INNOVATIVE TECHNOLOGIES AND CLINICAL APPLICATIONS FOR INVASIVE AND NON-INVASIVE NEUROMODULATION: FROM THE WORKBENCH TO THE BEDSIDE

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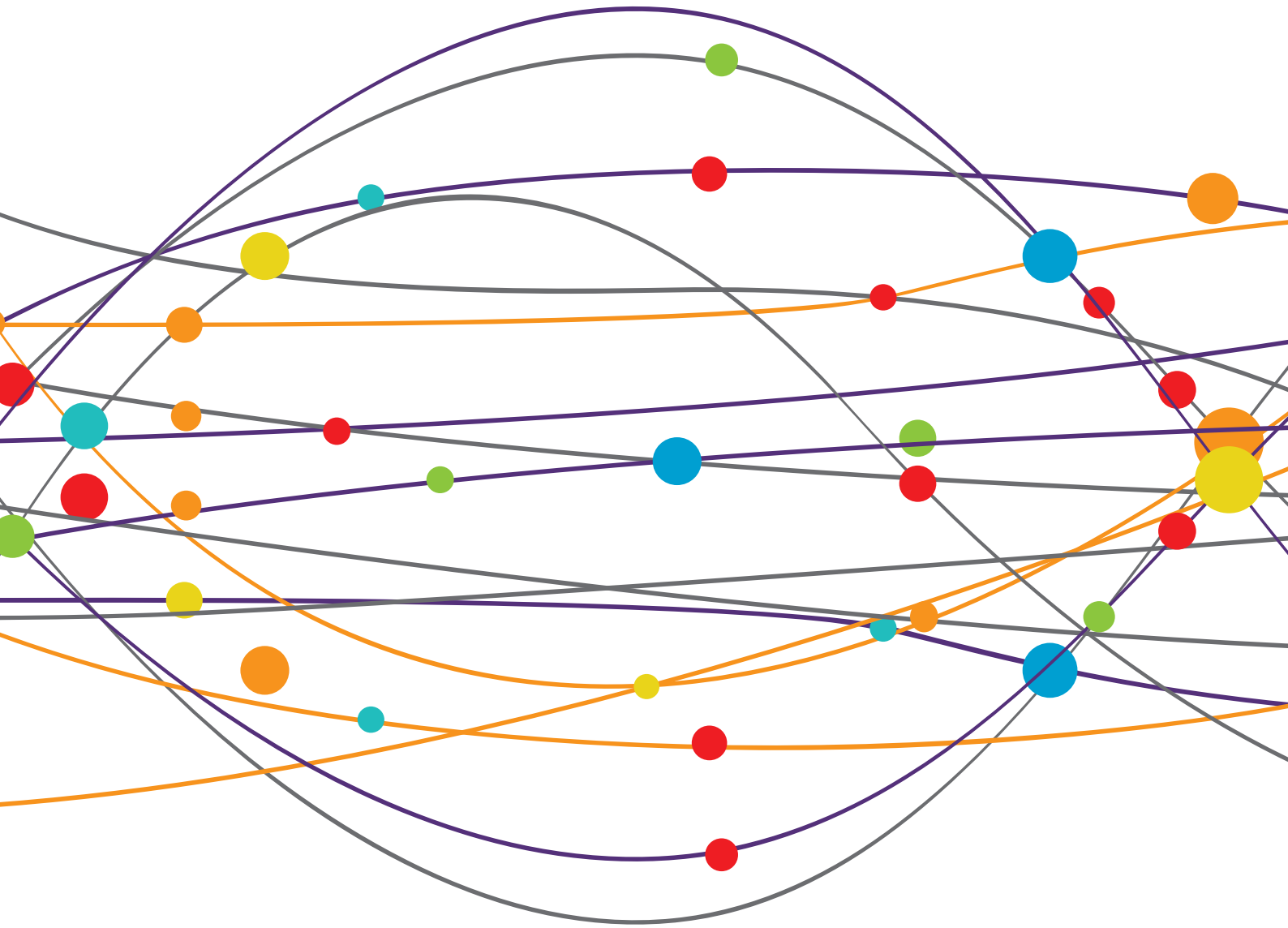

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INNOVATIVE TECHNOLOGIES AND CLINICAL APPLICATIONS FOR INVASIVE AND NON-INVASIVE NEUROMODULATION: FROM THE WORKBENCH TO THE BEDSIDE

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The possibility of harvesting the power of electric and magnetic impulses in the human body, commonly referred to as "neuromodulation," is one of the most recent and promising developments of the modern science. Since the late ´60s, multiple invasive and non-invasive technologies have been developed and tested in experimental and clinical settings with the final aim of modulating the function of the central and peripheral nervous system. Clinical applications include, but are not limited to, common neurological disorders such as Parkinson's disease and other movement disorders.

The bulk of evidence supporting the clinical efficacy of various invasive and non-invasive approaches for neuromodulation has progressively led scientific societies, patients' associations, and regulatory entities to acknowledge the critical role played by neuromodulation in the therapeutic algorithms of a wide range of neurological disorders. As a result, new technologies have been recently introduced into the market or are currently under validation. Their potential implementation into innovative protocols for neuromodulation demands a critical revision of what are the unmet needs for neuromodulation in movement disorders.

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EDITORIAL
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Editorial: Innovative Technologies and Clinical Applications for Invasive and Non-invasive Neuromodulation: From the Workbench to the Bedside

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Keywords: deep brain stimulation (DBS), Non-invasive focal mechanical vibrations (NIFMV), Parkinson's disease (PD), spinal cord stimulation (SCS), transcranial magnetic stimulation (TMS), transcranial ultrasound stimulation (tUS)

Editorial on the Research Topic

Innovative Technologies and Clinical Applications for Invasive and Non-invasive Neuromodulation: From the Workbench to the Bedside

Invasive and non-invasive brain stimulation represent one of the most promising scientific advances of the last decades (1). This special issue was designed to highlight and critically discuss innovative neurostimulation procedures for Parkinson's disease (PD) and other neurological conditions. Of the 17 papers initially submitted to the journal by international researchers, 13 were considered suitable for publication after a thorough peer-review process. These included five original researches, five reviews, one systematic review, one brief research report, and one case report. The following is a short summary of the main results of each of these manuscripts.

Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN), the ventral-intermediate nucleus (VIM), and the globus pallidus pars interna (GPi) are well-established therapeutic options for medically refractory PD, essential tremor, and dystonia (2, 3). However, several aspects related to DBS programming and post-surgical management of medications still remain to be clarified. In their manuscript, Koeglsperger et al. provide a concise review of strategies for DBS programming and dopaminergic medications adjustments following DBS. In another review from the same group, by Hell et al., summarizes and carefully discusses future perspectives for DBS, including target identification, adaptive closed-loop stimulation, and associated feedback signals.

Although STN- and GPi-DBS are both considered effective in reducing levodopa-induced dyskinesia (LID), the comparative efficacy of the two targets on dyskinesia remains unclear. Liu et al. conducted a meta-analysis of studies reporting data on STN- and GPi-DBS efficacy on LID. The authors found that GPi-DBS may reduce dyskinesia to a higher extent than STN-DBS at 12 months. This observation implies that mechanisms for dyskinesia reduction may be different between STN- and GPi-DBS. Future studies are needed to clarify the complex biological interaction with different systems of fibers involved in the modulation of motor symptoms in the two most common targets for DBS in the basal ganglia.

STN-DBS may also have a beneficial effect on balance and gait in PD. However, published results yielded variable conclusions. In their prospective controlled study, Szlufik et al. evaluated the impact of STN-DBS on balance disorders in PD. The authors found a beneficial effect of STN-DBS on static and dynamic instability in the short-term follow-up, while long-term data remain controversial. Zhang et al., report the case of a PD patient implanted with STN-DBS and complaining of severe speech problems. Tremor and speech problems were both effectively

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treated by a novel stimulation procedure, i.e., variable-frequency stimulation (VFS) consisting of a combination of high frequencies. This preliminary observation should be confirmed in future controlled studies. Again, concerning the possible detrimental effects of DBS, the review paper titled: "A Review of Cognitive Outcomes Across Movement Disorder Patients Undergoing Deep Brain Stimulation," by Cernera et al. discuss the issue of DBS-associated cognitive declines and adverse effects on quality of life in PD and other movement disorders. Pathophysiological mechanisms for cognitive changes occurring after DBS are also discussed.

Non-invasive neuromodulation, including Transcranial Magnetic Stimulation (TMS), in movement disorders is a challenging issue for both clinical and research purposes (4–6). Various non-invasive brain stimulation protocols have been studied in different conditions and settings. Hence, the reliability and validity of non-invasive neuromodulation techniques are still to be elucidated. In this regard, various methodological factors, possibly influencing the outcome measure, need to be better investigated. Fricke et al. developed an associative dual-site rTMS (1 Hz) targeting the premotor and primary motor cortex. The protocol aimed to activate different cortico-basal ganglia projections and, therefore, to target pathogenic oscillations at distinct STN subregions. The study results demonstrate that the stimulation was tolerated well, but did not improve motor symptoms in PD. Even though results were negative, this study raises interest toward non-invasive treatment options for PD symptoms. Furthermore, negative therapeutic results should not discourage the use of non-invasive stimulation techniques as a tool to investigate pathophysiological mechanisms underlying movement disorders. For example, dystonia is a relatively frequent movement disorder with unclear pathophysiology. However, the cerebellum is now considered a key area in the generation of dystonic symptoms. Odorfer et al. combined non-invasive cerebellar stimulation, i.e., continuous theta-burst stimulation and functional magnetic resonance imaging techniques, and investigated simple finger tapping in patients with cervical dystonia. Results indicate that finger movements, although clinically normal, are associated with altered cerebellar activity, further supporting the hypothesis of a prominent cerebellar involvement in dystonia. Finally, it should be considered that non-invasive stimulation techniques also allow to investigate physiological aspects not necessarily involved in the motor control. For example, mesial cortical areas in the frontal lobe and the ventral striatum are key nodes involved in decision-making and executive functions. In their original research study, including neuroimaging techniques, Popa et al. demonstrate how deep inhibitory rTMS can influence the underlying network functional connectivity of the targeted mesio-prefrontal-cingulo-striatal circuits regions. The study emphasizes that the modulation of resting neural activity in mesial prefrontal-striatal circuits by non-invasive techniques as a potential therapeutic tool for a wide range of psychiatric and neurologic disorders, particularly drug-cue reactivity processes relevant to addiction.

An increasing number of studies on animals and humans suggest that both the peripheral and the central nervous system can be targeted and potentially modulated by ultrasound stimulation techniques (7). An important aspect concerns the possibility to suppress or facilitate ongoing neural activity (during stimulation), as well as to induce long-lasting effects or even tissue ablation. In their review paper, di Biase et al. summarize mechanisms of actions, stimulation parameters, and therapeutic application of Transcranial Ultrasound Stimulation (tUS) in healthy humans and various disease states. In their original research article, Gibson et al. demonstrate that tUS delivered via a commercially available diagnostic imaging ultrasound system transiently increases excitability in the motor cortex. The results raise the intriguing possibility of new clinical applications for this technology, mainly as a diagnostic imaging for neuroplasticity induction not only in the motor cortex, but also in other brain areas. This initial but promising results encourage further research studies.

Alternative non-invasive stimulation techniques, like Spinal Cord Stimulation (SCS) and Non-Invasive Focal Mechanical Vibrations (NIFMV), may also improve motor control in different neurological diseases (8, 9). The review paper by Fonoff et al. summarizes the most relevant advances from experimental and clinical studies, including anecdotal reports, on SCS for gait disorders. The author discusses the potential mechanisms of action, neural substrates, and clinical outcomes of SCS, suggesting that gait abnormalities in parkinsonian syndromes, particularly freezing of gait, can improve with SCS. However, the authors acknowledge that future well-designed trials are needed to delineate the possible therapeutic applications for SCS. The results of the pilot open-label trial by Schirinzi et al. indicate that NIFMV represents a feasible, safe, and effective option of supportive therapy for patients with cerebellar ataxia. More extensive controlled studies are necessary to confirm these preliminary observations and to define other critical methodological aspects related to treatment and eligibility criteria.

In conclusion, the editors wish to thank all the authors, the reviewers, and the editorial board members for contributing to this special issue. We hope that this special issue might inspire future and novel research approaches in the field of invasive and non-invasive neuromodulation in Parkinson's disease and other movement disorders.

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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Abbreviations: DBS, Deep Brain Stimulation; GPi, Globus Pallidus internus; LID, levodopa-induced dyskinesia; NIFMV, Non-Invasive Focal Mechanical Vibrations; PD, Parkinson's disease; SCS, Spinal Cord Stimulation; STN, Subthalamic Nucleus; TMS, Transcranial Magnetic Stimulation; tUS, Transcranial Ultrasound Stimulation.

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BRIEF RESEARCH REPORT
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Non-invasive Focal Mechanical Vibrations Delivered by Wearable Devices: An Open-Label Pilot Study in Childhood Ataxia

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Non-invasive focal mechanical vibrations (NIFMV) now represent a strategy of increasing interest to improve motor control in different neurological diseases. Nanotechnology allowed the creation of wearable devices transforming thermal variations into mechanical energy with focal vibrations. This kind of wearable stimulators (WS) has produced encouraging preliminary results when used in the treatment of movement disorders and ataxia in adults. In this open label pilot study we first evaluated the feasibility, safety and effectiveness of NIFMV by WS in a cohort of 10 patients with childhood ataxia, a phenomenological category including different conditions still lacking of effective symptomatic therapies. Through the assessment of both clinical rating scales and spatio-temporal gait parameters via standardized gait analysis, we observed that a 4 weeks long treatment with WS Equistasi® was safe and provided significantly different effects in stride features of patients with slow/non-progressive cerebellar ataxia and Friedreich's Ataxia. Although limited by the sample size, the absence of a placebo-controlled group, the poor compliance of enrolled population to the original experimental design and the partial accuracy of outcome measures in pediatric subjects, we suggest that NIFMV by WS could support locomotion of patients with childhood slow/non-progressive cerebellar ataxia with preserved sensory system and no signs of peripheral neuropathy. Future studies are definitely necessary to confirm these preliminary results and define criteria for successful NIFMV-based treatment

Keywords: Ataxia, non-invasive stimulation, focal vibrations, equistasi, neuromodulation

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INTRODUCTION

Childhood ataxia (CA) is a phenomenological definition labeling patients suffering with an ataxic syndrome that appeared during childhood or at least in early adolescence. The group obviously encompasses several conditions with different etiology, including genetic and acquired forms, presenting either with pure cerebellar ataxia or complex syndromes with combined sensorial and/or strength deficit, neuropathy and mental disturbances (1, 2). Although in the absence of reliable epidemiological data, a prevalence of 26/1,00,000 has been recently estimated (1). However, regardless of clinical heterogeneity, all CAs lack of effective symptomatic treatments, such that patients are burdened by poor quality of life and high socio-economic costs (3).

Non-invasive focal mechanical vibrations (NIFMV) now represent an innovative strategy to enhance balance and motor control across different neurological diseases (4). Muscle vibrations indeed activate peripheral mechanoreceptors, leading to both short-term and long-term dynamic changes within somatosensory and motor systems, such that repeated applications may promote neuroplasticity with subsequent improvement in motor behavior (4–6).

NIFMV is usually delivered through electromechanical-based devices (6); however, a novel wearable tool has been lately introduced, which is nanotechnology-based, transforming minimal thermal variations into mechanical energy by self-producing of a focal vibration (7).

Encouraging results have been obtained from the use of such wearable stimulators (WSs) as a support to improve locomotor abilities in patients with Parkinson's Disease (PD) (8, 9) and, of interest, also in adult patients with hereditary cerebellar ataxias (10). Conversely, no data are available yet on patients with CA. In this pilot open-label trial, we thus attempted at evaluating the feasibility, safety and effectiveness of NIFMV by WS in CA, in order to explore novel therapeutic opportunities for this incurable condition.

METHODS

Study Population

The study included 10 consecutive patients with CA (onset of ataxia <18 years of age) afferent to Bambino Gesù Children's Hospital (Rome, Italy) between 2017 and 2018. Exclusion criteria were severe motor disability (Item 4 of Scale for Assessment and Rating of Ataxia, SARA > 4) and intellectual disability (IQ < 55). The cohort encompassed 6 Friedreich's Ataxia (FRDA) patients and 4 patients with other slow/non-progressive cerebellar ataxias (OA), specifically 3 with phosphomannomutase (PMM2) deficiency, 1 with isolated cerebellar atrophy. They all received brain MRI to exclude secondary causes of ataxia and nerve conduction study/electromyography to screen the presence of neuropathy. Diagnosis was obtained by appropriate genetic tests.

Intervention

The WS Equistasi® (Equistasi S.r.l., Milan, Italy) consists of a rectangular plate (10 × 20 × 0.5 mm, 0.17 gr), composed by nanotechnology fibers which produces, at body temperature, mechanical vibrations with a frequency of about 9000 Hz and a very low pressure of about 3-4 E-6 Pa. Equistasi® is a registered medical device (class 1, ministerial code n. 342577 on 05/08/2010), safe for humans (7) **(Figure 1C).**

Trial Design and Outcome Measures

All patients, after offering their consent (or parental consent, when minors), received a baseline assessment (T0). Participants were invited to wear three WSs, one over the seventh cervical vertebra and one on each soleus muscle tendons as previously described (8, 10), by using commercial patch/plasters. Application was prescribed for 60 min/day for 5 days in the first week, and then for 120 min/day (1 h in the morning, 1 h in the afternoon), 5 days/week for the following 3 weeks. At the end of the intervention, a second assessment was planned (T1). Then,

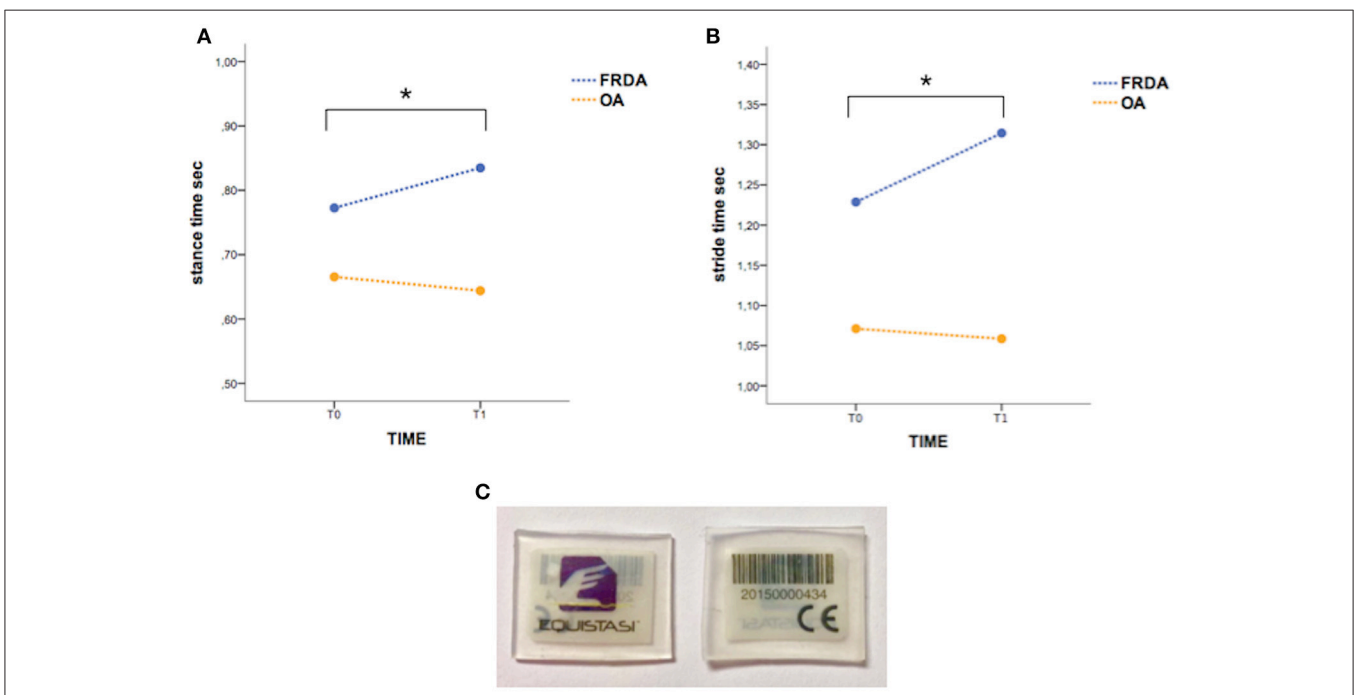

FIGURE 1 | The "stance time" **(A)** and "stride time" **(B)** variations in T0-T1 interval are significantly different between FRDA and OA. Asterisks indicate statistical significance ($p < 0.05$). **(C)** The picture shows WS Equistasi® devices.

a 4 weeks long period of WS wash-out was imposed, followed by the final assessment (T2). All patients were subject to the same protocol of physiotherapy (50 min individual session for gait and balance training, 3 times/week) over the entire trial. Also individual medical therapy continued unchanged.

Efficacy of WS was measured by means of the evaluation of clinical changes across the different time-points. Assessment performed at T0, T1, and T2 included full medical examination, clinical evaluation by SARA, 9 holes peg test (9-HPT) for both dominant and non-dominant hand, 6 min walking test (6MWT). Because of the age-related reliability of clinical rating scales (11, 12), also spatio-temporal gait parameters were considered as outcome measures to test WS effectiveness. Standardized gait analysis was conducted by an optoelectronic motion capture system with eight-camera (Vicon MX, UK) at the sampling rate of 200 Hz, as previously described (12–15). Subjects received 33 markers located on anatomical landmarks as indicated by the Plug-in-Gait protocol in order to reconstruct a full body kinematic and kinetic model. Collected data were normalized according to anthropometric features (12, 13). The following spatio-temporal parameters were specifically considered for this study: foot off (% gait cycle), stride width (meters), stance time (seconds), stride velocity (meters/second), stride time (seconds), swing time (seconds), stride length (meters), step length (meters), double support (seconds). For each variable, average values of three significant trials were analyzed. Given the non-variability between the two body sides, data from both lower limbs were analyzed together.

Safety of WS was monitored at every visit. E-mail and phone contacts were provided for adverse events communication.

The study was conducted in the context of the protocol code 1166/2016, approved by the local ethic committee (Bambino Gesù Children's Hospital). The intervention and all the procedures here performed were in agreement with the local ethical standards and the ethical principles of Helsinki declaration.

Statistical Analysis

Distribution of all collected variables was preliminary examined by the Shapiro-Wilk test. Differences in demographic, clinical and gait parameters between FRDA and OA groups were analyzed with parametric (one-way ANOVA) or non-parametric (U-Mann-Whitney) tests, as appropriate. To measure changes in clinical and gait parameters, the repeated measures ANOVA with TIME (T0, T1, T2) and GROUP (FRDA, OA) as within-subject factors was performed, by using the Greenhouse-Geisser correction for non-spherical data (Mauchley's test examined for sphericity). Statistical significance was set at $p < 0.05$. Analysis was conducted by IBM-SPSS software.

RESULTS

Demographic, clinical and gait features of study population are summarized in **Table 1**. No significant differences emerged between FRDA and OA groups in age, gender distribution and body mass index (BMI). FRDA patients all had peripheral

TABLE 1 | Summarizes main demographic, clinical and gait features of the whole study population and both FRDA and OA subgroups at T0 and T1 time-points.

	T0			T1		
	FRDA	**OA**	**All**	**FRDA**	**OA**	**All**
N	6	4	10	–	–	–
Age (y)						
mean	15.66	10.00	13.10	–	–	–
st.dev.	8.40	4.80	7.30	–	–	–
Gender						
(M/F)	2/4	3/3	5/6	–	–	–
BMI						
mean	18.40	15.98	17.32	–	–	–
st.dev.	4.05	2.72	3.58	–	–	–
SARA						
mean	13.83	12.13	13.15	11.70	11.75	11.72
st.dev.	6.53	5.54	5.89	5.07	6.76	5.48
9-HPT dominant (s)						
mean	44.82	43.67	44.36	38.04	45.16	41.20
st.dev.	14.45	15.96	14.19	7.34	13.57	10.49
9-HPT non dominant (s)						
mean	50.69	53.24	51.71	47.26	58.93	52.44
st.dev.	18.11	21.37	18.34	14.37	20.85	17.44
6MWT (m)						
mean	349.96	305.01	334.98	356.00	372.10	363.16
st.dev.	99.62	155.34	106.39	168.75	131.63	144.25
Foot off (%gc)						
mean	62.04	61.90	61.99	62.91	60.58	62.03
st.dev.	3.95	2.17	3.20	2.89	2.69	2.88
Stride width (m)						
mean	0.22	0.20	0.21	0.22	0.19	0.21
st.dev.	0.05	0.02	0.04	0.07	0.03	0.05
Stance time (s)						
mean	0.77	0.67	0.73	0.83	0.64	0.76
st.dev.	0.26	0.10	0.21	0.23	0.13	0.21
Stride velocity (m/s)						
mean	0.89	0.94	0.91	0.79	0.95	0.85
st.dev.	0.29	0.13	0.24	0.17	0.13	0.17
Stride time (s)						
mean	1.23	1.07	1.17	1.31	1.06	1.22
st.dev.	0.32	0.14	0.27	0.30	0.16	0.28
Swing time (s)						
mean	0.46	0.41	0.44	0.48	0.41	0.46
st.dev.	0.07	0.04	0.06	0.07	0.04	0.07
Stride length (m)						
mean	1.02	1.01	1.02	0.99	1.02	1.00
st.dev.	0.15	0.27	0.18	0.06	0.28	0.16
Step length (m)						
mean	0.51	0.51	0.51	0.50	0.51	0.50
st.dev.	0.08	0.14	0.10	0.04	0.13	0.08
Double support (s)						
mean	0.17	0.12	0.15	0.17	0.11	0.15
st.dev.	0.10	0.03	0.79	0.09	0.04	0.08

n, number; y, years; M, male; F, female; s, seconds; m, minutes; %gc, % gait cycle.

neuropathy and sensory impairment; none of OA patients showed neither clinical nor instrumental findings of peripheral nerves impairment and sensory deficit.

All subjects used WSs as prescribed, running normal daily activities along the treatment, avoiding sedentariness during WSs application, continuing usual medical and physical therapies. No adverse events were reported. Only 4 patients concluded the study; 6 patients dropped-out at T1 because the absence of subjective clinical improvement and discomfort of WSs application. Specifically they referred not being autonomous in the application of WSs and complained about patch application (pain, itch).

The rate of drop-out at T1 was particularly high (60%); for this reason, the statistical analysis was conducted by using T0 and T1 as time-points in TIME factor, whereas data obtained from the 4 patients accomplishing T2 were not included in the model. Repeated measure ANOVA did not show a significant TIME effect on both clinical scores (SARA, 9-HPT for both hands, 6MWT) and gait parameters in the whole population. Conversely, a significant TIMExGROUP effect resulted in either "stance time" [$F_{(1,6)} = 7.82$, $p < 0.05$] (**Figure 1A**) or "stride time" [$F_{(1,6)} = 5.54$, $p < 0.05$] (**Figure 1B**), suggesting that the clinical condition might affect the treatment outcome. Indeed, although in the absence of statistical significance, the gait parameters and the clinical scores (SARA, 6MWT) slightly improved in OA group according with an increase of gait speed (**Table 1**).

DISCUSSION

This small open-label study aimed at exploring safety, feasibility and efficacy of NIFMV delivered by WS in CA. Our preliminary results show that treatment is safe and that the underlying disease may condition the outcome. In fact, while no changes have been observed in the whole cohort, differences instead emerged by means the group analysis. Specifically, the gait parameters ("stance time" and "stride time") significantly differed between patients with slow/non-progressive cerebellar ataxia and FRDA after the treatment. Conversely, no significant effects were noticed in standard clinical scores (SARA, 9-HPT, and 6MWT).

The trial was definitely affected by several limitations. First, the small sample size, essentially due to both the rarity of the condition and inclusion/exclusion criteria of the study, may have influenced statistical significance of the results. Then, the study was not placebo-controlled. At this regard, the original experimental protocol was including a second follow up (T2), 1 month after the treatment wash-out; however, the high rate of drop-out (60% at T1) due to the poor compliance of enrolled population led us to perform a comparison between T0 and T1, excluding the few T2 data. The peculiar age of the study cohort (13.1 ± 7.3 years) influenced not only the compliance to the trial, but also the reliability of adopted outcome measures, which are typically age-dependent. Actually, SARA score is inaccurate in children < 11 years old (11). Moreover, gait analysis may have been conditioned by the inconstant collaboration of younger subjects. Nevertheless, no other age-specific ataxia outcome measures are available. All this should be thus considered in the final interpretation of the results and in the setting of future confirmative studies.

Despite these limitations, our study seems to highlight the mild beneficial effects of NIFMV by WS in gait features of a selected group of CA patients. These findings, if on the one hand, overlap with a **previous work** (10) showing the WS-induced improvement of gait ataxia in adult patients, on the other hand, provide adjunctive information on the specific action of NIFMV. In fact, we observed that NIFMV by WS did not change relevantly gait parameters in a small group of young FRDA patients, whereas they tended to be more effective in patients with pure slow/non-progressive cerebellar ataxia without peripheral neuropathy and sensory deficit, although in the absence of full statistical significance.

It has been demonstrated that the WS Equistasi® exerts neuromodulatory effects via the stimulation of proprioceptive reflexes, increasing the H-reflex inhibition and reducing alpha-motoneuron excitability, which in turn probably induces other adaptive changes within the proprioceptive pathways (7). Furthermore, NIFMV are able to modify sensory-motor cortical activity, contributing to the regulation of motor behavior at higher level (5). The integrity of sensory system is thus crucial to mediate the effects of NIFMV and determining the clinical effects. According with this data, we can refer the differences in treatment outcome between OA and FRDA groups to the impairment of sensory conduction, which is a stigmata of FRDA (16, 17). In addition, since FRDA is a neurodegenerative disease whose progression is faster and greater in patients with younger onset (18), clinical decline of this group of patients might also have contributed to different results.

Existing evidence indicates that NIFMV modulate neural transmission at different levels of CNS, contributing to motor control in deficient conditions (4). The availability of wearable devices for NIFMV, allowing easy, remote or home-based, continuative stimulations therefore should promote the use for symptomatic relief and supportive tool in neurorehabilitation of adult patients with ataxia or movement disorder (8–10).

Our preliminary findings also suggest that NIFMV by WS could represent a viable option of supportive therapy for patients with CA presenting with slow/non-progressive cerebellar ataxia in the absence of sensory involvement, although the individual compliance is fundamental for the final outcome. However, larger studies are necessary to confirm these preliminary observations, to define standardized schemes of treatment and the correct criteria of eligibility, especially in complex conditions such as CA.

AUTHOR CONTRIBUTIONS

TS, GV, AS, and MP conceived the study, analyzed data and wrote the manuscript. AR, MF, RB, and SS provided assessment and analyzed data. EB, EC, and GD contributed to interpretation of results and edited the manuscript.

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The Neuromodulatory Impact of Subthalamic Nucleus Deep Brain Stimulation on Gait and Postural Instability in Parkinson's Disease Patients: A Prospective Case Controlled Study

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Background: Subthalamic nucleus deep brain stimulation (STN-DBS) has been an established method in improvement of motor disabilities in Parkinson's disease (PD) patients. It has been also claimed to have an impact on balance and gait disorders in PD patients, but the previous results are conflicting.

Objective: The aim of this prospective controlled study was to evaluate the impact of STN-DBS on balance disorders in PD patients in comparison with Best-Medical-Therapy (BMT) and Long-term-Post-Operative (POP) group.

Methods: DBS-group consisted of 20 PD patients (8F, 12M) who underwent bilateral STN DBS. POP-group consisted of 14 post-DBS patients (6F, 8M) in median 30 months-time after surgery. Control group (BMT-group) consisted of 20 patients (11F, 9M) who did not undergo surgical intervention. UPDRS III scale and balance tests (Up And Go Test, Dual Task- Timed Up And Go Test, Tandem Walk Test) and posturography parameters were measured during 3 visits in 9 ± 2months periods (V1, V2, V3) 4 phases of treatment (BMT-ON/OFF, DBS-ON/OFF).

Results: We have observed the slowdown of gait and postural instability progression in first 9 post-operative months followed by co-existent enhancement of balance disorders in next 9-months evaluation ($p < 0.05$) in balance tests (Up and Go, TWT) and in posturography examination parameters ($p < 0.05$). The effect was not observed neither in BMT-group nor POP-group ($p > 0.05$): these groups revealed constant progression of static and dynamic instability ($p > 0.05$).

Conclusions: STN-DBS can have modulatory effect on static and dynamic instability in PD patients: it can temporarily improve balance disorders. mainly during first 9 post-operative months, but with possible following deterioration of the symptoms in next post-operative months.

Keywords: DBS (deep brain stimulation), neuromodulation, Parkinson's disease, gait, instability analysis

INTRODUCTION

Parkinson's disease (PD) in one of the most common neurodegenerative disorders with dominating motor symptoms such as bradykinesia, tremor and rigidity (1). The progression of the disease is often related to balance disorders and therefore can be a reason of falls with secondary injuries and increased possibility of hip fractures (2). Therefore the complex assessment of gait and postural instability in PD patients is crucial and can have a serious impact on quality of life in this group of patients (3).

Subthalamic nucleus deep brain stimulation (STN-DBS) has been a standard surgical procedure for PD patients with adverse effects after levodopa treatment or with motor fluctuations irrespective of best medical treatment (BMT) (4). STN-DBS has been shown to influence in addition to tremor, rigidity, and bradykinesia, also improves gait speed, step length and reduces gait variability (better postural control) (5–11). However, long-term observation of STN-DBS effect on balance disorders is not so clear, as some authors described the improvement in postural instability and gait difficulties only in first post-operative months after STN-DBS, but not in long-term assessment (12–14). To make these evidences more conflicting, there are also studies suggesting the aggravation of postural instability in PD patients after DBS (15).

Therefore, the aim of the study was to evaluate the impact of STN-DBS on gait and postural instability in PD patients in comparison with Best Medical Therapy (BMT) and Long-term Post-Operative (POP) groups.

MATERIALS AND METHODS

The study cohort consisted of clinically diagnosed as idiopathic Parkinson's disease patients that fulfilled UK Parkinson's Disease Society (UKPDS) Brain Bank criteria (16). All of the patients also met the CAPSIT-PD criteria (17) permissive to the qualification to bilateral STN-DBS. The patients were divided into three groups: BMT-group (Best Medical Therapy) consisted of 20 patients (56.7 mean age, 11 females, 9 males) treated only with pharmacotherapy through the whole time of observation, DBS-group (Deep Brain Stimulation) consisted of 20 patients (51.1 mean age, 8 females, 12 males) which underwent surgical procedure and pharmacotherapy, POP-group (Postoperative) consisted of 14 patients (51.4 mean age, 7 females, 8 males) which were operated in 30-months median time before the study began (this group was created to estimate a long-term effect of DBS on balance disorders). Demographic data of patients are described in **Table 1**. All of the patients signed an informed consent. The Ethics Committee of Medical University of Warsaw approved the study. The experiments were conducted in accordance with the ethical standards of the Declaration of Helsinki.

All study patients were examined during 3 visits (V1, V2, V3) in 9 ± 2-months periods. In POP-group, pre-operative demographic data and UPDRS III score were also included to this study in order to enable the comparison between three groups.

The balance tests and posturographic assessment were performed by physiotherapist experienced in movement disorders. The parametric evaluation included:

(1) posturographic assessment (stage 1: open eyes, stage 2: closed eyes) and biofeedback analysis on TecnoBody Prokin-M-line stabilometric platform with Prokin 3 software
(2) clinical balance tests:

- quantitative tests: Timed Up and Go (TUG), Dual Task-Timed Up And Go Test (DT-TUG)
- qualitative tests: Tandem Walking Test (TWT), 180° Tandem Pivot Test (TPT)

The motor assessment of study patients (UPDRS scale and parametric stability evaluation) was performed two times during each visit in BMT-group and preoperative assessment in DBS-group (BMT-ON and BMT-OFF phase) and four times (Total-ON, DBS-ON/BMT-OFF, DBS-OFF/BMT-ON, Total-OFF) during postoperative evaluations (V2, V3) in DBS group and during all visits (V1, V2, V3) in POP group. The neurological examination and UPDRS scale evaluation were performed by neurologist experienced in movement disorders. They were performed after 12-h time of levodopa stopping or 24-h time of stopping of other antiparkinsonian drugs in BMT group and in preoperative assessment in DBS group. The neurological evaluation and UDPRS scale during post-operative assessment were performed after 30-min time of switching off both the stimulators (left and right) with 12-h time of levodopa stopping and with 24-h time of other antiparkinsonian treatment stopping (**Table 1**).

All patients qualified to surgical treatment, underwent bilateral subthalamic nucleus deep brain stimulation (STN-DBS). Pre-operatively fusion of 1,5T MRI and stereotactic contrast-CT was performed with the use of Stereotactic Planning Software (Brainlab). Then, microrecording (MER) and macrostimulation were conducted using Leadpoint®(Medtronic) followed by macrostimulation evaluated by neurophysiologist and movement disorders neurologist. If motor adverse effects appeared below 2V from the M path and visual sensations appeared below 2V from

TABLE 1 | Study population.

	BMT-group	DBS-group	POP-group
Gender	11 F, 9 M	8 F, 12 M	7 F, 8 M
Age at study beginning	56.7 ± 15.4 years	51.1 ± 15.3 years	51.4 ± 8.7 years
Time of onset	46.3 ± 15.1 years	39.7 ± 13.3 years	40.9 ± 8.3 years
Symptoms' duration time	10.4 ± 4.9 years	11.3 ± 3.9 years	10.5 ± 3.5 years
Time of dyskinesia	1.8 ± 2.6 hours daily	4.9 ± 2.9 hours daily	5.9 ± 2.6 hours daily
OFF time	2.7 ± 1.3 hours daily	4.6 ± 3.2 hours daily	4.4 ± 1.8 hours daily
LEDD—Visit 1	1254.0 ± 511.6 mg	1379.5 ± 510.0 mg	(pre-operative): 1273.2 ± 464.3 mg (post-operative): 585.4 ± 409.7 mg
LEDD—Visit 2	1564.0 ± 542.2 mg	350.3 ± 262.2 mg	555.7 ± 499.6 mg
LEDD—Visit 3	1558.3 ± 622.1 mg	394.5 ± 319.2 mg	762.9 ± 589.8 mg
UPDRS III OFF—Visit 1	32.3 pts	34.1 pts	39.5 pts
UPDRS III ON—Visit 1	12.8 pts	11.5 pts	10.2 pts
UPDRS III OFF—Visit 2	37.0* pts	42.9* pts	43.0 pts
UPDRS III ON—Visit 2	12.8 pts	7.9 pts	10.8 pts
UPDRS III OFF—Visit 3	41.7* pts	45.1 pts	47.2 pts
UPDRS III ON—Visit 3	12.8 pts	9.3 pts	11.4 pts

*$p < 0.05$.

both paths at +2 bilaterally, microelectrodes were replaced by permanent electrodes (3389-28, Medtronic, Minneapolis, MN) bilaterally. Lateral control X-ray was performed to confirm the location of the electrode to be identical to the microelectrode, then the electrode was locked (Stimlock, Medtronic) at the burr-holes and the scalp wounds were closed. After removal of stereotactic frame, the connection of internal pulse generators (Activa SC, Medtronic, Minnneapolis, MN) to the electrodes was performer under general anesthesia. After 4-weeks time, the stimulators were switched on and tunned in order to start the stimulation without adverse effects. If the stimulation effect was balanced and stable, pharmacotherapy was then slowly reduced (**Table 1**). There were no observed surgical complications after DBS implantation through the whole time of the study.

Data analysis and statistical assessment consisted of the linear mixed model analysis, which was implemented by the use of LME4 (version 1.1) with intercepts for subjects included as random effects. Pairwise interactions between each fixed factor were included in the model. Tukey contrasts (from lsmeans package, version 2.25) were used to compare results between timepoints and treatments (18). All calculations were performed in statistical computing software R (version 3.3) (19). *P* values < 0.05 were considered significant.

RESULTS

Static balance evaluation on posturographic platform revealed alterations in early-post-operative assessment. Static instability in first post-operative Total-OFF phase evaluation (ΔV2-V1 assessment) of DBS group was relatively decreased ($p > 0.05$) in comparison to ΔV3-V2 assessment that revealed statistically significant deterioration of static stability. The mixed model analysis in DBS group showed a slower deterioration ($p > 0.05$) with following significant escalation ($p < 0.05$) in average AP-CoP velocity (average velocity of the center of foot pressure displacement in the anteroposterior direction), average ML-CoP velocity (average velocity of the center of foot pressure displacement in the mediolateral direction), perimeter (length of the path of the center of foot pressure) and ellipse area (area of the greatest sway of the center of foot pressure) in the tests with the eyes open as well as in the tests with eyes closed. The same alterations were not present either in BMT nor in POP-group ($p > 0.05$) (**Figure 1**).

Clinical balance tests' analysis also revealed different effects in DBS group in Total-OFF phase, which were similar to these observed on posturographic platform: ΔV2-V1 assessment showed improvement in Timed Up And Go tests and Tandem Walking Test ($p < 0.05$) with following deterioration in ΔV3-V2 evaluation in all clinical balance tests (Timed Up and Go tests, Tandem Walking Test, 180° Tandem Pivot Test) ($p < 0.05$). These alterations were not detected in BMT—and POP-group ($p > 0.05$) (**Figure 1**, **Table 2**).

Static and dynamic balance evaluations on posturographic platform and with the use of clinical balance tests, were also performed in Total-ON phase as well as in DBS-ON/BMT-OFF and DBS-OFF/BMT-ON in postoperative assessment in order to estimate the effect of STN-DBS on stability in PD patients. The mixed model analysis of both platform and clinical tests revealed the significant improvement in static and dynamic stability in DBS-ON phases only in V3 evaluation in DBS group ($p < 0.05$), except 180° Tandem Pivot Test assessment which was significantly improved in V1, V2, and V3 Total-ON vs. Total-OFF examination ($p < 0.05$) (**Figure 1**, **Table 2**). There was no significant effect of pharmacological treatment on static and dynamic stability within all study groups ($p > 0.05$), except 180° Tandem Pivot Test preoperative (V1) evaluation in DBS group ($p < 0.05$) (**Figure 1**, **Table 2**).

FIGURE 1 | (A–F) Posturography and clinical balance tests' parameters in study groups (BMT, DBS, POP) in visits 1–3 (V1, V2, V3) *$p < 0.05$. **(A)** AP-CoP velocity (mm) with open eyes in Total-OFF phase in study groups (BMT, DBS, POP) in visits 1–3 (V1, V2, V3). **(B)** ML-CoP velocity (mm) with open eyes in Total-OFF phase in study groups (BMT, DBS, POP) in visits 1–3 (V1, V2, V3). **(C)** Perimeter (mm) with open eyes in Total-OFF phase in study groups (BMT, DBS, POP) in visits 1–3 (V1, V2, V3). **(D)** Perimeter (mm) with closed eyes in Total-OFF phase in study groups (BMT, DBS, POP) in visits 1–3 (V1, V2, V3). **(E)** Timed Up And Go test in Total-OFF phase in study groups (BMT, DBS, POP) in visits 1–3 (V1, V2, V3). **(F)** Tandem Walking Test in Total-OFF phase in study groups (BMT, DBS, POP) in visits 1–3 (V1 ,V2 ,V3).

