair

TABLE 4 | Characteristics of studies that used other non-invasive brain stimulation in Parkinson's disease.

References	Design: randomization/ blinding/ sham	Sample number (age range in years); sex distribution; stage (disease duration)	Stimulation protocol		EEG		Other outcomes
			Type of stimulation; parameters used	Number of sessions	ON or OFF medication	Number of channels; condition of assessment; data analysis	
Lee et al. (35)	No/No/Yes	11 (62.1); 4 females; HY: NR (6, 9 years) + 11 healthy controls (59.8); 5 females	nGVS; bilateral and bipolar, over mastoid process, frequency 0.1–10 Hz, during 72 s, followed by a sham current for 60 s	1	OFF	19; eyes open focusing on a fixed target during 60-s pre and post GVS; interhemispheric connectivity analysis (IHC) by Partial Least Squares (PLS) regression and relative contribution percentage	_
Lee et al. (36)	Yes/No/Yes	16 (67.3); 7 males; HY 1–2 (4 ± 4, 3 years) + 18 healthy controls (67.6); 9 males	EVS; bilateral and bipolar, over mastoid process; applied at 90% of the individual threshold level; Three signals in different frequency bands (EVS1: 4–8 Hz; EVS2: 50–100 Hz; EVS3: 100–150 Hz)	4 (Sham, EVS1, EVS2, and EVS3)	ON/OFF	27; eyes open focusing on a fixed target before (20 s), during stimulation (60 s) and after EVS1, EVS2, EVS3 (20 s); analysis of PLV (mean, variability, entropy) and Sparse Discriminant Analysis (SDA)	_
Gálvez et al. (34)	Yes/Yes/Yes	14 (62); 8 females; HY 1–3 (7.2 ± 4, 9 years)	BBs (tones rhythmically at 120 bpm, sinusoidal waveform (154Hz in the left channel and 168Hz in the right channel), which created a 14Hz BB at the brainstem; 10 min. -Control stimulation: BBs without the rhythmically (pink noise); 10 min.	2 (1 BBs + 1 control sound)	ON	29; closed eyes at rest; immediately before and after both stimulations; analysis of power spectral density and functional connectivity	Gait; anxiety; cognition; EKG

HY, Hoehn and Yahr Scale; NR, Not reported; UPDRS, Unified Parkinson's Disease Rating Scale; EKG, electrocardiogram; PLV, Phase locking value; nGVS, noisy galvanic vestibular stimulation; EVS, electrical vestibular stimulation; BBs, binaural beats.

in 3 of the 7 manuscripts based on criteria of Downs and Black.

According to our findings, anodal tDCS, tACS, rTMS, GVS, and BBs consistently showed positive results related to quantitative EEG in the papers reviewed. The majority, but not all the studies, reported clinically significant improvement in patients and a strong relationship between the EEG activity and the movement-related (desynchronization/synchronization), which happens in PD at smaller amplitude (37, 38).

On the other hand, although most studies have shown motor and non-motor improvements that occurred concurrently with changes in the EEG, none of the studies included the analysis of the relationship between EEG at baseline and NIBS-induced changes on clinical outcomes. Additionally, many of the reviewed studies used heterogeneous samples and did not consider possible confounders related to the response rates and adjustments made to control for these variables. Evidence points out that patients with similar clinical characteristics of PD may present different responses to the same treatment, depending on demographic or clinical modifying variables, such as age and disease duration (39, 40). For instance, EEG oscillations have a direct relation in the response to treatment involving synaptic plasticity, thus baseline dysfunction may be also a functional and therapeutic marker for individual and personalized NIBS.

The regions of interest for the treatment of PD varied concerning the type of stimulation and the symptoms treated. Although the NIBS techniques described in these studies have different routes and action mechanisms, all of them aim to induce depolarization mechanisms in an attempt to directly alter brain activity in an extensive neuronal network involved in motor and cognitive processing. It is also important to consider that most of the included studies have consistently failed in detailing the functional impairment of patients which made it difficult to establish a relationship between clinical symptoms and the patterns of the quantitative EEG. PD patients with distinct clinical characteristics could answer differently to excitatory or inhibitory NIBS due to the different brain pattern activation (41). While these results related to aftereffects of NIBS are encouraging, further studies are necessary to elucidate the link between the cortical target, excitatory/inhibitory stimulation, and neural endophenotypes of PD.

It should be noted that all included studies assessed the effects of NIBS on the outcomes in the short term. In fact, the number of sessions ranged from 1 to 10. The study with the longest NIBS intervention and outcome assessment period was of Del Felice et al. (32) with 10 sessions of tACS (over 2 weeks) and outcome assessment at baseline, post-intervention (2 weeks), and 4 weeks after the end of the intervention. They found significant changes in quantitative EEG and improvement in bradykinesia and cognitive performance (32). However, so far, no study has assessed if there would be a significant long-term clinical improvement and quantitative EEG changes. Future

TABLE 5 | Quality assessment based on the tool proposed by Downs and Black.

Study / Questions	Tanaka et al. (30)	Marchesi et al. (31)	Lee et al. (35)	Lee et al. (36)	Schoellmann et al. (33)	Del Felice et al. (32)	Gálvez et al. (34)
1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1
3	1	1	1	1	1	1	1
4	1	1	1	1	1	1	1
5	0	1	0	1	1	1	1
6	1	1	1	1	1	1	1
7	1	1	1	1	1	1	1
8	0	0	0	0	0	0	0
9	1	1	1	1	1	1	1
10	0	1	1	1	1	1	1
11	0/UD	0/UD	0/UD	0/UD	0/UD	1	1
12	0/UD	0/UD	0/UD	0/UD	0/UD	1	0/UD
13	0/UD	0/UD	0/UD	1	0/UD	0/UD	0/UD
14	0/N	1	0/UD	1	1	1	1
15	0/N	0/UD	1	0/UD	1	1	1
16	1	1	1	1	1	1	1
17	0/N	1	1	1	1	1	1
18	1	1	1	1	1	1	1
19	1	1	1	1	1	1	1
20	0/N	1	1	1	1	1	1
21	0/UD	0/UD	0/UD	1	0/UD	1	0/UD
22	0/UD	0/UD	0/UD	0/UD	0/UD	1	1
23	0/N	1	0/N	0/N	1	1	1
24	0/N	0/UD	0/N	0/N	1	1	1
25	0/N	0/UD	0/UD	0/UD	0/UD	1	0/UD
26	0/UD	0/UD	0/UD	1	1	1	1
27	0	1	1	1	1	1	1
Total	10/28	17/28	15/28	19/28	20/28	25/28	22/28
Classification	Poor	Fair	Fair	Good	Good	Excellent	Good

N, no; UD, unable to determine.

long-term trials would greatly advance the current knowledge on this issue since it is difficult to modify a complex dysfunctional network by acute stimulation (42) and it would present important clinical applicability.