DISCUSSION

Balance disorders are one of the most debilitating motor deficits in PD patients, which increase during the disease progression (20). STN-DBS has been initially shown to have a modest effect on static and dynamic stability (5–10) but long-term studies revealed more conflicting results (11–15, 21). Our study, for the first time, evaluated the long-term effect of STN-DBS on gait and postural instability in Total-OFF phase in PD patients what allows to estimate the possible modulatory effect of STN-DBS on stability disorders progression in PD in comparison to only-pharmacologically treated patients. We revealed the possible modulatory effect of STN-DBS on static and dynamic balance disorders in first post-operative 9-months period with following deterioration in consecutive months. This phenomenon has not been described yet, as our analysis was performed in Total-OFF phase unlikely to previous long-term studies (12, 14, 15), which mainly used UPDRS III examination in postural evaluation rather than posturographic platform or clinical balance tests.

The impact of STN-DBS on static and dynamic balance disorders in PD patients is not clearly established. One of hypotheses is, that the post-operative effect of STN-DBS on balance amelioration may be secondary due to decrease of dyskinesia and motor fluctuations (22). The other authors postulate that STN-DBS can (at least partially) restore functionally the dopaminergic systems (23, 24) and the instability amelioration is than the secondary effect to the decrease of increased STN neuronal activity, burst type activity and abnormal oscillations (25, 26) or due to changes within the entire cortico-striato-pallido-thalamo-cortical system (26, 27). The other hypothesis based on animal models claims that STN stimulation may induce locomotion per direct electrical stimulation of corticobasal locomotor control structures (28). More recent studies showed the possible functional connectivity between STN and sensorimotor and frontoparietal cortical regions' disruption in PD patients with freezing of gait (29) which might be improved directly by STN-DBS electrical effect on the cortico-striato-pallido-thalamo-cortical system and explain the

TABLE 2 | Posturography and clinical balance tests' parameters in study groups: Δ = inter-visit differences.

	BMT group				DBS group				POP group			
Δ Visit:	**Δ (V2–V1)**		**Δ (V3–V2)**		**Δ (V2–V1)**		**Δ (V3–V2)**		**Δ (V2–V1)**		**Δ (V3–V2)**	
Phase:	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF
Parameter:												
Δ AP-CoP velocity [mm/s] /eyes open/	4.07	1.60	2.41	7.71	−17.62	−2.08	0.75	6.75	3.23	5.0	−3.21	−4.71
Δ ML-CoP velocity [mm/s] /eyes open/	1.24	2.91	5.01	6.72	−8.91	−3.31	0.55	9.5*	5.53	5.64	−4.18	−5.57
Δ perimeter [mm] /eyes open/	101.3	81.84	132.9	279.9	−505.4	−101.3	26.75	297.9*	162.0	204.9	−135.5	−175.6
Δ ellipse area [mm^2] /eyes open/	360.6	416.7	832.8	773.0	−47.84	−277.9	167.3	214.1	31.15	629.4	−172.5	−467.6
Δ AP-CoP velocity [mm/s] /eyes closed/	5.49	3.09	0.06	5.13	−17.76	−3.49	−2.35	16.4*	1.91	7.14	−3.40	−5.5
Δ ML-CoP velocity [mm/s] /eyes closed/	2.75	3.65	3.75	2.87	−9.04	−3.65	−0.4	30.85*	5.55	5.21	−2.82	−5.0
Δ perimeter [mm] /eyes closed/	158.0	133.7	72.9	148.2	−502.1	−128.1	−53.1	899.2*	129.3	237.1	−115.1	−203.6
Δ ellipse area [mm^2]/eyes closed/	870.7	1058	400.2	−299.5	583.5	−515.5	89.45	1677*	682.0	631.1	−1269	−1169
Δ Timed Up And Go tests [sek]	−1.26	−1.05	0.21	−0.61	0.57	−3.15*	0.54	−1.58*	0.0	0.69	0.35	5.25
Δ Dual Task—Timed Up And Go test [sek]	−0.91	−1.83	0.23	−0.35	0.85	−8.23*	0.20	−0.75	−0.56	−1.49	1.30	5.98
Δ Tandem Walking Test	−2.98	−0.14	1.17	0.85	0.18	−5.93*	−0.35	2.97	−0.83	−1.12	4.98	8.52*

*$p < 0.05$.

declining impact of STN-DBS on balance disorders in long-term observations (11–14), also observed in our study. Some studies also describe the frequency-dependent effect of STN-DBS on balance instability, with noticeable improvement in low-frequency stimulation (30–32). We have not allocated DBS patients to low- and high-frequency stimulation subgroups as the purpose of this study is to establish the impact of the STN-DBS surgery and long-term electrical stimulation in Total-OFF treatment phase, not to estimate the effect of STN-DBS ON-stimulation on the motor improvement of PD patients, what has been previously reported (30–32).

To conclude, our study revealed, for the first time, the modulatory short-term gait and postural instability improvement with following deterioration of balance disorders in PD patients after STN-DBS surgery. The long-term effect of STN-DBS has not been detected, similarly to lack of noticeable effect of levodopa and other dopaminergic treatment.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Bioethics Committee of Warsaw Medical University with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Bioethics Committee of Warsaw Medical University.

AUTHOR CONTRIBUTIONS

SS, AF, and DK contributed conception and design of the study. SS, MK, IP, KG, TM, AP, JD, MF, and PH organized the database. SS and DK performed the statistical analysis. SS, AF, AP, and DK wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Increased Excitability Induced in the Primary Motor Cortex by Transcranial Ultrasound Stimulation

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Background: Transcranial Ultrasound Stimulation (tUS) is an emerging technique that uses ultrasonic waves to noninvasively modulate brain activity. As with other forms of non-invasive brain stimulation (NIBS), tUS may be useful for altering cortical excitability and neuroplasticity for a variety of research and clinical applications. The effects of tUS on cortical excitability are still unclear, and further complications arise from the wide parameter space offered by various types of devices, transducer arrangements, and stimulation protocols. Diagnostic ultrasound imaging devices are safe, commonly available systems that may be useful for tUS. However, the feasibility of modifying brain activity with diagnostic tUS is currently unknown.

Objective: We aimed to examine the effects of a commercial diagnostic tUS device using an imaging protocol on cortical excitability. We hypothesized that imaging tUS applied to motor cortex could induce changes in cortical excitability as measured using a transcranial magnetic stimulation (TMS) motor evoked potential (MEP) paradigm.

Methods: Forty-three subjects were assigned to receive either verum ($n = 21$) or sham ($n = 22$) diagnostic tUS in a single-blind design. Baseline motor cortex excitability was measured using MEPs elicited by TMS. Diagnostic tUS was subsequently administered to the same cortical area for 2 min, immediately followed by repeated post-stimulation MEPs recorded up to 16 min post-stimulation.

Results: Verum tUS increased excitability in the motor cortex (from baseline) by 33.7% immediately following tUS ($p = 0.009$), and 32.4% ($p = 0.047$) 6 min later, with excitability no longer significantly different from baseline by 11 min post-stimulation. By contrast, subjects receiving sham tUS showed no significant changes in MEP amplitude.

Conclusion: These findings demonstrate that tUS delivered via a commercially available diagnostic imaging ultrasound system transiently increases excitability in the motor cortex as measured by MEPs. Diagnostic tUS devices are currently used for internal imaging in many health care settings, and the present results suggest that these same devices

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may also offer a promising tool for noninvasively modulating activity in the central nervous system. Further studies exploring the use of diagnostic imaging devices for neuromodulation are warranted.

Keywords: brain-stimulation, magnetic stimulation, excitability, neuroplasticity, excitation, pulsed ultrasound

INTRODUCTION

Neuroplasticity is fundamental to many neurobehavioral processes, including learning and memory (1). It is believed that neuroplasticity is associated with behavioral changes during normal development, and clinically for post-stroke recovery, traumatic brain injury (2), and adaptation to physical changes in the body (3) among other neural and behavioral changes across the lifespan. It has been suggested that changes in cortical excitability may be related to changes in neuroplasticity (4). Some methods of non-invasive brain stimulation (NIBS) have been found to be effective for inducing changes in brain excitability and, subsequently, neuroplasticity. A number of NIBS techniques have been developed that utilize different forms of energy, including direct and alternating current, magnetic, light, and others (5–8). Each of these techniques have a variety of advantages and disadvantages. Light stimulation, or photobiomodulation, is a promising but as yet little underexplored method of NIBS (9). Transcranial direct current stimulation (tDCS), while inexpensive and associated with minimal side-effects (10), can produce variable results across individuals and time points (11, 12). TMS has a longer history of clinical and experimental application (13), but also comes with more contraindications (14), and is subject to variable effects across individuals (15–17). Recently, ultrasound has received increased interest for NIBS. While the possibility of modulating peripheral nervous system function through ultrasonic stimulation was originally explored in the early twentieth century (18–21), interest subsequently declined, only to be rekindled recently with an emphasis on central nervous system modulation and transcranial ultrasound (tUS) (22–24).

Ultrasonic waves (administered via tUS) are able to pass through the scalp and skull (25–27), where they can safely interact with brain tissue at low intensities (28–30). A number of parameters govern the characteristics of tUS waves, including the fundamental frequency, pulse repetition rate, intensity, duty cycle, and duration of stimulation. Each of these parameters alone, or in combination and in consideration of the precise anatomical regions targeted, has the potential to alter how tUS affects brain activity. However, the exact relationship between tUS parameters and the subsequent effects are not yet fully understood (31–33).

Two common variants of tUS are transcranial focused ultrasound (tFUS), and diagnostic tUS. tFUS typically employs frequencies below 1 MHz, while diagnostic tUS utilizes frequencies ranging from 1 to 15 MHz (34, 35). This distinction is important in tUS, as the human skull is believed to attenuate the energy of higher frequency US more greatly than lower frequencies (36–38), with the degree of energy absorption and wave aberration varying across individuals (26, 39). Diagnostic tUS can be used to image brain tissue through the skull (26, 40–43), demonstrating that energy can be successfully passed into and out of the skull and brain at higher frequencies than those typically used in tFUS applications. Whether or not the amount of energy passed into the skull with diagnostic tUS is sufficient to produce neurophysiological effects is a question that has not been examined previously.

A growing body of literature has formed around the use of various forms of tUS in small mammals (35, 44–47) and non-human primates (48, 49), paving the way for research with human subjects (50). In separate studies, tFUS applied to the human somatosensory cortex improved performance on a tactile discrimination task (51), and elicited transient tactile sensations in the contralateral hands and fingers (52). Diagnostic tUS has also been applied for the purpose of neuromodulation. Administering 8 MHz diagnostic tUS over the temporal window, Hameroff and colleagues reported that 15 s of stimulation acutely improved subjective mood (53). While similar, longer term effects following tUS stimulation have been observed (54, 55), the brain processes underlying these changes are yet to be fully elucidated (56).

Here we examined whether tUS administered using a diagnostic ultrasound system modulates cortical excitability in healthy adults by using motor evoked potentials (MEPs) induced by transcranial magnetic stimulation (TMS) (57, 58).

METHODS

Subjects

Sixty-six healthy participants (42 female) participated in this randomized, single-blind study exploring the effects of tUS on cortical excitability. Individuals were required to pass a tUS and TMS screening form which included the following: Right-handed, age 18–45, no personal or family history of seizure, mood, or cardiovascular disorders, no facial or ear pain, no recent ear trauma, no metal implants including pacemakers, not pregnant, no dependence on alcohol or recent illicit drug use, and no use of any pharmacological agents known to produce significant changes in CNS function or increase seizure risk. A between-subjects design was chosen because, while TMS elicited MEPs have been shown to be reliable across sessions (59, 60), the intra-individual reliability of other forms of NIBs across sessions is still debated (61–64). This is especially a concern for forms of NIBS that are neuromodulators, like TUS, where daily changes in endogenous brain activity can have a large impact on the outcome of stimulation (6, 65, 66).

All experimental procedures were approved by Chesapeake IRB and the U.S. Army Research Laboratory's Human Research Protection Program.

Experimental Overview

Participants were seated in a reclining chair, informed about the study, and consented. To check for changes in subjective psychological state over the length of the protocol, subjects then completed a brief mood questionnaire that asked them to endorse 10 statements using a 6-point (0–5) Likert scale (**Table 1**). This same questionnaire was administered again at the conclusion of the study. Following measurement of baseline cortical excitability, subjects received either verum or sham tUS to their motor cortex for 2 min. Cortical excitability was measured immediately after stimulation at 1 min, and at 5 min intervals up to 16 min post-stimulation (**Figure 1**). Sham control was accomplished through application of the freeze function on the machine prior to transducer application, as has been employed in other studies using diagnostic tUS (53, 67). Subjects completed sensation questionnaires following acquisition of the motor threshold and again following tUS. These asked subjects to separately rate the degree of itching, heat/burning, and tingling on a 0–10 scale.

Cortical Excitability Recording Using TMS-Induced MEPs

TMS-induced MEPs (57, 58) were administered using a neuronavigation-assisted eXemia TMS system (Nextstim Ltd., Helsinki, Finland) with a 70 mm figure of eight coil and NBS software (version 3.2.0). Electromyography (EMG) was recorded from disposable Ambu Neuroline 720 electrodes attached to the abductor pollicis brevis and opponens pollicis muscles of the right hand with the reference electrode attached to the base of the extensor digitorum tendon of the right-hand middle finger. This enables recording of MEPs elicited from contraction of the thumb.

Subjects were instructed to rest their hand on a pillow in a relaxed position, where it remained for the duration of the study. MEPs are highly variable (68, 69), less variable resting motor thresholds (RMT) were determined for each subject (70). Subject's RMT was determined through adaptive parametric estimation via sequential testing (PEST) procedure and software (TMS Motor Threshold Assessment Tool, MTAT 2.0, (http://www.clinicalresearcher.org/software.html), which reliably determines the motor threshold (71–73). Prior to baseline, TMS power output was set at 110% of the power associated with an individual subject's RMT, where it remained for the duration of the experiment. In a given subject, if the PEST procedure found that acquisition of the RMT required a TMS power output that exceeded the total possible power output of the TMS system, then the experimental session was discontinued and the subject was regarded as not having consistently measurable MEPs.

The motor hotspot associated with abductor pollicis brevis activation was identified through a combination of visual inspection and EMG, with the area most consistently eliciting MEPs above 1 mV coupled with isolated thumb movements being selected for the RMT procedure, using similar methodology as Nitsche and Paulus (58). Stimulated areas of the motor cortex were tracked and mapped via neuronavigated TMS through the eXemia system. Neuronavigated TMS has demonstrated a higher probability of finding consistent MEPs compared to referencing external landmarks (74–77), as it allows the experimenter to maintain the location of the motor hotspot as well as the ideal coil orientation for an individual subject (78, 79).

Baseline excitability was measured through a series of 10 single TMS pulses delivered an average of 4 s apart. Following tUS, 4 additional blocks of 10 single TMS pulses were performed: 1 min after tUS application and then 3 more blocks of 10 pulses each separated by 5 min intervals.

TABLE 1 | Questionnaire administered prior to and after stimulation to probe possible changes in subject-reported psychological state.

Mood questionnaire items
1) I feel nervous
2) I feel excited
3) I feel tired or fatigued
4) I feel confused or disoriented
5) I feel sad or down
6) I feel tense or frustrated
7) I feel dizzy or light-headed
8) I feel nauseous
9) Physically, I feel pain or discomfort
10) I feel unable to concentrate or pay attention

Ultrasound Stimulation

We used a Phillips CX50 Diagnostic Imaging Ultrasound System, with a Phillips S5-1 broadband plane sector transducer array. This transducer has 80 piezoelectric elements, an aperture of 20.3 cm, and a frequency range of 1–5 MHz. The system was set in HGen, B-mode with harmonics on and a focal depth of 10 cm. The waveform generated by this transducer occurs in a plane wave where the energy deposited is homogenous across the field of view. The central frequency was 2.32 MHz, which

FIGURE 1 | Study Design. The experimental visit lasted between 70 and 100 min. MH, acquisition of the motor hotspot; RMT, acquisition of resting motor threshold.

represents the median frequency emitted by the transducer, with the absolute range of frequencies normally distributed between the limits of 1.53 and 3.13 MHz (80). SonicEaze ultrasound conductive gel was used to create an acoustic medium when applying the transducer to the scalp. To ensure fidelity to the previously identified hot spot, neuronavigation was again employed for tUS transducer placement. In order to measure maximum acoustic output, a hydrophone (HNR 500, Onda Corporation, Sunnyvale, CA, United States) calibrated 1 month prior to testing was used. The peak negative pressure associated with our transducer settings was 1.02 MPa as measured in free, degassed water with a manual stage.

Statistical Analysis

To explicate excitability changes associated with tUS, data was analyzed in SPSS using a between-subjects repeated measure ANOVA with 2 conditions, verum and sham, and 5 time points as described above. Student's *t*-tests (independent samples, two-tailed, $p < 0.05$) were then performed to test between-group differences at each post-stimulation time point. Individual subject MEPs were averaged across the 10 stimuli given per block. Individual TMS pulses that elicited an MEP amplitude of 0 were discarded and not counted in the 10 MEP average. The researcher performing the analysis was not blind to the experimental groups; however, there were no subjective steps involved in the MEP analysis that could be unduly influenced by unblinding. Due to the limited extant literature utilizing higher frequency tUS, no *a-priori* hypotheses were made about the direction of any possible neuromodulation effects.

RESULTS

Subjects

Eighty subjects were assigned to the current study after passing screening. Fourteen of these (17.5%) canceled due to scheduling conflicts or could not participate to due illness or other issues, leaving 66 subjects that were enrolled and consented. Measurable MEPs could not be obtained in 23 subjects (35%), and these were excluded from further analysis. We collected MEP data from the remaining 43 subjects, 21 who received verum tUS and 22 who received placebo tUS. The mean MEP averages at baseline were 0.932 mV for the verum group and 0.849 mV for sham (see **Figure 2**). This difference in baseline means between groups was not significant ($p = 0.55$). Subjects with baseline intra-block variability >1 standard deviation (> 0.812 mV) above the average variability for all baseline trials ($N = 420$) were excluded, which led to 2 additional exclusions in the verum group and 1 in the sham group. No subjects had more than 2 MEPs of 0 within a single block. A total of 40 subjects were used in the analysis, with 19 in verum (11 females) and 21 in sham (14 females). The mean age was 20.58 ($SD = 1.5$) and 22.05 ($SD = 5.0$) for verum and sham, respectively. The median age in the verum group was 21, with a range of 19 to 23. In the sham group, the median age was 20, with a range of 18 to 38. There were no significant differences between these final groups in gender or age composition ($p > 0.05$). Additionally, the difference in RMT as percentage of TMS power output between groups was not significant ($p > 0.05$; **Table 2**).

Safety

The most commonly reported sensation was tingling, both before baseline measurement ($M = 1.44$, $SD = 1.58$), and after tUS ($M = 1.32$, $SD = 1.65$). No significant differences were found between these pre- and post-stimulation measures for any of the sensation questions regarding itching, heat/burning, and tingling, nor were there any significant differences between verum and sham groups at either time point.

The mechanical index during tUS observed during hydrophone measurement was 0.67, well below the mechanical

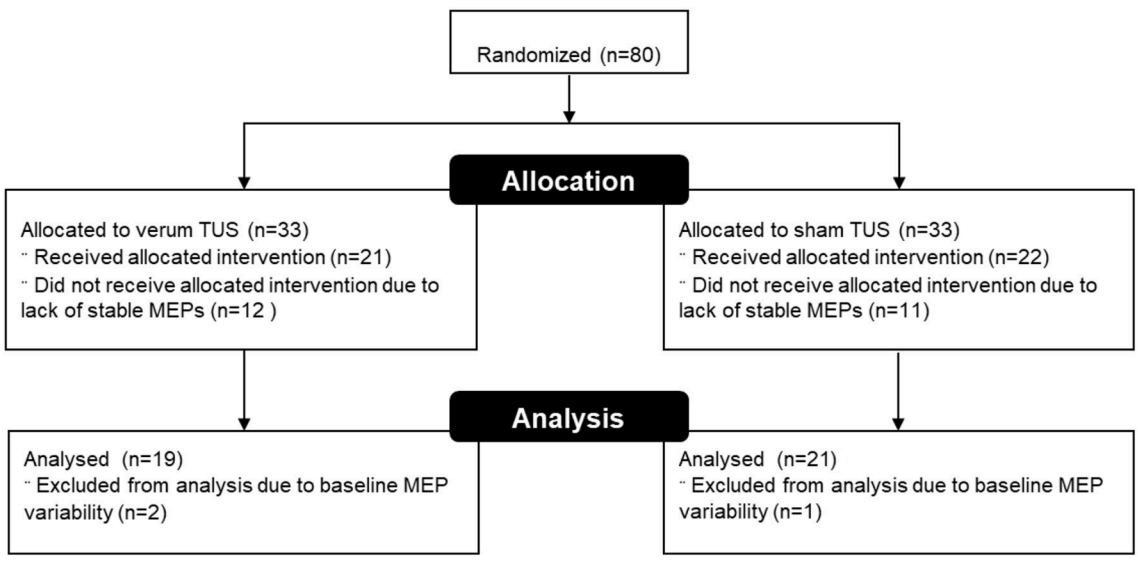

FIGURE 2 | Flow chart showing subject randomization and exclusion.

TABLE 2 | One hundred and ten percent resting motor thersold as percentage of TMS machine output.

	110% RMT		
	n	***M (SD)***	**Range**
Sham	21	78.6(10.84)	51–94
Male	7	81.71(10.14)	66–94
Female	14	77.29(11.24)	51–93
Verum	19	72.05(11.03)	51–94
Male	8	70.38(12.33)	56–94
Female	11	73.27(10.42)	51–88

index limit of 1.9 recommended by the Food and Drug Administration (81). The thermal index reading of 2.6 was also well within established safety parameters (28), where tissue can safely be exposed to similar temperatures for up to 100 min (82). The low duty cycle of our device, <1%, led to an I_{sppa} of 34.96 W/cm^2 and an I_{spta} of 132.85 mW/cm^2 before transcutaneous and bone transmission (i.e., in free water), well below recommended limits of 720 mW/cm^2.

As an additional safety measure, we assessed the possibility of motor cortex stimulation eliciting acute changes in subject mood with a brief questionnaire. Across both groups, paired samples *t*-tests indicated significant changes in 2 items over time. On a scale from 0 to 6, subjects reported feeling less nervous ($M = 0.96$, $SD = 1.11$) and less excited ($M = 2.44$, $SD = 1.56$) after completion of the study (nervous $M = 0.32$, $SD = 0.63$, $p = 0.003$; excited $M = 1.72$, $SD = 1.48$, $p = 0.011$). No significant differences between groups were found either before or after stimulation for any of these measures.

Effects on Cortical Excitability

Mauchly's test was significant, χ^2 (9) = 18.51, $p = 0.03$, indicating unequal variances between verum and sham groups, therefore a Greenhouse-Geisser correction was used ($\varepsilon = 0.851$). There was a significant interaction between condition and time point [ANOVA, $F_{(3.404,129.349)} = 3.501$, $p = 0.014$, $\omega^2 = 0.059$]. For subjects that received verum tUS, stimulation produced an average 33.7% ($SD = 0.457$ mV) increase in average MEP amplitude 1 min post stimulation (post measure 1) that declined slightly to 32.2% ($SD = 0.511$ mV) over baseline 6 min post stimulation (post measure 2; **Figure 3**). This contrasted with sham subjects whose average MEP amplitude was 7.6% ($SD = 0.187$ mV) smaller than baseline at post measure 1 and 1.2% ($SD = 0.290$ mV) smaller at post measure 2. Follow up comparisons revealed a significant difference between sham ($M = 0.785$ mV, $SD = 0.460$ mV) and verum tUS ($M = 1.246$ mV, $SD = 0.600$ mV) at 1 min post-stimulation (post measure 1), t (38) = −2.750, $p = 0.009$; and at 6 min post-stimulation (post measure 2), verum tUS ($M = 1.232$ mV, $SD = 0.694$ mV), sham tUS ($M = 0.839$ mV, $SD = 0.510$ mV), t (38) = −2.054, $p = 0.047$. Effect sizes for between-groups comparison were calculated using a pre-post control technique that accounts for groups of unequal sample size (83). At post measure 1 the observed effect size was $d = 0.86$, and $d = 0.71$ for post measure 2. No significant differences in MEP amplitude were found between groups for post-measures 3 ($p = 0.129$) and 4 ($p = 0.359$), collected at 11 and 16 min post stimulation.

DISCUSSION

This study demonstrated effects of tUS on MEP amplitude, amounting to a 33.7% increase in average MEP amplitude 1 min and a 32.2% increase 6 min after stimulation. Thereafter, MEP amplitude decreased toward baseline, and was not significantly different than sham for the remainder of testing times. Control subjects' average MEP amplitude was not significantly different than baseline at any post-stimulation timepoint. The 2 min duration of tUS used here produces neurophysiological effects that are limited in time, in this case approximately 4 times the duration of stimulation. Studies using other forms of NIBS, such as tDCS and TMS, have observed a similar relationship (57, 84–86), and have found that a longer duration of stimulation led to longer effects. Results using these other modalities suggest that the duration of tUS effects might be controlled in part by varying the duration of stimulation.

The length of tUS induced changes we observed corresponds with previous research, where suppression of visual evoked potentials and somatosensory evoked potentials following tFUS lasted between 5 and 10 min in (54, 87). Importantly, neither of these studies found evidence of tUS induced tissue damage in histological analyses. In humans, Hameroff et al. found mood effects that persisted up to 40 min after stimulation (53). While we did not find similar mood changes following stimulation, our questionnaire was designed to be a brief status check on subject well-being and not a nuanced accounting of mood effects, so subtle changes in mood may have been missed. A possible alternative explanation might be that tUS effects are specific to the location of stimulation, and that stimulation of the temporal lobe produces mood effects, while stimulation of the motor cortex does not.

Our study is also one of many to have found excitatory effects from tUS. At the neuronal level, ultrasound stimulation has directly evoked electrical responses from extracted cells (23, 88), opened voltage-gated sodium and calcium channels (24), and increased the concentration of excitatory neurotransmitters (46, 89). In small mammals, *in vivo* tUS excitation of the motor cortex has also often been observed, accompanied by increases in BOLD activation, EMG amplitude, and evoked movement (44, 45, 87, 90). Beyond the motor cortex excitation has been measured by visual evoked potentials (91, 92), EMG (93), directly evoked movement (35, 94–96), and increased glucose uptake (97). Similar excitation has been found in humans as well, measured by increased somatosensory evoked potentials (52), increases in BOLD activation (93, 98), and increases in the volume of activated cortical tissue in the motor cortex (99).

Our findings of increased MEP amplitude with tUS contrast with recent work that investigated the effect of transcranial tFUS on MEPs where a reduction in MEP amplitude was demonstrated (100). There are a number of differences between these studies

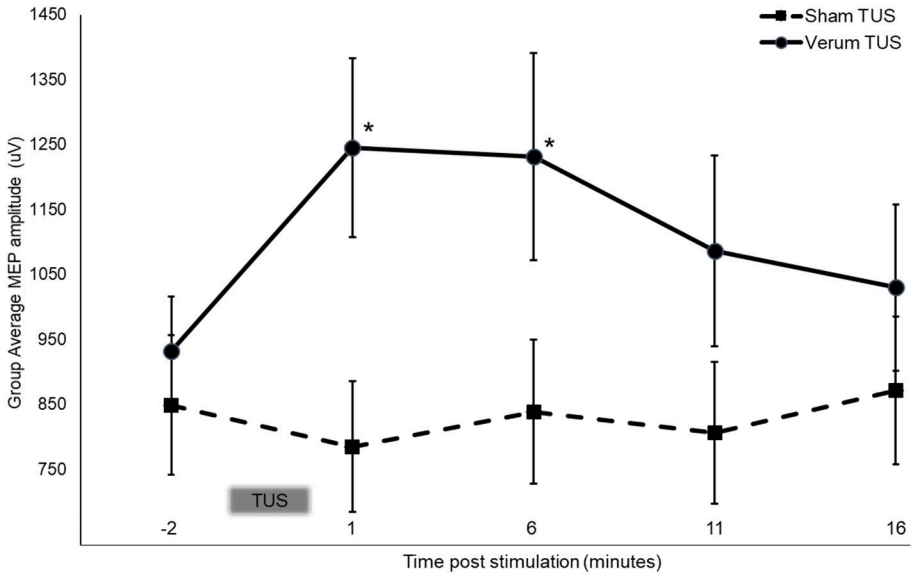

FIGURE 3 | Stimulation dependent changes in MEP amplitude at baseline and following 2 min of tUS. Asterisks indicate significant between group differences (two-tailed *t*-test, independent samples, $P < 0.05$) Error bars = ±SE.

that might account for the difference in response polarity observed. The precise tUS system, transducer types, and the tUS protocols used were all different between studies. TFUS and tUS using a diagnostic ultrasound system potentially penetrate to different cortical depths, with higher frequency diagnostic tUS possibly affecting more dorsal cortical tissue nearer to the scalp, and tFUS affecting deeper tissues that are out of the direct reach of subsequent TMS stimulation (100, 101). The differences in findings might also be due to contrasting methodologies between the present study and others, where applying tUS simultaneously with TMS leads to inhibitory (100), or null effects (67), whereas serial application as used here leads to excitatory effects.

While supported theories exist for the effects of tUS (32, 102, 103), researchers are still coming to grips with how tUS effects the brain above the level of individual neurons. Further complication comes from trying to parse how the numerous parameters of tUS interact with each other and with the stimulated medium. Another difference between our study and that of Legon and colleagues is the volume of tissue stimulated, a factor that might be crucial in interpreting the effects of tUS generally. Holding all other parameters constant, unfocused transducers impact upon more brain area than focused transducers, and analogously, each decrease in frequency within a focused transducer serves to increase the stimulated area. The greater brain volume affected by unfocused stimulation, as compared to focused stimulation, might thus be conceptually similar to the increased brain volume that is affected by lowering the frequency of focused ultrasound. In both cases, the sheer volume of brain tissue involved might be more important than the total energy delivered. If acoustic force was the most important parameter for induced effects, higher frequencies would generally equate with stronger effects; however, lower frequencies, and thus larger stimulated areas, have been found to be more likely to get a response (35, 44, 45). TFUS has also been shown to require greater energies to elicit an excitatory motor response, I_{sppa} of 12.6 W/cm^2, than unfocused tUS, I_{sppa} of 0.23 W/cm^2 (45, 87, 104). The same might hold true for human studies, where higher frequencies, >0.500 MHz, lead to inhibition (51, 100, 105), and lower frequencies, <0.350 MHz (52, 93, 106), or unfocused stimulation (53) induce excitation. The present study used a center frequency of 2.32 MHz, further suggesting that frequency may not be an important parameter in comparing excitatory and inhibitory effects, and that the volume of tissue affected may be the critical parameter. Furthermore, given our use of an unfocused transducer operating a relatively high fundamental frequency, acoustic energy reaching the brain may have been distributed across an even larger area due to diffuse refection occurring within the diploë layer of the skull (31, 107).

A limitation of this study was the use of a single blind experimental design. While the results of any single blind study must be interpreted with caution, no significant differences in outcome measures have been observed in prior studies from our laboratory comparing single- vs. double-blind NIBS on objective outcome measures (108). Two other points also help to mitigate the potential impact of the use of a single-blind design here. First, studies have shown that objective measures, such as the MEPs collected here, are less sensitive to expectancy effects compared with more subjective measures (109, 110). Second, and most importantly, a chi-square test was conducted and no significant relationship was found between assigned condition and condition guessed by the subject at the conclusion of the experiment, $\chi^2\,(1, N = 40) = 1.50, p = 0.22$. In addition, a greater percentage of sham subjects, 71.4%, reported that they believed they were in the verum condition, compared to 52.6% of actual verum subjects.

Another limitation was the relatively high number of participants excluded from the study. This was due in part to the power output of our TMS system, where we found that the average RMT was 68.7% of TMS power output. Thus, for excluded participants, our baseline TMS power of 110% RMT exceeded the total possible power output of the TMS machine, and so could not be performed for those participants. It should also be noted that the average age in our sample was 21.35. Replication with older subjects is thus needed, as age has been previously shown to impact NIBS mediated plasticity (111). Such replication is essential for possible clinical application. Other forms of NIBS have been explored as possible therapies for movement disorders (112–115), and given the observed tUS-induced changes in the primary motor cortex, this might be a productive avenue for future tUS research.

CONCLUSION

Our results demonstrate that tUS produced by a diagnostic imaging ultrasound system increased short-term cortical excitability in the motor cortex. This suggests that diagnostic tUS systems may be used as a neuromodulatory tool to alter the activity of the primary motor cortex. Following similar evidence demonstrating the effect of tDCS on excitability of the primary motor cortex as measured by TMS-evoked MEPs (57, 58), future research should determine how the observed tUS effects translate to other cortical areas and other measures of neuromodulation. By contrast to tES and TMS, tUS offers the advantage of greater anatomical precision and also greater depth without significant effects in more superficial regions, which together may allow for greater precision and rigor in this research, and ultimately may offer improved methods of treatment. Our finding of excitatory effects from tUS contrasts with a recent report of inhibitory effects (100), suggesting the potential for a wide dynamic range in cortical excitability using tUS. Ultrasound imaging has been used for many years and has an excellent safety record. The present results warrant further research into the use of diagnostic imaging ultrasound to modulate cortical excitability and neuroplasticity beyond the motor cortex, as well as the development of new clinical applications for this technology. If further study and development confirm that diagnostic imaging ultrasound is effective for producing neuromodulation, and given that diagnostic imaging ultrasound devices are found in many clinical settings worldwide alongside technicians trained in their use, this could potentially make neuromodulatory tUS highly accessible to clinical and research communities.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Chesapeake IRB and the U.S. Army Research Laboratory's Human Research Protection Program, with written informed consent from all subjects in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

Conceptualization JS and VC; methodology BB, BG, JS, and VC; software JS and BG; formal analysis BG and JS; investigation BG, JS, and EK; resources AY, JH, and VC; writing—original draft preparation, BG and JS; writing—review and editing, all authors; supervision, JS and VC; project administration, VC; funding acquisition, VC.

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Improvement of Deep Brain Stimulation in Dyskinesia in Parkinson's Disease: A Meta-Analysis

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Background: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus internus (GPi) have been proven to be equally effective in improving motor-symptoms for advanced Parkinson's disease (PD) patients. However, it is unclear that which target stimulation is more effective in reducing dyskinesia. We conducted the meta-analysis to evaluate the efficacy of STN and GPi-DBS in the dyskinesia.

Methods: A systematic search was performed in PubMed, Embase, and the Cochrane Library databases. Controlled trials about the dyskinesia comparing the efficacy of GPi and STN DBS were included. Clinical data of dyskinesia and levodopa equivalent doses (LED) were collected for the meta-analysis.

Results: Eight eligible trials containing a total of 822 patients were included in this meta-analysis. Our results showed that GPi DBS offered a greater reduction of dyskinesia than STN DBS at 12 months after surgery, with an overall pooled SMD of 0.32 (95% CI = 0.06 to 0.59, $P = 0.02$). Treatment of STN DBS was associated with a greater reduction of LED compared with GPi DBS, with a change score of −320.55 (95% CI = −401.36 to −239.73, $P < 0.00001$).

Conclusion: GPi DBS is superior to reduce dyskinesia than STN DBS at 12 months after surgery for advanced PD patients. Further studies should focus on the different mechanism for dyskinesia reduction by GPi or STN DBS.

Keywords: Parkinson's disease, deep brain stimulation, subthalamic nucleus, globus pallidus interna, dyskinesia

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INTRODUCTION

Parkinson's disease (PD) is a chronic and neurodegenerative disorder which affects 1% of the population over 60 years old (1). Dopamine replacement therapy remained the most effective symptomatic treatment of PD since Levodopa was first introduced for the treatment with PD in the 1960s. However, dopaminergic therapies are eventually associated with motor fluctuations and levodopa-induced dyskinesia. In a community-based study, the mean times of onset of dyskinesia were 6.6 years (2). Other studies have reported that 50% of PD patients experienced dyskinesia after 5 years from introduction of L-dopa (3), and this percentage up to 95% after 15 years of therapy (4). The clinical manifestations of the dyskinesia

included head, hand, foot, body, and trunk of involuntary movement. General types of dyskinesia could be divided into peak-dosed dyskinesia (PDSK), diphasic dyskinesia (DDSK), and off-period dystonia according to the course of the disease, clinical manifestation, and the relationship with medicine. As the curative effect decreased gradually, off-period dystonia appeared in the early morning or night, resulting in leg and foot cramp (5). Different types of dyskinesia were observed in PD patients. PDSK, off-period dystonia and DDSK were accounted for about 80, 30, and 20%, respectively. Furthermore, different types of dyskinesia could appear or appear alternately in the same patient at the same time (6). Previous studies have shown that incidence of dyskinesia was positively correlated with following factors, including youth, women, long course of levodopa treatment, high dose levodopa treatment and low weight (7). Moreover, some studies demonstrated that PD patients with stiffness had a higher incidence of dyskinesia than tremor (8).

Dyskinesia is unfavorable for quality of life, sometimes being more disabling than PD itself (9, 10). Lower doses and more frequent administration of levodopa may reduce dyskinesia in some patients. However, parkinsonian symptoms and motor fluctuations became worse with the reduction of L-dopa in many cases (11). So patients were encountered with the difficult choice between accepting more serious dyskinesia with better control of PD and less dyskinesia but accompanied by a worsening of PD symptoms. Consequently, it is critical to focus on more effective strategies in order to reduce dyskinesia in the on-state.

Deep brain stimulation (DBS), officially approved by the FDA in 2002, has been proven to improve motor symptoms and dyskinesia. STN and GPi are the two most commonly selected targets. Increasing evidence from randomized clinical trials indicated that the STN DBS and GPi DBS are equally effective in improving motor symptoms and suggests the same in improving dyskinesia (12–15). However, there has been discrepancy as to dyskinesia reduction between two targets. Several randomized controlled trials (RCTs) demonstrated that dyskinesia reduction from GPi DBS was superior to STN DBS (16), whereas other studies indicated there was no significant difference between two targets (17, 18). Up to now, it still remains inconclusive about which target stimulation is more effective in reducing dyskinesia. In the present study, we performed this meta-analysis to evaluate the efficacy of STN and GPi-DBS in the dyskinesia.

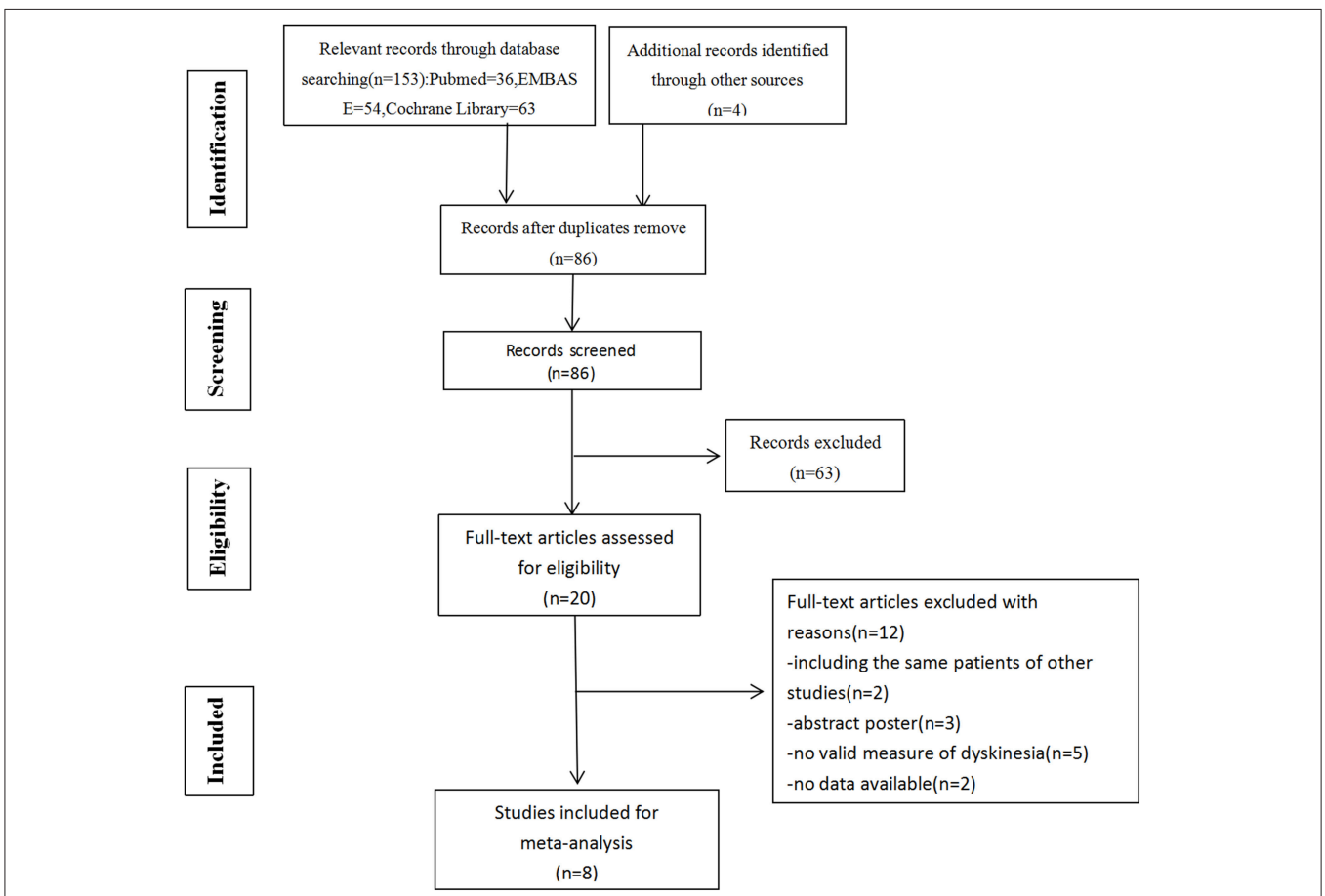

FIGURE 1 | Flow diagram of selection of studies. Among 157 articles screened, 5 randomized controlled studies and 3 non-randomized controlled trials were included in our meta-analysis.

METHODS

Search Strategy and Selection Criteria

A systematic search for articles written in English was performed in PubMed, Cochrane library, and Embase databases according to PRISMA guidelines (19). Databases were searched from inception to January 2018. Medical Subject Headings (MeSH) terms and corresponding keywords were exploded in the electronic search process. The search terms were (MeSH exp Parkinson Disease, and keywords Idiopathic Parkinson's disease, Primary Parkinsonism), (MeSH exp Deep Brain Stimulation and keywords Electrical Stimulation of the Brain and Deep Brain Stimulations), and (MeSH exp Dyskinesias and keywords Dyskinesia). We also examined reference lists of all eligible studies and reviews in the field for further possible titles. The process was repeated until no new titles were found.

The initial search was conducted by two reviewers independently (YL and FL). Retrieved literatures were imported into endnote, with duplication discarded. Unrelated literatures were excluded after scanning of titles and abstracts carefully. Full-text articles of the remaining literatures were acquired to identify eligibility. Any discrepancy was resolved by discussion or decided by a third reviewer (HL). The PRISMA statement flow diagram displayed the process of literature search and selection, as shown in **Figure 1**. Published studies were included by meeting the following criteria: (1) population: patients with PD were responsive to levodopa; (2) intervention: GPi DBS or STN DBS (either bilateral or unilateral); (3) comparison: STN DBS or GPi DBS (either bilateral or unilateral); (4) reporting clinical data of dyskinesia before and after surgery. Literatures were excluded for the following reasons: (1) maximum follow-up time <6 months; (2) data from conference abstracts or literatures that could not be extracted.

Data Extraction

Key characteristics of studies were extracted independently by two authors (QH and LC), ready for comparative analysis. All data were tabulated onto a predefined spreadsheet. For each included study, the following were extracted: authors, title, journal, year of publication, participant characteristics, dyskinesia scores, LED scores, and assessment time points in relation to DBS.