The EEG data acquisition protocols varied among studies, concerning the medication status (i.e., ON vs. OFF), "eyes condition" (i.e., closed vs. open), and activity state (i.e., resting-state vs. cognitive/motor tasks). The recording of EEG data and NIBS application during the ON medication may decrease inter- and intra-individual variability. During the OFF-medication motor and/or non-motor PD symptoms appear or are worsened, which are improved after the next dose of levodopa (43). Moreover, studies have shown marked differences in EEG comparing ON and OFF medication in spectral power, coherence, and phase-amplitude coupling (13, 44–46). Hence, when recording EEG, it should be considered that the apparent or intensified motor and non-motor PD symptoms may result in worsened performance, interference in EEG signal, or even data loss (33, 36). For instance, Gálvez et al. (34) calculated the levodopa equivalent dose for each individual and the intervention sessions accompanied by EEG recordings took place on different days, but at the same time of the day to reduce variability due to medication action and time of the day.

Concerning the eyes condition, previous studies were able to differentiate and classify patients with PD and healthy controls at rest with the eyes closed and during tasks with eyes opened (47–50). On the other hand, Railo et al. (51) demonstrated that patients with PD in the initial to intermediate state can be classified with relatively high sensitivity using EEG data recorded at rest with eyes open with about 10 electrodes, located over the motor and occipital areas. Contrary, the classification was not possible with the eyes closed (51). At present, it should be recommended to record EEG both with eyes opened and closed, whenever possible to test if the NIBS-induced changes are detectable at one condition or another or in both conditions.

Concerning the quantitative EEG parameters, the specific parameters measured may depend on the research purpose and study design. For instance, while some studies included in this review have assessed the EEG at rest and analyzed the frequency band spectral power (32), others have assessed

the event-related synchronization/desynchronization or corticocortical connectivity during motor tasks (31, 33). Despite strict guidance on quantitative EEG measures to monitor the effects of NIBS may not be provided, future studies should build on previous studies investigating changes in the EEG associated with PD and include at least more common measures used in previous NIBS studies to allow for comparability. For instance, a recent systematic review by Shirahige et al. (52) that includes 19 studies with 312 patients with PD and 277 showed that patients with PD present slower EEG frequencies (i.e., increased slower frequencies and decreased faster frequencies) at rest and during the performance of complex movements. Such results may serve as a starting point to define possible quantitative EEG parameters.

Furthermore, adding EEG measures to predictive models could provide fundamental prognostic value for motor recovery. In this light, the benefit of measuring both white matter tracts integrity and beta oscillatory activity in addition to clinical measures needs to be further explored. Most importantly, computational models could be needed for the design of brain stimulation protocol, considering EEG parameters and individual variability of cortical mapping.

Regarding the quality of the included studies, we identified potential critical bias in different categories. Most of the studies presented no sample size calculation, blinding procedure, and lack of information about the stage of the disease and medication intake dosage. Despite not being clinically representative, these medications can certainly alter treatment outcomes and "mask" the therapeutic effects of these techniques (53).

The main limitation of this systematic review is the heterogeneity of protocols between the included studies could somehow limit our conclusion. Moreover, a high risk of bias is present in several studies, which calls for caution in interpreting the results.

There are multiple sources of potential heterogeneity within the EEG and brain stimulation literature relating to the variability in stimulation parameters and outcomes measured, dose, and clinical characteristics. One of the main factors lacking in half of the studies was robust concordance regarding the enhancement of motor recovery associated with the clinical application of brain stimulation and EEG. Moreover, completeness of evidence is lacking regarding electrophysiological markers reflecting tDCS effects and cognitive outcomes in PD. This is an important factor to take into account when talking about brain modulation techniques and progressive impairment. This diversity of metrics and the lack of clear underlying hypotheses regarding the electrophysiology of motor and cognitive parameters make it hard to interpret the effect of treatment. There is currently insufficient high-quality evidence to make conclusions about the benefits or harms of NIBS and electrophysiologic correlates on PD.

CONCLUSION

In this systematic scoping review, current evidence suggests that NIBS could change cortical activity in patients with PD, however, we are not yet able to use the EEG outcomes to predict the cognitive and motor treatment response after brain stimulation. Further studies are also necessary to identify the clinical and neurophysiological optimal parameters associated with NIBS outcomes, taking into consideration these individual cortical pathways. In addition to performing higher quality care of patients. It is important that more funding be directed not only to neuromodulation studies but also to neurobiological studies in PD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

TC participated in conceptualization, methodology, software, and writing—original draft. SS participated in resources and investigation. RS participated in writing and review. DM, SA, and CG participated in writing—review and editing. All authors contributed to the article and approved the submitted version.

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Use of Functional MRI in Deep Brain Stimulation in Parkinson's Diseases: A Systematic Review

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Deep brain stimulation (DBS) has been used to modulate aberrant circuits associated with Parkinson's disease (PD) for decades and has shown robust therapeutic benefits. However, the mechanism of action of DBS remains incompletely understood. With technological advances, there is an emerging use of functional magnetic resonance imaging (fMRI) after DBS implantation to explore the effects of stimulation on brain networks in PD. This systematic review was designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to summarize peer-reviewed articles published within the past 10 years in which fMRI was employed on patients with PD-DBS. Search in PubMed database provided 353 references, and screenings resulted in a total of 19 studies for qualitative synthesis regarding study designs (fMRI scan timepoints and paradigm), methodology, and PD subtypes. This review concluded that fMRI may be used in patients with PD-DBS after proper safety test; resting-state and block-based fMRI designs have been employed to explore the effects of DBS on brain networks and the mechanism of action of the DBS, respectively. With further validation of safety use of fMRI and advances in imaging techniques, fMRI may play an increasingly important role in better understanding of the mechanism of stimulation as well as in improving clinical care to provide subject-specific neuromodulation treatments.