Data Analysis

Data analysis was performed by the RevMan 5.3 (The Cochrane Collaboration, London, UK). All the outcomes were displayed in consistent data. Standardized mean differences (SMD) with 95% confidence intervals (CI) were calculated for dyskinesia, since the analyzed domains involved multiple testing instruments. Mean differences (MD) with 95% CI were reported for the LED. The heterogeneity across studies was calculated using I-square and chi-square. Once the heterogeneity was small ($I^2 < 50\%$), the fixed-effects model was used; otherwise, the random effects model was used. $P < 0.05$ was considered statistically significant.

Quality Assessment

The methodological quality of the selected studies was assessed using Cochrane collaboration's tool. The risk of bias tool included six domains: selection, performance, detection, attrition, reporting and other bias (20). Methodological Index for Non-randomized Studies (MINORS) was used for assessing the quality of non-randomized controlled studies. MINORS

TABLE 1 | Characteristics of included controlled trials.

Study	Targets	Surgical modus	Subject size, *n*	Age (years)	Disease duration (years)	Outcome measure	Assessment time points
Anderson et al. (22)	STN	Bilateral	12	61.0 ± 9.0	15.6 ± 5.0	Dyskinesia severity rating	Baseline, 12 months
	GPi		11	54.0 ± 12.0	10.3 ± 2.0		
Burchiel et al. (18)	STN	Bilateral	6	62.8 ± 12.0	13.6 ± 5.0	Dyskinesia severity rating	Baseline, 12 months
	GPi		4	46.5 ± 11.0	10.6 ± 2.0		
Rodriguez-Oroz et al. (23)	STN	Bilateral	49	59.8 ± 9.8	14.1 ± 5.9	A dyskinesia scale	Baseline, 12 months 3-4y
	GPi		20	55.8 ± 9.4	14.4 ± 5.7	LED	
Odekerken et al. (16)	STN	Bilateral	63	60.9 ± 7.6	12.0 ± 5.3	CDRS	Baseline, 12 months
	GPi		65	59.1 ± 7.8	10.8 ± 4.2	LED	
Nutt et al. (24)	STN	Bilateral	6	56.5 ± 15.1	9.5 ± 2.2	Dyskinesia severity rating	Baseline, 12 months
	GPi		6	56.8 ± 11.5	19.5 ± 3.9		
Follett et al. (17)	STN	Bilateral	147	61.9 ± 8.7	11.1 ± 5.0	Motor function with Dyskinesia LED	Baseline, 24months
	GPi		152	61.8 ± 8.7	11.5 ± 5.4		
Weaver et al. (25)	STN	Bilateral	70	60.7 ± 8.9	11.3 ± 4.7	Motor function with Dyskinesia LED	Baseline, 6 months 24 month, 36 months
	GPi		89	60.4 ± 8.3	11.4 ± 4.9		
Obeso et al. (26)	STN	Bilateral	96	59.0 ± 9.6	44.6 ± 8.9	Motor function with Dyskinesia LED	Baseline, 6 months
	GPi		38	55.7 ± 9.8	41.2 ± 9.5		

CDRS, clinical dyskinesia rating scale; DBS, deep brain stimulation; GPi, globus pallidus interna; LED, levodopa equivalent doses; STN, subthalamic nucleus; UPDRS IV, unified Parkinson's disease rating scale IV.

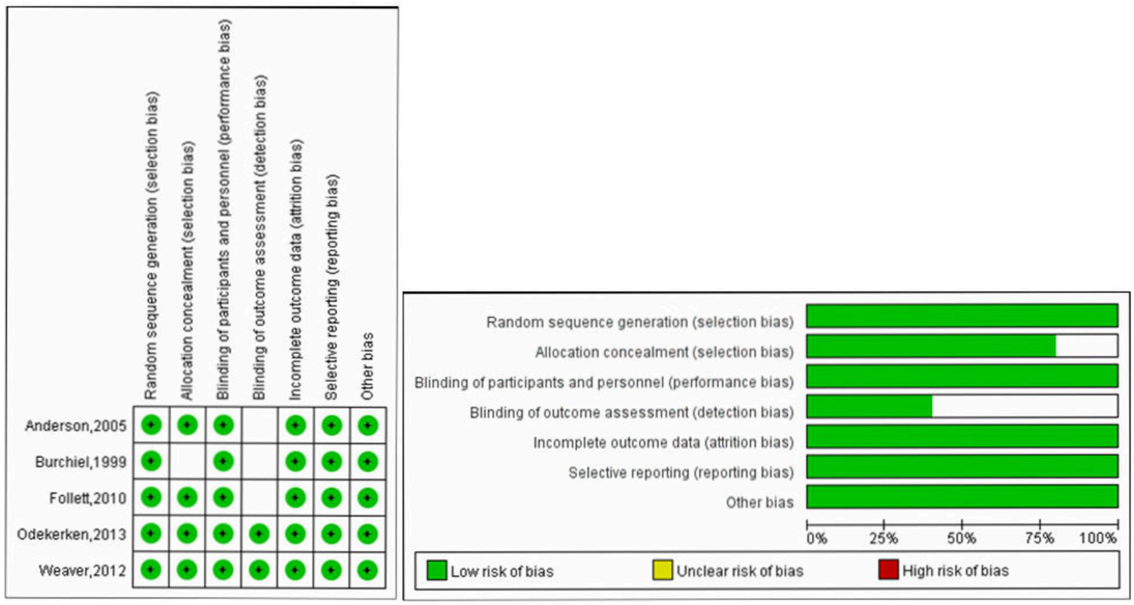

FIGURE 2 | Quality assessment of RCTs using Cochrane collaboration's tool for assessing risk of bias.

involved 12 items for comparative studies, subsequently each item was scored from 0 to 2; 0 indicating that it was not reported in the article, 1 indicating that it was reported but inadequately, and 2 indicating that it was reported adequately (21).

RESULTS

Study Characteristics

Initially, we identified 157 articles, 86 of which remained after removal of duplicates. A total of 20 full-text articles were assessed for eligibility, 5 randomized controlled studies and 3 non-randomized controlled trials were included in our meta-analysis at the end. Totally, 822 patients were included, among which 453 had been implanted with STN DBS, 369 with GPi DBS. The characteristics of the studies were presented in **Table 1**.

Study Quality

Study quality of RCTs was evaluated by Cochrane collaboration's tool, Two RCTs were classified as high quality (16, 25), and the other three RCTs were classified as moderate quality (17, 18, 22). Quality assessment results were presented in **Figure 2**. For the other three cohort studies evaluated by Methodological Index for Non-randomized Studies (MINORS), two studies (24, 26) scored 16 points and one study (23) scored 18 points, which could be regarded as at moderate-quality (**Table 2**). Thus, all included studies were deemed to be of the moderate or high quality. Most RCTs lost points because of the lack of blinding and allocation concealment. While most cohort studies lost points because of a statement of the outcome of interest at the beginning and non-blind outcome assessment.

TABLE 2 | Risk of bias results assessed with methodological index for non-randomized studies (MINORS).

Study	A	B	C	D	E	F	G	H	I	J	K	L	Total score
Rodriguez-Oroz et al. (23)	2	2	2	2	0	2	2	0	2	2	0	2	18
Nutt et al. (24)	2	0	2	2	0	2	2	0	2	2	0	2	16
Obeso et al. (26)	2	0	2	2	0	2	2	0	2	2	0	2	16

A, a stated aim of the study; B, inclusion of consecutive patients; C, prospective collection of data; D, endpoint appropriate to the study aim; E, unbiased evaluation of endpoints; F, follow-up period appropriate to the major endpoint; G, loss to follow-up not exceeding 5%; H, prospective calculation of the study size; I, an adequate control group; J, contemporary groups; K, baseline equivalence of groups; L, adequate statistical analyses.

Profile Comparison

Meta-analysis results of pretreatment profiles were shown in **Table 3**. Significant heterogeneity was detected in duration of disease ($I^2 = 87\%$) and dyskinesia ($I^2 = 46\%$). The heterogeneity was greatly reduced ($I^2 = 0\%$) when two studies (24, 26) were excluded. A significant difference in pretreatment age was observed in STN DBS group compared with GPI DBS group, with an overall pooled MD of 1.34 (95% CI = [0.12, 2.56]), indicating that the patients with STN DBS were generally older than the patients with GPi DBS. There were no significant differences and heterogeneity in the other comparisons of pretreatment profiles. Forest plots of each comparison were presented in **Supplementary Data (S1–S6)**.

Changes in Dyskinesia Scores

Based on the results of meta-analysis, GPi DBS did not yield any significant improvement in the dyskinesia score over STN DBS, with a change score of 0.13 (95% CI = −0.01 to 0.27, *P*

= 0.006; **Figure 3**). No significant differences in heterogeneity was observed between treatment groups ($X^2 = 4.33$, df = 7, $p = 0.74$, $I^2 = 0\%$). We conducted subgroup analyses according to follow-up periods. A greater reduction of dyskinesia was observed in GPi DBS group compared with STN DBS group at 12 months after surgery, with an overall pooled SMD of 0.32 (95% CI = 0.06 to 0.59, $P = 0.02$; **Figure 4**), with evidence of no heterogeneity ($X^2 = 1.62$, df = 4, $p = 0.81$, $I^2 = 0\%$). However, no significant differences and heterogeneity were observed in the other follow-up periods.

Changes in LED Scores

Treatment of STN DBS was associated with a greater reduction of LED compared with GPi DBS, with a change score of −320.55 (95% CI = −401.36 to −239.73, $P < 0.00001$; **Figure 5**). Based on the Chi-square and I-square analyses, there was small difference in heterogeneity between treatment groups ($X^2 = 4.47$, df = 4, $p = 0.35$, $I^2 = 10\%$). The heterogeneity was greatly reduced ($I^2 = 0\%$) when two studies (17, 24) were exclude [**Figure 6**, for example, the study by Follett et al. (17) was excluded]. However, even after excluding one or the other of those studies, LED were still reduced to a greater extent after STN DBS than GPi DBS.

TABLE 3 | Meta-analysis results of Profile comparison for STN DBS vs. GPi DBS.

Item	I^2 statistic	Mean and 95%CI (fixed-effect model)	Mean and 95% CI (randomized-effect model)
Age	31%	1.34 [0.12, 2.56]	1.78 [0.09, 3.47]
Duration of disease (month)	87%	−0.16 [−0.57, 0.89]	−0.06 [−2.30, 2.17]
LED (mg/day)	39%	−17.34 [−97.39, 62.71]	−2.56 [−109.97, 104.84]
UPDRS off-med	0%	1.58 [−0.34, 3.49]	1.58 [−0.34, 3.49]
UPDRS on-med	0%	0.40 [−1.11, 1.90]	0.40 [−1.11, 1.90]
dyskinesia	46%	−0.10 [−0.24, 0.04]	−0.11 [−0.33, 0.11]

CI, confidence interval; GPi, globus pallidus interna; LED, Levodopa equivalent doses; STN, subthalamic; UPDRS, unified Parkinson's disease rating score.

Publication Bias

Publication bias was estimated by funnel plots. No obvious asymmetry was identified in funnel plots, indicating that there was no publication bias (**Supplementary Data S7**).

DISCUSSION

The current meta-analysis provides a review of the efficacy of STN and GPi DBS in the dyskinesia in the treatment of advanced PD. Eight controlled clinical trials were included in this meta-analysis. Changes in dyskinesia scores and LED scores from baseline values after DBS were used to assess improvements in dyskinesia and medication use in patients with PD. Our findings revealed that there was a greater reduction of dyskinesia scores from GPi DBS compared with STN DBS at 12 months follow-up. There were two randomized clinical trials that revealed that GPi stimulation was superior in dyskinesia reduction to STN stimulation at 12 months after surgery (16, 22). However, there was no statistically significant difference between GPi DBS and STN DBS in the other follow-up periods, which was consistent with the VA Cooperative Study (25). Furthermore, STN DBS allowed for medication dosages to be reduced to lower levels than GPi DBS. Therefore, our results indicated that GPi DBS offered a greater reduction of dyskinesia than STN DBS at 12 months after surgery.

DBS has been established as an important therapeutic strategy to relieve motor symptoms in advanced PD patients when motor symptoms are no longer managed adequately with levodopa treatment (27). STN and GPi are the two most commonly selected targets. Moreover, mounting evidence has confirmed similar effect of the two targets stimulation on improvement of motor function and dyskinesia observed in several meta-analyses of RCTs involved in DBS therapy (28–30). Nevertheless, the mechanisms of dyskinesia reduction in STN and GPi DBS are fundamentally different. GPi stimulation improved dyskinesia through direct stimulation effects on dopaminergic pathways to inhibit abnormal electrical activity of GPi (22, 31, 32), while STN stimulation reduced dyskinesia by lowering greater dopaminergic medication to minimize dyskinesia (16, 33). Further investigations are needed to focus on the exact

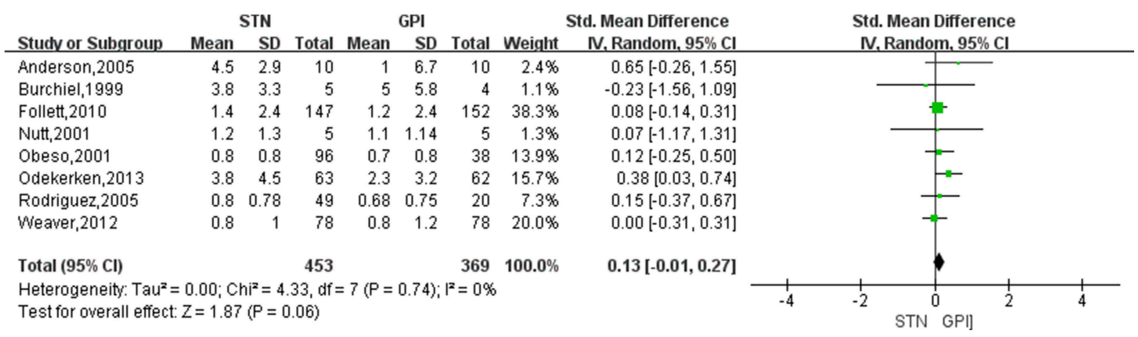

FIGURE 3 | Forest plot of mean difference of dyskinesia score in the on-medication/on-stimulation state between STN DBS and GPi DBS. GPi, globus pallidus interna; STN, subthalamic nucleus; IV, inverse variance; CI, confidence interval; Std, standardized.

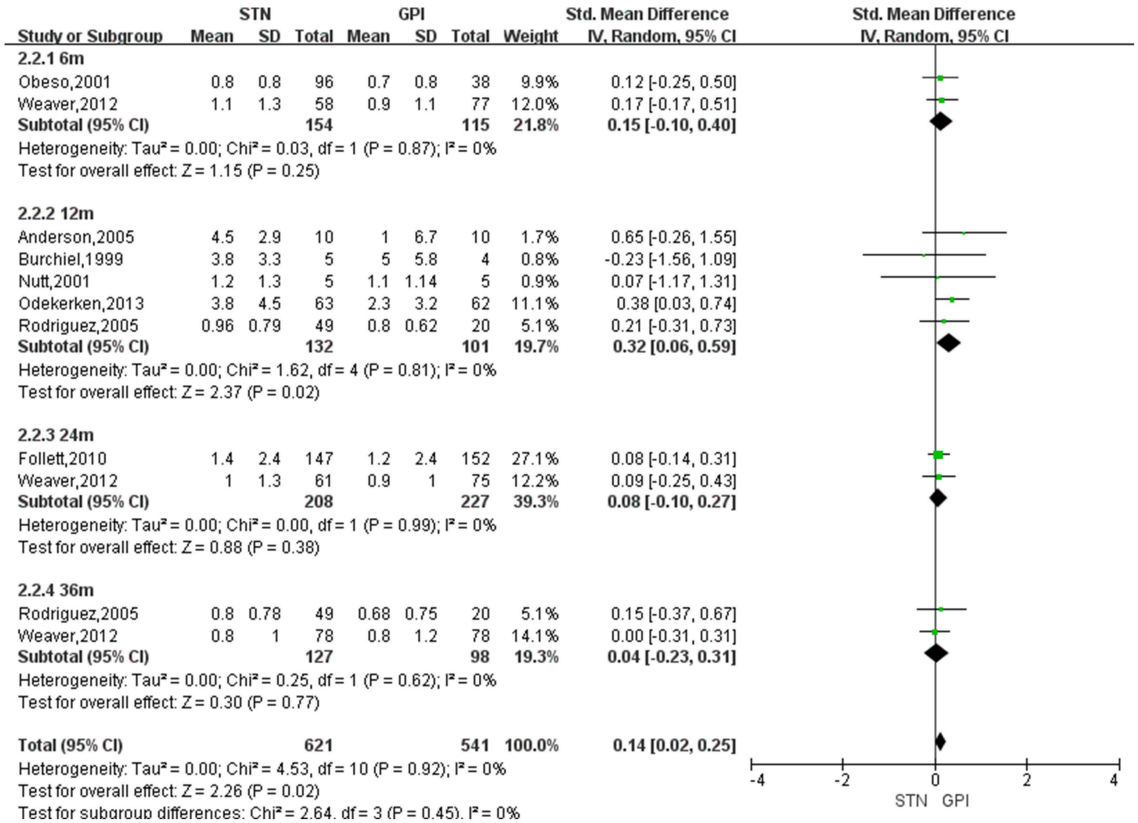

FIGURE 4 | Forest plot: subgroup analyses were conducted according to follow-up periods in dyskinesia score between STN DBS and GPi DBS. GPi, globus pallidus interna; STN, subthalamic nucleus; IV, inverse variance; CI, confidence interval; Std, standardized.

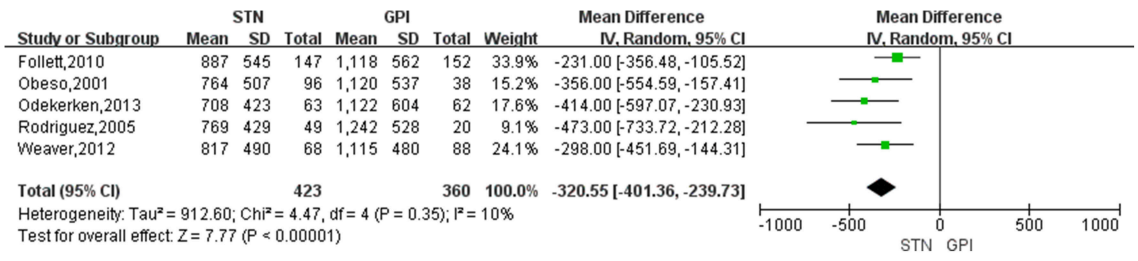

FIGURE 5 | Forest plot of standardized mean difference of levodopa equivalent doses between STN DBS and GPi DBS. GPi, globus pallidus interna; STN, subthalamic nucleus; IV, inverse variance; CI, confidence interval.

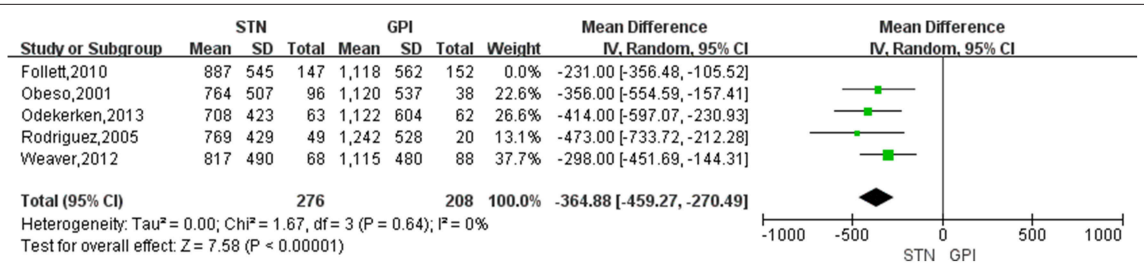

FIGURE 6 | Forest plot: sensitivity analysis. GPi, globus pallidus interna; STN, subthalamic nucleus; IV, inverse variance; CI, confidence interval.

mechanisms of dyskinesia changes after stimulation of the two targets.

Targets election for DBS should be assessed based on the patient's specific characteristics and goals. Deep brain stimulation of the STN is advantageous if the main goal is dopaminergic medication reduction. However, medication reduction may aggravate depression and apathy, even increase suicidal ideation (34). GPi stimulation rather than STN stimulation can be considered in patients with cognitive decline or mood changes (25). In patients with prominent gait disorder, axial symptoms, or falls, GPi DBS may be preferable (35). Successful GPi DBS was also applied in cases of persistent or severe dyskinesia, especially if they were unable to sufficiently reduce dopaminergic treatment (36).

The changes in LED observed in our analysis were consistent with the results of the meta-analysis (29) and the outcome of other recent studies, which indicated that medication was markedly reduced after STN DBS compared with GPi DBS. Although medication reduction is not the primary goal of surgery, dopaminergic requirements are reduced, with the additional advantageous of decreased fluctuations in "on" and "off" state, drug-induced dyskinesia, and other complications of medications (28–30). However, the reduction in medication should be managed cautiously, neurosurgeons have to avoid aggressive medication reduction after STN DBS, since apathy, depressive symptoms, and increased suicidal ideation may occur once levodopa was rapidly withdrawn (34). Previous study demonstrated that the loss of prior positive effects of STN stimulation in the medication "on" phase especially for gait and balance was related to a reduction in dopaminergic medication, not observed in GPi-DBS patients which retained stable scores (37). This contributed to various thoughts such as the desirability of medication reduction in the absence of side effects, the relationship between medications and stimulation.

Some limitations should be considered in our study. First, three studies lacked LED data (18, 22, 24). The involved studies were conducted with various implantation techniques, stimulators, stimulation parameters, and postoperative management. Therefore, potential risks of significant heterogeneity were undefined. Both randomized and non-randomized studies were included in the same analysis, which might result in potential bias. However, even after excluding the non-randomized studies, the outcomes were still stable (**Supplementary Data S8**). Second, the analyzed domains about dyskinesia involved multiple testing instruments, and the measurements in those studies of our meta-analysis were performed in different times after surgery, which might cause bias. Finally, we only included studies published in English, which might result in potential bias.

CONCLUSION

GPi DBS is superior to reduce dyskinesia than STN DBS at 12 months after surgery for advanced PD patients, and the mechanisms of dyskinesia reduction in STN and GPi DBS are fundamentally different. STN DBS allowed for significant dopaminergic medication reduction. Further studies should focus on the different mechanism for dyskinesia reduction by GPi or STN DBS.

AUTHOR CONTRIBUTIONS

YL and ZX: conception and design, drafting the article. QH and LC: acquisition of data. YL, FL, and HL: analysis and interpretation of data. ZX: approved the final version of the manuscript on behalf of all authors. ZX, WZ, YC, LC, and YL: study supervision. All authors critically revising the article, reviewed submitted version of 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.2019.00151/full#supplementary-material

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Dual-Site Transcranial Magnetic Stimulation for the Treatment of Parkinson's Disease

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Abnormal oscillatory activity in the subthalamic nucleus (STN) may be relevant for motor symptoms in Parkinson's disease (PD). Apart from deep brain stimulation, transcranial magnetic stimulation (TMS) may be suitable for altering these oscillations. We speculated that TMS to different cortical areas (primary motor cortex, M1, and dorsal premotor cortex, PMd) may activate neuronal subpopulations within the STN via corticofugal neurons projecting directly to the nucleus. We hypothesized that PD symptoms can be ameliorated by a lasting decoupling of STN neurons by associative dual-site repetitive TMS (rTMS). Associative dual-site rTMS (1 Hz) directed to PMd and M1 ("ADS-rTMS") was employed in 20 PD patients treated in a blinded, placebo-controlled cross-over design. Results: No adverse events were noted. We found no significant improvement in clinical outcome parameters (videography of MDS-UPDRS-III, finger tapping, spectral tremor power). Variation of the premotor stimulation site did not induce beneficial effects either. A single session of ADS-rTMS was tolerated well, but did not produce a clinically meaningful benefit on Parkinsonian motor symptoms. Successful treatment using TMS targeting subcortical nuclei may require an intervention over several days or more detailed physiological information about the individual brain state and stimulation-induced subcortical effects.

Keywords: Parkinson's disease, TMS, dual-site, hyperdirect tract, coordinated reset, paired associative stimulation

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INTRODUCTION

Bradykinesia and tremor impair quality of life in patients suffering from Parkinson's disease (PD), (1). Dopamine replacement therapy is limited by dyskinesia and its symptomatic benefit may be insufficient. Although some motor symptoms can successfully be ameliorated by deep brain stimulation (DBS) of the subthalamic nucleus (2), many patients are reluctant to undergo invasive procedures or are not eligible. In those patients, add-on therapies based on noninvasive brain stimulation techniques may be a promising alternative.

A key element in Parkinsonian pathophysiology is an alteration of information processing within cortico-basal ganglia networks. In particular, the off-motor state has been linked to abnormal beta-oscillatory neuronal activity in a network comprising basal ganglia and motor cortical regions, with the strength of these oscillations being correlated to motor impairment (3–7) and dopamine replacement therapy (8–12). Abnormal beta oscillations within the STN circuitry likely depend on neuronal coupling and synchronized activity. Tass (13) and Popovych and Tass (14) have hypothesized that

pathogenic STN oscillatory activity may be dampened using a stimulation protocol tailored to the oscillatory properties which they termed "co-ordinated reset" (CR). In their model, STN neurons may be desynchronized using specific stimulation patterns. Evidence in favor of this approach has been provided in Parkinsonian monkeys (15). An important feature of CR-based DBS is the notion that effects substantially outlasted the duration of the stimulation. This raises the possibility that long-term depression (LTD) has been induced by a Hebbian mechanism in synapses interconnecting STN neurons. In a pilot study the possible efficacy of the method has also been demonstrated in humans (16).

In a systematic review of therapeutic approaches that were based on non-invasive transcranial magnetic brain stimulation (TMS) Chou et al. (17) concluded that TMS was effective in ameliorating bradykinesia when either the primary motor cortex (M1) was stimulated at high ($\geq$5 Hz) frequencies, or more frontal motor regions outside M1 were stimulated at low frequencies ($\leq$1 Hz). Although these therapeutic effects might be mediated by induction of changes in cortical excitability another possibility may be a modulatory effect on subcortical structures connected to the cortex via a direct cortico-basal ganglia projection, known as the "hyperdirect tract" (18). This tract has also been discussed as the decisive structure activated by STN-DBS (19–21) and may constitute an interesting target for TMS. Furthermore, evidence exists for a direct short-latency effect of TMS on STN neurons (22, 23) which may have been propagated by the hyperdirect tract. Targeting this tract with TMS may open up a pathophysiologically founded therapeutic stimulation approach targeting pathological oscillatory activity in the STN using TMS. Importantly, as TMS can be timed very precisely it may be able to induce spike-timing dependent plasticity effects in neuronal synaptic connections. Indeed, paired-associative stimulation (PAS) protocols (24, 25) which involve time and location specific activation of neuronal inputs by TMS have been shown to induce LTD-like effects outlasting the intervention for tens of minutes. Plasticity resembling spike-timing dependent plasticity can be induced in cortical neurons by directing timed TMS pulses to two cortical regions (26–28) and subcortically, at the level of the spinal cord, by pairing TMS to M1 with appropriately timed peripheral stimulation (29).

Considering these facts, we aimed to develop a new TMS treatment protocol. We based our protocol on the assumption that different groups of STN neurons may be targeted by TMS mediated by the parts of the hyperdirect tract that originate from premotor and primary motor cortex. As STN neurons oscillate together in the Parkinsonian state, decoupling of these different populations could perhaps be achieved by targeting them with TMS applied in such a way that pulses act on these populations at different times during their oscillatory cycles. We hypothesized that a TMS protocol targeting both primary and premotor areas in a coordinated fashion may achieve this and thus be capable of attenuating pathogenic oscillatory activity in STN neurons which may outlast the stimulation due to LTD-like plasticity effects as shown in CR and PAS protocols.

MATERIALS AND METHODS

All procedures were approved by the local Ethics Committee (University of Leipzig, file-no.: 351-13-26082013) and written informed consent was obtained from each participant.

Patients and TMS Protocol

PD patients were recruited through the outpatient clinic of the Department of Neurology, University Hospital of Leipzig. Inclusion criteria were: age of 18–75 years, Hoehn and Yahr stage 1–3 and a baseline MDS-UPDRS-III of $\geq$8 points. Exclusion criteria were relevant cognitive impairment (Mini-Mental State Examination <24), manifest depression (Beck Depression Inventory $\geq$18), atypical Parkinsonian disorder, other severe illness interfering with safe participation, participations in other studies at the moment of inclusion and known contraindications to TMS (epilepsy, medication with antidepressants, neuroleptics, benzodiazepines, antibiotics, and implanted electrical/metal devices near the head).

Patients received two interventions—VERUM (supposedly effective) and SHAM (control)—in a cross-over design following overnight withdrawal of their PD medication. They were randomized to receive either VERUM or SHAM as the first intervention, then they received the complementary procedure at least 1 week later (**Figure 1A**). Subjects were blinded to the condition and told that "one of two different interventions" would be used. At the day of the intervention, subjects were assessed before (BASELINE), immediately after (POST0H) and 1 h after (POST1H) the intervention (30), comparable to a standardized Levodopa test. Administered tests are detailed below.

We devised an associative dual-site repetitive TMS ("ADS-rTMS") protocol inspired by CR stimulation (15, 16) and paired associative stimulation (24, 26, 27, 31) protocols. Our TMS protocol included stimulation of a premotor and the primary motor area (M1) (32) to activate distinct regions within STN. We used two coils targeting the hemisphere corresponding to the clinically more impaired body side of the patient (right body side in 12 cases, left side in 8 cases). As a premotor area we primarily targeted the dorsal premotor cortex which we identified physiologically in a localizer experiment (see **Supplementary Material**). Additionally, we conducted experiments with different premotor sites (see **Supplementary Material**). One thousand pairs of stimuli were applied in 40 blocks of 25 stimuli each with 5 s pause between each block. Stimuli (double TMS pulses) were delivered at a stimulation frequency of 1 Hz. This frequency ensured rapid completion of the intervention and rendered it unlikely that beneficial stimulation effects were induced by each stimulation site alone (17). Assuming an oscillatory frequency of 20 Hz (8, 33) within the targeted STN, the interstimulus interval (ISI) between premotor and motor TMS pulses was set to 25 ms, with motor cortex stimulation leading premotor stimulation (**Figure 1B**). This ISI corresponds to a half wave of an oscillation of 20 Hz and, therefore, is supposed to optimally disturb coupled oscillators at this frequency (13). As both stimulation targets are located very close to each other on the scalp, it was not

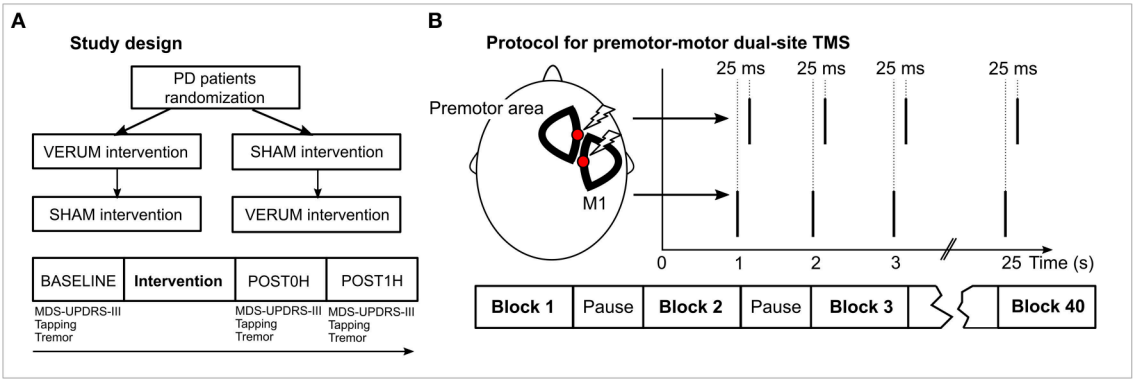

FIGURE 1 | Study design and experimental procedures. **(A)** The general study design is depicted in the panel. PD patients were randomized to receive VERUM or SHAM intervention. A week later each subject received the complementary procedure. At each day of an intervention, motor performance was assessed using MDS-UPDRS-III videography, tapping and tremor analysis prior to the intervention (BASELINE), immediately after the intervention (POST0H) and 1 h later (POST1H). **(B)** During the intervention two stimulation sites (a premotor area and M1) of the hemisphere contralateral to the clinically more affected body side of the patient were stimulated. M1 stimulation was delivered 25 ms before premotor stimulation. Forty blocks of 25 double pulses were applied. Intensity during VERUM stimulation was 95% of the resting motor threshold of the abductor pollicis brevis muscle, 20% during SHAM stimulation.

possible to conduct the experiment using conventional figure-of-eight coils. Therefore, we used two custom built D-shaped coils ("Cool-D50 research coils," external diameter 80 × 59 mm, active cooling) together with two MagPro X100 TMS devices which allowed stimulation of the same cortex area (coils and device MagVenture, Willich, Germany). Despite the different coil geometry, the efficiency of D-shaped coils was comparable to conventional figure-eight coils as indicated by the fact that stimulator outputs for suprathreshold stimulation of M1 were only marginally higher compared to those customarily required with figure-eight shaped coils.

At the start of the TMS intervention we identified the hot spot for stimulation of the abductor pollicis brevis muscle (APB) employing low frequency (<0.2 Hz) stimulation at multiple sites supposedly overlying M1 while recording MEPs using surface EMG from the APB. We then used threshold hunting (34) to identify the APB resting motor threshold (APB-RMT). This was done for both coils. VERUM stimulation was applied at an intensity of 95% APB-RMT at each coil. For the SHAM stimulation everything was kept identical except we used only 20% APB-RMT. We chose a marginally subthreshold stimulation intensity to stay within safety limits. At 95% APB-RMT corticospinal volleys can be recorded epidurally in patients undergoing spinal surgery (35). This indicates that although this stimulus intensity is insufficient to generate action potentials in spinal motor neurons, it is sufficient to activate corticofugal projection neurons. Additionally, previous studies using TMS to treat PD have successfully used subthreshold intensities (17). We used the BrainSight 2 Neuronavigation (Brain Products, Gilching, Germany) system to control coil positioning. During the intervention subjects were comfortably seated in a reclining position with cushions for their arms and instructed to relax but stay alert and attentive to the tasks. We refrained from testing bradykinesia during the ongoing intervention because LTD-like effects need time to build up and because we aimed to avoid interference by voluntary activity with the intervention.

Tests and Endpoints

MDS-UPDRS-III, finger tapping performance and tremor activity were recorded for VERUM and SHAM interventions at BASELINE, POST0H, and POST1H as markers for PD motor symptom severity.

MDS-UPDRS-III

Global endpoint was improvement in the third part of the Unified Parkinson's Disease Rating Scale of the Movement Disorder Society (MDS-UPDRS-III). The MDS-UPDRS-III was videotaped and later rated by two experienced and certified MDS-UPDRS-III raters (C.F. and T.B.W.) in a randomized order, blinded for condition and time of the recording. As we could not effectively record rigidity on video we excluded this item. We determined the inter-rater agreement using Pearson's and intraclass correlations.

Other clinical, lateralized endpoints were (i) change in a hemibody akinesia score of the treated side (MDS-UPDRS-III items 4–8, range 0–20), (ii) change in a hand akinesia score of the treated side (sum of MDS-UPDRS-III items 4–6, range of 0–12), and (iii) total tremor score (sum of items 15–18) for the treated hand. We hypothesized that VERUM intervention would reduce MDS-UPDRS-III or lateralized MDS-UPDRS-III scores compared to SHAM and/or BASELINE.

Finger Tapping Analysis

Subjects performed a finger tapping task during BASELINE, POST0H, and POST1H with tapping performance as a lateralized endpoint. Finger tapping was done on a force transducer (Grass Instruments, West Warwick, USA) which was mounted on a wooden box (size 50 × 30 × 5 cm^3) with the level of the transducer slightly above the surface of the box. Subjects were instructed to "tap as quickly as possible" on the force transducer following a go-signal by the experimenter until they were told to stop (after 30 s). The task was performed twice with each hand, starting with the clinically better (untreated) side.

Data pre-processing is described in the **Supplementary Material**. In order to determine relevant parameters we employed a linear mixed effects model predicting the MDS-UPDRS-III akinesia hand score (sum of items 4–6) from the extracted parameters, which were modeled as fixed effects, while we included the subject specific average tapping force as a random effect. The latter was done to account for individual tapping forces which scale for each subject but are also expected to be different between the clinically worse and the clinically better hand. Significant fixed effect coefficients ($p < 0.05$) were considered relevant parameters for the prediction of the MDS-UPDRS-III hand akinesia score. We hypothesized that VERUM intervention would improve tapping on the treated side. We had to exclude one dataset due to technical issues with the recording devices.

Tremor Analysis

Tremor was recorded using triaxial wireless accelerometers (Noraxon, Scottsdale, USA) mounted to either the proximal phalanx of either thumb or index fingers (depending on which finger showed a larger tremor amplitude) of both hands. First, subjects were asked to sit with their hands resting in a semipronated position in their lap (resting tremor). Data was recorded for 30 s, then subjects were given a command to raise both arms and hold them extended in front of them for another 30 s (postural tremor).

Data pre-processing is described in the **Supplementary Material**. We compared the spectral power of the peak tremor frequency separately for resting and postural tremor analogous to the analysis employed for MDS-UPDRS-III. We hypothesized that tremor power was reduced in response to VERUM stimulation, which was regarded as another lateralized endpoint of the study. We had to exclude one dataset due to movement artifacts.

Statistical Analysis

We used custom written software in Matlab in combination with the Statistics Toolbox (MathWorks, Natick, USA) for offline data analysis and statistical testing. Presence of normal distributions for outcome parameters was assessed using one-sample Kolmogorov-Smirnov tests, which were non-significant for each parameter. Thus, parametric tests were used for evaluation of all outcome parameters. Primarily, repeated-measures analysis of variance (rmANOVA) in a 2 × 3 within subject design with factors CONDITION (VERUM vs. SHAM stimulation) and TIME (BASELINE vs. POST0H vs. POST1H) or—for baseline-normalized data—in a 2 × 2 within subject design with factors CONDITION (VERUM vs. SHAM stimulation) and TIME (POST0H vs. POST1H) were employed to evaluate effects of VERUM stimulation. We hypothesized that the VERUM but not the SHAM intervention would improve the clinical and technical outcome parameters (MDS-UPDRS-III, tapping performance, tremor power) resulting in a significant CONDITION × TIME interaction and/or a significant main effect for CONDITION. Bonferroni-corrected *post-hoc* *t*-tests were used to further analyze rmANOVA results. One-sample *t*-tests were used for normalized data to test against unity (with null-hypothesis that test distributions are centered at 1 after normalization). Statistical significance was defined at an alpha level of below 0.05. Average values are usually reported together with their standard deviation in the text while the standard error of the mean is displayed in the figures.

RESULTS

Twenty PD patients (age 58.5 ± 14.1 years; 15 male, 5 female, **Table 1**) were included in the experiment (right-handed 16 out of 20). All patients tolerated the procedure well and no adverse events were noted.

Effects on MDS-UPDRS-III

Inter-rater agreement was high with respect to MDS-UPDRS-III throughout the experiments (**Figure 2A**, Pearson's correlation of MDS-UPDRS-III scores: $r = 0.925$ $p < 0.001$; intraclass correlation ICC(3,k) = 0.952, 95%-CI 0.931–0.967).

With respect to TMS efficacy repeated measures ANOVA revealed neither a significant main effect of CONDITION [VERUM vs. SHAM, rmANOVA, $F_{(1,19)} = 0.652$, $p = 0.430$], nor an interaction CONDITION * TIME [$F_{(2,38)} = 0.872$, $p = 0.427$], nor a strong numeric trend in favor of or against the VERUM intervention (**Figure 2B**). After normalization of POST0H and POST1H MDS-UPDRS-III scores to BASELINE we also found no significant main effect for CONDITION [VERUM vs. SHAM, rmANOVA, $F_{(1,19)} = 1.432$, $p = 0.246$] nor a significant effect for the interaction CONDITION * TIME [$F_{(2,38)} = 0.071$, $p = 0.794$]. POST0H and POST1H average values did not differ significantly from unity after normalization to BASELINE neither in the VERUM nor in the SHAM condition (one-sample *t*-tests, $p \geq 0.212$, Bonferroni-corrected). Thus, VERUM stimulation had no influence on the global endpoint of the study.

Improvement in the MDS-UPDRS-III hemibody and hand akinesia scores of the treated side as well as MDS-UPDRS-III-tremor scores were assessed as lateralized endpoints. Again we found no significant effect of the intervention—hemibody akinesia score of treated side (**Figure 2B**): main effect of CONDITION [$F_{(1,19)} < 0.001$, $p = 0.999$], interaction CONDITION * TIME [$F_{(2,38)} = 2.610$, $p = 0.087$], hand akinesia score of treated side: main effect of CONDITION [$F_{(1,19)} = 0.092$, $p = 0.765$], interaction CONDITION * TIME [$F_{(2,38)} = 0.267$, $p = 0.767$], tremor score: main effect of CONDITION [$F_{(1,19)} = 3.401$, $p = 0.081$], interaction CONDITION * TIME [$F_{(2,38)} = 1.570$, $p = 0.221$].

In summary, there was no significant effect of the VERUM intervention on MDS-UPDRS-III and selected subscores.

Effects on Tapping Performance and Spectral Power of Tremor Movements

Tapping performance was assessed as another lateralized endpoint. A mixed model analysis was used to identify tapping parameters that optimally predicted the MDS-UPDRS-III akinesia score of the corresponding arm.

The MDS-UPDRS-III hand akinesia scores were well-predicted by the model ($r^2 = 0.755$, $r = 0.875$, $p < 0.001$; **Figure 2C**). Out of 8 parameters we determined (i) mean tapping

TABLE 1 | Patient characteristics.

Subject no.	Age (years, range)	Disease duration (years)	H&Y stage	Clinically worse side	L-Dopa ED (mg/d)	MMSE	BDI
1	70–80	2	2	Left	550	30	5
2	70–80	4	2	Right	0	30	2
3	50–60	7	2	Right	310	30	6
4	50–60	10	2	Right	560	29	2
5	40–50	11	2	Left	1,092	29	7
6	70–80	10	2	Left	550	30	3
7	60–70	9	2	Right	1,220	28	4
8	40–50	9	2	Right	730	28	10
9	50–60	5	3	Left	580	28	17
10	70–80	6	3	Right	600	29	7
11	40–50	3	2	Left	600	30	14
12	60–70	10	2	Right	845	28	0
13	60–70	5	2	Right	500	29	3
14	20–30	10	2	Right	275	30	12
15	70–80	17	3	Left	450	28	3
16	20–30	14	1	Right	300	30	13
17	60–70	19	2	Left	240	28	1
18	60–70	4	2	Right	610	29	7
19	60–70	9	2	Left	880	24	4
20	50–60	1	1	Right	254	30	3
M ± SD	58.5 ± 14.1	12.8 ± 20.9			557 ± 297	28.9 ± 1.4	6.2 ± 4.7

H&Y stage, Hoehn and Yahr stage; ED, equivalence dose; MMSE, Mini-Mental State Examination; BDI, Beck Depression Inventory. Units, disease duration and age in years; L-Dopa ED in mg/d. M, mean; SD, standard deviation.

force ($p = 0.021$), (ii) mean interval between taps ($p = 0.034$), (iii) standardized tapping force ($p = 0.007$), and (iv) standardized tapping interval ($p < 0.001$) as significant for MDS-UPDRS-III prediction. The effect of ADS-rTMS intervention on this set of informative parameters was then evaluated, for the treated hand only, using repeated measures ANOVA. For the mean tapping force, there was a trend for CONDITION [$F_{(1,18)} = 4.409$, $p = 0.050$], but no interaction CONDITION * TIME [$F_{(2,36)} = 0.536$, $p = 0.590$; **Figure 2C**]. The effect of CONDITION was driven by a slightly higher tapping force throughout the day of the VERUM intervention. For the remaining parameters, we found neither a significant main effect of CONDITION [$F_{(1,18)} \leq 2.182$, $p \geq 0.157$] nor an interaction CONDITION * TIME [$F_{(2,36)} \leq 0.817$, $p \geq 0.450$].

Resting and postural tremor power were also evaluated as lateralized endpoints (**Figure 2D**). For resting tremor there was a significant main effect for spectral power of the treated hand for CONDITION [$F_{(1,18)} = 7.541$, $p = 0.013$] and TIME [$F_{(2,36)} = 6.111$, $p = 0.005$], but no significant CONDITION * TIME interaction [$F_{(2,36)} = 1.686$, $p = 0.200$]. The effect for CONDITION was driven by a lower spectral power after VERUM intervention ($p = 0.031$, uncorrected, **Figure 2D**), while the effect of TIME was driven by a lower spectral power at POST0H and POST1H ($p \leq 0.045$, Bonferroni-corrected). For postural tremor we found no main effect of CONDITION [$F_{(1,18)} = 1.321$, $p = 0.265$] nor for the interaction CONDITION * TIME [$F_{(2,36)} = 3.070$, $p = 0.059$], but again a significant main effect of TIME [$F_{(2,36)} = 10.305$, $p < 0.001$]. *Post-hoc t*-tests revealed that the main effect of time was driven by a significant decline in spectral tremor power following the intervention at POST0H and POST1H for both conditions ($p \leq 0.024$, Bonferroni-corrected). As there was no significant interaction CONDITION * TIME we interpret the decrease in tremor power following both interventions as an unspecific effect (e.g., anxiety before the intervention).

In summary, there were neither meaningful beneficial nor detrimental effects of the intervention on either tapping performance or tremor.

We conducted additional experiments involving stimulation of M1 and either SMA or M1+50 as a premotor site as detailed in the **Supplementary Material**. These interventions did not yield any beneficial effect either (for details, see **Supplementary Material)**.

DISCUSSION

We designed a TMS intervention aiming to ameliorate Parkinsonian motor symptoms by employing principles of associative stimulation. The protocol was well-tolerated. None of the tested variants of this stimulation protocol had any significant impact on motor parameters. Our experimental strategy was based on a variety of assumptions. Below, we examine possible violations of these assumptions and additional reasons explaining why results were negative, and outline consequences for future attempts of non-invasive treatment protocols.

The anatomical basis for a short latency effect of motor cortical stimulation on STN neurons is the presence of a

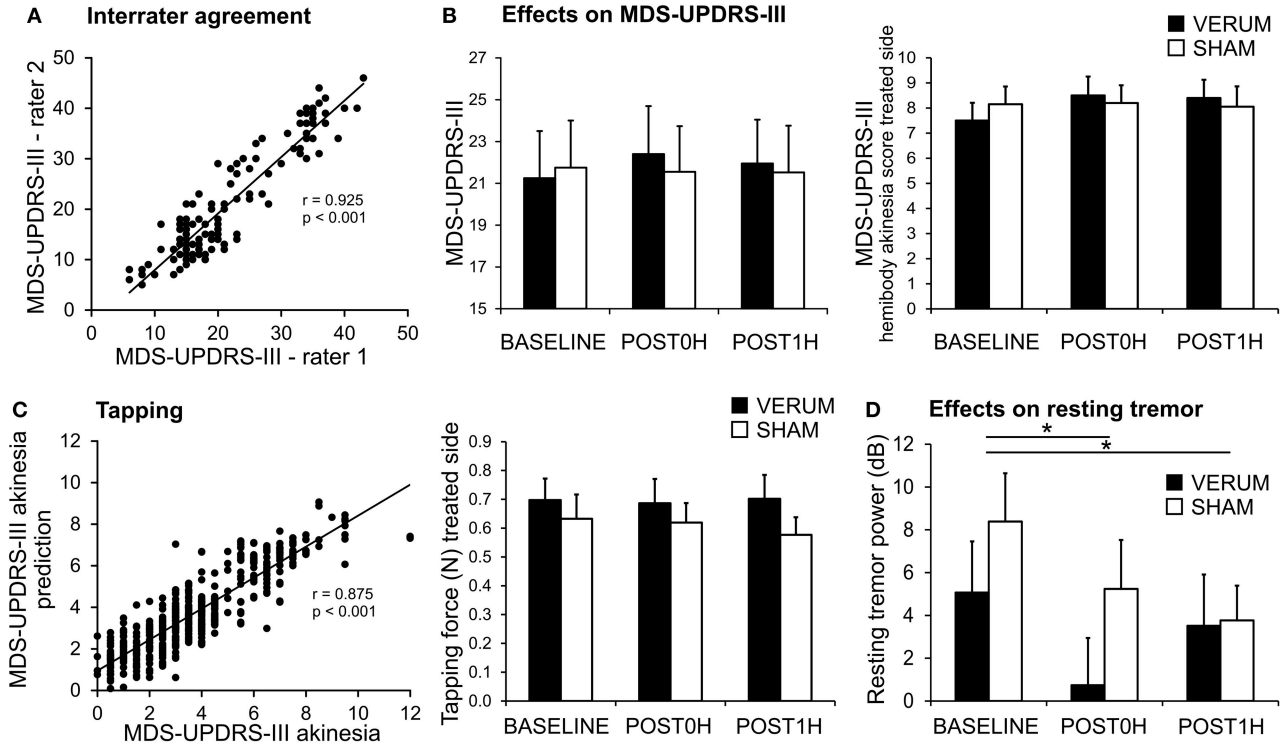

FIGURE 2 | Effects of associative dual-site rTMS on PD motor symptoms. **(A)** MDS-UPDRS-III was videotaped and rated by two certified and blinded MDS-UPDRS-III raters. There was high inter-rater agreement between both raters (C.F. and T.B.W.) as demonstrated in the scatter plot. **(B)** MDS-UPDRS-III was similar for VERUM (filled bars) and SHAM (empty bars) interventions at BASELINE and did not change significantly after the stimulation (left panel). There was also no significant effect on the MDS-UPDRS-III hemibody akinesia score (sum of items 4–8) of the treated side (right panel). **(C)** MDS-UPDRS-III hand akinesia scores (sum of items 4–6) were modeled using a linear mixed model from tapping performance parameters. The model was highly predictive for the MDS-UPDRS-III hand akinesia score when employing mean tapping force, mean interval between taps, standardized tapping force and standardized interval between taps (Left). These parameters were further analyzed (see results section). Tapping force for the treated side is depicted as an example (Right). We found a significant effect for CONDITION (BASELINE, POST0H, POST1H) without an interaction with TIME. Thus, no effect of the VERUM intervention can be inferred. **(D)** Resting tremor power tended to be reduced after VERUM intervention, but it decreased significantly after both interventions (*$p < 0.05$).

hyperdirect tract connecting cortex and STN monosynaptically. This tract has been shown to exist in animal studies (18) and there is increasing evidence of a hyperdirect tract in humans (36–38). A small number of studies showed that TMS directed to motor cortical areas induces STN activity (22, 23). The ability to activate this tract may, on the other hand, be compromised in PD patients as there is evidence for some degree of degeneration in the tract (39).

Little is known how cortico-basal ganglia projections may be specifically activated by TMS and how they would influence individual STN neurons. Fibers originating from SMA or PMd (18, 40, 41) may predominantly terminate in non-motor subregions within STN instead of motor regions. TMS pulses were intended to induce co-activation in a group of STN neurons. Although stimulation intensities near the motor threshold have been shown to induce volleys in descending fibers (35), stimulation intensities may have been too low to modulate the activity of a sufficiently large number of neurons, or to generate action potentials in cortico-fugal projection neurons targeting the STN in particular. Previous studies also successfully employed subthreshold TMS in PD patients (17, 42) and variably achieved beneficial effects in single sessions (43, 44) or only after multiple days of treatment (45, 46). Therefore, effects may be present after a first session but may also become apparent only after repeated applications. Hence we cannot exclude the possibility that ADS-rTMS might have been effective if higher stimulation intensities or multiple sessions had been used.

The interstimulus interval (ISI) of 25 ms used in our TMS protocol was based on the theoretical assumption that pathogenic oscillations are present at about 20 Hz. However, the relevant beta oscillations may peak at any frequency between 15 and 30 Hz (33, 47) or exhibit even two peaks at distinct frequencies (48). Therefore, an ISI of 25 ms may have been less effective to desynchronize STN neurons. Because we had no means of assessing individual beta oscillations in STN, it was not possible to individually adjust the ISI for optimal effects. Furthermore, studies using PAS found that synaptic plasticity may be deficient in the absence of dopaminergic medication in the motor cortex of patients with PD (49, 50). This has been recently shown to correlate with motor performance and be in part reversible by dopamine

replacement (51), suggesting not only a pathophysiological link between plasticity and dopamine availability, but also between motor cortical plasticity and akinesia in PD. The human STN receives dopaminergic projections from midbrain dopamine neurons (52). Studies in rat striatal slices have shown dopamine to be an essential component of activity-dependent synaptic plasticity at the input to the basal ganglia (53). Therefore, overnight withdrawal of dopaminergic medication in the present study may have compromised the ability of neuronal synapses in the STN to undergo long-term depression. On the other hand, Shirota et al. (46), Strafella et al. (54) and Strafella et al. (55) have shown that TMS delivered to a single cortical site, if anything, may facilitate striatal dopamine release. Therefore, ADS-rTMS is unlikely to have augmented the dopamine deficiency induced by overnight withdrawal of dopaminergic medication.

Whether the intended cortical targets have been activated remains another possible area of uncertainty. PMd or SMA stimulation effects cannot be verified physiologically as easily as M1 effects by assessing MEPs. Additionally, physiological localization of PMd is not trivial as evidenced by the considerable heterogeneity with respect to PMd stimulation sites used in previous studies. In the present study we employed TMS mapping which yielded a possible PMd site 32 mm anterior to M1 (M1+32). This site is near a PMd site at 25 mm anterior of M1 used previously (56–59). More precisely, M1+32 was based on the absence of significant known effects tied to M1 conditioning and on suggestions of a physiological effect of conditioning stimulation on M1 excitability whose timing (at 23 ms) would be consistent with latencies of effects on M1 excitability observed in STN-DBS (60) suggesting subcortical processing. Civardi et al. (61) also described conditioning effects at M1+50 mm which we tested in an additional experiment. In line with reports of another group (62) we could not replicate the described physiological effects, neither did we find any clinical effect on PD symptoms at this stimulation site. SMA stimulation proved difficult due to its deep location in the interhemispheric fissure as we found that even maximal stimulation intensities were insufficient to reliably activate the leg-associated motor area in 2 participants.

Despite the fact that the present study failed to reach a clinical improvement, we believe that it may stimulate future attempts at non-invasive treatment of PD by targeting pathogenic oscillations at subcortical targets. Apart from the limitations discussed above, our study has certain strengths that may inform the design of future intervention trials: The assessment of PD symptoms was based on randomized videography of the MDS-UPDRS-III and on objective parameters. This ensured that researcher bias was minimized. Furthermore, a novel coil design enabled us to stimulate two cortical areas located very close to each other.

CONCLUSIONS

In summary, associative dual-site rTMS did not generate a clinically meaningful beneficial effect on Parkinsonian motor symptoms. The present findings leave us with a very large number of TMS parameters and other parameters to be optimized. Although future information may help to constrain this vast space, a more promising strategy may consist in estimating parameters individually with optimized parameter estimation paradigms (e.g., Bayesian optimization) and on brain-state markers of PD pathology as potentially accessible from EEG.

ETHICS STATEMENT

All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the University of Leipzig, file-no.: 351-13-26082013.

AUTHOR CONTRIBUTIONS

CF: conception, fund raising, data acquisition, data analysis, writing of the manuscript. CD: data acquisition, data analysis, writing of the manuscript. TW: data acquisition, data analysis, writing of the manuscript. JH-H: patient recruitment, data acquisition. J-JR: conception, data acquisition. DW: conception, data acquisition. JC: conception, fund raising, data analysis, writing of the manuscript. All authors 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.2019.00174/full#supplementary-material

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Increased Finger-Tapping Related Cerebellar Activation in Cervical Dystonia, Enhanced by Transcranial Stimulation: An Indicator of Compensation?

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Background: Cervical dystonia is a movement disorder causing abnormal postures and movements of the head. While the exact pathophysiology of cervical dystonia has not yet been fully elucidated, a growing body of evidence points to the cerebellum as an important node.

Methods: Here, we examined the impact of cerebellar interference by transcranial magnetic stimulation on finger-tapping related brain activation and neurophysiological measures of cortical excitability and inhibition in cervical dystonia and controls. Bilateral continuous theta-burst stimulation was used to modulate cerebellar cortical excitability in 16 patients and matched healthy controls. In a functional magnetic resonance imaging arm, data were acquired during simple finger tapping before and after cerebellar stimulation. In a neurophysiological arm, assessment comprised motor-evoked potentials amplitude and cortical silent period duration. Theta-burst stimulation over the dorsal premotor cortex and sham stimulation (neurophysiological arm only) served as control conditions.

Results: At baseline, finger tapping was associated with increased activation in the ipsilateral cerebellum in patients compared to controls. Following cerebellar theta-burst stimulation, this pattern was even more pronounced, along with an additional movement-related activation in the contralateral somatosensory region and angular gyrus. Baseline motor-evoked potential amplitudes were higher and cortical silent period duration shorter in patients compared to controls. After cerebellar theta-burst stimulation, cortical silent period duration increased significantly in dystonia patients.

Conclusion: We conclude that in cervical dystonia, finger movements—though clinically non-dystonic—are associated with increased activation of the lateral cerebellum, possibly pointing to general motor disorganization, which remains subclinical in most body regions. Enhancement of this activation together with an increase of silent period

duration by cerebellar continuous theta-burst stimulation may indicate predominant disinhibitory effects on Purkinje cells, eventually resulting in an inhibition of cerebello-thalamocortical circuits.

Keywords: cervical dystonia, functional MRI, cortical excitability, transcranial magnetic simulation (TMS), continuous theta burst stimulation (cTBS), motor-evoked potentials (MEP), cortical silent period

BACKGROUND

Cervical dystonia (CD) is a movement disorder leading to involuntary muscle contractions which cause repetitive and twisting head movements and abnormal, sometimes painful head postures (1). Dystonic disorders have been regarded as psychogenic diseases for decades (2) before pathophysiological research provided evidence for underlying basal ganglia dysfunction (3, 4). Only over the last years, a growing body of evidence points to the cerebellum (CRB) as an important node in dystonia pathophysiology (5–8). Most of this evidence originates from magnetic resonance imaging (MRI) studies, particularly from advanced techniques like functional (9, 10) and resting-state MRI (11), voxel-based morphometry (VBM) (12–15), or probabilistic tractography (16) in different cohorts of dystonia patients. While this leaves little doubt as to cerebellar involvement in dystonic disorders, the exact nature of this involvement remains unclear. In the case of cervical dystonia, functional imaging faces additional challenges: While brain activation associated with dystonic head movement would be of particular interest, data acquisition requires subjects to keep the head still. As the interpretation of task-free functional imaging studies in CD may be ambiguous (17, 18), simple hand motor tasks have been used instead to study activation patterns in functional MRI (fMRI). Although clinically non-dystonic, such hand movements have been shown to be associated with altered activity in ipsilateral putamen, insula and cingulate cortex (19) as well as caudate nucleus, putamen and thalamus (20). In an upper limb force task, increased severity of CD was associated with decreased functional activity of the somatosensory cortex and increased activity of CRB (21). Only recently, Prudente et al. used a new paradigm to assess the functional imaging correlate of isometric head movements (22). They found increased activation of the anterior CRB during constant tension on muscles rotating the head into the pathological direction of torticollis (22). However, while fMRI is able to reveal brain activity associated with a certain condition, the technique is unable to discriminate pathophysiological from compensatory activation. Here, additional neurophysiological approaches like repetitive transcranial magnetic simulation (rTMS) can prove useful (23): By interfering with neuronal processes of a specific brain area, the functional role of this region can be probed (24). In this way, for instance, rTMS over the premotor cortex has been shown to improve symptom severity in CD patients (25). Moreover, a significant reduction of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) score following a 2 week cerebellar continuous theta-burst stimulation (cTBS) treatment has been reported (26). However, similar clinical improvement of CD has recently been described in a study applying cerebellar intermittent TBS (iTBS) over 10 working days (27), along with an improved performance in the pegboard task, i.e., an enhancement of motor function in a non-dystonic body part (27). From a mechanistic point of view, the results of these two studies appear conflicting: Given their opposite impact on excitability at the primary motor cortex (28), one might not expect that both stimulation protocols can induce clinical improvement when applied to the cerebellum. However, as cerebellar physiology and cytoarchitecture is largely different from the motor cortex, effects of cTBS on M1 may not easily be transferred one-to-one to the CRB. Therefore, rather than a dichotomic issue, the behavioral impact of cerebellar TBS might be considered a net effect of various neuromodulative effects of different direction.

In the present study, we applied a complementary approach to challenge the role of CRB in CD: First, we examined functional MRI (fMRI) brain activation during a simple finger tapping task along with neurophysiological measures of cortical excitability in CD patients as compared to healthy controls. Second, we assessed the effects of an excitability-modulating TMS protocol at the lateral CRB on (i) finger-tapping associated brain activation in fMRI, (ii) measures of cortical excitability, and (iii) clinical scores of CD severity. Changes in physiological and/or clinical measures were anticipated to allow an informed interpretation of fMRI data later-on.

METHODS

Participants

Sixteen patients (7 females) with idiopathic cervical dystonia (CD) were recruited from our outpatient clinic for movement disorders. Neurological or psychiatric conditions other than CD led to exclusion from the study. All CD patients were treated with botulinum neurotoxin injections on a regular basis. The experiments were scheduled at an interval of at least 10 weeks from the last injection, with no or minor treatment effects remaining as judged both by the experimenter and by the patient. In addition, a control group (CTRL) of 16 healthy volunteers matched for age and sex (6 females) was recruited. Handedness was determined by a modified version

Abbreviations: AMT, active motor threshold; BOLD, blood oxygen level dependent; CD, cervical dystonia; CGI-I, Clinical Global Impression Improvement subscale; CRB, cerebellum; CSP, cortical silent period; CTRL, control group; cTBS, continuous theta-burst stimulation; EMG, electromyography; FDI, first dorsal interosseous muscle; fMRI, functional magnetic resonance imaging; iTBS, intermittent theta-burst stimulation; M1, primary motor cortex; MEP, motor-evoked potential; PD, Parkinson's disease; PMd, dorsal premotor cortex; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

of the Edinburgh Handedness Inventory (29). The protocol conformed to the principles of the declaration of Helsinki and was approved by the Ethics Committee of the Medical Faculty at the University of Würzburg. All participants gave their written informed consent for participation in the study.

Study Design

Participants were randomized to two arms of the study (fMRI or TMS), with eight CD patients and eight controls per arm (**Figure 1**). In the TMS arm, participants underwent an electrophysiological work-up before and after cTBS at dorsal premotor cortex (PMd) and CRB, respectively, or sham stimulation (three sessions). In the fMRI arm, brain activation during simple finger tapping was assessed before and after cTBS at PMd or CRB (two sessions). In support of feasibility, the fMRI arm did not comprise an additional sham condition to reduce the single patient's burden within the study. The reason for using two experimental groups, rather than doing all experiments in one group, was the long total duration of five sessions which may overtax the compliance of participants [see also (30)].

TMS and EMG Recording

All participants received high resolution MRI including T1-weighted (T1w) 3D MP-RAGE sequences (1 mm isotropic) to allow the localization of cortical regions by neuro-navigation (Brainsight, Rogue Research, Montreal, Canada). TMS was applied by a MC-B70 double coil connected to a MagPro X100 stimulator (Medtronic A/S 2140 Skovlunde, Denmark).

Electromyography (EMG) was recorded from first dorsal interosseous muscle (FDI) via surface cup electrodes with the reference placed over the metacarpophalangeal joint of the index finger. Signals were amplified using a differential amplifier (CED 1902, Cambridge Electronic Design, Cambridge, UK) and bandpass-filtered between 1 and 200 Hz. EMG signals were sampled at 5,000 Hz and digitized by an analog-converter (CED 1401 plus, Cambridge Electronic Design, Cambridge, UK).

The left motor hotspot (M1), defined as the optimal position for eliciting motor-evoked potentials (MEPs) in the right FDI muscle, was localized both functionally (TMS) and according to the landmarks described previously (31), with excellent congruence of the two. PMd was considered to be represented in the posterior part of the middle frontal gyrus, which was located around 2 cm anterior and 1 cm medial to the motor hot spot (32, 33). CRB was marked 3 cm lateral and 1 cm inferior to the inion (31, 34–36). Targeting M1 and PMd, the coil was held in a 45° angle to the sagittal plane with the handle in backward direction, while during cerebellar stimulation, the handle pointed upwards.

Resting motor threshold (RMT) was defined as the lowest stimulation intensity evoking MEP amplitudes of at least 50 μV in 5 out of 10 trials (monophasic pulse-shape). Active motor threshold (AMT) was determined during voluntary FDI activation at about 20% of maximal innervation (visual feedback) and defined as the lowest stimulation intensity evoking MEP amplitudes of at least 200 μV in 5 out of 10 attempts (biphasic pulse-shape).

Continuous Theta-Burst Stimulation (cTBS)

cTBS was applied at 80% AMT (biphasic pulse shape) for a total duration of 40 s (total amount of 600 pulses) (28). Cerebellar stimulation was applied bilaterally (left side first, 60 s break between stimulations), while unilateral stimulation of the left PMd and unilateral cerebellar SHAM stimulation (20% AMT, outer edge of the TMS coil touching the back of the head) served as control conditions.

fMRI Arm

fMRI (Magnetom Trio, Siemens, Munich, Germany) data [EPI, 3 mm isotropic, repetition time (TR) = 3,000 ms, echo time (TE) = 30 ms, 164 volumes] were acquired during a straightforward tapping task of the right index finger and thumb before and after cTBS. Via a simple block design paradigm (plus and minus signs) visually presented with OLED goggles [NordicNeuroLab AS (NNL), Bergen, Norway] patients were instructed to press buttons on a response grip (NNL) in a moderate frequency or to rest for the same duration of 30 s. The two conditions were run equally in a randomized order over a total time frame of 8 min. Feedback data was recorded with high accuracy (Presentation, Neurobehavioral Systems Inc., Berkeley, CA, USA.) To minimize artifacts due to head movements, the participant's head was properly fixed during image acquisition.

TMS Arm

The MEP amplitude (mean of 30) at 130% RMT was taken as an estimate of corticospinal excitability. The CSP duration (mean of 10) as recorded during voluntary FDI pre-innervation (about 20% of maximal innervation) at 150% AMT (biphasic stimulation) was taken as a measure of cortical inhibitory mechanisms. Neurophysiological measures were recorded in the same sequence (RMT–MEP–AMT–CSP) before and after cTBS intervention.

Clinical Assessment

Clinical severity of CD was rated on the motor subscale of the TWSTRS (37) and the TSUI scale (38) in a blinded manner by providing standardized video sequences of CD examination to an experienced clinical investigator uninvolved in the experiment. In addition, CD patients were asked to rate their personal impression of symptom improvement or deterioration after cTBS by using the Clinical Global Impression Improvement subscale CGI-I (39).

Data Analysis

First level and group analysis of the fMRI data was carried out with FEAT, part of the FMRIB Software Library (FSL v5.0, FMRIB, Oxford, UK) (40, 41) (FMRIB Software Library). Fieldmap-based distortion-correction was applied to unwarp the data to increase registration accuracy. MCFLIRT was applied for motion estimation and correction (40). Finger tapping feedback data was added as an additional event variable to account for motor activation and variance. A 2 × 2 × 2 design was set up to test for site and group differences and also to verify that there has been no significant baseline variance between runs on different days. A whole brain correlation analysis was performed with

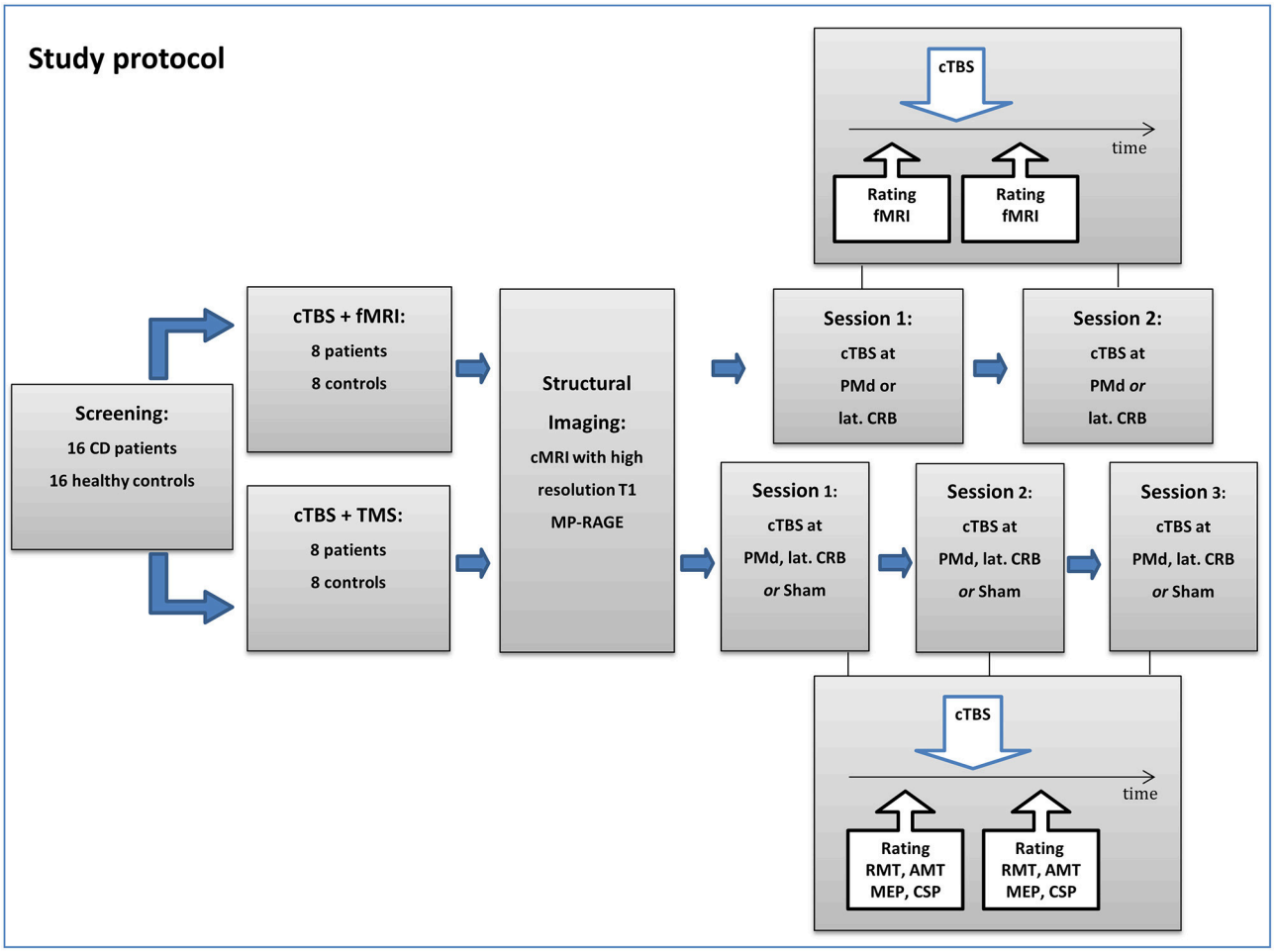

FIGURE 1 | Flowchart of the study protocol. CD, cervical dystonia; cTBS, continuous theta-burst stimulation; TMS, transcranial magnetic stimulation; fMRI, functional magnetic resonance imaging; PMd, dorsal premotor cortex; lat. CRB, lateral cerebellum; RMT, resting motor threshold; AMT, active motor threshold; MEP, motor-evoked potential; CSP, cortical silent period.

cluster thresholding to correct for multiple comparisons. This method is based on Gaussian random field theory and is more sensitive to activation than a voxel based thresholding and is also less overly-conservative with respect to the familywise error rate than the Bonferroni correction (42).

GraphPad Prism (GraphPad Software, San Diego, CA, USA) was used for statistical analyses of TMS data. MEP amplitudes were measured peak-to-peak and averaged. CSP duration was determined by the time interval from MEP onset to the restarting point of EMG activity with 50% amplitude of pre-MEP level. We tested for normality using the Anderson-Darling-Test. In case of normal distribution, baseline TMS data were compared by two-tailed *t*-tests, otherwise by non-parametric Mann-Whitney-U test. Repeated measures two-way ANOVA was applied to compare between the three stimulation conditions within each group, and Sidak's multiple comparisons test was used for *post-hoc* analysis. Effects were considered significant if $p < 0.05$. If not stated otherwise, all values are given as mean ± standard deviation (SD).

RESULTS

Demographics and clinical baseline data of CD patients are shown in **Table 1**.

fMRI

At baseline, finger tapping of the right hand was associated with brain activation in the right cerebellar hemisphere and left motor cortex region across groups. Activation of the right lateral CRB was significantly increased in CD patients as compared to healthy controls (**Figure 2A**, MNI152 coordinates X 21, Y−54, Z−18). Following bilateral cerebellar cTBS, this increased activation was even more pronounced in CD patients (**Figure 2B**, MNI152 coordinates X 19, Y−59, Z−16). Two other significantly increased activations were found adjacent to the gyrus angularis (MNI152 X−57, Y−42, Z 21) and adjacent to the postcentral sulcus (MNI152 X−55, Y−27, Z 48, **Figure 2C**). Comparison within the patient group (cTBS on CRB vs. baseline or vs. cTBS on PMd) also showed these elevated activations at the

TABLE 1 | Clinical characteristics of patients.

Patient no.	Age*	Age of onset*	Dominant pattern	Second pattern	TWSTR baseline	TSUI-score baseline
1	41–45	31–35	LC right	TC left	14	3
2	45–50	41–45	TC left	LS right	15	5
3	51–55	11–15	DHT	LC left	15	6
4	55–60	31–35	TC left	SE left	19	5
5	61–65	16–20	DHT	TC right	22	13
6	41–45	35–40	DHT	TC left	16	4
7	41–45	41–45	TC left	LC left	21	6
8	45–50	21–25	TC left	DHT	21	9
9	61–65	56–60	TC left	LC right	19	3
10	36–40	26–30	RC	DHT	17	4
11	51–55	35–40	DHT	TC left	16	8
12	61–65	55–60	TC left	LC right	20	6
13	51–55	51–55	TC right	DHT	24	13
14	46–50	41–45	TC left	DHT	21	6
15	51–55	51–55	LC right	SE right	22	10
16	46–50	41–45	DHT	LC left	18	5
Means	51.9**	38.5			18.8	6.6
± SD	7.5	13.5			3.0	3.2

**presented in age of range in order to avoid providing indirectly identifiable patient data. **for comparison, healthy control group: mean age 45.0 ± 15.6 years (p = 0.125). TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; LC, laterocollis; TC, torticollis; LS, lateral shift; DHT, dystonic head tremor; SE, shoulder elevation; RC, retrocollis; AC, anterocollis.*

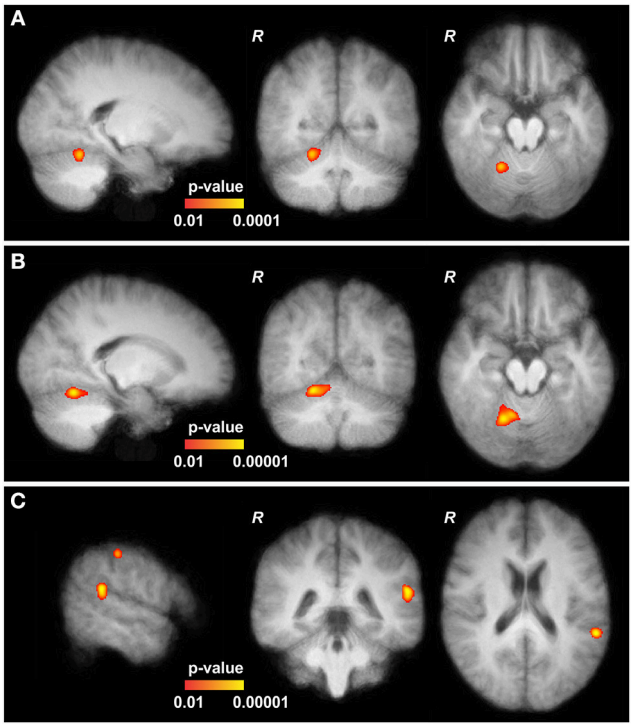

FIGURE 2 | Functional MRI data of cervical dystonia (CD) patients**. (A)** At baseline, the upper part of the cerebellum (CRB) of CD patients showed slightly increased activation in comparison to controls (MNI152 21, −54, −18). **(B)** After continuous theta-burst stimulation (cTBS), main and significantly increased activations in CD patients are shown in the upper part of the right CRB (MNI152 19, −59, −16, adjacent to the baseline results, further pronounced). **(C)** Two other significantly elevated activations were found adjacent to the gyrus angularis (MNI152 −57, −42, 21) and the postcentral sulcus (MNI152 −55, −27, 48). All depicted activations are overlayed on the average coregistered and linearly transformed brains of the subjects. Some moderate but significantly elevated activations in the left primary motor and primary somatosensory cortex and the left premotor cortex are not shown. Comparison with patients at baseline and after stimulation of the left dorsal premotor cortex (CRB vs. PMd) showed increased activations at the same locations and at the same significance levels with only minimal differences (not shown).

same locations and at the same significance levels with only minimal differences. In contrast, bilateral cerebellar cTBS had no significant effect on brain activation in healthy controls, and PMd stimulation had no effect on tapping-related fMRI activation in both groups. Continuous monitoring of motor performance (timing, duration and frequency) did not reveal significant correlation between groups or stimulation sites.

TMS

At baseline, MEP amplitudes were significantly higher (2.6 ± 1.4 vs. 1.3 ± 1.0 mV, $p = 0.002$) and CSP duration significantly lower (132 ± 23 vs. 147 ± 26 ms, $p = 0.036$) in CD patients as compared to controls (**Figure 3A**). RMT was lower in CD patients (54.5 ± 16.7 vs. 65.5 ± 12.1, $p = 0.019$), while AMT was comparable between groups ($p = 0.216$). In CD patients, repeated measures two-way ANOVA with the factors STIMULATION MODE [PMd, CRB, sham] and TIME [pre, post] revealed a significant effect of the factor TIME [$F_{(1,21)} = 19.59$, $p = 0.0002$] on CSP duration. *Post-hoc* analysis showed a significant increase of CSP duration following CRB stimulation (123 ± 27 ms vs. 130 ± 29 ms; adjusted $p = 0.004$), but not after PMd or sham stimulation (**Figure 3B**). In controls, repeated measures two-way ANOVA with the same factors revealed a significant effect of the factor TIME [$F_{(1,21)} = 5.565$, $p = 0.028$] and a significant interaction effect of STIMULATION MODE x TIME [$F_{(2,21)} = 3.636$, $p = 0.044$] on CSP duration. *Post-hoc* analysis showed a significant increase of CSP duration following PMd stimulation (143 ± 30 ms vs. 160 ± 34 ms; adjusted $p = 0.006$), but not after CRB or sham stimulation (**Figure 3B**). cTBS did not have a significant effect on MEP amplitudes, neither in CD patients, nor in controls (**Figure 3B**).

Clinical Assessment

There were no significant changes of TWSTRS and Tsui scores following cTBS at PMd (TWSTRS −1.4 ± 2.0, $p = 0.146$; Tsui −0.3 ± 1.8, $p = 0.837$), at CRB (TWSTRS −0.2 ± 2.7, $p = 0.816$; Tsui −0.4 ± 1.1, $p = 0.746$), or sham stimulation (TWSTRS −0.8 ± 2.4, $p = 0.705$; Tsui + 0.2 ± 0.9, $p = 0.898$). Similarly, CGI-I remained stable after cTBS at any site.

DISCUSSION

The present study assessed the role of CRB in CD. Employing a multimodal approach comprising functional MR imaging,

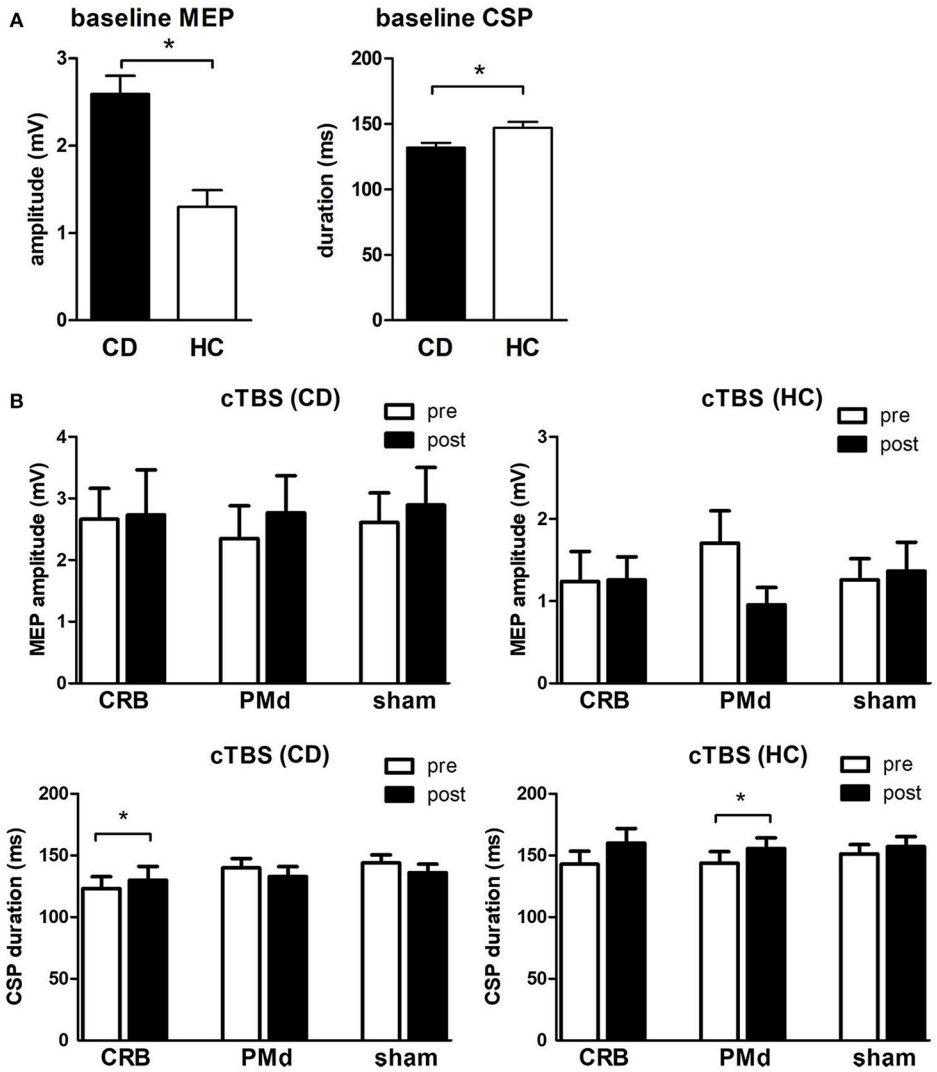

FIGURE 3 | Transcranial magnetic stimulation data**. (A)** Baseline mean motor-evoked potential (MEP) amplitudes and cortical silent period (CSP) duration in CD patients (CD) vs. healthy controls (HC). **(B)** Mean MEP amplitudes and CSP duration before and after cTBS at the cerebellum (CRB), dorsal premotor cortex (PMd), and sham in CD patients and healthy controls. * indicates significant difference.

neurophysiological assessment, and blinded clinical rating, we found CD to be associated with increased brain activation during movement of the (clinically non-dystonic) right hand. Moreover, CD involves an impairment of cortical inhibitory mechanisms, as evidenced by a reduction of CSP duration. Cerebellar interference by TMS enhanced overactivation of CRB while it partially normalized cortical disinhibition. In the following, possible implications of our findings will be discussed.

Finger-Tapping Related Brain Activation in CD

Finger tapping of the right hand was associated with activation of contralateral M1 and ipsilateral CRB both in CD patients and controls. This is in line with a number of previous studies [e.g., (43–45)] and concurs well with common neuroanatomical knowledge. Combined anatomical, physiological, and imaging evidence suggests that voluntary movements are controlled by a network of regions, comprising motor cortex, basal ganglia, thalamus, dentate nucleus, and cerebellar cortex. CRB is commonly accepted to play a major role in motor task planning and coordination, integration of multisensory peripheral input, and feedback generation to the motor cortex.

At baseline, activation of the right cerebellar hemisphere was significantly increased in CD patients as compared to healthy controls. The elevated activation was located in the anterior lobe of the CRB. Projection of this area onto a map of the human CRB based on functional connectivity to cerebral networks (46) indicated that this part of the CRB is tightly connected to the hand motor area (**Figure 4**). Notably, increased cerebellar activation occurred during a simple motor task performed by a non-dystonic limb—a new finding as compared to previous studies in CD patients which did not report cerebellar

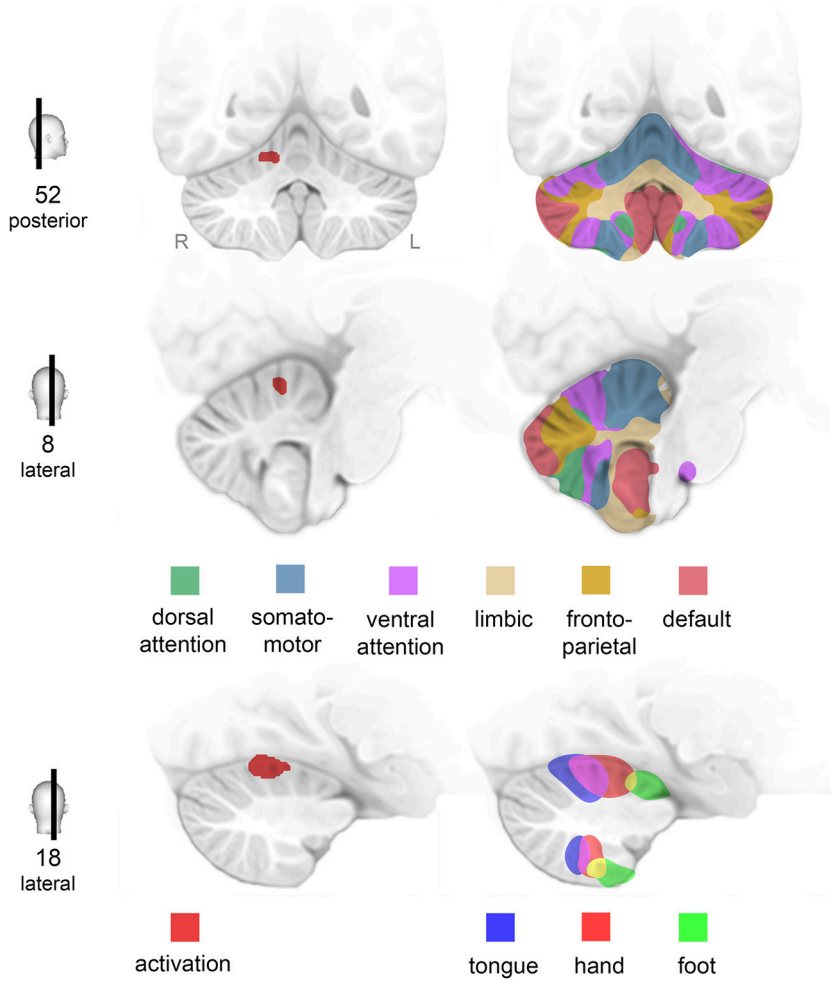

FIGURE 4 | Activation of specific networks in the cerebellum. Finger tapping of the right hand was associated with increased activation ($p < 0.0001$) of the right lateral cerebellum (CRB) in patients with cervical dystonia compared to healthy controls **(middle column)**. Projection on a map of the human CRB based on functional connectivity to seven major brain networks (46) reveals that this area of overactivation is strongly connected to the contralateral hand motor area **(right column)**. Numbers **(left column)** indicate MNI-coordinates (posterior corresponds to y-coordinate, lateral to x-coordinate).

abnormalities during simple hand motor tasks (19, 20, 47). Both the application of different motor tasks and the use of a scanner with higher magnetic field strength in our study (20) might contribute to this difference.