Keywords: Parkinson's disease, functional connectivity, DBS, deep brain stimulation, fMRI, functional MRI, neuroimaging

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INTRODUCTION

Deep brain stimulation (DBS) is a well-established neurosurgical treatment for Parkinson's disease (PD) that works by modulating aberrant neural circuits *via* electrical stimulation to a key structure, most commonly the subthalamic nucleus (STN) or globus pallidus internus (GPi) (1). DBS has shown both rapid and sustained improvements of PD motor symptoms (1, 2). The effects of DBS on non-motor symptoms have been described, such as PD-related pain (3) and cognitive functions (4), although the efficacy is still controversial (5, 6). Individual PD patients may respond to DBS differently (7) and the underlying therapeutic mechanism of stimulation action remains incompletely understood (1, 2). This is partially due to the complexity of neural circuits, electrical stimulation affecting both locally and globally, the innumerous possible combination of parameters for DBS programming, and the inter-individual variability (1, 2, 8).

Studies have utilized multiple neuroimaging techniques to investigate the modulatory effects of DBS on brain activity, including non-invasive methods, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) (8, 9). Compared with PET and SPECT, fMRI provides better spatiotemporal resolution for detecting brain activity across small but distributed areas associated with the basal ganglia (2, 10). Moreover, fMRI can be continuously acquired while DBS is switched on and off (11). It does not require the use of tracers, which introduces confounding variables between subjects due to different metabolic kinetics (8). The challenges of using fMRI in DBS-implanted patients are related to hardware artifact, as well as safety concerns, including the possibilities of lead migration, heating, and DBS hardware malfunction (2, 8); however, both 1.5 and 3 T fMRI scanning have been shown to be feasible and safe with DBS systems both turned OFF and ON (2, 12–14).

This will likely pave the way for additional DBS neuroimaging studies, thereby providing a more comprehensive understanding of the mechanism of DBS and improving clinical care for individual patients with PD. The purpose of this systematic review is to summarize the available literature on the use of fMRI in PD patients who have undergone DBS treatment in terms of important recent findings and the significance of fMRI as a highly informative tool.

METHODS

This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15) to collect scientific studies in which fMRI was employed in PD patients who had undergone DBS implantations. The search was performed in PubMed database to find English-language articles published from January 2010 to May 2021 (last searched date: June 1, 2021) using the combination of keywords: ("function*"[All Fields]) AND ("MR"[All Fields] OR "MRI"[All Fields] OR "magnetic resonance"[All Fields]) AND ("DBS"[All Fields] OR "deep brain stimulation"[All Fields]) AND ("parki*"[All Fields]). The resulting references were imported to Covidence.org, which automatically removes duplicate articles. Then, the abstracts and titles of the references were screened by two authors for relevance to fMRI in PD-DBS patients. Full text articles were reviewed by five reviewers working independently to screen articles that met the inclusion criteria: human subjects with PD treated with DBS, fMRI acquired after DBS implantation with a purpose relevant to PD. Articles involving patients with PD as controls to study other diseases were not included. Two reviewers resolved possible conflicts to select articles included in this review.

The assessment of study risk of bias was carried out following the Cochrane guidelines (Chapter 8) (16) by evaluating each included article from the following domains: selection, performance, detection, attrition, reporting, and other biases. For each domain, a judgment of high-risk, low-risk, or unclear was determined. Extracted variables from each article were numbers of participants and subjects' states during scanning, fMRI paradigms, timepoints of fMRI acquisition, and analysis methods. Customized table formats were used to group articles and explore possible heterogeneity. Meta-analysis was not performed, as the purpose of this review is to provide qualitative rather than quantitative evaluations.

RESULTS

Article Selection

The search strategy described above yielded 353 articles. Following the abstract and title screening, 295 articles were excluded as they were not relevant to the use of fMRI and PD-DBS patients that resulted in 58 articles. Full-text screening excluded 34 articles, which led to 24 articles included for narrative synthesis. Five articles were not comparable due to the type of articles and purposes of their studies, and finally, 19 studies were included for qualitative synthesis (**Figure 1**).

The assessment of the risk of bias (**Figure 1**) revealed that 5 studies had high risk of "sequence generation" due to non-counterbalanced scanning conditions of DBS settings (1, 10, 13) or the nature of the study design (17, 18). Most of the studies did not specify if the assessors were blinded (allocation concealment), however, the nature of voxel-based fMRI imaging analysis (such as, preprocessing and FDR corrected *p*-values lowered the risk of bias.

Study Characteristics

The fMRI design paradigms that were used in the included articles were categorized into three groups: (1) resting-state fMRI (rs-fMRI), during which subjects were asked to remain relaxed for 6–10 min (2, 4, 7, 10, 14, 19–26). (2) A DBS ON/OFF block design, wherein stimulation was cycled ON and OFF while the subject laid still in the scanner, to investigate the mechanism of action of DBS (1, 2, 11, 13, 18, 27). (3) Behavior-dependent task-based design, where a behavioral or stimulus task was interleaved with rest while DBS was either ON or OFF during each session (9, 17, 22, 28, 29) (**Table 1**). The main approaches of fMRI data analysis used in the reviewed studies included functional connectivity (FC), effective connectivity (EC), eigenvector centrality mapping (ECM), and contrast images (**Table 1**). In addition, these metrics were correlated with clinical measurements, such as UPDRS-III score, and/or imported to machine learning models. The 19 studies included for qualitative synthesis were grouped according to study purposes and fMRI paradigms: the mechanism of action of DBS, the acute phase after lead implantation, the effects of chronic stimulation, the effects of DBS on non-motor symptoms in PD, and DBS vs. Levodopa (**Table 2**).