To interpret our finding, it seems crucial to discriminate reports on abnormalities derived from a clinically dystonic area from findings associated with a non-dystonic movement or even at rest. To our knowledge, only one functional imaging study assessed brain activation during head rotation in CD patients. While isometric (i.e., motionless) head rotation into the direction of the torticollis was associated with an increase of activation in the ipsilateral anterior CRB, isometric rotation into the opposite direction came along with increased activation in ipsilateral precentral and contralateral postcentral cortex regions (22). The authors propose a pathogenic role of the CRB, but compensatory role of the sensorimotor cortex in CD, acknowledging that intentional muscle contraction might differ from involuntary head movements in CD (22).

In contrast, CD patients in the present study were asked to keep their head relaxed while performing a simple tapping task or resting. Within block design, any BOLD signal associated with task-free, CD-related or compensatory muscle contraction was dissolved by subtraction. Thus, cerebellar overactivation can be directly attributed to finger tapping. This may be interpreted as a result of motor overflow, i.e., an unintentional extension of tonic cervical activation into the representations of finger movements, which has become a core feature within the motor phenomenology of dystonic disorders (1, 48). Alternatively—though not mutually exclusively—cerebellar overactivation may be viewed as an indicator of a global "dystonic trait." Indeed, in a PET study, even completely asymptomatic DYT1 carriers showed increased cerebellar activity at rest (49). Similarly, non-manifesting DYT1 mutation carriers performing at matched levels overactivated the lateral CRB and the right inferotemporal cortex during motor sequence learning compared to age-matched controls (50). Moreover, resting state fMRI revealed an increase

of negative cerebello-cortical functional connectivity in patients suffering from writer's cramp who typically are asymptomatic during rest (51). Taken together, one might speculate that cerebellar overactivation during non-dystonic movements or rest may indicate an increased "demand" of tonic cerebellar activity to counter motor cortical overexcitability, well in line with a mainly compensatory role of the CRB (5, 16, 52).

Cortical Excitability

At baseline, we found higher MEP amplitudes and decreased CSP duration in CD as compared to healthy controls, which is well in line with earlier studies providing evidence of motor cortical disinhibition and concurs with the overall pathophysiological concept of disturbed sensorimotor integration in CD.

Findings about MEP amplitudes in different forms of dystonia are inconsistent, with most studies describing normal (53–58) and only few describing higher (53, 57, 59) amplitudes.

CSP is commonly accepted as a marker of cortical inhibitory capacity mediated by GABAergic transmission (60, 61). Lower CSP duration has already consistently been described in patients suffering from writer's cramp (62), facial (63), and cervical dystonia (57, 64). In CD patients, a positive correlation of CSP duration recorded from the sternocleidomastoid muscle with symptom severity on the TSUI scale was reported, suggesting an impairment of inhibitory motor control to underlie the dystonic symptoms (57, 64). However, as CSP has been assessed remote from a clinically dystonic muscle in the majority of studies, reduced CSP duration may be viewed as another indicator of a global "dystonic trait" in CD patients.

In healthy controls, there was an increase of CSP duration after PMd stimulation. This is well in line with previous data showing reduced M1 excitability after applying this inhibitory protocol to PMd (65), possibly by depression of excitatory connections to M1. Conversely, the lack of an effect of PMd stimulation in the CD group might be interpreted as a further indicator of motor cortical disorganization in dystonia.

Effects of Cerebellar cTBS on Finger-Tapping Related Brain Activation and CSP

We applied cTBS to the lateral CRB in order to probe the effects of an excitability-modulating protocol on finger tapping related brain activation. We observed even pronounced additional activation of the ipsilateral CRB as well as significantly elevated activation of the contralateral sensorimotor region and the angular gyrus after cerebellar cTBS in CD patients—both compared to healthy controls and compared to baseline and PMd stimulation within the group of patients.

Suprathreshold TMS of the CRB has an inhibitory effect on contralateral M1 excitability, which is usually explained by activation of Purkinje cells leading to an inhibition of dentate nucleus and consequently less excitatory tonic output onto contralateral M1 via dentate-thalamo-cortical connections (34, 66–68). Notably, unilateral cerebellar cTBS, which is performed at subthreshold intensity, has also been shown to decrease contralateral MEP amplitudes (34, 69–71). We therefore suggest that cTBS, rather than directly affecting the Purkinje cells, acts via transsynaptic modulatory effects on stellate and basket cells or parallel fibers within superficial layers of the CRB. As superficial layer cells are known to have inhibitory influence on Purkinje cells, cTBS-induced depression of these cells would eventually result in an inhibition of M1 excitability (34, 70, 72).

It remains open whether activity dependent metaplastic effects, which have been shown to occur at M1 following muscle contractions prior to cTBS (73, 74), might also play a role at cerebellar stimulation. To this end, future studies in healthy subjects will need to disentangle the complex interplay of parameters with potential impact on the net effects of cerebellar cTBS, including motor activity and per interventional head position (58), respectively.

Following cTBS at CRB, we found a significant increase of CSP duration in CD patients. Given shortened CSP at baseline, this may indicate normalization of inhibitory mechanisms acting on M1 by a virtual lesion at the cerebellar hemispheres. The lack of an effect of cerebellar stimulation on CSP in the control group indicates differences between CD patients and controls in respect of their susceptibility to cerebellar "virtual lesions."

Application of cTBS to bilateral (as opposed to unilateral) CRB in our study confines direct comparison to a small number of previous studies (26, 70, 75). Indeed, CSP did not change following unilateral cerebellar cTBS in CD patients (26), in PD patients (75), nor in healthy subjects (26, 70, 75).

Clinical Outcome

We did not detect significant effects of cTBS on blindly-rated symptom severity of CD, irrespective of the target site. A simple explanation might be that the impact of a single session of cTBS on the motor network is just too weak to provoke obvious clinical effects, e.g., due to network redundancy (76) and/or fast adaptive mechanisms (77). Our finding is here in line with comparable approaches using single session TBS (78). Notably, previous studies which reported clinical improvement of CD have applied at least 10 sessions of TBS (26, 27). Another reason might be a lack of sensitivity of our rating scales (TWSTRS, Tsui) for small clinical changes. Furthermore, it must be acknowledged that the aforesaid studies (26, 27) used the TWSTRS total score, while we exclusively collected the TWSTRS motor subscale. For instance, interventional effects on the pain subscale, as reported by Bradnam et al. (27), might have contributed significantly to changes of the TWSTRS total score. Finally, potential clinical effects were only assessed once, immediately after the intervention. Bearing in mind the delayed effects of deep brain stimulation in dystonia, it cannot be ruled out that protracted effects of cTBS have escaped our attention.

The fact that two protocols of TBS with opposite effects on the primary motor cortex, applied daily for 2 weeks, previously improved CD symptoms (26) might reveal that their global input on the network disorder itself is quite the same in spite of manifold local effects on cerebellar cortical structures (27). In view of the complex functional network of activating and inhibiting connections, parallel fiber and Purkinje cell interplay, and their dependency on climbing fiber activity, effects of interference by non-invasive stimulation of the cerebellar cortex

is obviously hard to predict. A focal effect of TBS on one type of cerebellar neurons may therefore remain an over-simplified view.

LIMITATIONS OF THE STUDY

While our subgroups are rather small, they are comparable to previous physiological studies on CD (22, 26, 27), and group size has proved sufficient to show significant differences of brain activation and of physiological measures between groups. It cannot be ruled out, however, that small group sizes contributed to the lack of a significant TMS effect on the clinical scales of CD.

Another limitation might be a potential influence of previous neurotoxin treatment on our neurophysiogical and clinical data in spite of the fact that the experiments were performed at least 10 weeks after the last injection. While an even longer interval between drug application and experimental sessions would have been preferable, this has not been possible both for ethical reasons and for the sake of patient recruitment.

CONCLUSION

According to our multimodal approach, interpretation of fMRI data may benefit from physiological and/or clinical input. Given the lack of behavioral changes, the neurophysiological arm of the study may prove most useful to interpret the present findings: CSP, an established measure of cortical inhibitory capacity (79), was reduced in CD patients at baseline, but significantly increased toward normal duration following cerebellar stimulation. In other words, cerebellar cTBS may have partially restored the inhibitory net influence of the CRB on M1 within the cerebello-thalamo-cortical network. On fMRI, we found increased cerebellar activation during simple finger movements in CD patients compared to controls, which were even enhanced by cerebellar cTBS.

Altogether, we interpret our findings in favor of a compensatory role of the CRB within a network disorder underlying CD: If cerebellar overactivation during non-dystonic finger movements indicate a higher "demand" of tonic cerebellar activity to countervail overexcitability of the motor cortex, an indirect, inhibitory net effect of cTBS on Purkinje cells may be able to enhance both cerebellar activation and M1 inhibition. This interpretation, though partly speculative, allows several predictions about measures of cortical excitability/inhibition and cerebello-cortical interactions which can be assessed systematically by future studies.

In conclusion, our combined approach of TMS and fMRI supports the hypothesis of general motor disorganization in CD, which remains subclinical in most body regions and therefore may be characterized a "dystonic endophenotype." Effects of non-invasive cerebellar interference point to a predominant compensatory function of cerebellar overactivation, which may act as a counterbalance of cortical disinhibition, a core feature of dystonic network disorders. Further research is needed to separate the specific contributions of the CRB in the control of dystonic vs. non-dystonic movements and to disentangle its complex interplay with basal ganglia circuits and the somatosensory system in the range of dystonic disorders.

AUTHOR CONTRIBUTIONS

DZ and JV designed the study protocol. DZ, TO, and GH planned the experiments. TO and GH carried out the study. DZ and JV advised on interpretation and analysis of the results. DZ, TO, and GH prepared the first draft of the manuscript. MR and JV reviewed the manuscript.

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Deep Brain Stimulation Programming 2.0: Future Perspectives for Target Identification and Adaptive Closed Loop Stimulation

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Deep brain stimulation has developed into an established treatment for movement disorders and is being actively investigated for numerous other neurological as well as psychiatric disorders. An accurate electrode placement in the target area and the effective programming of DBS devices are considered the most important factors for the individual outcome. Recent research in humans highlights the relevance of widespread networks connected to specific DBS targets. Improving the targeting of anatomical and functional networks involved in the generation of pathological neural activity will improve the clinical DBS effect and limit side-effects. Here, we offer a comprehensive overview over the latest research on target structures and targeting strategies in DBS. In addition, we provide a detailed synopsis of novel technologies that will support DBS programming and parameter selection in the future, with a particular focus on closed-loop stimulation and associated biofeedback signals.

Keywords: deep brain stimulation, machine learning, adaptive, feedback, DBS target, reinforcement learning

INTRODUCTION

Deep brain stimulation (DBS) has become the treatment of choice for movement disorder, such as Parkinson's disease (PD), medically intractable essential tremor (ET) and complicated segmental and generalized dystonia (1). In addition, DBS is increasingly used in other neurological disorders like neuropathic pain and epilepsy, and is being investigated for psychiatric disorders (2), such as obsessive-compulsive disorder, depression and Tourette syndrome and neurodegenerative diseases like Alzheimer's disease (3). DBS is thought to modulate the function of the target region by applying electrical current to the area (4). Recent reviews propose that DBS likely acts through multimodal, non-exclusive mechanisms including immediate neuromodulatory effects on local and network-wide electrical and neurochemical properties, synaptic plasticity and long-term neuronal reorganization, potentially also providing neuroprotective effects and leading to neurogenesis (4–7).

DBS surgery involves implantation of electrodes into one of several target regions and administering electrical current pulses that are generated by an implanted impulse generator. Although the effects of DBS on for example Parkinsonian symptoms and quality of life are generally satisfying (8), the clinical outcome may vary between patients (9) and side effects can be induced

(10) due to the stimulation of different functional pathways or structures nearby the original target. New approaches, such as current steering (11) are able to restrict the volume of tissue activated (VTA) (12) and therefore promise a more precise stimulation of neural structures. Improving the initial targeting and later stimulation of specific neural structures and pathways involved in the generation of pathological neural activity as well as avoiding others will be a crucial point for improving the clinical DBS effect and, at the same time, limiting side-effects.

The setting of DBS parameters to optimize therapy is time-consuming and will likely get more complicated with new technological developments, introducing an ever increasing combination of parameters like pulse duration, stimulation frequency, stimulation contacts and so forth. In open loop DBS, which is the current standard protocol, these stimulation parameters are set by a clinician in a trial and error procedure and remain constant until manually updated, irrespective of disease fluctuations. In a closed loop DBS system, a sensor continuously records a feedback signal, a so-called biomarker, which is ideally correlated or causally linked to a clinical symptom. A second major point of interest in DBS research therefore is to develop more sophisticated strategies and automated algorithms on how to program and adjust stimulation parameters in a precise and effective manner.

TARGET STRUCTURES

Contemporary research in humans features investigations into different network structures connected to individual DBS targets and explores structural networks (13, 14) involved in the generation of disease symptoms. There are currently a handful of FDA approved DBS targets, including the subthalamic nucleus (STN), the internal segment of the globus pallidus (GPi), the nucleus ventralis intermedius (ViM), as well as several other investigational targets used for, often more than one for a given disorder or symptom (15). A popular target for DBS in medically intractable tremor, like Parkinsonian or essential tremor is the ViM. Studies using tractography show structural connectivity between ViM and motor cortical, subcortical, brainstem and cerebellar sites (16). Various other research groups show that the dentato-rubro-thalamic tract in the subthalamic region is implicated in tremor control (17) and report successful guidance of DBS surgery based on fiber tracking (18). Comparing STN DBS near tremor frequency in PD and DBS of the ventrolateral thalamus in ET, Cagnan and colleagues describe differences in the response of the behavioral tremor characteristics. They reason that different networks could be involved in essential and Parkinsonian rest tremor and conclude that these differences will be important in developing future strategies for closed loop DBS for tremor control (19).

Studies in dystonia patients have shown that ventral GPi stimulation is more efficient in alleviating dystonic symptoms (20). Using diffusion tensor tractography for investigating the connectivity patterns of different target structures and DBS electrode locations, Rozanski et al. report substantial differences in connectivity of dorsal and ventral GPi. The authors interpret their results in favor of functional differences in the ventral and dorsal GPi and recommend that specific targeting could play an important role in promoting distinct effects of DBS (21).

While PD patients show similar improvement in motor function after GPi- and STN-DBS (22), STN DBS is superior in improving off-drug phase motor symptoms (23). Therefore, the STN is often the preferred target to treat Parkinsonian symptoms, such as bradykinesia, tremor and rigidity. Accola et al. used STN LFP recordings from PD patients to investigate the relation between subthalamic fiber connectivity and oscillatory activity. The dorso-lateral portion of the STN, which shows the highest beta power in the STN, predominantly projected to premotor, motor, but also to associative and limbic areas. Ventral areas are connected to medial temporal regions, like hippocampus and amygdala (13). Recently, Tinkhauser et al. reported that beta oscillations recorded from directional contacts can be used as a predictor of the clinically most efficient contacts for stimulation in patients with PD (24). Various research groups (25–30) suggest that the posterior dorsolateral subthalamic region next to the red nucleus could be a "sweet spot" to help guiding DBS electrode placement in PD. However, the small size of the STN and its proximity to different axonal projections (31) can result in multiple side effects during high-frequency stimulation.

In summary, these results highlight the relevance of targeting specific (sub)-structures and networks in improving the clinical outcome after DBS surgery.

Improving Surgical Planning, Evaluation, and Stimulation

Functional neurosurgery has been driven by technological innovations and DBS has evolved over the years, including new approaches to surgical targeting, evaluation and in the delivery of therapy at the target. For a detailed overview see Gross and McDougal (32). Improving and personalizing the targeting of specific (sub)-structures and avoiding others will be crucial for improving the clinical effect and limiting stimulation induced side-effects. New evolving technologies are turning away from classical cylindrical electrodes toward directional stimulating leads. The VANTAGE study, a multi-center study investigating the benefits of using segmented electrodes and multiple-source axially asymmetric directional DBS could show that such an approach leads to similar therapeutic effects as the standard approach without steering. A follow up study reports that axially asymmetric current can reduce adverse effects as well as efficacy thresholds in a highly individual manner, while also expanding the therapeutic window as compared to ring-mode DBS (33).

New software now allows for a patient-specific reconstruction of DBS leads based on MRI and post-operative CT imaging, the reconstruction of nuclei and fiber tracts adjacent to stimulation sites and the mapping of intra- and perioperative electrophysiological recordings (34, 35). For instance, Lead-DBS, now available in version 2.0, is a semi-automated toolbox to model deep brain stimulation electrode locations based on structural and neurophysiological imaging (34, 36). This toolbox now contains PaCER, a fully automated tool for electrode trajectory and contact reconstruction (37). Lauro et al. provide

the open source software systems DBSproc and DBStar for clinical research which co-register CT and MR data for individual target localization and diffusion tractographic analysis from automatically detected DBS contacts (38, 39). On the industry side, Boston Scientific bought Cicerone DBS (40), a platform for stereotactic neurosurgical planning, recording, and visualization for DBS initially developed by the McIntyre lab and turned it into the commercial available software GUIDE. Medtronic initially offered comparable software called Optivize and recently replaced it with its sequel, SureTune 3. The company Brainlab, which has recently partnered with Boston Scientific to develop GUIDE XT, also offers a DBS surgery planning software called ELEMENTS which enables displaying target structures, fiber tracts as well as electrode trajectories.

The VTA is a concept to model the spatial dimension of stimulation for a given set of stimulation parameters (12, 41–43). It can be calculated from individual therapeutic impedance and stimulation energy (total electrical energy delivered, TEED) (44). With a 3D brain atlas and MRI data, the VTA can provide an approximate reconstruction of brain structures surrounding the DBS electrode as a 3D activate/non-activate image. A clinical application of the prediction of the spatial extent of VTA was reported to be helpful in optimizing DBS parameter settings in PD patients (45). However, the application of VTA remains limited due to a lack of impedance calculation in the model and differential strength-duration curves of the response of axons with different diameters because VTAs are derived from volume conductor models with a homogenous and isotropic tissue medium and the axonal trajectories are assumed to be perfectly straight and perpendicular to the electrode shaft, as for example in DBSproc and DBStar (38, 39).

As the electric fields generated during multi-contact stimulation become more complex, new approaches are needed minimize the prediction error for VTA and to quantify axonal and pathway responses in patients-specific models (46, 47). The clinical software StimVision provides another algorithm to calculate the VTA using the artificial neural network technique to facilitate tractography-based DBS targeting (48). Tractography is a modeling technique used to visually represent nerve tracts in 3D space using data collected by diffusion MRI (49). Results from tractography can be combined with post-operative computational modeling to determine the VTA based on electrode contacts, as the implanted electrodes can influence activity not only in gray matter structures but might also influence activity in surrounding white matter structures, thereby potentially influencing networks (50–52). The influence of fiber pathways in DBS has been shown with blood flow, glucose metabolism and blood oxygenation level dependence (BOLD) imaging techniques in multiple studies (53–55), supporting the hypothesis that DBS affects larger neuronal networks with subsequent downstream axonal activation. Sweet and colleagues combined results from tractography with post-operative computational modeling in patients with tremor-dominant PD identifying that the most efficient VTA stimulates the dentatothalamic fiber tract. As mentioned above, this tract probably plays an important role in the occurrence of tremor in PD and targeting it may alleviate tremor symptoms (43).

Advancements in imaging methods, such as ultra-high field MRI and new learning algorithms (34, 56–59) promise to refine our conception and understanding of different neural structures and their wiring in health and disease and will support the investigation of personalized target structures, thus possibly individualizing DBS surgery.

NEW SENSING DEVICES AND FEEDBACK SIGNALS

Today, DBS systems stimulate in an open-loop manner, meaning that stimulation parameters are pre-programmed and are not responsive to changes in the patient's clinical symptoms or in the underlying physiological activity. Although open-loop stimulation is state of the art, limitations like overall efficiency, reduction of efficiency over time or side-effects have become more obvious with growing clinical experience. DBS therapy adjustment also remains time-consuming, requiring clinicians to evaluate numerous combinations of stimulation parameters in order to achieve the optimal outcome. Selecting the right combination among many possibilities can have a major impact on the therapeutic effect (60). DBS practice currently requires patients to follow-up for months post-operatively to optimize the clinical effect of DBS. Disease and patient specific biomarkers could ideally help optimize therapy and help finding the right DBS parameter.

Medtronic now offers the implantable and rechargeable neurostimulator Medtronic® ACTIVA RC + S, a research system following the Activa PC + S system, which records electrophysiological signals from the implanted DBS electrodes and also offers inertial measurements. New miniature implants (61) with names like Neural dust (62) or Neurograins (63) will push the boundary of signal collection even further and ultimately promise to provide read and stimulation capabilities with a far greater spatial and temporal detail than available at present. There now are several companies actively pursuing brain computer interface technology by developing new neural implants, ranging from traditional medical device manufacturers like Medtronic, St. Jude Medical or Boston Scientific to tech start-ups like Neuralink, Kernel or Cortera, which in part work in close cooperation with several research institutes and are driven by funding from the DARPA program.

Looking forward, adaptive closed-loop stimulation systems that integrate feedback signals will ideally be able to rapidly respond to real-time patient needs and make human programming unnecessary (64). NeuroPace (California, USA) for example already provides a responsive neurostimulation system (RNS) for closed-loop cortical stimulation with FDA-approval in patients with drug-resistant epilepsy. It is capable of continuously sensing electrocorticography (ECoG) potentials (65). When recognizing a seizure-related pattern, the stimulator is activated to stop the seizure and store the ECoG potentials, date and time of seizure occurrence.

Optimally, biomarkers for adaptive closed loop DBS should be usable continuously after DBS implantation to make them applicable for clinical practice. Local field potentials and network

connectivity measures based on electrophysiological signals with their high temporal resolution can already be measured with sensing DBS electrodes or other implanted neural sensors and hold great promise as biomarkers.

Biomarkers and Control Mechanisms

Regarding closed loop adaptive DBS, a distinction has to be made between feedback signals (biomarkers) and mechanisms of control. A biomarker describes a correlative or causal relation to a clinical symptom. Adaptive control mechanisms then define how to adjust stimulation based on the evolution of biomarkers.

Biomarkers

Electrophysiological measurements

Recordings of LFPs in the basal ganglia of PD patients show oscillations at several frequencies, including oscillations at low frequencies in the delta and theta band (1∼7 Hz), alpha and beta band (8–35 Hz), gamma band (35–200 Hz) and high frequency oscillations (>200 Hz). It has been demonstrated that the beta activity amplitude is correlated with motor symptom severity without medication (66–68). Moreover, it has been reported that the reduction of rigidity and bradykinesia is correlated with a decrease in beta activity (69, 70). In line with this, STN DBS and dopaminergic medication has been shown to attenuate beta activity locally (71–75), while the degree of beta activity suppression has been shown to correlate with improvement in Parkinsonian motor symptoms (71, 76). Whereas, exaggerated beta activity is associated with bradykinesia and rigidity, dyskinesia symptoms are reported to be linked to increases in low (4–8 Hz) and gamma frequencies (60–90 Hz) (77, 78), akin to oscillatory activity observed during normal movement (79–82). High frequency oscillations (HFO), which are reported to be coupled to the phase of beta oscillations, are another promising biomarker associated with Parkinsonian symptoms, such as bradykinesia, rigidity as well as tremor, even in the ON medication state (83–85). They are typically found at ∼250 Hz, while not being attenuated by dopaminergic medication, but rather shifted toward higher frequencies at 350 Hz (84–86).

Early approaches using local field potentials (LFP) as feedback signals for adaptive DBS incorporated the beta frequency amplitude as a mechanism to trigger the stimulation (87) demonstrated clinical improvement of symptoms compared to standard DBS. An approach by Meidahl et al. targets potentially pathological long beta bursts sparing supposedly functionally important short-term beta bursts (88, 89). Several other oscillatory biomarkers, such as pathological cross-frequency coupling (85, 90) or pathological coherence of neural activity between cortical and subcortical structures (91) have been reported to correlate with clinical symptoms and are discussed as potential feedback signals. Despite early success, challenges have yet to be overcome. Beta power in the STN for example correlates with rigidity and bradykinesia, but not with tremor (92, 93), which is linked to field potentials at tremor frequency. PD patients for example often show heterogenous clinical symptoms, a single, one-dimensional feedback signal might be only useful to a certain degree. Body measurements using electromyography or kinematic sensors allowing for the assessment of symptom severity and behavior could be a promising additional feedback source for adaptive DBS. For instance, Cagnan and colleagues stimulated patients with essential tremor and thalamic electrodes, while recording tremor amplitude and phase with inertial sensor units. They report that the amplitude of the tremor was modulated depending on the phase relative to the tremor cycle, at which stimulation pulses were delivered (94). Most neural biomarkers like beta frequency oscillations are multifaceted and not only linked to clinical symptoms, but also modulated during normal behavior like movement or cognition (95, 96) and are associated with medication (71, 97). Although biomarkers like beta activity seem to be stable months after DBS surgery (98, 99), it is also conceivable that they evolve with disease progression, as they are correlated with symptom severity (67), which naturally increases over time in neurodegenerative diseases.

The use of electrophysiological biomarkers in aDBS is also restricted due to an often unfavorably low signal-to-noise ratio and interference with external artifacts like movement, speaking and cognition (100). Also, stimulation can lead to artifacts when sensing is done near the site of stimulation, e.g., the sensing of β-bands in the STN with e.g., Activa PC + S can be contaminated by stimulation. This may be avoided by using ECoG sensing (101). ECoG is another invasive electrophysiological biomarker which directly records electrical potentials associated with brain activity from the cortex. When using ECoG as a biomarker in aDBS the sensing strip is implanted subdurally over the primary motor cortex during the same procedure as the electrode implantation subcortically. Gamma band activity (60–90 Hz) for example is associated with dyskinesia in PD patients and can therefore be used as a feedback signal to trigger stimulation (101).

For a detailed overview of oscillatory features related to pathological and physiological states in DBS patients, see Neumann et al. (102).

Neurochemical sensing

Neuronal sensor devices that detect local alterations in neurotransmitter release in response to DBS have been developed. The stimulation-evoked changes that resemble physiological neurotransmitter release are associated with the therapeutic effect of DBS (103). Grahn et al. developed a device that detects changes in dopamine concentration in rodents to adapt stimulation parameters (104). Lee et al. have developed a wirelessly controlled device, WINCS Harmoni®, which can measure *in vivo* neurotransmitter concentration across multiple anatomical targets using implanted neurochemical sensors. These devices provide real-time neurochemical feedback for closed loop control (105). Until now, the method has been used in preclinical DBS studies, but it is a promising tool for a better understanding and future improvement of a clinical application of closed loop DBS.

External mechanistic sensors

External wearable devices, such as accelerometers or EMG sensors can be used to infer symptoms and symptom severity like rigidity, bradykinesia and gait disorders (106, 107). Studies show that the measurement of tremor with accelerometers that adjust the stimulation frequency to tremor frequency lead to a

better clinical result than conventional stimulation in patients with essential tremor (52, 94). In PD, the severity of motor dysfunction can be measured with a wireless external sensor device which is integrated into a smart glove containing two touch sensors, two 3D-accelerometers and a force sensor to assess tremor, rigidity and bradykinesia of hand and arm (108). Heldman et al. devised software to automatically optimize stimulation settings based upon objective motion sensor-based motor assessments. To assess symptom severity, a motion sensor was placed on the index finger of the more affected hand. The software then guided a procedure during which stimulation on each contact was iteratively increased. This was followed by an automated assessment of tremor and bradykinesia severity. After completing assessments at each setting, a software algorithm determined stimulation settings, leading to improved tremor and bradykinesia scores by an average of 35.7% (107, 109).

Control Mechanisms

Beta threshold targeting

One of the earliest approaches to adaptive closed loop DBS was beta threshold targeting. When the amplitude of oscillatory activity in the β-band exceeds a defined threshold, stimulation is turned on. It has already been shown that this approach can improve the therapeutic effect compared to standard DBS (87). Alternatively to threshold targeting, excessive β-synchronization in PD patients may selectively be regulated via aDBS by targeting pathological long β bursts while leaving possibly functionally relevant short bursts of β activity unaffected (88). However, as described above, one problem of this approach is that not only beta oscillations but also beta oscillatory characteristics, such as burst length are not only related to symptom severity, but also to medication and behavior (75, 110).

Noise cancellation

Cagnan et al. suggest a tool to detect the patient's tremor with an accelerometer attached to the affected hand, as described above. Using the effect of noise cancellation, a control mechanism based on this external mechanistic sensor switches on the thalamus stimulation in specific phases of the essential tremor (52). In this work the modulation of tremor turned out to depend on the phase of stimulation relative to the tremor cycle. However, only stimulation during the first half of the tremor cycle resulted in a reduction of tremor whereas during the second half of the tremor cycle harmonics in tremor were inducted (52). Also in PD patients, the effect of noise cancellation was used to cancel cortical oscillations within the tremor network with non-invasive transcranial alternating current stimulation (tACS) which can reduce the amplitude of resting tremor by 50% (111).

Stimulation on demand

Measuring biomarkers in real-time can be used for stimulation on demand in aDBS. Herron et al. used cortical electrodes sensing β-band desynchronization in ET patients when a movement was started. This desynchronization then triggered the stimulation to reduce the tremor while stimulation was switched off in resting state (112). Due to a delay in stimulation initiation, tremor at the beginning of a movement could not be prevented. One way to improve this would be if one is able to predict movement before it occurs.

Coordinated reset stimulation

An alternative stimulation protocol is the temporal stimulation pattern coordinated reset stimulation for research application (113). Abnormal neuronal synchrony in neurological diseases can be addressed by coordinated reset stimulation that delivers brief high-frequency pulse trains through different stimulation contacts of the DBS lead to reset abnormal synchronization. In PD the basal ganglia structures STN and GPe are known to generate rhythmic synchronized oscillations which are associated with PD symptoms(114). Coordinated reset stimulation can decrease these abnormal synchronous beta oscillations and hence improve bradykinesia and rigidity (115).

LIMITATIONS AND FUTURE PERSPECTIVES

Moving From Invasive to Non-invasive DBS

Although the implantation of DBS electrodes is a well-established procedure in movement disorders, it comes along with surgical risks and complications. Thus, a non-invasive approach could be a future direction. Non-invasive aDBS is proposed by Grossman et al. who have developed an experimental strategy in mice to target deeply situated neurons without manipulating the overlying cortex by applying high-frequency oscillating fields in different locations outside the brain (116). The interference between two applied fields cancels out the high-frequency activity, while an oscillation of low frequency corresponding to the difference between the two frequencies can emerge. With this low frequency neurons situated deeply in the hippocampus can be activated. The suggested approach is limited by the size of human brain that is much bigger than mouse brain and hence, more difficult to target deeply located structures, and by whether neural networks in the stimulation paths remain unaffected also in a larger brain (117). Another non-invasive approach is optogenetic stimulation, which was developed over the last decade. Optogenetics can selectively activate neurons deep in the rodent brain by using light to control neuronal ion channels *in vivo*. Thus, neural circuits can be manipulated by precise excitation and inhibition of specific circuit elements, moving from invasive toward non-invasive DBS (118, 119). Currently, optogenetics still require a chronically implanted optical fiber, hence, it is not yet a completely non-invasive technique.

However, the non-invasive approaches still need to be investigated much further. So far they have only been studied in animal models.

Future Perspectives

Most existing approaches to adaptive DBS so far have in common that they are carefully engineered based on a core principle and allow for a specific action given a certain signal. However, these approaches do not allow for learning optimal individual signal properties and control algorithms. In addition, each biomarker and control mechanism has its specific drawback as discussed above.

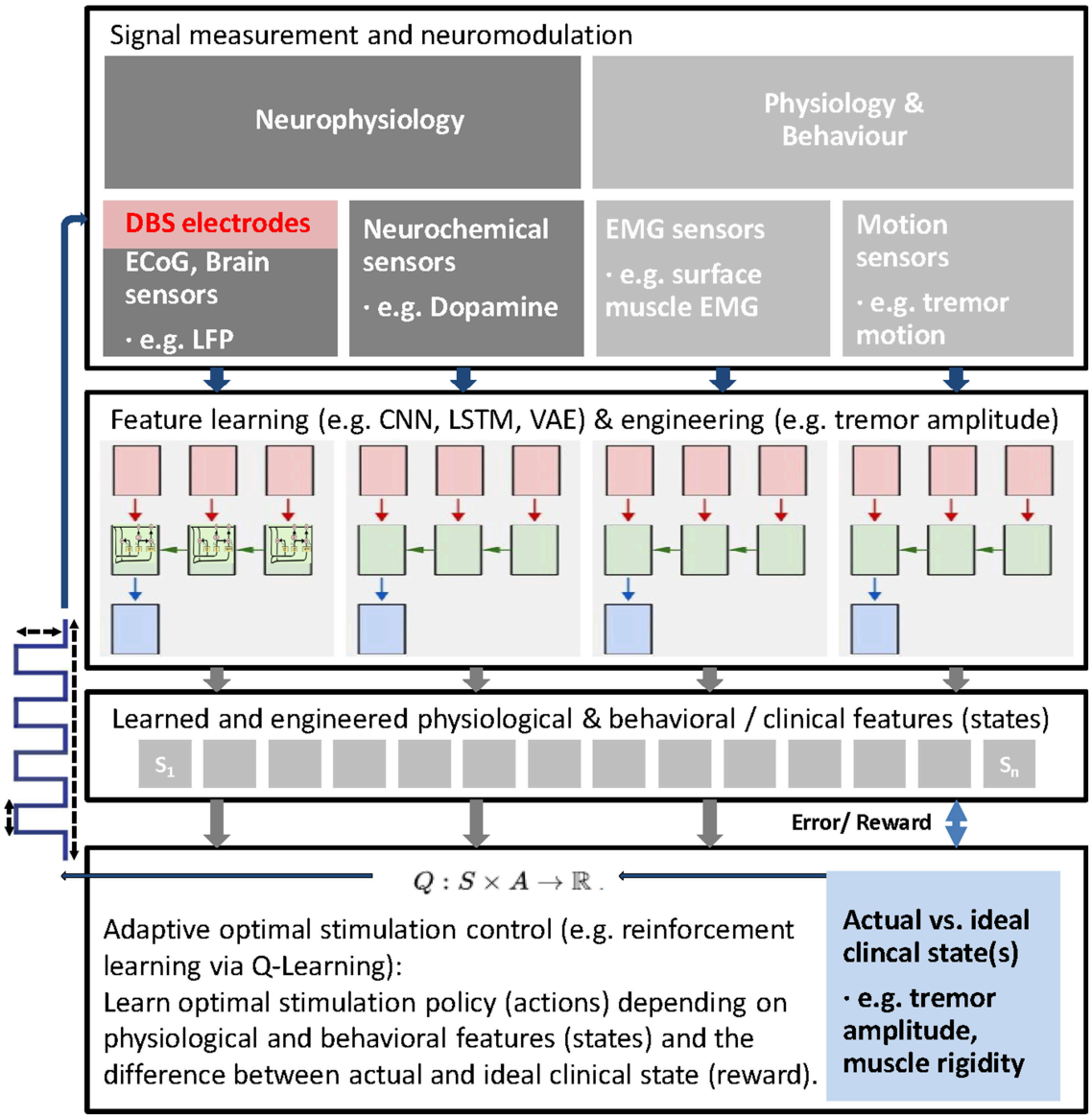

FIGURE 1 | Schematic of general adaptive closed loop DBS for adaptive adjustment of deep brain stimulation (DBS) parameters based upon real time patient measurements, such as electrophysiological signals (e.g., LFP, ECoG, EMG), neurochemical parameters and behavioral measurements and machine learning. First, latent features from different possible signal sources are learned using machine learning approaches to extract behavioral (clinical) states (e.g., bradykinesia, rigidity, tremor) and corresponding and predictive latent neural states (e.g., beta and high frequency oscillations). Then, actual states are compared with ideal states to compute a reward and stimulation parameters (e.g., VTA, stimulation frequency, etc.) adjusted and finally learned via reinforcement learning (Q-Learning is shown as an example). In this closed-loop paradigm, the stimulation parameters (actions) are adjusted within clinical limits based on the reward and the extracted latent states.

As a future direction, latent features derived from different signal sources could be used in parallel to establish a feedback driven stimulation algorithm based on the analysis of behavioral and physiological data and a suitable control mechanism. By integrating parameters derived from different sources, such as kinematic and electrophysiological measurements and other sensor like electromyography, patient state and disease symptoms severity and underlying neural activity could be ultimately learned and classified end to end (102, 120–122), using machine learning algorithms (**Figure 1**).

In case that physiological and behavioral features, describing the neural and clinical state of the patient, can be reliably decoded and ideally predicted from measurements, reinforcement learning could be another option to learn and optimally control stimulation paradigms and optimize the clinical state (**Figure 1**). Reinforcement learning can provide optimal control in an environment with unknown transition probabilities (123). In reinforcement learning, an agent, in this case the DBS stimulation controller interacts with an uncertain environment, i.e., stimulating a mixture of neural structures

with certain stimulation parameters with the goal to maximize a numerical long term reward, in this case the (long term) clinical improvement of the patient. Through the learned policy after training the controller ideally has identified the right stimulation action in every state (124).

A simple version of this idea could be realized in patients with tremor dominant PD. The amplitude of the tremor can be measured with kinematic sensors and then be used to describe the clinical state of the patient. Such a signal could then serve as a reward signal for reinforcement learning, with the reward simply being the difference between optimal clinical state (no tremor amplitude) and actual clinical state (actual tremor amplitude). With such an approach, the optimal stimulus could be learned and adjusted based on feedback signals, closing the loop. Alternative stimulation protocols and parameters (such as electrode contact, VTA, pulse-frequency, -width, -amplitude, -shape, timing relative to neural activity, etc.) could then be evaluated within a clinically acceptable range of stimulation energy. However, the vast amount of free parameters in DBS programming introduces a potentially very large search space to evaluate during reinforcement learning, even when constraining the search space to clinically acceptable parameters. Algorithms for reinforcement learning are commonly either model-free or model-based. While in model-free learning, the agent simply relies on trial-and-error experience to learn a policy that optimizes immediate and future reward, in model-based learning, the agent exploits previously learned lessons (125). Although model-free deep reinforcement learning algorithms are suited for learning a wide range of applications, they often require millions of training iterations to achieve good performance (126, 127), rendering this approach inappropriate for adaptive DBS trials in humans. In model-based reinforcement learning, experience is used to construct a model of the world, describing the transitions between states and associated outcomes, while suitable actions are chosen by searching or planning in this world model (128). To learn such models in the first place, however, a large number of training trials would also likely be required. Possibly animal models could help pioneering such an approach (129). Ultimately, only interventional studies can prove causal relationships and in this case the effects of adaptive deep brain stimulation on the clinical and overall state of the patient. However, applying countless experimental perturbations, which are necessary to gather enough observational data to learn from, can be costly and time consuming, even when done in animal models. Inferring the causal structure of brain networks from neuroimaging data is an important goal in neuroscience (130, 131) and various methods, such as Granger causality (132, 133), dynamic causal modeling (134, 135), structural equation modeling (136, 137) and causal Bayesian networks (138, 139) have been developed to infer causal relations from brain imaging data. Recently, van Wijk et al. applied dynamic causal modeling to explore the cortical-basal ganglia-thalamus loop in patients with PD and to study pathways that contribute to the suppression of beta oscillations induced by dopaminergic medication (140). Also recently, Bogacz et al. described a coupled oscillator model to predict the effects of deep brain stimulation (141). Ideally, causal inference methods based on i.e., causal Bayesian networks could also help give testable predictions on the effects of external manipulations (142), such as the effects of deep brain stimulation. In this way, different adaptive approaches could be explored or learned *in silico* and the number of interventional studies, that are required to establish an approach, could be reduced substantially (143).

SEARCHING STRATEGY

This review is based on expert opinions and does not follow a systematic searching strategy.

AUTHOR CONTRIBUTIONS

FH, JM, TK, and KB conceived the project. FH and CP did the literature search and wrote the manuscript. TK, JM, and KB wrote the manuscript.

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CASE REPORT
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Variable High-Frequency Deep Brain Stimulation of the Subthalamic Nucleus for Speech Disorders in Parkinson's Disease: A Case Report

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Background and Importance: It is known that subthalamic nucleus deep brain stimulation (STN-DBS) at a fixed high frequency (>100 Hz) improves the primary motor symptoms of Parkinson disease (PD), but this stimulation does not improve or may even exacerbate the later-occurring axial symptoms and signs in PD (e.g., problems with gait or speech). Recent evidence suggests that STN-DBS at a fixed lower frequency (< 100 Hz) can improve speech and gait, but may worsen the tremor in PD.

Clinical Presentation: The case involved a female patient who developed severe speech problems after 16 years high-frequency STN-DBS for PD. The tremor and dysarthria symptoms were both effectively treated by applying variable-frequency stimulation (VFS) containing only a combination of high frequencies.

Conclusion: VFS containing several higher frequencies improved both the tremor and axial signs including speech problems in our patient. This case report suggests that VFS may be of clinical utility in the management of advanced PD, but this should be further verified in larger well-controlled studies.

Keywords: variable high frequency, subthalamic nucleus, deep brain stimulation, dysarthria, Parkinson's disease

BACKGROUND AND IMPORTANCE

High-frequency deep brain stimulation of the subthalamic nucleus deep brain stimulation (STN-DBS) improves the primary motor symptoms of Parkinson's disease (PD). However, this stimulation at a fixed high frequency does not improve or may even exacerbate the axial symptoms and signs (such as problems with gait, speech, or swallowing) that often emerge over the long-term course of treatment and disease (1). Recent evidence suggests that STN-DBS at a fixed lower frequency (< 100 Hz) could improve speech and gait (2, 3). However, the tremor might worsen significantly with fixed low-frequency stimulation (4). Here, we present a case of PD that was treated effectively by applying variable-frequency stimulation (VFS) containing only a combination of high frequencies. A written informed consent was obtained from the patient, both for participation and for the academic publication of this case report.

CLINICAL PRESENTATION

The case involved a female patient who developed severe speech problems after long-term high-frequency STN-DBS for PD. In 1998, at the age of 23, she was diagnosed with PD. In 2002, she received bilateral STN-DBS (Kinetra 7428, Medtronic, Minneapolis, MN, USA) for severe medication-resistant tremor. The position of the most ventral DBS contacts was shown in **Figure 1**. After STN-DBS onset, she first decided to reduce the dosage of anti-Parkinson medications and then stopped taking the drugs altogether. One year after surgery, she was medication-free and gave birth to a baby. She received subsequent battery replacements in 2006, 2009, and 2012. For over a decade, her motor symptoms responded well to DBS at 170 Hz. However, from April 2015 onwards, she experienced increasing difficulties in standing up from a sitting position and with her speech/phonation. The adjustments made to her DBS parameters and medication were not helpful. Post-operative magnetic resonance imaging confirmed that the DBS leads were correctly located in the STN and had not migrated. In December 2015, we replaced the DBS battery of the patient with a rechargeable battery (G102, PINS, Beijing, China). As stimulation at a fixed low frequency might exacerbate the tremor evident in this patient, we explored the value of VFS in treating her motor symptoms, which was made possible by the battery change (5). The same parameters were selected: right, 1-2-3-Case+, 3.55 V, 100 us, 170 Hz; left, 6-7-C+, 3.35 V, 90 us, 170 Hz.

We evaluated the effects of three different sets of VFS on the patient's motor function. Initially, the frequencies used in each set were randomly chosen from a group of six frequencies (170, 160, 145, 125, 90, 60 Hz). Ten minutes after the delivery of each VFS stimulus, a speech therapist assessed the patient's vocal and speech performance by taking into account (a) the quality of articulation when she pronounced her name, date of birth, and an 8-syllable Chinese tongue-twister; (b) the maximum phonation time when pronouncing /ah/; and (c) the loudness of the sound of her voice, as indicated by the maximum sound pressure level while the patient produced a loud, clear sound for as long as possible (UT-352, Uni-Trend Technology, Ltd., Shenzhen, China). A movement disorder specialist also performed follow-up motor assessments using established clinical instruments. Other stimulation parameters (i.e., the contacts, amplitude, pulse width) were kept the same while frequencies were varied across VFS sets.

The first set of VFS parameters used contained two low-frequency components (90 and 60 Hz). Following the application of this set, the patient could no longer speak, and her tremor immediately recurred. We therefore excluded these low frequencies from further consideration. Next, we evaluated our second set, involving 160 Hz (10 s), 145 Hz (15 s), 125 Hz (10 s), 145 Hz (15 s), and 160 Hz (10 s). Note that 145 and 160 Hz were used twice within this set as a 1-min loop. The second VFS set was found to alleviate her bradykinesia, muscle rigidity, and axial symptoms on day one and 1 month follow-ups (**Table 1**). We then evaluated our third set involving 160, 155, 145, 130, and 125 Hz (10 s) at the 1 month follow-up. Similar to the second parameter set, the third VFS set improved the patient's bradykinesia, rigidity, and axial symptoms at the 3 months follow-up, as compared to no STN-DBS treatment or fixed high-frequency STN-DBS (**Table 1**). Thus, the two VFS sets were both effective for primary motor symptoms, but the third set improved the axial symptoms better than the second set.

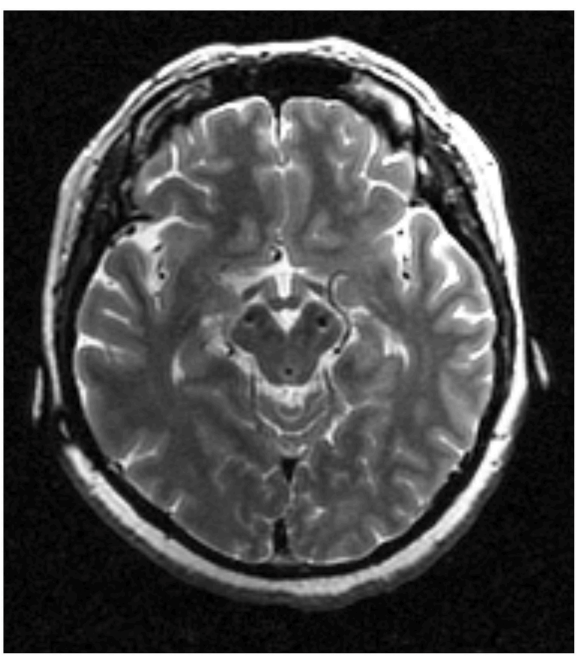

FIGURE 1 | The most ventral DBS contacts location.

DISCUSSION AND CONCLUSION

In PD, axial symptoms, and signs involving problems with gait and speech are common, especially in advanced stages of the disease. For the affected, these symptoms often lead to functional impairment and a lower perceived quality of life. It is known that STN-DBS treatment using fixed high frequencies, while being effective in controlling the primary motor symptoms of PD, may induce or aggravate speech and voice dysfunctions (1). VFS containing low frequencies has been reported to relieve severe subthalamic stimulation-induced dysarthria, yet this stimulation has also been found to worsen the tremor (2). Our results confirm the latter observation by showing that VFS containing low frequencies alone worsened the tremor in the present case. By contrast, VFS containing several higher frequencies improved both the tremor and axial signs including speech problems in our patient.

This case report describes the application of new paradigms for DBS programming, made possible by technological advances. Unfortunately, for the different sets of VFS tested here, the stimulation amplitude and pulse width could not be varied. One possible explanation for the scarce efficacy of the first VFS set (containing high and low frequencies) could be that low frequencies typically require a higher stimulation intensity to be at least as effective as the high frequencies. The differences between the two high-frequency sets of VFS implied that switching more frequently seems to be advantageous. Although

TABLE 1 | Patient's motor symptom severity before and after variable-frequency stimulation.*

Clinical variable	Off	HFS	2nd VFS (1-day follow-up)	2nd VFS (1-month follow-up)	3rd VFS (3-months follow-up)
Total	90	50	45	39	35
Tremor	10	6	6	5	5
Rigidity	20	8	8	2	2
Bradykinesia	40	24	22	22	22
Axial symptoms	20	12	9	10	6
Speech	4	3	3	2	2
Gait	4	2	2	2	1
Posture	4	2	1	2	1
Postural stability	4	2	2	2	2
Arise from chair	4	3	1	2	0
TUG (sec)	Unable to complete	10	12	10	11
Hoehn-Yahr Stage	5	3	3	3	3
GFQ	NA	36	32	32	32
Voice loudness	NA	Max duration = 2.2, max SPL = 89.0	Max duration = 3.3, max SPL = 98.1	Max duration = 2.3, max SPL = 93.2	Max duration = 3.4, max SPL = 97.6

**Motor symptom severity was assessed by using the Unified Parkinson's Disease Rating Scale (UPDRS)-III, unless indicated otherwise. Off, no STN-DBS; HFS, 170 Hz; HFS, High Frequency Stimulation; LFS, Low Frequency Stimulation; TUG, Time Up and Go test; GFQ, Gait and Falls Questionnaire; SPL, Sound Pressure Level; NA, Not Available.*

assessment is usually done 30 min after stimulation, we assessed her speech after 10 min because this patient is very sensitive and reached a stable clinical effect quickly. Furthermore, the data is comparable as the conditioning followed the same protocol.

These observations indicate that VFS may be of clinical utility in the management of advanced PD. Future large-scale studies are needed to confirm our findings and elucidate the mechanism of VFS, and to establish whether it alleviates the detrimental effect of HFS, DBS or has a beneficial effect.

ETHICS STATEMENT

This study was approved by the ethics committee of Ruijin Hospital, Shanghai Jiaotong University. The patient gave her consent for participation and anonymity publication.

AUTHOR CONTRIBUTIONS

CZ, BS, DL, and CN designed this study. QX and CN performed the speech assessment. YP, DL, and HZ conducted the DBS programing and motor assessment. CZ, DL, and CN wrote this paper with input from all co-authors.

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REVIEW
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A Review of Cognitive Outcomes Across Movement Disorder Patients Undergoing Deep Brain Stimulation

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Introduction: Although the benefit in motor symptoms for well-selected patients with deep brain stimulation (DBS) has been established, cognitive declines associated with DBS can produce suboptimal clinical responses. Small decrements in cognition can lead to profound effects on quality of life. The growth of indications, the expansion of surgical targets, the increasing complexity of devices, and recent changes in stimulation paradigms have all collectively drawn attention to the need for re-evaluation of DBS related cognitive outcomes.

Methods: To address the impact of cognitive changes following DBS, we performed a literature review using PubMed. We searched for articles focused on DBS and cognition. We extracted information about the disease, target, number of patients, assessment of time points, cognitive battery, and clinical outcomes. Diseases included were dystonia, Tourette syndrome (TS), essential tremor (ET), and Parkinson's disease (PD).

Results: DBS was associated with mild cognitive issues even when rigorous patient selection was employed. Dystonia studies reported stable or improved cognitive scores, however one study using reliable change indices indicated decrements in sustained attention. Additionally, DBS outcomes were convoluted with changes in medication dose, alleviation of motor symptoms, and learning effects. In the largest, prospective TS study, an improvement in attentional skills was noted, whereas smaller studies reported variable declines across several cognitive domains. Although, most studies reported stable cognitive outcomes. ET studies largely demonstrated deficits in verbal fluency, which had variable responses depending on stimulation setting. Recently, studies have focused beyond the ventral intermediate nucleus, including the post-subthalamic area and zona incerta. For PD, the cognitive results were heterogeneous, although deficits in verbal fluency were consistent and related to the micro-lesion effect.

Conclusion: Post-DBS cognitive issues can impact both motor and quality of life outcomes. The underlying pathophysiology of cognitive changes post-DBS and the identification of pathways underpinning declines will require further investigation. Future

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studies should employ careful methodological designs. Patient specific analyses will be helpful to differentiate the effects of medications, DBS and the underlying disease state, including disease progression. Disease progression is often an underappreciated factor that is important to post-DBS cognitive issues.

Keywords: deep brain stimulation, cognition, Parkinson's disease, essential tremor, dystonia, Tourette syndrome, cognitive domains

INTRODUCTION

Deep brain stimulation (DBS) has become an area of active scientific inquiry for the treatment of movement and other neuropsychiatric diseases (1–3). Decades of research have largely focused on optimizing the preoperative evaluation, refining neurosurgical technique, advancing target selection, and improving postoperative management (4). The efficacy of DBS depends on quality clinical outcomes along with an acceptable adverse event profile. The prospect of short or long-term complications, particularly non-motor issues (e.g., cognitive changes), can dampen efficacy and enthusiasm for continued use. Information on adverse events and selection criteria can also help to better define the populations who will most benefit. Thus, careful attention must be devoted to the investigation of cognitive issues (5).

One of the most commonly reported non-motor issues that may emerge after DBS surgery for movement disorders has been neuropsychological dysfunction, including cognitive and emotional changes. DBS outcomes can be hindered by negative neuropsychological outcomes and by mild decrements revealed in detailed testing. These deficits may have demonstrable effects on quality of life (5–7). However, cognitive decline is a complex topic and may be associated with disease progression in many movement disorders such as Parkinson's disease (PD).

To progress toward a more precise understanding of cognitive decline after DBS surgery, we conducted a detailed review of the DBS literature focusing on cognitive outcomes across movement disorder cohorts. Separate cohorts are addressed in dedicated sections with neurosurgical target in subsections. We present an overview of current evidence to elucidate the present state of the field and to motivate improved methodological design of future studies, analyses, and devices. Consequently, improved surgical techniques, novel devices, expanding indications, and complex device management issues all may be impacted by cognitive issues.

METHOD

A PubMed search was conducted using the keywords "cognitive effects," "executive function," "cognition," "neuropsychology," and "neuropsychological" along with "deep brain stimulation." The retrieved abstracts as well as their references were reviewed for relevant studies. Studies focusing on dystonia, Tourette syndrome (TS), essential tremor (ET), and PD were included. Studies which included both preoperative and postoperative cognitive outcomes were included. Studies which included only postoperative assessments or acute tests (i.e., DBS on/DBS off) were considered if the testing was performed at least 3 months after lead implantation in order to control for postoperative cognitive dysfunction. Case studies were excluded, unless applied to less common implantation sites or diseases. **Table 1** summarizes the included cognitive domains and relevant tests associated with each domain.

DYSTONIA

Fifteen studies (12 globus pallidus internus (GPi), 2 subthalamic nucleus (STN), 1 GPi/ventralis intermedius (VIM) nucleus of the thalamus) reported the cognitive effects of DBS for primary and secondary dystonias. Contained within these studies, 243 patients were included in the analyses. In some studies, participants were unable to complete assessments due to disabilities from the disease state, thus, the number of participants completing each task could not be reported as absolute, especially in pediatric DBS cases (8–10). We summarize the cognitive tests administered and the significant changes reported within each dystonia paper (**Supplementary Table 1**).

Globus Pallidus Internus

Overall, cognitive measurements in chronic GPi stimulation remained stable among the 12 identified studies. No changes in cognitive battery were observed in Vidailhet et al.'s multi-center, prospective trial of 13 patients with dystonia-choreoathetosis cerebral palsy. This study examined measures of general intellect and executive functions one year after surgery (11). Two larger prospective trials that only used measures of global cognition [e.g., Mattis Dementia Rating Scale (DRS) and Mini-Mental State Exam (MMSE)] also reported no significant changes from pre- to post-DBS (2, 12). Improvements were observed in tests assessing memory (13, 14), cognitive set shifting (13), perceptual reasoning (8–10, 14), processing speed (15), verbal comprehension (8, 10, 14), verbal fluency (16), and executive function (14, 17).

Motivated by the limited cognitive battery used and varying results reported within previous GPi-DBS studies, de Gusmao et al. published a prospective study involving 12 patients with either primary or secondary dystonia. The authors reported a considerable improvement in their cohort post-DBS (average of 13.1 months) compared to pre-DBS on the Letter-Number Sequencing test of the Wechsler Adult Intelligence Scale (WAIS) or the Wechsler Intelligence Scale for Children (WISC) (a test of working memory). The cohort also experienced an improvement in Trail Making Test-B (TMT-B), which is a measure of executive function and processing speed, specifically cognitive

TABLE 1 | Cognitive domains and associated tests.

Cognitive domains	Tests
General cognition	Mini-Mental State Examination, Mattis Dementia Rating Scale, Reading subtest of the Wide Range Achievement Test, Montreal Cognitive Assessment, Parkinson Neuropsychometric Dementia Assessment
Attention, processing speed and working memory	Paced Auditory Serial Addition Test, Digit Span—WAIS/WMS, Letter-Number Sequencing—WAIS/WMS, Elevator Counting—Test of Everyday Attention, Self-Ordered Pointing Test, Benton Visual Retention Test, Arithmetic—WAIS, Digit Ordering Test, Conner's Continuous Performance Test, Trail Making Test—A, Symbol Digit Modalities Test, Coding—WISC/WAIS, Symbol Search—WISC/WAIS, Letter Cancellation—WISC/WAIS, Brief Test of Attention, Alertness—TAP, The "A" Test
Executive function	Wisconsin Card Sorting Test, Controlled Oral Word Association Test, Stroop Color-Word Test, Trail Making Test—B, Tower of London, Temporal Rule Induction, Frontal Assessment Battery, Delis-Kaplan Executive Function System, Go/nogo Test—TAP
Verbal memory	Hopkins Verbal Learning Test, Verbal learning—WRAML, Verbal Learning and Memory Test, Paired Associate Learning, Stories and Word Pairs—WMS/CMS, Rey Auditory Verbal Learning Test, Bi-syllabic Words Repetition Test, California Verbal Learning Test, Grober and Buschke Test
Visual and spatial memory	Faces—WMS/CMS, Dot Locations—WMS/CMS, Block Span—WMS, Nonverbal Learning Test, Recognition Memory for Faces, Corsi's Block Tapping Test, Complex Figure Test, N-back Task, Figural Memory—WMS, Brief Visual Memory Test
Language	Boston Naming Test, Graded Naming Test, Complex Ideational Material Test
Visuospatial perception	Judgement of Line Orientation, Hooper Visual Organization Test, Visual Object and Space Perception, Clock Drawing, Block Design (non-verbal)—WISC/WAIS, Copying Drawings, Line Cancellation, Multi-features Target Cancellation, Benton Facial Recognition Test, Constructional Praxis
Verbal fluency	Semantic Fluency, Letter Fluency, Phonemic Fluency, Category Fluency, Alternating Fluency
Intellectual ability	Vocabulary (verbal)—WISC/WAIS, Block Design (non-verbal)—WISC/WAIS, Matrix Reasoning (non-verbal)—WISC/WAIS, Picture Concepts (non-verbal)—WISC/WAIS, Picture Completion (non-verbal)—WISC/WAIS, Similarities (verbal)—WISC/WAIS, Comprehension (verbal)—WISC/WAIS, Multiple Choice Vocabulary Test, Graded Difficulty Arithmetic Test, National Adult Reading Test, Leistungsprüfsystem
Abstract reasoning	Raven Color Matrices, Raven Progressive Matrices
Motor speed and coordination	Halstead-Reitan Finger Oscillation, Luria's Fist Edge Palm Test, Grooved Pegboard, Sequential and Simple Tapping, Purdue Pegboard

WAIS, Wechsler Adult Intelligence Test; WMS, Wechsler Memory Scale; CMS, Children's Memory Scale; WRAML, Wide Range Assessment of Memory and Learning; TAP, Test Battery for Assessing Attentional Disorders.

set-shifting. There was a trend toward a decrease in semantic verbal fluency. There were no other evident changes on tests evaluating visual memory, language, and higher order visual processing (13). Improvements were noted in one retrospective review of 40 children with secondary dystonias who received bilateral GPi-DBS implants. The cohort had a substantial improvement in Picture Completion scores of the WAIS\WISC (9). Pillon et al. attributed post-DBS improvements in concept formation and reasoning [Raven Progressive Matrices (PM38)], executive function [Wisconsin Card Sorting Test (WCST)], and memory (Grober and Buschke Free Recall) to a reduction in anticholinergic medication. Anticholinergic therapy has been shown to be associated with a deleterious effect on memory and information processing (14). Another paper reported that individuals whose medication was unchanged after DBS experienced decrements in reaction times compared to subjects with medication reduction (15). Additionally, improvements within other cohorts were attributed to medication reduction, to the lessening of dystonic burden, and to compounding practice effects (9, 13–15). Although in one study whose only group level cognitive change was a significant improvement in Trail Making Test-A (TMT-A), the authors indicated that individual *post-hoc* analyses revealed both improvements and declines across the cognitive battery, stressing the importance of the need for both tailored therapies and reporting individual scores (15).

While some patients undergoing GPi-DBS for dystonia experienced improvement, several studies utilizing calculated methodologies [i.e., Reliable Change Indices (RCIs)] did not describe such results. RCI is a statistical measure that determines whether or not a change is clinically significant according to an individual's state before the initiation of therapy by considering a test measurement's reliability (18). In Jahanshahi et al.'s follow-up investigation of 14 patients with bilateral implants for primary generalized dystonia, the authors observed a worsening in the scaled score on Digit Span, fewer items recalled on Rey Auditory Verbal Learning Test (RAVLT), and a notable increase in errors on the Paced Auditory Serial Addition Test (PASAT). After calculating RCIs for each of these scores to determine which ones were statistically reliable, only the increase in errors on PASAT was significant. This result suggested a decrease in sustained attention in this cohort of patients, although the cohort did improve in tests of executive function, specifically on Stroop Color and the WCST (17). In another randomized, multi-center sham-controlled trial with 13 cervical dystonia patients, the only cognitive test that demonstrated detriments after 12 months was the number of words produced on alternating categories, which is a verbal fluency task. The authors hypothesized that

this impairment could be due to an interruption of fronto-subcortical circuits (i.e., dorsomedial GPi), which are involved in cognitive flexibility, caused by either current spread from DBS or a micro-lesion from electrode insertion (19). Interestingly, in a follow-up analysis from Gruber et al., patients with tardive dystonia tended to improve in category verbal fluency up to 7 years after surgery (16), suggesting that a decline in verbal fluency could be a micro-lesion rather than stimulation induced effect.

Within the only paper that reported bilateral implants in both the GPi and VIM for patients with myoclonus-dystonia, no change was observed within the cognitive battery, which included tests of general cognition, reaction time, executive function, working memory, verbal memory, processing speed, and verbal fluency (20). Patients were assessed at baseline (pre-surgery), 6 months, 12 months, and long-term at an average of 62.3 months. At these follow-ups, patients were also assessed in the following stimulation patterns (VIM/GPi): OFF/OFF, OFF/ON, ON/OFF, OFF/OFF. These stimulation patterns demonstrated a substantial difference between simple reaction time, a test used to assess alertness, with impairment observed in GPi in relation to VIM stimulation. These results suggested that stimulation may have a mild effect on cognitive outcome, or on specific cortical loops influenced by either the GPi or the VIM (assuming DBS leads are optimally placed).

Subthalamic Nucleus

Two investigations focused on cognitive outcomes in dystonia patients treated with STN-DBS. In Kleiner-Fisman et al.'s case series, four idiopathic dystonia patients experienced declines in executive function, verbal memory, visual memory, and language skills; however, no statistical testing was performed. As a whole, these patients were already impaired at baseline in multiple cognitive domains (21). In a prospective pilot study, 9 cervical dystonia patients were implanted with bilateral STN leads. Patients were impaired at baseline on tests for information processing speed (TMT-A and -B) and verbal delayed recall. Cognition was stable within 12 months after DBS implantation, suggesting that impairments in executive function and verbal fluency observed in STN PD patients may be due to underlying circuitry abnormalities inherent to PD, rather than stimulation or micro-lesion effects on the STN (22).

TOURETTE SYNDROME

Eight studies (3 GPi, 4 Centromedian-parafascicular (Cm-Pf), 1 GPi/Cm-Pf) reported the cognitive effects of patients undergoing DBS for TS. Within these studies, 52 patients were included in analyses. We summarize the cognitive tests administered and the significant changes reported within each TS paper in **Supplementary Table 2**.

Globus Pallidus Internus

All studies assessing the effect of GPi-DBS in TS patients revealed no change in assessments from baseline to follow-up (23–25). In Smeet and colleagues' open-label study with five TS patients, tests in attention, working memory, verbal fluency, and executive function were stable between preoperative and postoperative assessments (12–38 months) (25). In one case study, no change was observed at one year in the cognitive tests Verbal Learning Memory Test and Stroop, which are measures of verbal memory and executive function, respectively (23). Finally, Kefalopoulou et al.'s double-blind, randomized crossover trial in 15 bilateral patients demonstrated no alterations in cognitive functioning between baseline and open-label conditions; however, there was a significant effect of time on the California Verbal Learning Test (CVLT) Immediate Recall, on which patients performed worse in off-stimulation conditions (24).

Centromedian-Parafascicular Complex

Ackermans et al. explored the cognitive effects of DBS in a case study of two patients with follow-ups of 6 and 10 years. Case 1 (10-year follow-up) had stable scores in measures of verbal and non-verbal memory, executive function, mental speed, and attention. Case 2 had variable outcomes over the course of 6 years. This patient experienced post-operative worsening in letter verbal fluency, total numbers learned in 5 trials of the RAVLT, and a substantial increase in the time to perform the Stroop task, which eventually returned to baseline at 6 years (26). Although only two cases, this paper demonstrates the differential outcomes that can be observed under similar DBS paradigms, suggesting both the practicality of personalized stimulation paradigms or devices and the potential advantages of reporting individual outcomes rather than group averages. Ackermans et al. continued exploring this topic in a double-blind, randomized controlled trial, where there was a significant increase in the time required to perform the Stroop Color Word Test (SCWT) one year after DBS, which suggested a decrease in response inhibition and selective attention. The authors proceeded to perform RCIs, which concluded that only one patient performed worse in the SCWT (27). Much like Jahanshahi's analyses, RCIs explained which factors or patients drove significance and *post-hoc* tests proved essential to better appreciate the true effects of DBS (17).

To further eliminate confounding factors such as learning effects, Schoenberg et al. conducted a prospective, randomized trial with 4 TS patients, where they utilized alternate test forms. At baseline, the cohort was impaired in TMT-B, the written version of Symbol Digit Modalities Test, Continuous Performance Test (CPT-2) hit rate, and SCWT. At 5 months, the group demonstrated impairments in these measures as well as RAVLT-total words, letter fluency, and semantic fluency. The authors conducted Cohen's *d* tests to observe the effect sizes of these deficits. Deteriorations in semantic and phonemic verbal fluency were large, whereas the declines in CPT-2 hit rate and immediate memory from the visual memory task were moderate. Additionally, the improvement observed on the visuo-constructional skill task (Complex Figure Test) was a medium sized effect (28). Another prospective study found no changes in 15 patients after 24 months with bilateral implants in the Cm-Pf ventralis oralis anterior area except for an improvement on TMT scores. However, this paper did not explore measures of sustained attention or verbal memory (29). The differences in findings from these two studies suggested a potential micro-lesion effect from DBS surgery, which was demonstrated in the immediate deficits captured from Schoenberg's investigations. Furthermore, the

opposing results could have been attributed to the heterogeneity found between the two studies in the neuropsychological battery, implant area, sample size, or statistics. For instance, Porta's analyses used Wilcoxon-Signed Rank Tests; whereas, Schoenberg used standardized paired *t*-tests, corrected for multiple comparisons, and controlled the small sample size using false discovery rate.

Finally, Welter et al.'s double-blind, randomized, controlled, crossover trial reported the cognitive results of 3 TS patients with bilateral implants in both the GPi and the Cm-Pf. Neuropsychological battery remained stable between preoperative and postoperative follow-ups. The follow-ups were 2 months after surgery without stimulation, followed by four different stimulation conditions, which were applied and sustained for 2 months. The stimulation conditions were bilateral Cm-Pf, bilateral GPi, both bilateral GPi and Cm-Pf, and sham. Although this experiment involved stable cognitive functioning, conclusions should be approached with caution due to low sample size (30).

ESSENTIAL TREMOR

Six studies [1 caudal zona incerta (cZi), 2 ventrolateral nucleus (VL) of the thalamus, 3 VIM] reported the cognitive outcomes of patients following DBS for ET. Additionally, one analysis compared VIM-DBS in ET patients with STN-DBS in PD patients, whereas another study compared stimulation of the VIM between ET, PD, and multiple sclerosis (MS) cohorts. The complete cognitive batteries administered, and results have been summarized in **Supplementary Table 3**.

Caudal Zona Incerta

Fytagoridis et al.'s prospective pilot trial investigated the effects of DBS on verbal fluency in 17 patients at baseline and off stimulation at 3 days. There were also 10 patients tested at one year both on and off stimulation. There was a considerable reduction in verbal fluency 3 days after surgery, but this effect dissipated at one year both on and off stimulation. Therefore, this may have been a micro-lesion effect, however the sample size was too small to determine (31).

Ventrolateral Nucleus of the Thalamus

In their open-prospective study, Heber et al. conducted a series of neuropsychological tests on 9 ET patients implanted into the VL region of the thalamus. The subtest "Alertness" of the Test for Attentional Performance was used to assess patients. This subtest is a simple reaction time test that requires a patient to press a button upon detecting a visual stimulus. The patient performs four blocks, in which two blocks consist of no warning tone before the visual stimulus appears and two blocks consist of a warning tone before the stimulus appears. At one year, the patients were remarkably slower with DBS-OFF compared to both pre-surgery and DBS-ON, specifically in the blocks without warning tone. Using *post-hoc* analyses, the authors demonstrated that the differences between DBS-ON and -OFF were statistically different, whereas differences between DBS-ON and -OFF against pre-surgery reaction times were negligible. These results were consistent at 6 years as well. Tests of verbal fluency, memory, executive function, and intellect were preserved at 1 and 6 years after surgery. The authors noted that the surgical electrode trajectory did not impact reaction time tests, and those patients who had implantations through supplementary motor area and through other cortical entry points did not differ (32). Another investigation evaluated the acute effects of stimulation settings (i.e., high frequency vs. low frequency) on measures of verbal fluency (parallel versions), executive function, and working memory. There was a difference in both measures of verbal fluency under different stimulation conditions. Low frequency stimulation led to both better phonemic and semantic verbal fluency compared to high frequency stimulation (33). Similar results were demonstrated in a group of STN-DBS PD patients, where 10 Hz stimulation hindered motor improvement but improved verbal fluency (34). Since low frequency stimulation exacerbated tremor and high frequency suppressed tremor, Pedrosa et al. concluded these results potentially supported the idea of segregated networks for motor control and for higher cognition (33).

Ventralis Intermedius Nucleus of the Thalamus

In Tröster et al.'s outcomes study ($n = 40$), which compared baseline scores to 3 month post-operative scores, there were significant improvements in DRS-Construction subtest, visual span backwards, Hooper Visual Organization Test, Grooved Pegboard, Delayed Word Recognition of the CVLT and Delayed Prose Recall, measured by Logical Memory II of Weschler Memory Scale (WMS) (35). The only significant decrement was observed in lexical verbal fluency, however, concurrently, there was an improvement on the communication score measured by the Parkinson's Disease Questionnaire-39, which is a quality of life scale. Although most of the group level comparisons demonstrated improvement in scores, individual analyses revealed reductions on the DRS subscales Attention, Initiation, and Perseveration. Additionally, the authors speculated that improvements in visual attention, working memory, and visuoperceptual functioning may have been caused by thalamic stimulation facilitating an attentional gating mechanism, therefore, stimulation aided in filtering out extraneous information and enhanced interhemispheric information transfer. This hypothesis could additionally support Heber et al.'s finding of improved reaction time during on stimulation trials compared to off (32). In a tandem study, Fields et al. investigated the cognitive outcomes at 12 months in mostly the same cohort as Tröster's outcomes study (36). All improvements were maintained at 12 months, with additional improvements in CVLT Immediate Recall, Short-Delay Recall, Long-Delay Recall, and Recognition Hits from baseline to 12 months, and in CVLT Immediate Recall and DRS Conceptualization scores from 3 to 12 months. Although, the authors stated that the gains observed may be due to practice efforts. In terms of cognitive declines, lexical verbal fluency remained diminished at 12 months, with 4 additional patients demonstrating declines in semantic verbal fluency.

Determined to tease apart the underpinnings of cognitive decline, one study separated patients who experienced cognitive decline after DBS from those who did not (37). The authors defined those who had decrements (ET-D) as patients who decreased by one standard deviation compared to baseline assessments in one or more cognitive tests and in at least two domains of function, which included global cognitive functioning, attention, executive function, language, visuoperception, and learning and memory. This study demonstrated that ET-D patients did not have more severe tremor and were not significantly older or cognitively lower functioning at baseline. ET-D patients had significantly higher pulse width settings and were more likely to have undergone left hemisphere DBS compared to stable participants. Patients with greater pulse width settings ($> 120\ \mu s$) were 10 times more likely to exhibit postoperative cognitive decline, which the authors attributed to current spread into adjacent VIM association fiber tracks. Additionally, pulse width settings and age at disease onset accurately predicted whether a patient was in the stable or decrementing cognitive group. These results demonstrate the attention to detail that must be utilized within the clinic to safely and effectively determine programming settings. Furthermore, these results highlight the importance of patient selection to ultimately minimize the risk of cognitive deficits.

Comparative Studies

One paper investigated the differential effects of stimulation on verbal fluency in patients with PD (STN), ET (VIM), and healthy controls (38). Both DBS groups uttered fewer words when compared to healthy controls, however there were no substantial differences between the DBS cohorts. There was a considerable effect of task demand (i.e., phonemic vs. semantic). When comparing DBS-ON vs. -OFF, there was a significant interaction between group and stimulation state. *Post-hoc* analysis revealed that there was a notable reduction in the number of words produced during DBS near the VIM, particularly in phonemic fluency. Conversely, DBS in the STN improved phonemic fluency. The error rate, specifically the types of "wrong category" and "word stem repetition," was also substantially reduced by VIM stimulation. Furthermore, Ehlen et al. investigated the correlations of these outcomes in STN stimulation. Stimulation amplitude and the electrode trajectory were key predictors for the change in phonemic fluency, in which higher stimulation amplitude and more anterior locations correlated with better verbal fluency. The authors speculated that stimulation within the STN restored impaired left fronto-cortical functions. These same predictor variables were included in the VIM, but increasing stimulation caused decreased verbal fluency. Another relationship uncovered was that electrodes located more posterior and dorsolateral were associated with better verbal fluency scores, thus, electrode trajectories may have influence on cognitive outcomes (38). Similarly, Loher et al. investigated the effects of stimulation within the VIM in PD, ET, and MS patients. Stimulation deteriorated the number of words recalled on the short delay recall of the RAVLT in all groups, and demonstrated an alteration in episodic memory, which was related to left-sided stimulation and altered simple reaction times (39). These results verified that in this subset of patients, episodic memory was influenced by stimulation and not a micro-lesion effect. Additionally, impairments in frontal lobe tests (Stroop, verbal fluency, Go/nogo of the Test Battery for Attentional Disorders), constructional praxis, and cognitive processing speed (Alertness of the Test Battery for Attentional Disorders) were observed under stimulation off and on conditions, and changes were most evident in the PD cohort. These studies ultimately stress the importance of truly delineating the underlying causes of cognitive declines post-DBS.

PARKINSON'S DISEASE

There are numerous papers investigating the cognitive side effects following DBS for PD, and we have divided the summary into the following sections: outcome studies with a control group, outcome studies without a control group, correlation studies, studies that included new DBS techniques, and studies that compared the outcomes of GPi- vs. STN-DBS.

Within the literature search, 19 studies (all STN) included a control group, 29 studies did not include a control group (24 STN, 4 GPi, 1 VIM), 10 (9 STN, 1 GPi) were correlation studies, 3 included either new stimulation or surgical techniques for DBS (1 STN, 2 GPi and STN), and 12 compared STN and GPi outcomes. Within the controlled studies, 650 DBS patients were included with 433 controls (40 with DBS implants). Within studies without a control group, 704 (60 GPi, 9 VIM) DBS patients were included. Correlation studies included 304 (14 GPi) patients, new technique studies included 160 patients (25 GPi) with 65 controls, and studies that compared pallidal vs. subthalamic outcomes had 519 GPi patients and 579 STN patients. Information regarding the cognitive assessments utilized and the outcomes are in **Supplementary Tables 4–8**, respectively.

PD Outcome Studies With a Control Group

In studies that followed both patients that had undergone DBS and patients solely being treated with drug therapy, DBS patients either experienced declines in performance over time that were not evident in controls or were significantly impaired when directly compared to controls, namely in the following cognitive domains: verbal fluency (40–49, 51–55), executive function (40, 45–49, 51–54, 56), general cognition (49, 51, 54, 55), visuospatial reasoning and memory (49, 53), processing speed (53, 56), and verbal memory (45–47, 49, 51, 56). In a two-year follow-up analysis, STN-DBS patients exhibited impairments on tasks involving non-verbal recall, processing speed, and verbal fluency (both phonemic and semantic). A trend was observed for problems with SCWT. The authors used RCI to draw conclusions solely based on the effects of DBS on cognition and to delineate these effects from PD progression. After computing RCIs, the percentages of patients in both the STN-DBS ($n = 19$) and PD control group ($n = 18$) that deteriorated on non-verbal recall, processing speed, phonemic verbal fluency, semantic verbal fluency, and executive function were 47 vs. 25%, 53 vs. 28%, 26 vs. 11%, 29 vs. 29%, and 43 vs. 18%, respectively (53). Within the 6-month outcomes, the STN-DBS group deteriorated on verbal delayed recall and verbal fluency when compared to PD controls.

When the authors considered age of onset, education level, and dopamine dosage, the worsening of verbal fluency was negligible, even though 26% of patients in the STN group performed worse on the task compared to only 4% of the controls (56).

In a similar long-term analysis, Tramontana et al. noted that DBS patients had deficits in phonemic fluency and on several subtests of the WCST at two-year follow-up compared to controls. However, when the authors eliminated patients who suffered from an adverse event in the DBS cohort, these differences were trivial (52). Sáez-Zea et al.'s prospective, controlled study found a correlation between more reduction in medication and a greater reduction in phonemic verbal fluency (48). Similarly, Smeding et al. reported that decreases in DRS and the Auditory Verbal Learning Test were correlated to low levodopa at baseline, emphasizing the importance of preoperative screening for optimal patient outcomes (51). Additionally, the STN group performed worse on all measures of verbal fluency, on Attention and Initiation of the DRS, on delayed recall, and on SCWT compared to controls at 6 months, although, apart from delayed recall (verbal memory), these declines were not due to negative side effects from surgery, electrode misplacement, or reduction in medications. Thus, the authors stated the outcomes may be linked to executive dysfunction stemming from PD. All these papers collectively indicate the importance of controlling for confounding factors when analyzing the cognitive effects of DBS, and the importance of patient selection.

There were some instances when the DBS group either outperformed or remained stable in comparison to the control group. In one analysis, controls tended to perform slightly worse in TMT-B at follow-up. In addition, the authors found a correlation between higher age and an increase in time to complete TMT-B, which they attributed to PD progression (48). In Zangaglia et al.'s long-term controlled study, the authors observed trends for improvement on Verbal Span, Digit Span, Corsi's Block Tapping Test, and Logical Memory Test, which are all measures of memory at 3 years after surgery; whereas, controls had a considerable decrease in WCST and MMSE at 3 years. Although there was a trend toward increased scores in memory assessments, the authors stated that it could have been a learning effect that masked deterioration since alternate versions were not used. Furthermore, the test results were confounded by impairments noted in the WCST (55). Finally, when using RCIs, Williams et al. observed a significant interaction for clock drawing, a visuospatial task. PD controls tended to become more impaired at 2 years with 47% declining in contrast to only 16% in the STN-DBS group (53). However, in one investigation, visuospatial functioning was impaired in both groups at one year (45), and notably impaired only in the STN-DBS group at one year in another analysis (49). These results support the notion that treatment needs to be tailored toward the patient, and that more emphasis needs to be placed on follow-up times, neuropsychological batteries used (i.e., alternate tests), and how to control for confounding factors.

Although most studies reported in this review had control groups that were PD patients on optimal medical therapy, a few studies focused on other comparisons. For example, two studies focused on the underlying cognitive differences after DBS and pallidotomy (57, 58). In Gironell and colleagues' 6-month outcomes study, STN-DBS patients declined in semantic verbal fluency, whereas they remained stable in measures of executive function (SCWT and TMT-B) (57). However, in another study, STN-DBS patients at 6 months experienced an increase in the total number of errors on SCWT and TMT-B, while the control group demonstrated improvement (58). Additionally, the increase in errors on SCWT was significantly correlated with lower baseline DRS scores at 6 months post-operatively, further demonstrating that cognitive changes can be heavily influenced by the individual patient and test battery. Finally, Merola et al.'s retrospective observational study classified one group as normal cognition STN-DBS patients ($n = 134$) and another as mild-cognitively impaired (MCI) STN-DBS patients ($n = 40$). Both patient groups were comparable at their follow-up times in tasks quantifying visuospatial functioning, memory, and processing speed, except for one-year follow-up, where normal cognition patients performed worse on phonemic verbal fluency. The authors credited this result to the baseline of the MCI group which revealed significant impairment. Though the two groups were comparable on neurocognitive assessments, the MCI group had a markedly lower estimated time until dementia (6.03 years) compared to 11.08 years in the normal cognition group (50). These results support that STN-DBS is cognitively safe, even when used to treat patients that are mildly impaired.

PD Outcome Studies Without a Control Group

When analyzing studies not including a control group, impairments observed were remarkably similar to DBS patients within controlled studies. DBS patients exhibited deteriorations after surgery compared to preoperative performances in tasks of verbal fluency (59–77), memory (59, 62, 64, 66–68, 71, 72, 75, 77), executive function (59, 60, 64, 67, 69, 71, 72, 76–80), attention (66, 71), visuospatial functioning (59, 72, 75), global cognition (62, 74, 78), abstract reasoning (62), and processing speed (64, 72, 76, 77). A few studies observed no cognitive changes up to 3 months (81), in which individuals who did decline were significantly older, had higher levels of levodopa at baseline, and all had left implants in the GPi, up to 6 months (82, 83), and up to 5 years (84), in which there was a trend for a decline in verbal fluency. Within other studies, the outcomes of verbal fluency were variable. Some authors described an improvement, albeit not to baseline levels, of verbal fluency in the long-term compared to an initial substantial reduction in scores, supporting the possibility of a micro-lesion effect (60, 70, 76). In Lefaucheur et al.'s short-term outcomes, patients had an acute significant reduction in verbal fluency 3 and 10 days post-operatively, however their scores had a reliable improvement at 6-month follow-up (70). In another study, patients had a significant reduction at one month on both semantic and phonemic verbal fluency, but phonemic completely recovered and semantic was improved at the 12-month follow-up (76). However, most studies reported verbal fluency impairments one or more years later after DBS as compared to baseline (61–63, 65–67, 69, 71, 72, 77, 85),

suggesting disease progression rather than lesion effects. In GPi-DBS outcomes papers, most studies did not identify a reduction in verbal fluency, with the exception of one (74), suggesting the possibility that the STN and related circuits may have a more substantial role in verbal fluency processing (78, 81, 86).

In four studies that followed patients post-operatively 5 years or more, patients had a significant decrease at 5 years on total and Perseverative Errors on the WCST (executive function) (77), verbal fluency (62, 77, 85), Raven's color matrices (reasoning) (62, 77), and delayed recall of the RAVLT (memory) (85). In Kishore and colleagues' study ($n = 47$), there were no significant cognitive declines at 5 years, however, when analyzing individual scores, there were 10 patients who declined in verbal fluency compared to one at baseline (84). Similarly, individual analyses revealed several cognitive declines that were not observed in Contarino et al.'s group assessments (62). At their long-term follow-ups, 8 (85) and 9 (77) years, patients had deteriorations in the Bi-syllabic Words Repetition Test (BWR) (77), TMT-B (77), verbal fluency (77, 85), and Immediate Recall on the RAVLT (85). In Zibetti et al.'s study, dementia developed in one patient at one-year, 2 patients at 5 years, and 4 patients at 9 years or more (77). These decrements could possibly have been due to disease progression.

Many studies reported deficits in executive function and memory. In Rizzone et al.'s 12-year long-term follow-up, patients had a significant worsening in contrast to baseline on short-term memory (Corsi's Block Test Forward), episodic memory (Immediate and Delayed Recall on the RAVLT), executive function (WCST) and attention (Attentive Matrices). The authors attributed these findings to be expected in advanced PD patients, especially since 22.7% of patients developed dementia in their cohort (71). Another investigation with a one-year follow-up initially reported a notable impairment on tasks of executive function (Stroop) but the scores eventually recovered, although were considerably worse than baseline measures (76). Heo et al.'s one-year follow-up study also reported a substantial reduction on both tasks for verbal memory and Stroop test at both 6 and 12 months (67). These effects were not solely in STN-DBS patients with Bonenfant and colleagues reporting a significant worsening in SCWT and Stroop Interference at 3 years in comparison to baseline within a GPi-DBS cohort. Although the authors reported stable scores on the WCST, there was an overall reduction in general cognition (78). One study observed an improvement in memory, which the authors attributed to practice efforts (73) and another investigation observed increased memory until one year after the surgery followed by deficits at 5 and 10 years (69). Similarly, one study reported improvement in TMT-B in 24 unilateral STN patients (87). Interestingly, in the only study involving the VIM in PD, there were significant improvements in Delayed Recognition of the CVLT and Delayed Recall of WMS-Logical Memory (88), although the authors stated that they could not demonstrate if these improvements were clinical relevant. The heterogeneity of these results reveal the complexity of PD post-DBS. Such variations in outcomes within and across studies may relate to age, disease duration, medication, neuropsychological instruments, electrode localization, and time of follow-up and reassessment. These factors should be controlled and considered, especially in studies lacking a control group.

Correlation Studies

Many studies investigated the influence of the following factors on neuropsychological outcomes: volume of tissue activation (VTA), white matter lesions (WML), electrode trajectory, active contacts, brain perfusion, and microelectrode (MER) tracks. One retrospective study explored the relationship between deficits in verbal fluency and number of MER passes, and concluded that there were no correlations between PD duration, MER passes, baseline cognition, stimulation parameters and verbal fluency. However, verbal fluency scores were correlated with age (89). Mikos et al. investigated the relationship between VTA, which represents neuronal activation, within the STN and verbal fluency (alternate forms) in 17 PD patients (90). The stimulation paradigms examined were no stimulation, optimal stimulation, ventral stimulation, and dorsal stimulation. There were no differences in verbal fluency scores among the three electrode contacts, but other relationships were reported. Optimal stimulation correlated positively with VTA inside the STN and letter fluency change scores, meaning more VTA within the STN was associated with better fluency scores compared to off stimulation, which corroborated results from Ehlen and colleagues' study (38). However, with ventral stimulation, there was a negative association with VTA and STN, implying that a larger volume of VTA inside the STN was associated with worse letter fluency performance relative to off stimulation. These relationships were not observed with category fluency, which the authors attributed to category fluency relying more on the temporal lobe. Whereas, letter fluency relies more on fronto-subcortical structures with an abundance of projections to the STN, making letter fluency potentially more susceptible to stimulation (90). This assertion was the opposite of what Cilia and colleagues reported using brain perfusion imaging, where they noted that decrements in category fluency were related to hypoperfusions in dorsolateral prefrontal and anterior cingulate, both frontal lobe regions, in addition to the ventral part of the caudate and premotor cortex (91). However, Mikos' study demonstrates that a reduction in verbal fluency may not only be due to surgical impact, but also influenced by stimulation. Interestingly, these methods were repeated in 14 GPi patients, and no significant relationship was discovered between the magnitude or location of VTA and verbal fluency performance (92). This finding supported the possibility that GPi stimulation and surgery impact verbal fluency less than STN. Bonenfant et al.'s study was supportive of this idea (78).