The Mechanism of Action of DBS

Six original studies employed the DBS ON/OFF block paradigm in their fMRI scans to investigate the immediate changes in BOLD signals induced by stimulation ON vs. OFF at various post-operative timepoints ranging from the same day of patients' lead implantation surgery (11, 27) to over 2-year post-implantation (1, 2, 13, 18). Nearly all recruited patients had DBS

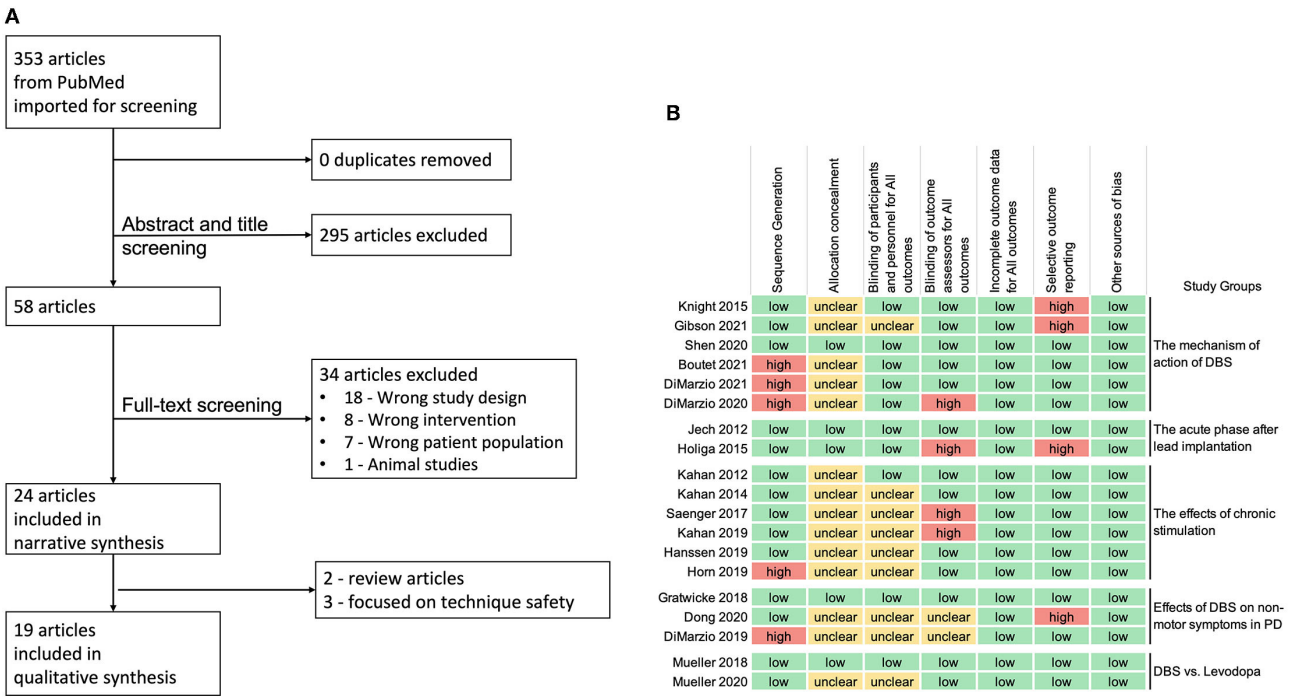

FIGURE 1 | (A) Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart. **(B)** Review authors' judgments about each risk of bias domain for the 19 articles included in qualitative synthesis, following the Cochrane guidelines (high-risk in red, low-risk in green, and unclear risk of bias in yellow).

implanted in the STN, except that two studies also included a number of GPi DBS patients and analyzed both targets as a single group (1, 18).

Contrast images of DBS ON-OFF revealed some similar neurocircuit responses across independent cohorts regardless of ON/OFF block length or duration post-operation: (a) significant activation of thalamus was observed in all of six studies, (b) significant activation of pallidum in three studies (2, 13, 18), (c) significant deactivation of cerebellum in two studies (1, 2), while increased cerebellar activity found to be associated with side effects (27), and (d) significant changes of the primary motor cortex (M1) of which increased activation seen in rigidity phenotypes (18, 27), whereas significant deactivation seen in tremor-dominant phenotypes (1, 2, 13, 18). Of these regions of interests (ROIs), two circuits were identified showing opposite responses to DBS: the activated GPi-circuit covering the GPi, thalamus, and deep cerebellar nuclei and the deactivated M1-circuit covering the primary motor cortex, putamen, and cerebellum. They were found functionally dissociable based on the pre-operative resting state FC analysis (2).

Moreover, BOLD responses to STN DBS were demonstrated to be correlated with motor symptom subscales and specific clinical outcomes (2, 18, 27). The rigidity subgroup responded with activated M1 and SMA (18), and its improvements were significantly correlated with the higher activation in M1 (27) and the GPi-circuit (2). The tremor-dominant subgroup responded with deactivated M1 (18), and its improvements were associated with the higher activation in thalamus (27). Activation in the cerebellar and sensorimotor cortices were correlated with paresthesia and nausea side effects; and activation in the caudate and putamen regions were correlated with dystonia side effects (27). In comparison with STN stimulation, GPi DBS induced BOLD responses were similar in the rigidity and tremor subgroups; however, in the subgroup with postural instability gait disorder, GPi DBS induced M1 deactivation whereas STN stimulation resulted in the M1 activation and better clinical improvement (18).

Using the same fMRI paradigm, three studies explored how stimulation parameters (i.e., contact, voltage, or frequency) affect the functional activity by assessing stimulation-induced BOLD responses obtained under clinically optimized settings, followed by non-optimized settings during which only one parameter was altered (1, 2, 13). Compared with the fMRI signatures of the optimal DBS settings (activation in the thalamus and deactivation in M1 and anterior cerebellum), stimulation at non-optimal contacts led to a diminished magnitude in M1 and increased signals in non-motor cortex (1). Lower-voltage stimulation did not change the topographic pattern but reduced the magnitude of BOLD signals; while high-voltage stimulation produced stronger BOLD signals but accompanied by increased activation in non-motor regions (1). The frequency parameter significantly affected the GPi-thalamus-cerebellum circuit, but not the M1-putamen-cerebellum circuit (2). The optimal stimulation frequency induced the strongest activation in the GPi-circuit, while slightly increased frequency (+30 Hz) resulted in decreased activation in primary somatosensory cortex

TABLE 1 | Summary of the types of functional MRI (fMRI) paradigms and analyses.

fMRI paradigm	Descriptions
Resting-state fMRI	Subjects remain relaxed for 6–10 mins, during which the DBS was either ON or OFF
DBS ON/OFF block design	Subjects laid still while the DBS was switched ON and OFF for 30 s in each state. This is to mimic the conventional task-based fMRI paradigm
Behavior-dependent task-based design	Subjects were asked to perform a task (or receive stimulus), while DBS was either ON or OFF during the scan session
fMRI analysis	**Descriptions**
Functional connectivity (FC)	A statistical correlation of brain activity indicating the synchronization between regions and/or voxels
Effective connectivity (EC)	The directional influence that a brain region has over another region indicating a causal relationship between these two regions
Eigenvector centrality mapping (ECM)	A data-driven and parameter-free analysis technique based on graph theory, which can detect central hubs that are strongly connected to a brain network
Contrast images	Differences in brain activation during task/DBS-ON compared to that during baseline/DBS-OFF

(13). Another important modulatory factor of DBS treatment is time. Deactivation of the M1-putamen-cerebellum circuit gradually increased over time within 12 months post-surgery (2). This issue of timing of the postoperative MRI scan may be able to explain the inconsistent findings of brain activity in M1 (1, 2, 11, 27).

The Acute Phase After Lead Implantation

Two studies focused on changes in brain activation associated with the microlesion effect (MLE)—a phenomenon where electrode implantation into the STN or GPi is associated with motor improvement prior to the onset of stimulation (9, 21, 30, 31). The mechanism behind MLE was assessed by fMRI scanned with DBS-OFF 0–3 days after implantation compared with pre-operative fMRI data (9, 21). In movement state, *via* finger tapping task-based fMRI, the amplitude of BOLD responses was found significantly decreased in the motor cortex, insula, thalamus, and basal ganglia, after edema scores were considered as covariates. Besides, the improvements of rigidity and axial UPDRS-III scores were significantly correlated with the BOLD signals in the putamen and globus pallidus (9). In resting state, a data-driven ECM analysis of the whole brain revealed that the brainstem (specifically 2 clusters in the upper and lower brainstem) acted as a compensatory hub in the motor network to likely counterbalance the physical disruption from electrode penetration and microlesion. The EC in the brainstem hubs were inversely correlated with the sub-scores of the UPDRS-III, regardless of surgery stage (combined pre- and post-operative DBS-OFF UPDRS-III scores). After DBS was activated, EC in the left premotor cortex increased, and FC analysis seeded in the brainstem hubs showed significant increased connectivity with the cerebellum (21). These fMRI study findings indicated that microlesion affected BOLD responses to stimulation with a compensating activation in the brainstem, which is different from the mechanism of action DBS described in previous section, even though UPDRS-III scores obtained during and after the microlesion effect were similar.

Effects of Chronic Stimulation on Motor Networks

Six studies investigated the effects of chronic stimulation therapy in patients who had received STN DBS treatment for at least 3 months, and conducted fMRI, during which each patient was at rest with DBS either ON or OFF (10, 14, 20, 22, 24) or was performing a voluntary movement task (22, 28). The order of DBS ON/OFF was counterbalanced in five studies with no mentioning of the washout time before fMRI with DBS OFF (14, 20, 22, 24, 28); one study acquired fMRI with DBS-ON first, then turned off the stimulation and waited until symptoms reappeared before scanning with DBS-OFF (10).

Various analyses approaches were used. Horn et al. assessed voxel-wise FC of the motor network within the basal ganglia-cerebellar-cortical circuit in two different scenarios: DBS ON vs. DBS OFF. There was increased average connectivity within motor network during DBS ON vs. OFF, specifically by increasing the FC between thalamus and motor cortex while reducing the coupling between striatal and three regions, namely, GPe, STN, and cerebellum. Moreover, the amount to which average connectivity increased was found to be associated with the volume of activated motor STN (10). Kahan et al. constructed a number of hypothetical neural architectures using the dynamic causal models (DCMs) from 5 ROIs (M1, putamen, thalamus, cerebellum, and STN). The DCM of best fit indicated that, at resting state, DBS mostly affect the cortico-basal ganglia circuit by increasing the coupling strengths of M1-putamen, thalamo-M1, and putamen-thalamus pathway and significantly reducing the connectivity of M1-STN, putamen-STN, and STN-thalamus pathways, with no impacts on cerebellar connectivity (22). Another study by Hanssen et al. used a similar approach but with 7 ROIs (M1, SMA, PMC, PFC, putamen, thalamus, and cerebellum). Cerebellar effective connectivity was significantly increased comparing DBS ON vs. OFF, specifically the cerebello-putamen and prefronto-cerebellar circuits. Additionally, the resting tremor improvement was found to be correlated with DBS-induced increased prefronto-cerebellar interaction (20). Kahan et al. performed the same DCM analysis on task-based fMRI data during voluntary movement from the same cohort and revealed a different architecture model with an additional recruitment of cerebellar-basal ganglia interactions.

TABLE 2 | Summary of included articles for qualitative analyses.

References	Subj # PD (HC)	Target	MRI scanner	fMRI category	Major fMRI measurements timepoints and scanning conditions		Notes *
The mechanism of action of DBS							
Knight et al. (11)	10	STN	1.5 T	DBS ON/OFF block	0-3 days post-op	· DBS ON/OFF cycling (6 s ON and 60 s OFF) · 2 V, 90 microsecond, 130–180 Hz · Awake or under general anesthesia	
Gibson et al. (27)	20	STN	1.5 T	DBS ON/OFF block	0–3 days post-op	· DBS ON/OFF cycling (6 s ON and 60 s OFF) · 3 V, 90 ms, 130 Hz · Under general anesthesia	
Shen et al. (2)	14	STN	3 T	DBS ON/OFF block	1, 3, 6, 12 mos post-op	· DBS ON/OFF cycling (36 s ON and 24 s OFF) · Stimulation with low (60 Hz) or high (120 Hz) frequency · 60 min wash-out between fMRI sessions	Bilateral stimulation
Boutet et al. (1)	39	STN GPi ($n = 4$)	3 T	DBS ON/OFF block	Mean 20.5 mos post-op	· DBS 30 s ON/OFF cycling · Left stimulation with optimal, followed by non-optimal contact or voltage ** · Bilateral stimulation with low or high frequency · 15 min wash-out time only before the first fMRI scan	
Dimarzio et al. (13)	14	STN	1.5 T and 3 T	DBS ON/OFF block	Post-op after DBS optimized	· DBS 30 s ON/OFF cycling · Medication doses continued · Stimulation with optimal settings (mono- or bipolar-) · Followed by altered frequency by ± 30 Hz, ± 60 Hz relative to individual's optimal frequency ** · <5 min between fMRI sessions	Some subjects were scanned with meds-ON
DiMarzio et al. (18)	23	STN GPi ($n = 8$)	1.5T and 3T	DBS ON/OFF block	Post-op after DBS optimized	· DBS 30 s ON/OFF cycling · Medication doses continued · DBS with clinically optimal settings · 5 min wash-in time before ON/OFF cycling session	Subjects were scanned with meds-ON
The acute phase after lead implantation							
Jech et al. (9)	12	STN	1.5T	Finger-tapping task	Pre-op 0–3 days post-op	· Med-off and DBS-OFF	
Holiga et al. (21)	13	STN	1.5T	Resting state	Pre-op 0–3 days post-op	· Med-off, DBS ON and OFF · Unilateral bipolar stimulation · 2.64 ± 0.44 V, 60 microsecond, 130 Hz	
The effects of chronic stimulation							
Kahan et al. (28)	10	STN	1.5 T	Joystick-motion task	>6 mos post-op	· Med-off, DBS-ON and OFF	
Kahan et al. (14)	12	STN	1.5 T	Resting state	>6 mos post-op	· Med-off, DBS-ON and OFF	
Saenger et al. (24)	10 (56)	STN	1.5 T	Resting state	>6 mos post-op	· Med-off, DBS-ON and OFF	
Kahan et al. (22)	11	STN	1.5 T	Resting state	>3 mos post-op	· Med-off, DBS-ON and OFF	
				Joystick-motion task		· Med-off, DBS-ON and OFF	