In Blume et al.'s retrospective review focusing on WML, 40 patients with bilateral STN implants were analyzed. The authors developed a cognitive composite score (CSS) to correlate cognitive dysfunction with WML. All tests scores were transformed into z-scores by averaging the scores of five domains (attention, executive function, language, memory, visual-constructive). After 3 years in 17 patients, substantial reductions were reported in semantic verbal fluency, TMT-A, and the Block Design Test. Fifteen of these patients fulfilled the criteria for PD-MCI or PD dementia (PD-D), in which 10

patients developed PD-D 3 years after DBS with four occurring within the first post-operative year. The only considerable differences between PD-D and non-demented patients were age and occurrence of hallucinations at baseline. WML were associated with age and one or more cardiovascular risk factors. Patients who developed PD-D had a higher volume of WML at baseline compared to non-demented patients. Likewise, a worsening of CSS was correlated to the volume of WML after correction for age in a linear regression analysis (93). This study demonstrated that declines in cognition could be influenced by several factors.

Five studies investigated STN electrode trajectory or contacts. One study considered if lead trajectory involving the caudate was correlated with cognitive dysfunction. TMT-B decreased substantially more in the caudate involved group in contrast to the group that did not have caudate disruption at 3 months. At 12 months, TMT-B was markedly reduced in both groups with a greater decrease in the caudate involved group. Verbal fluency notably worsened in both cohorts compared to baseline assessment. Since performance was decreased in both groups, these results contradict the hypothesis that caudate involvement has a substantial effect on verbal fluency (94). In Witt and colleagues' lead trajectory analysis, patients who exhibited decrements on DRS and Digit Span Backwards had trajectories that were more medially located which resulted in a greater overlap in the caudate nucleus compared to stable performers. Whereas, stable performers had more lateral trajectories, resulting in greater lesions within the basal ganglia, specifically the globus pallidus. Patients that worsened on both Stroop task and semantic verbal fluency had electrode positions outside the stimulation area of the left STN, which, for semantic verbal fluency, confirmed the results of Mikos et al.'s investigation that more VTA within the STN region resulted in a better performance on verbal fluency (90, 95). Additionally, patients who performed worse in semantic fluency had ventral electrodes positioned in the left STN. This result was similar to Smeding et al.'s case study, where ventral contact activation in both hemispheres demonstrated declines in verbal fluency, but this effect was lessened after dorsal contact stimulation (96). Ventral stimulation in the STN has been speculated to produce more cognitive and mood-related effects, since the sensorimotor region is located posterior and dorsolateral (97). However, the authors noted that the ventral contacts were located outside the STN, namely placed within the internal capsule and dorsomedial globus pallidus externus (96).

York et al. found that if a patient's ventricles, not the caudate nucleus, were involved within the DBS lead trajectory, they demonstrated greater impairments on verbal long-term memory and verbal fluency following DBS surgery. Declines in MMSE, DRS, long-term verbal memory, short-term verbal memory, verbal fluency and semantic fluency were correlated with electrodes placed more lateral in either hemisphere, superior in the left, posterior lateral in the left, lateral in the right, posterior and superior in the left hemisphere, and superior in the right, respectively (98). One study found that patients who had trajectories with a more anterior cortical entry, which ultimately spared or passed through less of the thalamus, had greater reductions on semantic fluency, while there were no relationships between lead trajectory and phonemic verbal fluency (99). Finally, Floden et al. explored the relationship between active contact and cognitive alterations. Semantic fluency decreased with more medially located active contacts in the left hemisphere; whereas, phonemic fluency decreased with more posterior left-sided contacts. In the right hemisphere, there was a significant relationship between increasing stimulation voltage and worse single trial learning on the RAVLT (verbal memory) (100). These studies demonstrate that cognitive outcomes may be tricky to interpret and that pre- vs. post-operative scores may not be enough. In the future, directional DBS leads may be shown to be advantageous for avoiding cognitive deficits (100).

Different Study Designs and Techniques in PD

One trial explored the effects of constant current DBS devices vs. the standard constant voltage (101) with neuropsychological outcomes reported in a second study (102). In this randomized controlled trial, 101 patients were treated with active stimulation, while 35 underwent delayed stimulation until the 3-month follow-up. At 3 months, both groups had significant impairments in category and switching fluency. The stimulation group had notable reductions on all parts of the Stroop and on letter verbal fluency, with improvements on several measures of memory; whereas, the control group had considerably worsened in the Initiation score of the DRS. At 12 months, the Vocabulary subtest of WAIS, verbal fluency and Stroop significantly declined, while measures of working memory increased (102). These results are comparable with devices using constant voltage. This study revealed that verbal fluency was primarily a surgical and not stimulation induced effect, though stimulation may also possibly be a minor factor in the decline.

Two studies explored the outcomes of using image-guided DBS instead of the traditional MER technique. In Brodsky et al.'s study, patients who underwent image-guided DBS (7 STN and 23 GPi) had a substantial improvement in category fluency at 6 months, while patients who underwent standard DBS surgery (MER-guided) had a decline in category fluency (18 STN and 21 GPi). Additionally, the difference in verbal fluency was significant between both groups. Phonemic fluency was unchanged in the asleep group but was considerably worsened in the awake group. DRS remained stable in both groups at 6 months (103). However, the sample size was too small to definitively conclude the superiority of one approach. Although, another study assessing asleep guided DBS (16 STN and 4 GPi) found a mild decrease in scores for category fluency, Complex Figure Copy and memory at one-year follow-up (104). Though, this study did not use statistical techniques. The difference between these two studies could have possibly been the time between follow-ups, selection of patients or differences within targeting methods.

Comparison of GPi vs. STN Stimulation in PD

Whether GPi or STN stimulation offers equal motor benefits while avoiding long-term cognitive or mood side effects has

been an important question within the DBS field (105). Several longitudinal studies have sought to answer this question by comparing both DBS groups (106–114), while others compared each stimulation group against one another and a control group (115–118). Determined to enhance the evidence supporting the difference in cognitive outcomes between unilateral STN (n = 22) and GPi (n = 23), Okun et al. conducted a prospective, randomized trial (111). To evaluate regional settings, the investigators stimulated under four different paradigms: ventral, dorsal, optimal, and off. In the optimal setting, the STN group had a worsening in letter verbal fluency compared to GPi, but this finding did not reach pre-defined significance. This phenomenon persisted regardless of stimulation setting, suggesting that this was an insertion or lesion effect. When observing post-surgical cognitive adverse events across groups, the GPi-DBS group had 12 (2 serious) adverse events with difficulty in speech and language, while STN had 8. Additionally, GPi-DBS had 3 adverse events in worsening of memory, whereas STN had 2, suggesting the importance of both individual and group level analyses.

In Odekerken et al.'s one-year follow-up study, bilateral STN (n = 56) and GPi (n = 58) groups notably differed on SCWT, TMT-B, and were borderline different on WAIS Similarities, which were all worse in the STN-DBS group. These results suggested STN-DBS may have a considerable effect on mental speed, attention, and language. Seventeen patients in the GPi group exhibited cognitive decline, whereas 22 patients exhibited worsening in the STN group. Moreover, the authors reported independent predictors of cognitive decline, which included age and semantic fluency at baseline (110). Within the 3-year follow-up of the same cohort, no clinically relevant differences were evident on cognitive measures between the two groups. Dementia incidence was similar between both groups, with 4 patients in the GPi group and 5 in the STN (107). In another 2-year follow-up study, the only difference between the GPi (n = 152) and STN (n = 147) groups was within the processing speed index driven by the digit symbol visuomotor task, which declined more in the STN group (108). After 3 years in the same cohorts, the groups differed substantially on the DRS between 36 months and baseline and on the Hopkins Verbal Learning Test (HVLT) total and Delayed Recall (36 months vs. 6 months and baseline), which showed no change in the GPi group (114). The authors did not adjust for differences found at baseline between the groups or other covariates. Overall, these studies demonstrated potential differences in cognition between targets.

Other studies investigated the differences between the two surgical targets and a control group. In Rothlind et al.'s prospective, randomized, controlled trial, two between group differences were observed at 6 months between GPi and STN. STN worsened to a greater extent in Stroop Word Reading; whereas, the GPi group declined more in performance on the HVLT. Since the differences were minimal, the two DBS groups were pooled and contrasted with the best medical therapy cohort. This resulted in the DBS group demonstrating greater deficits in multiple measures of processing speed and working memory. After performing RCIs, the two DBS groups considerably differed on Digit Symbol Coding, a measurement of processing speed, with 11.1% of the STN group indicating impairment compared to only 1.3% in the GPi-DBS cohort (116). The next two studies attempted to address two methodological issues within the literature, namely, lack of PD control groups and focusing solely on group mean differences. The first study focused on a specific collection of cognitive tasks that activated the dorsolateral prefrontal cortex (DLPFC), stemming from the hypothesis that current spread to the associative basal ganglia-thalamocortical loop of the GPi and STN would affect the DLPFC. The control and DBS group markedly differed on letter fluency and semantic fluency compared to baseline, but letter fluency issues persisted and were notably impaired in the DBS group even after controlling for disease duration and Unified Parkinson's Disease Rating Scale-III off-score in the analysis of covariance. In the GPi group, medication dosage change negatively correlated with change in letter fluency. Additionally, the side of surgery was significantly related to the change in semantic fluency. Patients who underwent right-sided surgery presented with an increase in performance, albeit slight, of 0.88 points; however, patients who underwent left-sided surgery experienced a decrease of 14 points. Using RCIs, only one out of 8 patients worsened on semantic fluency for right-sided surgery; whereas, 8 out of 14 patients with left-sided surgery declined on the same measure (118). In another study, there was a main effect of time for the visuospatial multivariate analysis of covariance, implying all participants (DBS and PD controls) demonstrated lower scores on visuospatial tests. *Post-hoc* analyses revealed a worsening only on the Judgement of Line Orientation, not facial recognition test. At 12 months, DBS patients performed remarkably worse on tests of processing speed. For TMT-A, there was a significant interaction between group and time, but for Stroop Word Reading, there was only an effect of time, suggesting both groups were impaired. Using RCIs, a greater proportion of DBS patients demonstrated a reliable decline from baseline to 12 months on the HVLT Immediate and Delayed Recall, TMT-A, Stroop Word Test, TMT-B, and SCWT. However, a greater proportion of DBS patients also displayed reliable improvement from baseline to 12 months on SCWT and Judgment of Line Orientation (115).

In one study, the control group was composed of patients who underwent unilateral pallidotomy (117). Across groups (left pallidotomy, STN-, GPi-DBS), there was a significant decrease in phonemic verbal fluency. Within left unilateral pallidotomy patients, a worsening of working memory, measured with Digit Span Backwards, was reported, whereas only a trend was observed in STN-DBS patients. Additionally, left pallidotomy patients were impaired on verbal learning, specifically total score of the CVLT. Pallidotomy patients also improved in attention measured with PASAT. DBS, specifically STN, declined on executive functions (TMT-B), Long Delay Free and Cued Recall of CVLT, and visuospatial reasoning measured by the Battery for Memory Efficiency. The authors noted that there was a significant effect of age in the STN-DBS group, warning that patients >69 years of age are at more of a risk for cognitive changes. Overall, the authors stressed the importance of baseline cognitive status, test sensitivity, and using alternate versions. These findings emphasize the importance of controlling for these confounding effects across any type of cognitive study.

To further delineate effects of stimulation vs. surgery, Pillon et al. assessed STN-DBS and GPi-DBS patients while the stimulators were both on and off 3 to 12 months post-DBS (112). Improvements in Graphic Motor Series, SCWT, TMT-A, and TMT-B were noted in the STN-DBS cohort, whereas no differences were marked in DBS-on and -off states for GPi. The authors attributed the improvements in the SCWT, TMT-A and -B to improvements in psychomotor speed, since no significant changes were noted in cognitive speed for Stroop Interference or the difference between TMT-A and -B. In a similar study by Jahanshahi et al., PD patients were assessed on several tests of executive function off-stimulation, on-stimulation, and then off-stimulation, again (109). While stimulation was off, there were no significant differences between bilateral STN- and GPi-DBS groups. While stimulation was on, the authors found four different outcomes within their neuropsychological testing results. Both STN and GPi stimulation demonstrated improvements in TMT-A, TMT-B, their difference, Paced Visual Serial Addition Test, missing digit, and Control of SCWT compared to off-stimulation conditions. For conditional associative learning, both STN- and GPi-DBS deteriorated performance. STN and GPi also demonstrated different outcomes on TMT-B, TMT difference, Perseverative Errors of the WCST, and measures of random number generation, which in all cases, STN substantially improved responses. The authors speculated that this result stems from STN's differential impact on DLPFC, compared to GPi. Finally, stimulation did not change results on verbal fluency and on measures of seriation within random number generation. The authors did caution that chronic DBS may have different cognitive outcomes compared to this study, since subjects were assessed 2–26 months after surgery (109). These studies were successful at measuring the acute effects of DBS with fairly similar results for STN- and GPi-DBS outcomes, but chronic studies have shown decrements rather than improvements in the same or similar neuropsychological tests within the STN (108, 110, 115, 117).

CONCLUSION

DBS therapy has mixed cognitive outcomes across studies, targets, and methodologies. The expansions to new indications such as Alzheimer's disease (119) or addiction (120), to various age groups (121, 122), and to novel surgical targets (123, 124) should prompt a consideration of the factors that may lead to cognitive decline. Overall, this review highlights the lack of large, well-controlled and powered studies reporting cognitive effects of DBS and highlights heterogeneity in methods. Additionally, it emphasizes the various contributions to cognitive alterations (**Figure 1**). The pathophysiological mechanisms of cognitive modifications post-DBS are intricate and individually variable, consequently, the evidence provided in this review can only partially delineate the true factors involved in cognitive ramifications. The primary DBS targets for movement disorders are within the basal ganglia, a set of nuclei linked to cortical areas (i.e., DLPFC, lateral orbitofrontal, and anterior cingulate) through several cortico-striato-thalamo-cortical loops (126, 127), which are known to not be anatomically separate; thus, these disorders present with a myriad of symptoms, including cognitive dysfunctions (128, 129). Additionally, DBS may propagate through these loops, initiating modifications of influenced brain circuits, increasing the difficulty in pinpointing the true causes of cognitive dysfunction post-DBS (130, 131).

From several electrophysiology studies, it has been speculated that dystonia arises from increased inhibition of both the STN and GPi by inputs from the globus pallidus externus, causing disinhibition of the thalamus and increased excitation to the cortex (132). Pathophysiology of cognitive modifications in dystonia after DBS is not concrete, but a few theories have been postulated to explain potential dysfunctions: anti-dystonic medications affecting memory (133, 134), concurrent mood disorders (i.e., depression or anxiety) leading to impairments in executive function or other cognitive domains (135–138), or severe motor impairments shadowing intact cognitive functioning (139, 140). Altogether, evidence suggests that dystonia patients have intact global cognition, language and memory, while isolated incidents of impaired executive function and sustained attention may stem from fronto-striatal abnormalities (137, 140, 141). The DBS studies reviewed do not recall potential cognitive circuits disrupted during DBS, but many conclude that changes post-DBS are congruent with a decrease in anti-cholinergic medication (14, 15), a lessening of burden from suppressing motor symptoms of dystonia (9, 13), already present executive dysfunction or impaired sustained attention (17), or practice effects of the task (9, 13). The evidence in this review for dystonia fails to separate effects of DBS and of the aforementioned factors. However, studies attributed decreases in verbal fluency to unspecific stimulation spread to neighboring structures, especially the dorsomedial GPi, disrupting the fronto-subcortical circuit, or to a micro-lesion effect (13, 16, 19). Altogether, the evidence suggests that DBS improves other burdens of dystonia (i.e., medication dose, motor fluctuation severity), which in turn improves or worsens cognition within dystonia cohorts. Although, this review does not separate the cognitive outcomes based on dystonia type, thus, the conclusions may not be accurate across the variations of dystonia. Dystonia studies could have benefited from a control group, which would be necessary to correct for confounding factors such as disease progression, aging, re-test efforts, and even teasing out stimulation or lesional effects.

Similar to dystonia, TS is thought to arise from disinhibition of thalamo-cortical circuitry due to decreased activity of the striatum causing excessive activation of fronto-cortical areas (142). Overall, the cognitive profile of TS has been associated with deficits of executive function, inhibitory control, and cognitive flexibility; however, these aspects are convoluted with comorbidities such as attention deficit disorder and obsessive-compulsive disorder, which can exacerbate neurocognitive impairments. Thus, it is difficult to disentangle the causes of such impairments within TS cohorts (143, 144). The DBS studies within this review reported stable cognitive scores after GPi-DBS (23–25) and some impairments reported after thalamic DBS, yet, many of these impairments were driven by one patient (26, 27) or convoluted by baseline cognitive impairments (28). Studies

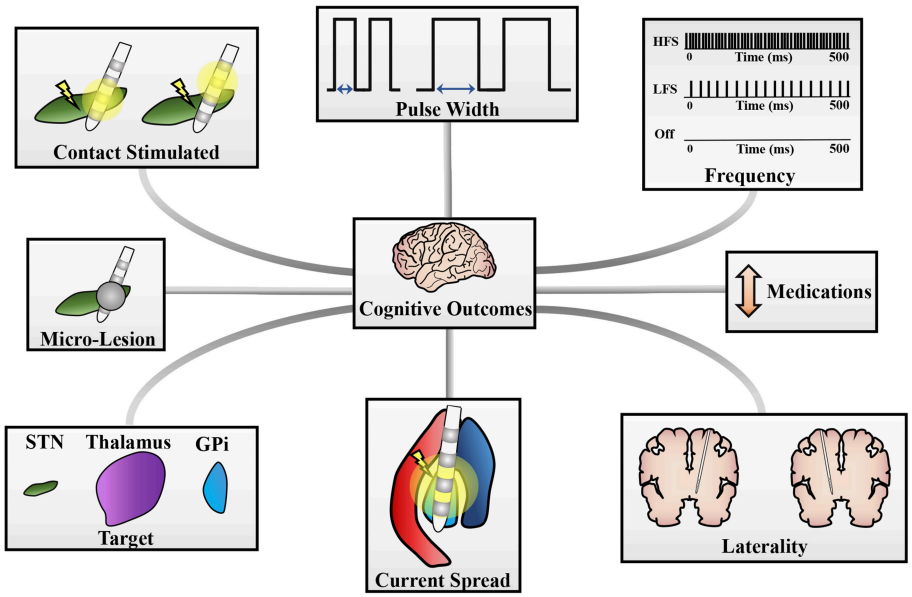

FIGURE 1 | Potential sources of cognitive changes post-DBS. Cognitive changes can stem from a variety of sources and pictured here are a few potential contributors to these changes. These include (clockwise): pulse width of stimulation, frequency of stimulation, changes in medication doses, laterality of DBS implantation, current spread to neighboring structures (i.e., GPi stimulation spreading to the internal capsule), target stimulated for therapy, a micro-lesion effect, or the contacts stimulated on the DBS lead [adapted with permission from figures originally published in Eisinger et al. (125)].

also reported stable cognitive functioning after thalamic DBS (29) and after both thalamic and GPi implants (30). Therefore, DBS seems to have a minimal effect on cognition in TS cohorts, but this can be due to bias from the studies sampled. To make more conclusive findings about DBS and TS, neuropsychological papers reporting DBS outcomes should attempt to separate groups based off comorbidities or severity of tics, since both of these factors can influence cognition (143, 145). Another limitation is the lack of control groups within TS studies.

ET was once thought to be a monosymptomatic condition, but reports have emerged describing cognitive deficits including problems with verbal fluency, memory, mental set-shifting, and executive function (146–150). These deficits have stemmed from various pathophysiological mechanisms including abnormalities in DLPFC through the thalamo-cerebellar loop (147), an underlying clinical cerebellar syndrome (151), or pathological oscillations disturbing the normal physiological dynamics of the nervous system (152). ET-DBS has been thought to exhibit little to no cognitive impairment in chronic studies, but the studies within this review reported minor reductions in verbal fluency (32, 33, 35, 36, 38), which could ultimately stem from already abnormal cerebello-thalamo-cortical loops underlying verbal fluency or stimulation spreading to cerebellar pathways (37). Interestingly, Pedrosa et al. reported that this phenomenon is frequency dependent, and could not simply be a micro-lesion effect since phonemic and semantic fluency were differentially modulated (33). Furthermore, Heber et al. reported no impairments in verbal fluency, although the authors stated that they used lower stimulation amplitudes compared to previous studies (32), suggesting that current spread was limited. These conflicting results welcome techniques, such as patient-specific VTAs, that could potentially be useful for understanding the underlying thalamo-cortical circuitry or fiber tracts affected by DBS (90, 92, 153). Additionally, the minimal decrements observed in ET-DBS within in this review may be accounted for by the location of the sensorimotor regions within the thalamus (lateral) compared to both the limbic and associative territories (97). There has been a paucity of studies focused on ET-DBS and cognition, and only one study within this review utilized a control group (38). With recent trials now examining targets beyond VIM including the posterior subthalamic area (154) and Zi (155), ET studies should expand their methodologies and correlations to consider influences such as changes in medication dosage, disease duration, and age to adequately assess the benefits and risks of each target. These considerations will be critical for future clinical trials.

Cognitive decrements in PD are heterogeneous in several regards, including the severity of impairment and the cognitive domain affected. These deficits have been well-reported, reviewed, and are comprised of reductions in memory, executive function, attention, language, and visuospatial functioning, resulting from degeneration of nigro-striatal dopaminergic neurons and subcortical abnormalities, ultimately interfering with frontal lobe functions through under activation (156, 157). Similarly, these cognitive issues are associated and heavily researched within DBS cohorts (50). Interestingly, the cognitive results were heterogeneous across the various studies, which is already observed in PD patients without DBS. However, declines in verbal fluency were observed in most studies similar to ET-DBS. Verbal fluency was clearly a surgical implantation effect,

with patients demonstrating an initial reduction in scores that returned to near baseline levels (60, 70, 76), though variation in stimulation parameters and location could also worsen outcomes (34, 90). There was a substantial difference in cognitive outcomes between STN- and GPi-DBS studies in regard to the amount of declines post-DBS, and this difference could have manifested from several factors. The STN and GPi are both basal ganglia nuclei with separate anatomical sensorimotor, associative and limbic areas, but the STN is sufficiently smaller compared to the GPi. Additionally, the aforementioned anatomical regions comprise about one-third of the nuclei within the STN, whereas the sensorimotor region within the GPi spans 53% of the structure (97). Therefore, unspecific current spread is easier to evoke in STN-DBS, potentially influencing cognitive circuits traversing in the nuclei's associative region (72). Furthermore, studies have primarily focused on STN-DBS compared to GPi-DBS, which could be another factor contributing to STN being associated with more frequent cognitive declines. However, in studies that directly compared the two targets, STN had a greater frequency of cognitive declines (107, 108, 110, 114). To add to the complexity of this debate, Ostrem et al. reported no cognitive dysfunction after STN implantation in dystonia patients, attributing PD-DBS decrements in executive function and verbal fluency to underlying circuit malfunctions (22). While, Merola et al. concluded that STN-DBS is safe for even MCI PD patients, supporting the idea that other factors are being overlooked in the search for understanding and quantifying cognitive dysfunction (50). Although there have been numerous studies attempting to quantify the cognitive effects of PD-DBS, important factors still need to be revised and further considered including follow-up times, surgical techniques, postoperative management, cognitive battery, and statistical methodologies. More investigations should be completed and should focus on relationships between cognitive outcomes and correlations such as VTA, electrode trajectory, and activated DBS contacts, since these investigations will be invaluable when mapping the networks affected. Furthermore, there has been emerging evidence of PD patients presenting with different cognitive subtypes, thus, separating different DBS patients into their appropriate subtypes may provide substantial meaning to group average cognitive comparisons (158–162).

Stemming from the lack of studies and various contributions, there is an urge to design larger, well-controlled, and sufficiently powered clinical studies to describe the effects of DBS on cognition, to refine and potentially standardize appropriate candidates for DBS, and to define criteria that substantiates or reflects what true clinical cognitive change is (163, 164). Additionally, there has not been a unified agreement of when exactly motor improvement is acceptable at the expense of cognitive dysfunction. The current standard of analyzing cognitive outcomes in DBS cases is still subpar especially if we want to reliably understand and report cognitive issues in post-DBS cohorts. Subsequently, cognitive issues can limit stimulation effectiveness, thus limiting the therapeutic window of DBS and negatively impacting quality of life. Although cognitive DBS issues and data have been available for more than a decade, the underlying pathophysiology of cognitive declines post-DBS will need further investigation. The identification of relevant pathways could lead to better device design and implementation (e.g., directional leads). This review stresses the importance of patient specific analyses and accurate lead localization, since there can be differential outcomes of DBS in similar cohorts (i.e., importance of defining patient criteria). Moreover, this review raises the question as to whether the results on a group level represent clinical significance, since even minor changes in cognition can advance a patient into a state of severe dysfunction (6). However, the data presented here are only descriptive findings and a formal meta-analysis may lead to a more precise understanding between cognitive declines and DBS. Finally, we should reflect on how we can better track cognitive changes in daily situations rather than using only a single test. Implementing these changes may help us to better understand true cognitive DBS related alterations.

AUTHOR CONTRIBUTIONS

SC conceptualized the paper and wrote the first draft, developed the first draft of figures and tables, and finalized the paper, figures and tables. SC, MO, and AG provided inputs and edits.

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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.2019.00419/full#supplementary-material

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REVIEW
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Deep Brain Stimulation Programming for Movement Disorders: Current Concepts and Evidence-Based Strategies

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Deep brain stimulation (DBS) has become the treatment of choice for advanced stages of Parkinson's disease, medically intractable essential tremor, and complicated segmental and generalized dystonia. In addition to accurate electrode placement in the target area, effective programming of DBS devices is considered the most important factor for the individual outcome after DBS. Programming of the implanted pulse generator (IPG) is the only modifiable factor once DBS leads have been implanted and it becomes even more relevant in cases in which the electrodes are located at the border of the intended target structure and when side effects become challenging. At present, adjusting stimulation parameters depends to a large extent on personal experience. Based on a comprehensive literature search, we here summarize previous studies that examined the significance of distinct stimulation strategies for ameliorating disease signs and symptoms. We assess the effect of adjusting the stimulus amplitude (A), frequency (f), and pulse width (pw) on clinical symptoms and examine more recent techniques for modulating neuronal elements by electrical stimulation, such as interleaving (Medtronic®) or directional current steering (Boston Scientific®, Abbott®). We thus provide an evidence-based strategy for achieving the best clinical effect with different disorders and avoiding adverse effects in DBS of the subthalamic nucleus (STN), the ventro-intermedius nucleus (VIM), and the globus pallidus internus (GPi).

Keywords: DBS programming algorithms, subthalamic nucleus, DBS side effects, segmented electrode, short pulse width

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INTRODUCTION

Since the pioneering work of Cooper et al. (1) and of Benabid et al. in the early 1990s (2), deep brain stimulation (DBS) has become the treatment of choice for advanced stages of Parkinson's disease (PD), for medically intractable essential tremor (ET), and for complicated segmental and generalized dystonia. Although overall considered an effective treatment in these diseases, a number of specific factors determine the treatment success: in addition to careful patient selection and accurate electrode placement, the effective post-operative programming of DBS devices is considered the most important factor for the individual patient outcome (3–5). Programming is

the only modifiable factor once a patient has been implanted with DBS leads and it becomes even more relevant in cases in which the DBS electrodes are located at the border of the intended target structure. Current implantation techniques, using either stereotaxic frames or surgical robots, exhibit an average precision in the range of 1–2 mm from the target area (6–12). In addition, the brain itself can shift by 2–4 mm during surgery (13–15), contributing to imprecise lead placement. According to previous studies, such errors occur in up to 40% of DBS surgeries (16–20), thus underscoring the importance of post-operative programming to compensate for such variability. Inefficient stimulation may result in unnecessary follow-up visits and reduced patient satisfaction with DBS (21). Conversely, sound programming has been shown to improve patient outcomes and to avoid unnecessary lead revisions (19). In addition, improvement with re-programming highlights that proper adjustment of stimulation parameters is a major factor for successful treatment and patient satisfaction (22).

Despite established strategies for adjusting neurostimulation (23–27), DBS programming remains time- and resource-consuming. New leads with two levels of tripartite electrodes (i.e., segmented electrodes) (Abbott®, Boston Scientific®) can improve the therapeutic window (**Figures 1A,B**) but increase the number of possible combinations of programming parameters (28) [For a thorough review of currently implanted pulse generators (IPGs) and electrodes see: (29)]. Therefore, there is a need for sophisticated strategies on how to adjust stimulation parameters and lead configurations in a precise and effective manner once the electrodes have been implanted. We here review the current evidence for adjusting neurostimulation in different movement disorders. Regarding the biophysical and physiological effects of DBS, the reader is referred to extensive reviews on this matter (30, 31).

CURRENT PROGRAMMING STRATEGIES

Specific Programming Strategies for DBS of the Subthalamic Nucleus (STN)

It is thought that adjustment of stimulation parameters is best carried out by trained clinicians (3) and depends to a large extent on personal experience, whereas detailed algorithms for a disease-specific programming strategy are rare, with the exception of expert recommendations (3, 27, 32).

Assessing the Response to DBS:

In order to judge the effect of STN-DBS, rigidity is typically used in PD because it does not fluctuate, responds to stimulation adjustments within seconds (**Figure 2A**), and does not depend on the patient's fatigue or cooperation (33, 34). When effective stimulation is switched on, rigidity disappears within 20 s, whereas after cessation of stimulation, rigidity returns within 1 min (35) (**Figure 2A**). This must be taken into account when subsequent tests are performed. In the absence of rigidity, bradykinesia or (rest) tremor can be used, although the response of bradykinesia to changing the stimulation parameters is slower (33) and may be biased by fatigue and the patient's discomfort or expectations and (rest) tremor may fluctuate spontaneously. Gait speed, arm swing during gait, finger tapping, or alternating hand movements can all be measured with a stopwatch to achieve numeric data to supply evidence for a certain stimulator setting. A list of appropriate tests has been suggested (36). Also, selected items from the UPDRS-III scale are used to judge the therapeutic effect and to document effects in a systematic manner. It is noteworthy that no single clinical sign or symptom should be used alone (such as e.g., rigidity) to judge the therapeutic effect. Our clinical experience suggests that one should select from a list of possible tests two or three which characterize the symptoms of the patient best and to apply these tests in a systematic manner during the programming sessions. The contact with the lowest threshold for beneficial effects and the widest therapeutic window is then selected for chronic stimulation (23–27).

Electrode Configuration Adjustment

It is commonly suggested that once the leads have been implanted, each ring contact should be tested in a monopolar configuration with the electrode as negative (cathode) and the IPG as positive (anode), a process referred to as monopolar review (3, 27, 32). In some centers, this is done prior to the implantation of the IPG using externalized leads, with the option to adjust the depth of the implanted electrode during the implantation of the IPG. In these cases, stimulation is applied by an external stimulator. Initially, the pulse width and frequency are kept constant at 60 μs and 130 Hz, respectively. Each of the ring electrodes is tested separately with increasing amplitudes to determine the threshold of beneficial effects and, with further increasing the amplitude, to detect the threshold of adverse effects (3, 37). In the case of segmented electrodes, all segments of one ring are activated simultaneously (38). Most authors suggest a gradual increase of stimulation amplitude in steps of 0.1–0.5 V or 0.1–0.5 mA up to a maximum of 5 V or 5 mA, or until side effects occur (3, 25, 37).

When newer DBS leads (Boston Scientific®, Abbott®) with two levels of tripartite electrodes are used, it is suggested that after determination of the clinically most efficient ring, single contacts of this ring are screened in a similar fashion (directional or current steering) (39, 40) (**Figures 1A,B**). Stimulation of single segments can result in a larger therapeutic window (38). In addition, the average current threshold for obtaining a therapeutic effect was noted to be lower with the best directional stimulation (41–44). In accord, Pollo et al. reported, in their study on intraoperative segmental stimulation, a reduced threshold for clinical efficiency as well as a better clinical efficiency with segmental stimulation (39). Even with small currents of 0.3 mA, these authors were able to induce clinical effects in individual patients, which suggests that the stepwise increase of current during testing may have to be considerably lower than 0.5 mA. In the VANTAGE study, stimulation was performed with the Vercise system (Boston Scientific®) that includes a separate current source for each segment of the lead which contains 8 contacts (45). These authors stimulated the best as well as the second best segment and instructed their patients to optimize the applied current via a patient control device. The authors reported an improvement of over 60% during the ON phase on the

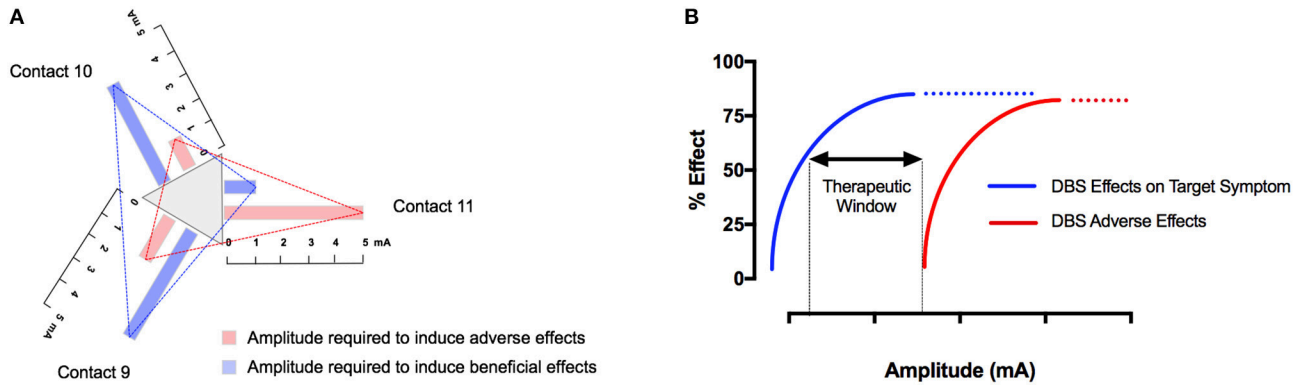

FIGURE 1 | The therapeutic window depends on stimulation parameters and the electrode configuration. In tripartite electrodes, the therapeutic window should be determined for each segment individually by examining the beneficial and adverse effects with increasing the stimulation amplitude under defined pulse width and frequency **(A)**. The therapeutic window in DBS is defined as the gap between the minimum stimulation current required to produce adverse effects and the current required to produce a beneficial effect. Similar to pharmacologic intervention, DSB is a tradeoff between beneficial and adverse effects. Numerous stimulation parameters, as well as the anatomical position of the respective contact, affect the therapeutic window. As a consequence, each electrode contact and each combination of pulse width and frequency thus has an individual therapeutic window **(B)**.

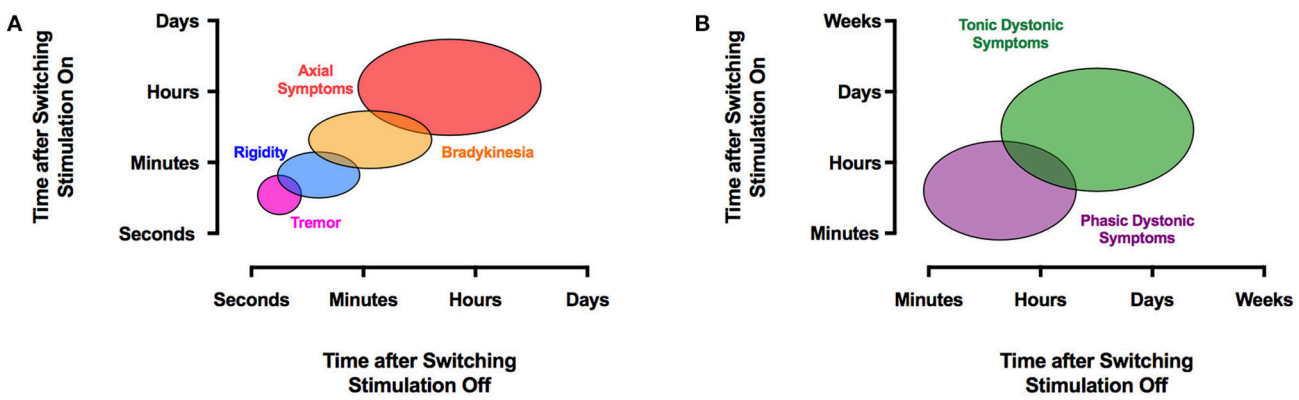

FIGURE 2 | The effects of DBS on clinical symptoms are time-dependent. PD signs and symptoms respond to STN-DBS variably. Axial symptoms may take hours or days to improve, whereas tremor typically disappears almost instantly with STN- or VIM-DBS **(A)**. A similar temporal disparity occurs with dystonia, where phasic dystonic symptoms respond quickly within minutes to GPi-DBS, and tonic dystonic movements may take much longer to resolve **(B)**. The reappearance of symptoms after discontinuation of DBS exhibits a similar temporal pattern.

UPDRS-III rating scale, which is above the average improvement seen with conventional ring electrodes.

Stimulation Parameter Selection

In order to achieve the best clinical effect, certain stimulation parameters have been determined empirically for STN-DBS. Previous studies investigating the specific contribution of frequency, pulse width, and amplitude found that the amplitude had the greatest effect on ameliorating PD motor signs relative to energy-equivalent changes in frequency and pulse width (23, 24). In one study that examined PD patients with STN-DBS, the amplitude required to improve wrist rigidity ranged from 0.7 to 1.7 mA, and the amplitude required to generate adverse effects was in the range of 1.3–3.4 mA (23). In an intraoperative examination of clinical STN-DBS effects in 17 PD patients, Sauleau et al. found that the threshold for the vanishing of wrist rigidity was 0.94 V (at 130 Hz and 100 μs) (46). Stimulation frequencies of 50 Hz and 130 Hz improved tremor, rigidity, and bradykinesia, with rigidity improving already above a threshold of 33 Hz. In these studies, there was no significant improvement above 185 Hz for either target symptom, although some reports suggest that tremor tends to respond to a higher frequency (47). Using frequencies below 50 Hz in STN-DBS did not improve motor signs, even when the total electrical energy delivered (TEED) was similar (23). In fact, very low frequencies of 5–10 Hz have been found to worsen motor symptoms, in particular, bradykinesia, compared with no stimulation (24, 48, 49). Moro et al. demonstrated that pulse widths between 60 and 210 μs were beneficial for improving tremor and rigidity, while reduction of bradykinesia relative to baseline was only significant at 60 μs. High-pulse-width stimulation (>210 μs) was generally not well-tolerated. No difference in tremor has

been observed with different pulse widths (23, 24). In addition to rigidity, tremor, and akinesia, STN-DB has a beneficial effect on off-dystonia (50, 51), whereas improvement in on-dyskinesia is predominantly a consequence of a reduced L-Dopa equivalent dose (LED) (52). Recently, IPGs became available which allow for even shorter pulse widths 60 μs. The CUSTOM-DBS study by Steigerwald et al. investigated 15 PD patients with STN-DBS and found that for STN stimulation, a shorter pulse width of 30 μs resulted in a larger therapeutic window with a non-inferior therapeutic efficacy (as measured by the UPDRS III score) when compared to the standard pulse width of 60 μs (53). Also, another group showed that stimulation using 30 μs pulse-width results in better walking and speech performance at a similar total electrical energy delivered (TEED) (54). Therefore, the previous recommendation for a fixed pulse width of 60 μs in STN DBS is clearly challenged, although future research needs to confirm these encouraging findings.

Typical Side Effects in STN-DBS

Most DBS side effects can be understood as a result of current spreading into brain regions adjacent to the target area. The STN is a relatively small, ovoid structure with a close anatomical relationship with other deep brain nuclei and tracts, including the *internal capsule* (lateral, anterior), the *substantia nigra* (ventral), the *red nucleus* (medial), *the fibers of the third cranial nerve* (medioventral), *the thalamic fasciculus,* also termed field H1 of Forel and composed of the ansa lenticularis and the lenticular fasciculus (mediodorsal), the *sensory thalamic nuclei* (dorsal), the *zona incerta (ZI) and cerebello-rubro-thalamic fibers* (medial dorsal, posterior), and the *hypothalamus and medial forebrain bundle* (anterior) (55, 56) (**Figure 3**). In addition to these anatomical relationships, the STN is subdivided into different territories (motor, oculomotor, associative, and limbic), each with different connections and specific functions (57). Previous studies that have analyzed the anatomical location of the most effective contacts used for chronic stimulation showed varying results: the majority of reports suggest that the most effective contacts to ameliorate PD symptoms segregate to the dorso-lateral, sensorimotor aspect of the STN (58–64), whereas current spread to the limbic and associative sub-segments may cause unwanted affective and cognitive side effects (65–68). Conversely, other studies recommended targeting other areas or even adjacent regions such as the zona incerta (ZI) or the Forel fields H1/H2 (69–76) and one study found no significant association between the position of the active contacts and the clinical effect (77). This heterogeneity may be a consequence of methodological differences among the studies, as different imaging techniques were applied to define the position of the electrodes including ventriculography, CT and MRI (78). In addition, classical studies applied numerical coordinates referenced to the stereotactic space to define the contact position, making the results difficult to interpret without knowing the patient's individual anatomy and because a volume of tissue is represented by a single point. The following adverse effects in STN-DBS can be derived from the function of the adjacent anatomical structures:

Spastic muscle contractions: The most frequent adverse effects include (spastic) contractions involving the facial muscles ("facial pulling"), which often affect bilateral upper facial and contralateral lower facial muscles (79, 80) and are a consequence of current spread into the internal capsule (IC) lateral and anterior to the STN (**Figures 3A,D**). By modeling the electric field caused by STN-DBS, it was found that even small deviations in the electrodeposition within the STN can result in activation of large diameter myelinated IC axons over a volume that spreads outside the borders of the STN (81).

Uni- or bilateral gaze deviation: Typical oculomotor side effects are reduced gaze ipsilateral to stimulation, sometimes progressing to contralateral gaze deviation. This resembles conjugate eye deviation during frontal epileptic seizures and is therefore assumed to be caused by activating fibers stemming from the frontal eye field (FEF) which run in the internal capsule in three bundles: a dorsal trans-thalamic trajectory, an intermediate bundle crossing the subthalamic region, and a ventral bundle in the medial portion of the cerebral peduncle, which projects, among other structures, to the subthalamic nucleus (82). Analyzing 22 electrode locations which intraoperatively could elicit conjugate eye deviations, these positions were found to lie within the lateral anterosuperior border of the STN (**Figures 3A,D**). This resulted in the recommendation to place the lead or deflect the field to a more medial, posterior, and inferior position (83). In a single case, this phenomenon was elicited with the STN contacts which provided the best clinical efficiency and could be compensated by bilateral STN stimulation (84). These eye movements consisted of several saccades and were accompanied by turning the head. Thus, contra-versive and conjugate eye deviation cannot be generally taken as evidence for electrode misplacement. Conversely, activating the fibers of the third nerve (N.III) that run inferomedial to the STN and within the red nucleus (RN) below the STN may result in unilateral gaze deviation and diplopia (**Figures 3A,C**). Tamma and co-authors claim that stimulation of oculomotor fibers causes adduction or reduced abduction or elevation of the superior eyelid in the ipsilateral *eye* (85). Also, in another report, unilateral eye deviations were frequently seen during intraoperative test stimulation when the electrode was medial, posterior, and ventral to the final target (46). However, this far medial position makes unwanted stimulation of these fibers an extremely rare instant. In experimental stimulation of the third nerve in macaques, only small adduction of the eye was seen but prompt miosis, as expected from physiology (86). Eyelid opening apraxia has also been observed (51), although this symptom may be present as part of PD itself, and is occasionally relieved by stimulation but also can be induced by stimulation above the clinically efficient threshold (87). Mydriasis is rather frequently seen during intraoperative test stimulation and post-operative adjustment along with ipsilateral perspiration. These are quickly adapting symptoms and are not considered as evidence for a misplaced electrode. The central sympathetic tract runs medial to the red nucleus anteriorly to the aqueduct and is therefore not involved, but sympathetic fibers within the zona incerta (ZI) (88) or within the STN (**Figures 3A,B**) are assumed to be stimulated when mydriasis occurs.