(Continued)

TABLE 2 | Continued

References	Subj # PD (HC)	Target	MRI scanner	fMRI category	Major fMRI measurements timepoints and scanning conditions		Notes *
Hanssen et al. (20)	26	STN	1.5 T	Resting state	3–78 mos post-op	· Med-on, DBS-ON and OFF	
Horn et al. (10)	20 (15)	STN	1.5 T	Resting state	>4 mos post-op	· Med-on, DBS-ON followed by DBS-OFF** · 5–15min wash-out time until symptoms reappeared	
Effects of DBS on non-motor symptoms in PD							
Gratwicke et al. (19)	6	NBM	1.5 T	Resting state	Post-op (after 6 weeks of DBS/sham)	· 2-week washout period	Symptom: dementia
Dong et al. (4)	23(14)	STN	1.5 T	Resting state	Pre-op >3 mos post-op	· Med-off, DBS-OFF	Symptom: executive functions
Dimarzio et al. (17)	15	STN	1.5 T and 3 T	Pain-stimulus task	Post-op	· Med-off, DBS-ON and OFF	Symptom: chronic pain
DBS vs. Levodopa							
Mueller et al. (23)	13	STN	1.5 T	Resting state	Pre-op	· Med-on and off	
					0–3 days post-op	· Med-off, DBS-ON and OFF	
Mueller et al. (29)	32	STN	1.5 T	Finger-tapping task	Pre-op	· Med-on and off	
	18				0–3 days post-op	· Med-off, DBS ON and OFF	

**Intraoperative timepoint is post lead implantation and before the implantation of stimulator. All of the post-operative fMRI acquisition was performed while the subjects were OFF medication, unless specified. All of the deep brain stimulation (DBS) stimulation settings during DBS-ON fMRI scan was unilateral bipolar stimulation, unless specified.*

***Order of fMRI sessions were not counterbalanced.*

STN, subthalamic nucleus; GPi, globus pallidus internus; NBM, nucleus basalis of Meynert.

Active stimulation resulted in an increased effective connectivity of STN afferent (M1-STN and putamen-STN) pathways during voluntary movement, whereas a reduced coupling strength during resting state (22).

Deep brain stimulation (DBS) modulatory effects were observed in both behavior independent and dependent statuses, but different inter-regional connectivity was affected: when subjects were at rest, basal ganglia pathways were modulated without the inclusion of cerebellum, while subcortical-cerebellar pathways were activated when subjects were performing voluntary movement (22). However, two other studies on resting state fMRI revealed inconsistent findings, in which cerebellar connectivities were also modulated by therapeutic DBS, but in the opposite directions, with one study representing increased (20) while the other study showing decreased striatal-cerebellum connectivity (10).

Two of the six studies recruited age-matched healthy control subjects for comparisons with each DBS-ON and DBS-OFF conditions, and demonstrated that therapeutic DBS helps in rebalancing resting state brain activities toward healthy controls on a local as well as global level (10, 24). Regarding static FC, FC maps were estimated by seeding from the activated motor STN to the rest of the brain from rs-fMRI acquired with DBS ON and OFF conditions, and a healthy age-matched control group (10). The similarity of FC maps, compared using spatial correlation values, were significantly higher between DBS-ON and healthy controls vs. DBS-OFF and healthy controls (10). Similarly, in terms of dynamic FC, which is used to describe the oscillation of inter-region synchronization throughout the scan time, therapeutic stimulation was found to increase "phase consistency" (defined as the mean and standard deviation (SD) of all windowed FC matrices of individual subject) toward the ones obtained from age-matched healthy controls (24).

Effects of DBS on Non-motor Symptoms in PD

Three of the reviewed studies looked into the effects of DBS with regards to non-motor symptoms in PD (e.g., chronic pain, dementia, and executive function) using rs-fMRI (4, 19) or block-design task-based fMRI (4). DiMarzio et al. investigated how STN stimulation affects pain perception in PD-DBS patients with chronic pain relief contrasted with those without pain relief. Brain activation corresponding to pain perception was measured using a task-based fMRI paradigm, during which mechanical pain stimulus alternated with resting periods while the DBS was ON or OFF throughout the scan time. Distinct patterns of brain activation were observed: PD patients with pain relief responded to pain with hyperactivation in primary sensory cortex (S1) and anterior cingulate cortex (ACC) during DBS OFF, and turning on the stimulation reduced such activation in these two regions;

conversely, PD patients without pain relief showed deactivation in S1 and ACC during DBS OFF, and stimulation ON increased the activation in the two regions (17).

Gratwicke et al. recruited PD patients with dementia and conducted two rs-fMRI scans on each subject after receiving 6 weeks of sham and DBS treatment in the Nucleus Basalis of Meynert (NBM), received in counterbalanced order with 2 weeks of washout intervals. FC in the default mode network revealed no significant differences between the NBM DBS and sham treatments, agreeing with their clinical measurements (19). Dong et al. studied the executive functions in PD patients, who received at least 3 months of STN-DBS, by assessing the intrinsic FC of the executive control network from pre- and post-operative rs-fMRI acquired in DBS-OFF condition. Although both pre- and post-operative rs-fMRI revealed significantly decreased FC comparing with a healthy control group, no significant differences were found between pre- and post-states (4).

DBS vs. Levodopa

Mueller et al. compared the effects of oral levodopa (L-DOPA) and STN-DBS in individual patients with PD (i.e., within-subject comparison) using the scores of UPDRS-III, rs-fMRI, and finger tapping task-based fMRI—all collected in four scenarios: pre-operative L-DOPA-OFF, pre-operative L-DOPA-ON, post-operative L-DOPA-OFF and DBS-ON, and post-operative L-DOPA-OFF and DBS-OFF. The UPDRS-III scores showed comparable improvements by L-DOPA and DBS from the baseline of the pre-op L-DOPA-OFF scores (23, 29). However, rs-fMRI data revealed different motor network connectivity modulations caused by these two interventions, specifically, DBS-ON increased EC in the bilateral motor cortices accompanied with the increased connectivity with the thalamus and cerebellum compared with L-DOPA-ON (23). In a later study, finger tapping task-based fMRI was assessed *via* the same study design, and beta images during TAPPING and REST were computed for each scan scenario. It was found that L-DOPA-ON reverted putamen activation to increased activation during TAPPING-REST, whereas these reversed patterns of putamen and motor cortex were not found in DBS-ON vs. OFF scenario (29).

DISCUSSION

This systematic review focused on summarizing the findings of articles published within the past 10 years in which fMRI was employed on PD-DBS patients. A direct comparison of results is complex due to the significant variability in fMRI design paradigm and connectivity analyses described in the previous section. Performing 1.5 and 3 T fMRI is safe in PD-DBS patients with the use of MRI-compatible DBS (2, 12, 18, 21, 28, 32, 33). The effects of DBS on functional activity and integrity can vary depending on factors, such as duration after the implantation, DBS programming parameters, if the scan is acquired at rest or with movement, PD subtypes, and the conditions of medication intake. Turning the DBS ON produces immediate modulation of the cortico-basal ganglia-thalamo-cortical loop in PD, leading to the increased activation in thalamus and globus pallidum (consistent with the DeLong Model of PD), deactivation in cerebellum, and changes of activation in M1 to correct the motor symptoms (i.e., activation in rigidity whereas deactivation in tremor phenotypes). Furthermore, when compared with age-matched healthy controls, DBS seems to rebalance brain activities at resting state toward healthy subjects. Correlations of BOLD signals with various DBS settings and UPDRS-III subscores demonstrate the advantages of fMRI technique to explore the effects of stimulation between PD subtypes and individuals. The use of fMRI in patients with PD-DBS is gradually growing and will enhance our understandings of the mechanism of DBS in PD with the respect of improving motor and non-motor clinical outcomes. This section addresses how the current data could be used in the clinical setting, such as providing patient-specific surgical planning and identifying the optimal or new targets for various symptoms.

Safety Concerns and Artifacts

Phantom tests conducted at multiple research centers have shown that patients with DBS implanted may safely undergo 1.5 and 3 T MRI (2, 12, 18, 21, 28, 32, 33). As MRI environment did not interrupt the implanted pulse generator functions, more recent studies used the body-transmit coil for the benefits of better signal-to-noise ratio (22). Although the imaging artifact caused by the DBS device appears as circumferences along the DBS leads and in the frontoparietal cortex area close to DBS wire coils, and although larger artifact is seen in 3 T compared with 1.5 T MRI, it is still limited to the superficial cortex and the signal loss adjacent to the electrode contacts is acceptable (12). Additionally, shorting scan time in 3 T MRI scanner (5.5 min compared with 8 min per scan in 1.5 T MRI scanner) seems to compensate the higher signal-to-noise ratio, and thus pooling fMRI data from 1.5 and 3 T scanners for further analyses becomes feasible (18). Therefore, with a priori safety testing, more recent studies have scanned patients with PD-DBS at their clinically optimal DBS settings, including monopolar stimulation (1, 13, 18).

The Mechanism of Action of DBS

It has been demonstrated that DBS achieves its clinical effects through modulating not only the local neuronal activity within the target region, but also larger brain networks by propagating along related circuitries (23, 27). However, the exact neuromodulatory mechanism of how active stimulation, and more specifically the changes of stimulation parameters, affect brain networks still remain unclear (1, 2). A fMRI paradigm with DBS ON/OFF cycling was employed by multiple studies in our systematic review to measure immediate BOLD signal changes induced by stimulation ON vs. OFF states (1, 2, 11, 13, 18, 27). This design was validated by a high test-retest reliability at the subject level as well as a high inter-subject consistency within the same group or scanning conditions (2). Variations of study designs existed among the reviewed articles, for example, the block lengths (ON-period ranged from 6 to 30 s, OFF-period ranged from 60 to 30 s), post-operative durations (ranging from the same day of the lead implantation surgery to over 2-year post implantation), wash-in/wash-out durations (e.g., unclearly reported, 5 min wash-in period and 60 min wash-out period), and medication on/off. Washout time following the discontinuation

of STN DBS is around 30–50 min, a rapid drop of 0–80% followed by further slow washout, which varies depending on individual disease duration, lead location (34, 35), and patients' maneuver (36). The rapid alternation of stimulation ON and OFF states (ON/OFF cycling) utilized by the studies in this review may not fully capture the entire effects of DBS on functional activation. Future studies should consider employing a longer wash-out period in order to overcome this limitation. Nevertheless, the reviewed studies reached generally consistent findings: STN DBS has significant effects throughout the motor circuitry in PD, preferentially the thalamus, primary motor cortex, pallidum, and cerebellum.

Effects of DBS on Networks

Although, the non-optimized DBS programming may lead these studies less relevant to conclusions of the therapeutic effects of DBS on neural networks in PD-DBS patients (8), the findings may contain predictive information in the matter of clinical outcomes (27). The current standard-of-care procedure for adjusting DBS parameters is labor-intensive and time-consuming. The complexity of this process has been further compounded by the recent introduction of segmented leads; this increased the possible combinations of parameter configuration (37). Furthermore, the optimization is mostly subjective and dependent on personal and clinical experience rather than objective detailed algorithms to generate personalized DBS settings. For instance, acquisition of fMRI following a programming session could have the potential to demonstrate if activation patterns associated with the improvement in UPDRS-III subscores occurred (such as, increased activation in thalamus and globus pallidum, deactivation in cerebellum, and the changes of activation in M1) with a specific set of parameters. Therefore, neuroimaging biomarkers could assist the efficiency and accuracy in the process of DBS programming for individual patients.

Better understanding of the mechanism of chronic stimulation may provide quantitative neuroimaging evidence for predicting DBS efficacy for individual patients. Of the six studies reviewed in this category, the order of fMRI sessions with DBS ON and OFF were counterbalanced, except for one study by Horn et al. (10), in which 5–15 min of DBS washout was included by waiting for the reappearance of symptoms. Consistent findings across these studies demonstrated the main effects of STN DBS on functional connectome at resting state: stimulation strengthens the couplings of the direct pathway and reduces those of the hyperdirect pathway. However, the results of how STN DBS affects the connectivity between cerebellum and striatum were inconsistent, which might be caused in part due to different conditions of medication intake (on or off). Even when two studies had their subjects continue the medication intake throughout fMRI scans, their results were contradictory (10, 20). Therefore, future studies with consistent fMRI scanning designs are necessary to confirm or further explore the specific connectivity changes between the cerebellum and the basal ganglia following chronic therapeutic DBS.

The complete circuitry involved in non-motor symptoms of PD remains unclear. Nevertheless, symptoms, such as pain are common in patients with PD and affect quality of life significantly (38). It has been shown that up to 80% of PD patients may receive pain relief from STN DBS with different effects depending on the types of PD pain phenotypes (39, 40). Yet, the mechanism behind has yet to be determined. Dimarzio et al. demonstrated the reduction of activation in primary sensory cortex and anterior cingulate cortex after turning DBS ON in patients who experienced pain relief, while the opposite finding in patients without pain relief. Although these findings do not elucidate the entire circuitry involved, the activation status of such areas could potentially be used for patient counseling prior to DBS implantation, e.g., managing expectations regarding pain reduction following DBS (17). The effects of DBS on cognitive functions in PD patients are controversial, with previous studies showing declined, stable, or improved cognitive functions at up to 8-year follow-up; DBS targets (STN vs. GPi) seemed to affect the cognitive outcomes as well (5, 6). The assessments of the resting state FC within the executive control network showed no significant changes in post-operative DBS OFF states from the pre-operative baseline in PD patients who received at least 3 months STN DBS (4). Future studies evaluating the effects of chronic therapeutic DBS on cognition should include both STN and GPi DBS, to provide better insight on the differences between both nuclei.

LIMITATIONS AND FUTURE DIRECTIONS

In this review, we only searched in PubMed database and focused on qualitative synthesis without meta-analysis of the studies. Reviewing of the included articles, fMRI has major advantages in studying PD patients following DBS implantation; however, the scanning and processing methodology of the reviewed studies are not uniform, which limited the generalizability and applicability of the results. Standardized fMRI scanning parameters (e.g., the time period of each block in fMRI DBS ON/OFF block design) and processing pipeline would maximize the benefits of fMRI application in PD patients. Other limitations include safety concerns and susceptibility artifacts which can hinder the proper assessment of FC between brain regions.

Machine learning simulation has emerged as a possible solution. Yan et al. (41) used the deep convolutional generative adversarial networks (DCGAN) model to reconstruct the lost BOLD signals in PD-DBS patients. Not only parts of the imaging data were recovered, but also the machine-learning-model-generated BOLD signals corresponded in time with the original signals. The main advantage of using the DCGAN machine learning model over an oversimplified diffusion model is that the DCGAN is able to reconstruct FC maps specific to individual patients. Further studies are needed to improve the reconstructive accuracy of such models and account for brain shift that occurs during surgery.

The location of DBS electrodes is paramount for clinical improvement in motor function, so identifying the exact location of the electrodes is essential for optimal clinical outcomes (33). The most effective stimulation occurs at places that are most strongly connected to the motor network. Therefore, future research may involve performing fMRI scans on patients

pre-operatively with a particular emphasis in identifying contact points that would strongly activate the motor network as this has been shown to result in the best clinical improvement. The ultimate goal would be to develop an artificial intelligence (AI) model that can use clinical data and pre-operative FC maps to accurately identify the best location of the DBS leads and stimulation parameters specific to each patient.

CONCLUSIONS

The recent years have witnessed major advances in fMRI use following the DBS implantation in PD patients. Studies at multiple research centers have provided evidence for performing 1.5 and 3 T fMRI safely in PD-DBS patients with properly designed phantom test and the use of MRI-compatible DBS (2, 12, 18, 32). The effects of DBS on functional activity and integrity have shown to be different depending on a number of factors, namely, the duration after the implantation (microlesion effect), DBS programming parameters, the subject's activity while being scanned (at rest or with movement), PD subtypes, and the conditions of medication intake. fMRI studies with a DBS ON/OFF block paradigm have shown that immediate modulation of the cortico-basal ganglia-thalamo-cortical loop in PD led to significant increased activation in thalamus and globus pallidum (consistent with the DeLong model of PD), deactivation in cerebellum, and changes of activation in M1 to correct the motor symptoms (i.e., activation in rigidity whereas deactivation in tremor phenotypes). Compared with age-matched healthy controls, DBS seems to rebalance brain activities at resting state toward healthy subjects. The findings of significant correlations of BOLD signals with various DBS settings and UPDRS-III subscores further signified the advantages of fMRI technique to explore the effects of stimulation between PD subtypes and individuals. Overall, the use of fMRI in PD-DBS patients is showing a growing attraction to clinicians and researchers, with the aims to enhance our understandings of the mechanism of DBS in PD with the respect of improving motor and non-motor clinical outcomes, providing patient-specific surgical planning, and identifying the optimal or new targets for various symptoms.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

JM did the conceptualization, methodology, screening, evaluation, syntheses, writing of the original draft, and visualization. MT did the screening, evaluation, and writing. VK, AZ, and VZ did the screening and writing. AS did the manuscript review and editing. CW did the methodology and manuscript review and editing. CM did the methodology, manuscript review and editing, and supervision. All authors contributed to the article and approved the submitted version.

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