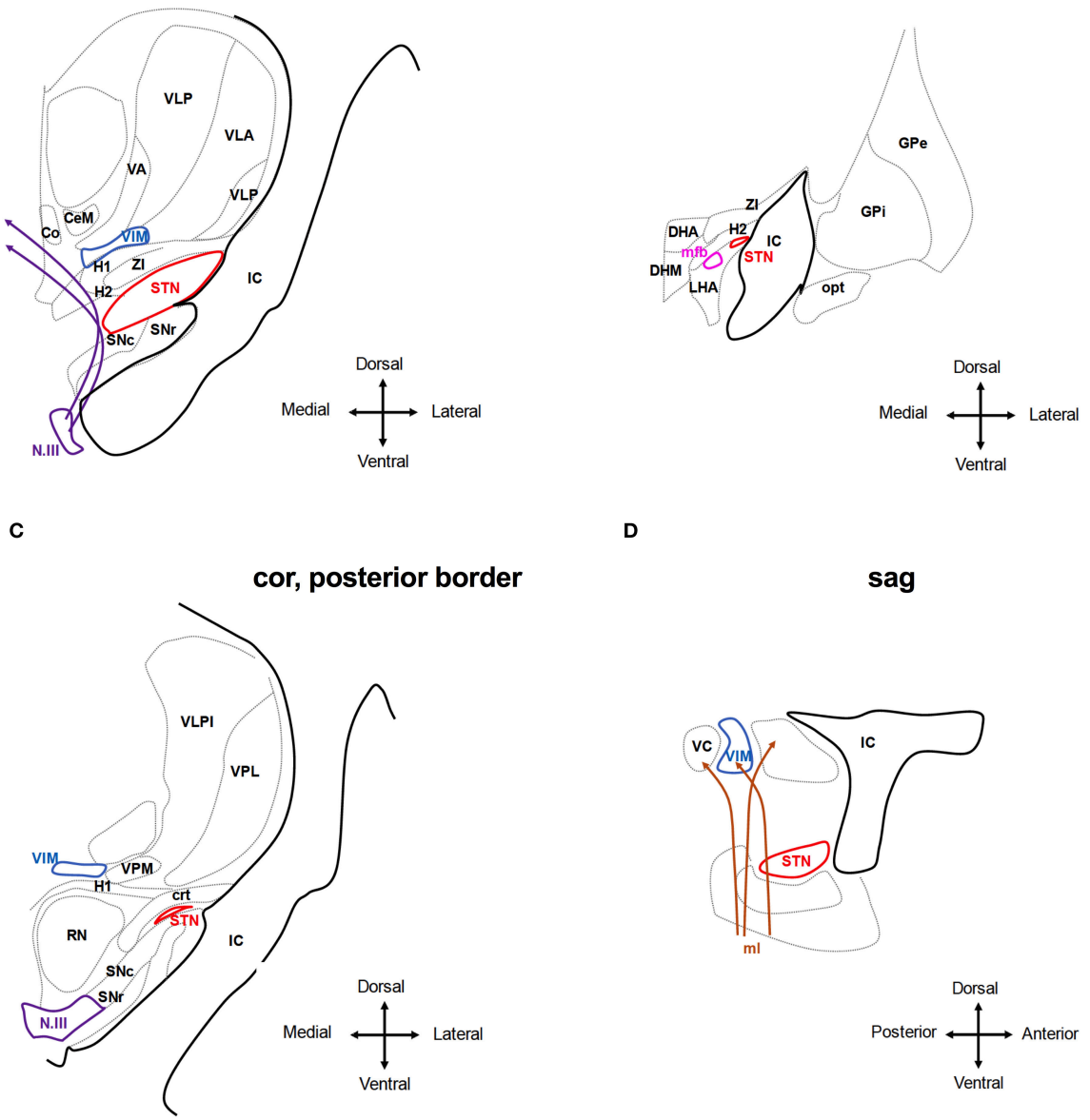

FIGURE 3 | Anatomical relationship of the subthalamic nucleus (STN) and the ventral intermedius nucleus (VIM) to adjacent structures. The schematic shows coronar **(A–C)** and sagittal **(D)** planes through the basal ganglia at the level of the STN and VIM. Co, Commissural nucleus; CeM, central medial thalamic nucleus; VA, ventroanterior thalamic nucleus; VC, ventrocaudal nucleus; VLP, ventrolateral posterior thalamic nucleus; VPM, ventroposterior medial thalamic nucleus; IC, internal capsule; SNr, Substantia nigra pars reticulate; and SNc compacta; H1, H2, H1 and H2 Fields of Forel; ZI, zona incerta; N.III, nucleus of the third cranial nerve; DHA, dorsal hypothalamic area; DHM, dorsomedial hypothalamic nucleus; LHA, lateral hypothalamic area; mfb, medial forebrain bundle; opt, optic tracts; RN, red nucleus; crt, cerebello-rubro-thalamic tract. Stimulating the tissue medial and dorsal to the STN activates the *H1* and *H2* fields of Forel and the ZI and may reach to the medio-dorsal thalamic nuclei incl. the Co, CeM, and VIM. Deflection of the field to more ventral areas will activate the fibers of the N.III and the SN **(A)**. Anterior of the STN, stimulation may activate hypothalamic nuclei and mfb as well as the IC **(B,D)**. At the posterior border of the STN, stimulation may activate the RN and ml, in particular, if the tissue medial of the STN is activated. Stimulation of tissue dorsal of the STN may activate the crt. **(C,D)**. Adjusted from Mai et al. (55).

Autonomic side effects: Nausea and excessive sweating are likely a consequence of medial and anterior current spread, presumably corresponding to tissue activation in the hypothalamus and red nucleus (85, 89) (**Figures 3B,C**). Approximately half of all STN-DBS cases experience dizziness, a sense of heavy- or lightheadedness, or malaise (51).

Paresthesia: Contralateral paresthesias may be due to stimulation of the medial lemniscus which conveys somatosensory information from the joints and skin and lies ventroposterior to the STN (**Figure 3D**). With the usual frontal entry of the lead the lowermost contacts may thus encroach on this structure (89). Mostly, paresthesias are

transient but when they persist, a more dorsal contact may be chosen, if clinically effective.

Speech impairment: The impairment of speech frequently occurs during the initial programming and long-term follow-up of STN DBS (37, 90) but can be ameliorated through proper programming (91). Dysarthria occurs in about 25% of STN-DBS cases and may be caused by current spread into the internal capsule (strained or spastic speech) or otherwise into the pallidal and cerebello-thalamic fiber tracts (crt) medial and dorsal of the STN (92–94) (**Figures 3A,C,D**). It is therefore important to distinguish the different causes of DBS-induced dysarthria to be able to adjust stimulation contacts and parameters. In addition, stimulation of the STN itself may account for speech impairment. In particular, medial left-sided stimulation in right-handed patients had a negative effect on prosody, articulation, and overall intelligibility (95–97). Accordingly, higher left STN voltage is associated with deterioration of speech (98). Similarly, other reports demonstrated a strong correlation between high voltages in the left STN and speech impairment (99–101).

One report suggested high stimulation frequency to increase the risk of speech impairment (102). Another report suggested high-frequency stimulation to have a negative effect on speech-related velopharyngeal control (103).

Dyskinesia: STN-DBS may induce dyskinesia, such as choreiform, ballistic, or dystonic movements reminiscent of levodopa-induced dyskinesia (52). Dyskinesias occurring during the initial post-operative programming period are thought to indicate a good outcome and the contact inducing dyskinesia is usually the most effective in ameliorating motor symptoms (52, 104–106). Rare dystonic effects in STN-DBS included dystonia of head and neck muscles with stridor and dysphagia (107, 108).

Gait impairment and postural instability: Overall, L-Dopa responsive axial symptoms are also more likely to improve with STN-DBS and indeed, various studies reported gait improvement with STN-DBS (109–115), in particular in terms of gait velocity and amplitude of arm and leg swing. On the other hand, long-term follow-up studies (116, 117) have consistently shown that axial symptoms including gait may worsen over time in contrast to the sustained improvement of cardinal motor signs, suggesting a differential effect of DBS on the distal and axial neural control circuits (118–120). Indeed, increasing the stimulation amplitude can worsen gait and increase freezing episodes similar to no stimulation as discussed further in detail in section Specific Programming Strategies to Counteract Side Effects in STN-DBS. However, the cause of gait impairment in DBS is most likely multifactorial (121) and, apart from stimulation-induced worsening through the current spread, disease progression, medication reduction, and cognitive decline may contribute. Postural instability is the least likely to respond to DBS and STN-DBS appears to be more detrimental to postural stability as compared to GPi-DBS (122, 123). Although there is no evidence to support a certain programming strategy to avoid worsening of postural stability, a recent study suggested that limiting current spread to the non-motor territories of the STN would liberate cognitive resources that could be used to maintaining a steady posture (124, 125) and to improve postural stability (126). Because certain studies suggested that trunk ataxia to be a consequence of activating the red nucleus, directing the current to more lateral areas might be also helpful.

Acute neuropsychiatric side effects: STN-DBS may cause acute neuropsychiatric alterations in addition to preexisting psychiatric comorbidities that can decompensate during or after surgery (106). Neuropsychiatric signs can be observed in individual subjects during initial programming and may include apathy (112, 127), mirthful laughter (66) as well as acute mania (68, 128) and acute depression (129–131).

Depression: In a case described by Bejjani et al., depression occurred while all contacts were screened in the post-operative setting. When contact the most ventral (**Figures 3B,C**) was activated, depression set in after 5 s. of stimulation with 2.4 V. This contact was not efficient in relieving PD symptoms and was shown to be located within the substantia nigra. Stimulation of more dorsal contacts provided relief from PD motor signs without causing depression. In addition, apathy and depression may be due to a "hypodopaminergic" state as a consequence of a quick or radical reduction in dopaminergic medication (132). Recognizing depression is highly relevant since these symptoms have an even bigger impact on the live quality of DBS patients than motor function (133, 134).

Mania: Manic episodes due to STN stimulation are assumed to be a consequence of stimulating the medial and ventral aspects of the STN (135, 136). Therefore, the use of more dorsal contacts is recommended in these cases. In addition, stimulating tributary fibers from the STN to the median forebrain bundle may contribute to these symptoms (65).

Impulse Control Disorders (ICD): The relationship between DBS and ICD is complex and in part controversial (137). In general, bilateral STN-DBS was found to either ameliorate or worsen decision-making or to have no effect (138–140). STN-DBS is associated with the risk of binge eating (141, 142) and punding behavior (143). Moreover, STN-DBS may induce hypersexuality, hypomania (144, 145), or compulsive gambling (146). These effects are most likely associated with using the most ventral contacts (147–150) and are assumed to be caused by stimulating the ventromedial, limbic area of the STN (66, 149, 151) as well as the SNr (128) and the medial forebrain bundle (65) (**Figures 3A,C**). One therapeutic option may, therefore, be to avoid current spread into STN-related limbic circuits by deflecting the electrical field to more dorsal and lateral parts. However, ICD may also resolve or improve after surgery (152, 153) and STN-DBS might in fact be considered to treat ICD in PD (152, 153). Long-term follow-up of patients with STN-DBS showed pre-surgery ICD was abolished in most patients once L-DOPA or dopamine agonist doses were reduced (141) as was the dopamine dysregulation syndrome (154). In these studies, the *de-novo* onset of ICD was rare and transient with the exception of compulsive eating (141). Similar to motor symptoms, the individual patient outcomes in regard to ICD depend on several factors, including target selection, electrode location, programming settings, appropriate medical management, age, and perhaps genotype (155) and is thus difficult to predict.

Cognitive side effects: The effects of STN-DBS on cognition remain controversial. A reduced verbal fluency is well-described

(156), but has been observed with and without stimulation and thus has been attributed to penetrating the caudate nucleus during surgery (157, 158). On the other hand, Morishit et al. and Isler et al. found no significant difference in cognitive decline between caudate-penetrated and caudate-spared groups. In addition, executive dysfunction and altered short term memory have been observed (159, 160). These effects are also considered to be a consequence of stimulating the ventral and medial aspect of the STN (160, 161). However, well-controlled studies did not find detrimental effects of STN-DBS on global cognitive function (162, 163). The etiology is therefore likely multifactorial and due to the surgical lesion of the frontal lobe and caudate nucleus and diseases progression (164).

Specific Programming Strategies to Counteract Side Effects in STN-DBS

Some adverse effects may be transient in nature and will disappear despite continuing stimulation (165). For instance, dyskinesia is a typical side effect of STN-DBS in PD but increasing the amplitude in minute steps and waiting for the dyskinetic symptoms to disappear after each incremental step might ultimately allow for an increase in amplitude required for symptom control despite transient dyskinesia (105). Moreover, it may be sufficient in some instances to adjust stimulation parameters in order to achieve a more symmetrical or asymmetrical DBS effect. For example, if gait disturbances are prominent in STN-DBS, reducing the stimulation amplitude on the side contralateral to the best motor response resulted in increased stride length, reduction of gait variability, and a reduction in freezing episodes (166). On the other hand, asymmetric stimulation may be helpful in ameliorating the emotional side effects of STN-DBS, that are thought to be lateralized (167). The latter study demonstrated emotional auditory stimuli to induce activity in the ventral non-oscillatory region of the right STN but not in the left ventral STN or in the dorsal regions of either the right or left STN. These results suggest that DBS of the right ventral STN may be associated with beneficial or adverse emotional effects observed STN-DBS. The authors suggest that the stimulation parameters in the right STN should be modified to counteract psychiatric side effects. This hypothesis is tempting but needs further confirmation from clinical studies. When permanent side effects occur, either the stimulating contact or the stimulation parameters may be changed or, as the last option, the electrode may be repositioned. The first step is to check the electrode position in case this is not done routinely after surgery or if post-surgical images are not available. The second step is to reduce the current of the activated contact(s) and/or choose another contact for stimulation. For example, choosing a more dorsal contact is recommended when persistent paresthesias occur as well as in psychiatric symptoms (see above). Alternative electrode configurations can be achieved by combining single contacts to a compound cathode (double or triple monopolar) or by setting another lead contact as an anode (bipolar). The latter allows the volume of tissue activated (VTA) to be restricted at the expense of higher energy consumption (3), although one should be aware that the extent of the computed VTA varies substantially with the material properties of the surrounding brain tissue (168–171). Alternatively, interleaving stimulation (Medtronic®) may be applied. Interleaving stimulation (ILS) consists of rapid and alternate activation of two electrode contacts with two distinct amplitudes and pulse widths but with the same frequency up to a maximum of 125 Hz and a delay of 4 ms between two stimuli. In general, ILS may be applied either to limit stimulation-induced adverse effects or else, to stimulate different brain regions with individualized settings in order to alleviate specific symptoms (47). For example, ILS was successfully applied for freezing of gait (additional stimulation of substantia nigra) (101) as well as tremor (additional stimulation of zona incerta) (172). However, with the exception of case reports and small case series (172–177), there are no larger prospective trials that have investigated the clinical effect of ILS. In accord with previous reports, a recent study from Kern et al. demonstrated improvement with ILS for adverse effect management predominately for the treatment of dyskinesia and improvement of PD motor symptoms with ILS (178), whereas ILS was less effective in ET and dystonia. Of note, a contact was added into the rostral zona incerta (ZI) (**Figure 3A**) in the majority of dyskinetic patients, thus suggesting a particular role of the ZI and the surrounding pallido-thalamic fibers for improving dyskinesia and a potential ILS target in STN-DBS. These alternative targets are under active investigation for treating dyskinesias (174, 179, 180), although sound evidence for using these structures is still lacking. A drawback of ILS is that battery drainage is likely increased with ILS as 2 independent programming settings are applied (181).

Short Pulse Width Stimulation (SPWS)

Decreasing the standard pulse width, which is currently only possible with Boston Scientific® or Abbot® devices, represents an alternative strategy to counteract unwanted side effects in STN-DBS (53, 182). For example, Reich et al. investigated pulse widths below 60 μs at a frequency of 130 Hz and found that compared to (standard) 60 μs stimulation, the therapeutic window increased by a mean of 182% with a PW of 30 μs, and decreased by 46% with a PW of 120 μs (183). Although the stimulation amplitude required for rigidity control increased with reducing pulse widths from a mean of 1.6 mA at 60 μs to 2.9 mA at 30 μs, the TEED required for the clinical effect of rigidity control decreased. This is thought to be mediated by more selective action of stimulation on the fiber tracts that are responsible for symptom relief while the neighboring thick and myelinated corticospinal and corticobulbar fibers are thought to be less affected by short pulse width stimulation (184–186).

Low-Frequency Stimulation (LFS)

If gait and balance issues such as freezing of gait (FOG) or other axial symptoms predominate, LFS (60–80 Hz) may be a good treatment strategy for PD patients with STN-DBS. FOG is a gait disorder featured by recurrent transient gait retardation and interruption that occurs in PD, PD-plus syndromes and vascular parkinsonism. Most FOG episodes are related to the OFF state in PD, but severe cases begin to suffer from ON state FOG (ON-FOG). FOG increases the risk of falls for PD

patients and has a large impact on the motor function and daily life of the patients. HFS-DBS of the STN can alleviate FOG in some patients, particularly if FOG is related to medication OFF state (187–189). On the other hand, HFS-DBS may induce FOG in PD (190, 191). Pharmacological treatment options for FOG include L-DOPA (192), methylphenidate and amantadine (193, 194). Alternatively, the stimulator may be switched to LFS. LFS (60–80 Hz), compared to HFS (130 Hz), has been shown to have beneficial effects on improving FOG and other axial symptoms, such as speech and swallowing function, in PD patients with bilateral STN-DBS in some studies (190, 191, 195–198) or selected patients (199), but not in others (200–203). Some found short-term but not long- term beneficial effect (204), while others found both short-term and long-term benefits after 6 weeks, 8 months and even 10 months study periods (190, 195, 197). It is not well-understood, which factors account for the different responses of FOG and other axial symptoms to LFS. Possible factors include the presence or absence of pre-existing FOG, the frequency used (60 vs. 80 Hz), the maintenance of the TEED [TEED = (voltage^2 × pulse width × frequency)/impedance)] with frequency adjustment and the location of the active contacts (ventral vs. dorsal). In most studies, adjusting for TEED appeared to be less relevant than the frequency (205). This in line with the finding that neuronal responses relative to frequency are highly non-linear as demonstrated by Huang et al. (206). In summary, it is currently unclear, which patients benefit most from LFS vs. HFS, but likely applies to patients that have pre-existing FOG at HFS-DBS on exam (190, 195–197). In some studies, switching from a high to low frequency (<100 Hz) stimulation also ameliorated speech intelligibility (207) and acoustic parameters such as hypophonia (196). On the other hand, tremor control has been observed to be worse with lower frequencies (190, 197, 204).

Alternative Electrode Targets for Axial Symptoms and Gait Disorders

If there is a beneficial effect of LFS on gait, it may be caused at least in part, by affecting neurons that project to the pedunculo-pontine nucleus (PPN) as unilateral or bilateral LFS of this structure directly and in combination with stimulation of additional target structures has been shown to improve FOG (99, 187, 208–213). The PPN has reciprocal cholinergic connections with the STN, its degeneration may be crucial in the pathophysiology of gait and balance deterioration in PD (214, 215) and stimulation of the PPN may improve axial symptoms in PD (216, 217). The PPN may be stimulated by leads in this region alone or in conjunction with the STN, the SNr, or the GPi (99, 211, 212). Interestingly, the optimal contact positions for LFS were more ventrally located in the STN than optimal contacts for 130 Hz-stimulation (198). More recently, there has been interest in the stimulation of the SNr, which is located ventrally and medially to the STN (218). One study found that among PD patients treated with STN-DBS at 130 Hz via the most distal contact of the quadripolar electrode resulted in an improvement of gait and posture (100). Subsequently, another group of researchers used interleaving to stimulate both the STN and the SNr (101) and found that FOG was significantly improved with combined STN/SNr stimulation, although other axial symptoms on UPDRS did not significantly differ. At the same time, stimulating the SN also comprises the risk of worsening akinesia and of inducing depressive symptoms. In summary, the combined stimulation of PPN plus STN, PPN plus GPi, or STN plus SNr, may be useful for the treatment of FOG in PD patients. The optimal combination of nuclei to be stimulated and the stimulation parameters need to be determined by future clinical trials. In addition to its effect on gait and balance, LFS may reduce stimulation-induced dyskinesia (219, 220). This may be particularly relevant for dorsal-projecting contacts in or close to the ZI above the STN, that have been reported to have an anti-dyskinetic effect with different stimulator settings (178, 221, 222).

Optimal Initiation Time for Programming and Adjusting Pharmacotherapy in STN-DBS

General Considerations on Post-Operative Care

The time point to initiate DBS after STN implantation surgery varies between institutions. Early programming (within the first days after surgery) satisfies the patient's wish for a timely treatment but may be hindered by a improvement in PD symptoms due to the lesion caused by the electrode (stun effect) which may last up to 2 weeks (223, 224) or even longer: the mean medication "ON" time improved 3 months after STN electrode implantation even in the absence of electrical stimulation (115), thus demonstrating an improvement with surgery alone. At which time point DBS is initiated after surgery thus depends on the procedures established in each institution. In any way, the initial programming should be performed after an overnight washout of dopaminergic drugs so that the effect of DBS can be assessed without the interference of medications (37). Adjusting anti-parkinsonian drugs typically occur after initial programming of STN-DBS. There is no specific evidence on how and when to adjust medication after STN-DBS is programmed. The insertional effect and the effect of the electrical stimulation synergize to ameliorate PD symptoms, thus requiring a reduction of the pre-operative LED to avoid dyskinesia. In addition, there may be significant placebo or nocebo effects subsequent to electrode implantation. Stopping dopaminergic medication altogether is not recommended, as this may induce a hypodopaminergic state including apathy and depression. Importantly, these symptoms may develop even weeks after the cessation of dopaminergic drugs (225–227). In particular, in patients that suffer from impulse control disorder, cutting dopamine agonists is advisable (152). Otherwise, L-Dopa should be reduced first (228, 229). Finally, reducing L-Dopa might unmask preexisting Restless Legs Syndrome that would have to be considered for treatment.

Constant Voltage vs. Constant Current Stimulation

In addition to the micro-lesion effect, the fluctuation of impedances may bias the determination of the therapeutic window in the early post-operative period (230) which might become more relevant hen using constant-voltage stimulation (CVS) where the current delivered is inversely proportional to the

electrode impedance. Conversely, current-constant stimulation (CCS) may offer more stable stimulation, in particular when programming soon after surgery (231, 232). Apart from possibly affecting the outcome in an individual patient, using CCS instead of CVS might allow for an improved generalization of outcome between subjects such that knowledge gained from one set of subjects can be generalized to others. Because the total current delivered current depends on both voltage and impedance, and since voltage is held constant with CVS, potential variations in current over time will be mainly a consequence of impedance fluctuations. Data from examining non-human primates using a small version of the human DBS lead supported this hypothesis (233) as the electrode impedance progressively increased over 7 days post-implantation, resulting in a reduction of current delivered. Benabid et al. reported impedance changes in patients with VIM stimulation for ET. These authors observed an increase in impedance of 33% (on average) over 3 months following the implantation of DBS leads. Thereafter the impedance stabilized (234). Sillay et al. measured impedances in 63 DBS patients with PD, essential tremor, and dystonia at various time intervals following DBS surgery (235). All measurements were performed at >25 days post-operatively, and in the absence of changes in the stimulation parameters between time points. On average, the authors found no significant intra-patient or intra-electrode impedance changes. However, over half had a small increase in impedance over time, and 40% had a small decrease in impedance, with the largest change observed being 23% in a single subject. Hemm et al. described similar results in patients with dystonia (236) observing that impedance values changed only slightly over time within a single patient but that there were differences between patients and between active and non-active DBS contacts. However, Cheung et al. analyzed a large database of impedance measurements from 94 subjects, ranging from 6 months to 5 years after implantation. They found that a significant amount of impedance variability could be expected in chronically implanted DBS electrodes, with a range spanning from 18 to over 600 Ω (237). Studies that compared CCS and CVS did not show any significant differences in non-motor outcomes, including cognition, mood, and quality of life in a double-blind crossover trial (238). A retrospective analysis of 19 patients with PD and dystonic syndromes switched from CVS to CCS reported no change in measured clinical outcomes and therapy satisfaction at 6 months (115, 239), whereas a more recent study found better outcomes with CCS (240). Taken together, the relevance of changes in the electrode impedance and, as a result, the total electric charge transferred, is uncertain and the specific consequences of using CCS vs. VCS stimulation are not yet clear (231, 241, 242) and currently, there is no clear evidence to support an early or late post-operative initiation of DBS.

VIM-DBS in Essential Tremor

Specific Programming Strategies in VIM-DBS

Compared to STN-DBS, the evidence for adjusting neurostimulation parameters in VIM-DBS is limited. In case of ET, kinetic tremor, the principal target of stimulation adjustments, the limb can be assessed with the finger-to-nose or finger-to-finger maneuver or by asking the patient to draw a spiral, drink water from a cup or pour water from a glass into another one. In addition, postural tremor can be assessed with the arms outstretched or elbows bent (wing-beating position). In general, the programming strategies outlined above can be applied for VIM-DBS. Using a pulse width of 60 μs and a frequency of 130 Hz, the current intensity is usually increased progressively until tremor stops or until side effects are encountered. If the tremor is not optimally controlled at 3.5 volts, pulse width and then the frequency of the stimulation may be increased (243). Studies evaluating the effect of different stimulation parameters in ET showed that tremor responds best to increase the amplitude and is further improved by 25% with longer pulse widths (90–120 μs). The frequency-response curve shows an inverse linear relationship between tremor magnitude and frequency between 45 and 100 Hz and a plateau above 130 Hz, although an additional but variable effect between 130 and 200 Hz has been documented (2) (244–247). Similar to what has been demonstrated for STN-DBS, reducing the pulse width has been shown to widen the therapeutic window in ET (248) where the minimum pulse width for suppression of tremor was shown to be significantly different to that for induction of ataxia, with values of 27 and 52 μs, respectively (249). Comparing directional stimulation with segmented electrodes to conventional ring stimulation, Rebelo et al. found an increased therapeutic window and reduced current with stimulation in the best direction compared to the best omnidirectional stimulation alternative (44) (**Figure 1**). Likewise, alternative targets directly adjacent to the VIM have been described for ET. For instance, the caudal ZI has been examined as a target for patients with tremor suggesting that ZI stimulation may even exceed tremor control through stimulation of the VIM (250–253). These findings are consistent with results from diffusion tensor imaging data suggesting that the best tremor control is obtained with stimulation of the cerebello-thalamic afferents, which are embedded in the ZI (249).

Typical Side Effects in VIM-DBS

The VIM nucleus of the thalamus is located close to the STN in the vicinity of the *internal capsule* (lateral), the *centromedian and parafascicular nucleus* of the thalamus and the *commissural nucleus* (medial), the *zona incerta (ZI) and H1/H2 field of Forel* (ventral), *the ventroanterior (VA), the ventrolateral anterior (VLA) and posterior (VLP) nuclei of the thalamus* (dorsal), and the *ventromedial thalamic nucleus (VM)* (anterior, posterior) (55) (**Figure 3**). Common side effects include the following:

Paresthesia is the most common short term side effect because the electrical field reaches into the thalamic sensory nuclei dorsal to the VIM (**Figure 3A**). It can be transient, lasting from a few seconds to minutes, or permanent, and only resolving with reducing stimulation (2, 234, 254).

Speech impairment: Dysarthria is a significant complaint in more than half of ET patients with bilateral VIM-DBS (255), although dysarthria is common in ET even in the absence of DBS. This is relevant because clinicians often choose suboptimal stimulation parameters to avoid stimulation-induced side effects, more frequently seen in patients with bilateral VIM-DBS (255,

256). Speech impairment appears to occur more frequently with higher stimulation amplitudes and with more ventral stimulation contacts. As with STN-DBS, dysarthria may be caused by interference with the cerebello-thalamic or with motor fibers of the internal capsule (**Figures 3C,D**) located laterally to the VIM causing spastic dysarthria (257) and appropriate contact adjustment may be beneficial.

Gait ataxia: Another common complaint in patients with VIM-DBS is balance issues with an unsteady gait. As with speech disturbances, current spread into dentato-thalamic afferents lateral and ventral the VIM (**Figure 3C**) may be the cause of such gait and limb ataxia (258–260), although gait and limb ataxia can be a sign of ET itself, commonly referred to as ET-Plus (261). Switching off DBS even for several days can help to distinguish between the two, but rebound tremor needs to be considered.

Loss of Stimulation Benefit: In ET, the energy required for tremor suppression and the number of active contacts typically increase as the disease progresses and this effect is more common in ET as compared to other tremor types (262–265). Indeed, some studies showed the initial improvement in activities of daily living evident at 1 year after the DBS implantation to be lost in the long run except the ability to eat (266). The loss of long-term benefit in ET has been attributed to DBS tolerance, natural disease progression, and other factors including brain atrophy (234, 266–271). Possible strategies to avoid the adaptation of neuronal networks in ET include switching the stimulation off at night (255), inverting the electrode configuration in patients using bipolar settings or on-demand stimulation.

GPi-DBS in Generalized and Segmental Dystonia

Specific Programming Strategies in GPi-DBS

GPi-DBS has been applied worldwide as a surgical treatment alternative for medical refractory segmental or generalized dystonia. Although GPi-DBS seems to be more effective for isolated than non-isolated dystonia (272), there is no evidence that non-isolated dystonia needs a different programming approach (273–275). The role of specific stimulation parameters on dystonic symptoms is probably even less established than with VIM-DBS for ET. This is likely a consequence of the

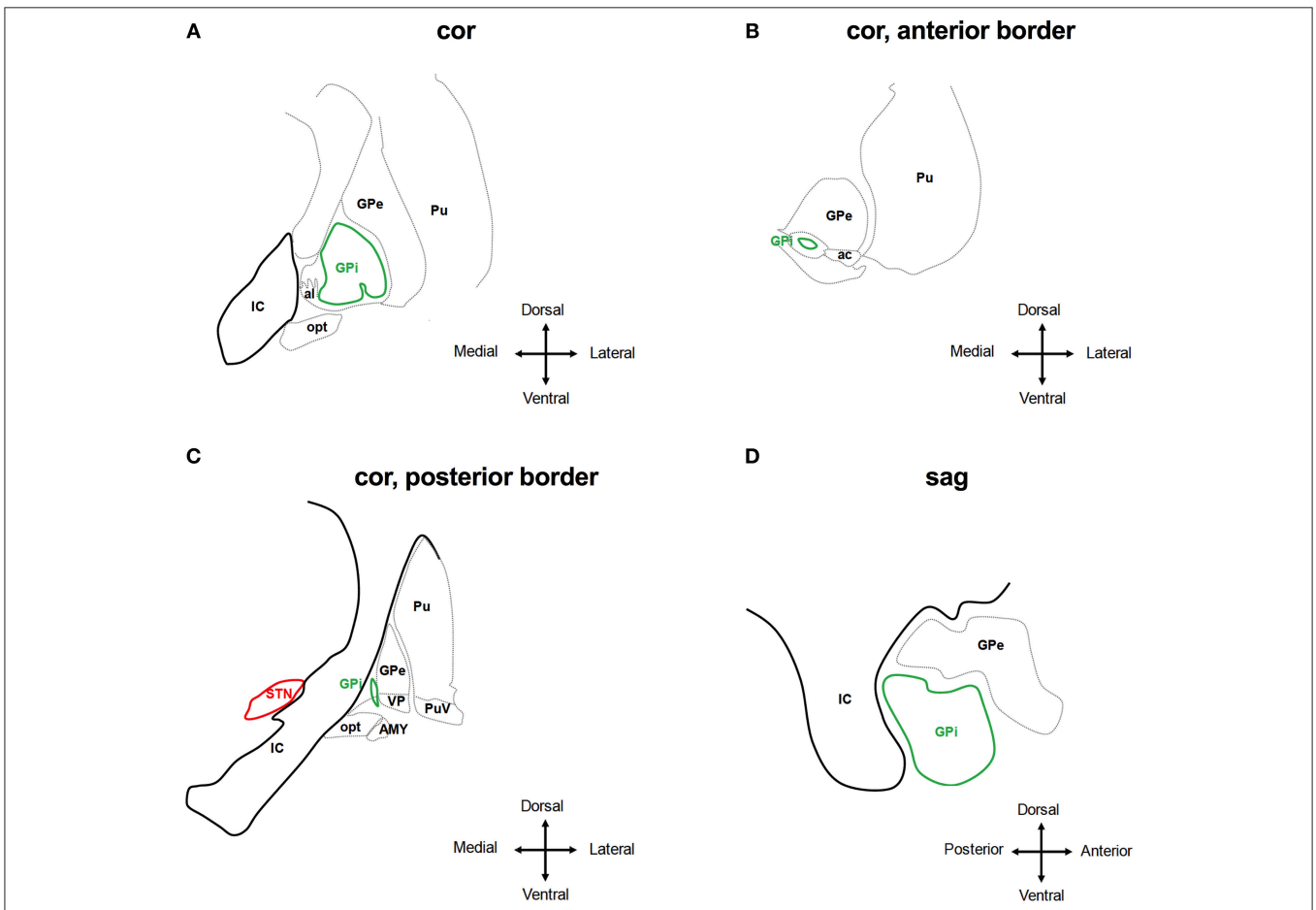

FIGURE 4 | Anatomical relationship of the globus pallidus internus (GPi) to adjacent structures. The schematic shows coronar **(A–C)** and sagittal **(D)** planes through the basal ganglia at the level of the GPi. IC, internal capsule; GPe, globus pallidus externus; al, ansa lenticularis; Pu, putamen; opt, optic tract; AMY, amygdala; VP, ventral pallidum; PuV, ventral putamen; STN, subthalamic nucleus. Deflection of stimulation to tissue medial of the GPi will activate the IC, which is less likely the case at the anterior border of the GPi **(A,B,D)**. The AMY and opt are activated by stimulating tissue ventral of the GPi **(C)**. Adjusted from Mai et al. (55).

heterogeneity of symptoms. In addition, and unlike in STN- and VIM-DBS, where the effect is observed within seconds to minutes, the effect of GPi-DBS on dystonia may not occur for hours, days, or in some cases even months (**Figure 2B**). For instance, Krauss et al. noted that phasic dystonic movements were often relieved within minutes of stimulation onset, whereas improvement in tonic posturing took several months to fully manifest (276). When adjusting neurostimulation in dystonia, phasic dystonic movements, such as dystonic neck movements, are therefore best suited for evaluation because tonic dystonic components usually need more time to improve (277). This may be in part be due to musculoskeletal abnormalities caused by long-standing dystonic posture. Accordingly, most GPi-DBS patients fail to show a clear insertional effect (277). In accord, tonic dystonic symptoms may take a lot longer to reappear upon cessation of GPi-DBS than phasic one (278–281) (**Figure 2B**). In some cases, discontinuing GPi-DBS may result in a clinical rebound effect with acutely severe symptoms (282, 283). The principal programming algorithm follows the same recommendations as with PD or ET with some modifications (3). For instance, a high frequency of 185 Hz has been proposed to be effective in GPi-DBS (284). There is a debate on the selection of the contact for chronic stimulation as there is a poor correlation between benefit and stimulation in different regions of the GPi. Cheung et al. recently identified a small area located squarely in the middle of the GPi as a potential specific therapeutic target for DBS for dystonia (285), whereas recent evidence from our own group suggests that most efficient DBS electrodes displayed a close anatomic proximity to the pallidothalamic tracts (ansa and fasciculus lenticularis) between the GPi and the pyramidal tract (286). Thus, stimulation is most commonly initiated in the ventral region of the GPi above the optic tract (contacts 0 and 1) (287) with a short pulse width (60–120 μs), high frequency (130–185 Hz) and amplitude just prior to eliciting adverse effects (284, 288, 289). Due to the anatomical location of the target, delayed side effects are less likely to occur than with STN- or VIM-DBS, thus favoring a top-down approach and starting the stimulation with the highest tolerated voltage. The use of high- vs. low-frequency stimulation in dystonia has shown mixed results. Alterman et al. suggested that the use of 60 Hz stimulation can be beneficial in some patients (290), whereas another group preferred high-frequency stimulation (289). Moro et al. concluded that high-amplitude and high-frequency stimulation predict better outcome in cervical dystonia (291). Various pulse widths have been recommended in GPi-DBS. Coubes et al. recommend the use of 450 μs (292). However, another study comparing 60, 120, and 450 μs did not show any significant differences between the three groups (293).

Typical Side Effects in GPi-DBS

The GPi is surrounded by the *globus pallidus externus and putamen* (anterior, posterior, lateral), the *internal capsule, ZI and MFB* (medial), the *ansa lenticularis* (mediodorsal), the *optical tract* (ventral), the *amygdala* (laterodorsal), the *ventral pallidum* (laterodorsal) (55) (**Figure 4**). As with STN- and VIM-DBS, side effects in GPi stimulation can result from current spreading into neighboring regions in many cases:

Hypo-/Bradykinesis: The occurrence of parkinsonian motor signs, such as micrographia and postural deficits, has been described as a possible adverse effect of GPi-DBS in dystonia (294–297). This may be the result of stimulating distinct regions within the GPi: whereas stimulation of the dorsal part of the GPi improves PD signs and symptoms like hypokinesia and rigidity, stimulation of the postero-ventral part suppresses levodopa-induced hyperkinesias but may lead to a deterioration of hypokinesia and gait (284, 298). As a consequence, stimulation-induced hypokinesia is more frequent with use of the ventral contacts and may be significantly reduced by switching to dorsal contacts. Because the ventral contacts are the most effective at controlling dystonic symptoms, this approach may lead to a worsening of dystonia (294, 299, 300).

Speech Impairment: In patients with primary dystonia treated with GPi-DBS, dysarthria is one of the most common stimulation-induced side effects reported in close to 30% in follow-up studies (277, 301). As with STN- or VIMN-DBS, this may be caused by current spreading into the internal capsule medial and posterior to the GPi (**Figures 4A–D**). In addition, stuttering may occur with GPi stimulation (257, 302), emphasizing the role of the GPi in speech fluency.

Phosphenes: These may be caused by current spread into the optic tract that is located ventral of the GPi (**Figures 4A,C**).

There is no specific evidence for general programming strategies to avoid speech disturbances in GPi-DBS other than the general strategies for avoiding side effects outlined above.

CONCLUSION

Programming the IPG is the only modifiable factor once DBS leads have been implanted and thus crucially impacts on the overall treatment success. Although our review does not provide a specific level of evidence for an overall programming strategy, we here summarized appraised strategies on how to adjust stimulation parameters and program settings in different movement disorders. Therefore, we reviewed previous studies that examined the significance of distinct stimulation strategies for ameliorating disease signs. We summarized the well-characterized significance of the stimulation amplitude, frequency and pulse width on clinical symptoms. In addition, we provided an in-depth review of potential side effects in DBS of the STN, VIM, and GPi. Based on these effects, we specifically examined more recent techniques for modulating neuronal elements, such as directional current steering, low-frequency, and short pulse-width stimulation as these strategies were shown to enlarge the therapeutic window and thus allow for a more favorable outcome in different movement disorders. In conjunction with a recommendation for managing pharmacotherapy in PD after initiation of DBS, we thus provide a concise review for STN-, VIM-, and GPi-DBS programming.

AUTHOR CONTRIBUTIONS

TK conceived the project, conducted literature research, and wrote the paper. CP, FH, JM, and KB wrote the paper.

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Modulation of Resting Connectivity Between the Mesial Frontal Cortex and Basal Ganglia

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Background: The mesial prefrontal cortex, cingulate cortex, and the ventral striatum are key nodes of the human mesial fronto-striatal circuit involved in decision-making and executive function and pathological disorders. Here we ask whether deep wide-field repetitive transcranial magnetic stimulation (rTMS) targeting the mesial prefrontal cortex (MPFC) influences resting state functional connectivity.

Methods: In Study 1, we examined functional connectivity using resting state multi-echo and independent components analysis in 154 healthy subjects to characterize default connectivity in the MPFC and mid-cingulate cortex (MCC). In Study 2, we used inhibitory, 1 Hz deep rTMS with the H7-coil targeting MPFC and dorsal anterior cingulate (dACC) in a separate group of 20 healthy volunteers and examined pre- and post-TMS functional connectivity using seed-based and independent components analysis.

Results: In Study 1, we show that MPFC and MCC have distinct patterns of functional connectivity with MPFC–ventral striatum showing negative, whereas MCC–ventral striatum showing positive functional connectivity. Low-frequency rTMS decreased functional connectivity of MPFC and dACC with the ventral striatum. We further showed enhanced connectivity between MCC and ventral striatum.

Conclusions: These findings emphasize how deep inhibitory rTMS using the H7-coil can influence underlying network functional connectivity by decreasing connectivity of the targeted MPFC regions, thus potentially enhancing response inhibition and decreasing drug-cue reactivity processes relevant to addictions. The unexpected finding of enhanced default connectivity between MCC and ventral striatum may be related to the decreased influence and connectivity between the MPFC and MCC. These findings are highly relevant to the treatment of disorders relying on the mesio-prefrontal-cingulo-striatal circuit.

Keywords: cingulate cortex, ventral striatum, mesial prefrontal cortex, transcranial magnetic stimulation, resting state connectivity

INTRODUCTION

Neuromodulation with magnetic stimulation is emerging as a valuable treatment alternative for a wide range of psychiatric and neurologic disorders (1). Repetitive transcranial magnetic stimulation (rTMS) is a technique that can be used to apply multiple brief magnetic pulses to neuronal structures, thus transiently modulating neural excitability in a manner that is dependent mainly on the intensity and frequency of stimulation (2). It is a non-invasive, non-pharmacological, and safe treatment, in which abnormal communication within neuronal networks can be entrained and modified. Depending on the target, the depth at which stimulation occurs appears to be a crucial factor underlying potential therapeutic efficacy in certain disorders, such as major depressive disorder (3–5). In this study, we investigate the modulation of resting neural activity in mesial prefrontal-striatal circuits in healthy subjects by inhibitory deep wide-field stimulation with an Hesed (H-)7 coil (6, 7).

Fronto-striatal circuits are critical for the processing of reward, anticipation of outcomes, and behavioral control (8–11). Latent neural network organization and behavioral mechanisms in humans can be explored with resting state functional magnetic resonance imaging (fMRI) connectivity (rsFC), a method that measures the synchronization between intrinsic low-frequency fluctuations of brain regions in the absence of any specific task (12–14). Since the connections identified at rest closely mirror anatomical connections (15) and predict brain activations associated with behavioral performance (16), rsFC is an important tool for characterizing *in vivo* circuit-level dynamics, which may support particular behavioral responses (17, 18).

Studies of substance use disorders have revealed the critical role of fronto-striatal circuits, highlighting large scale disruptions in functional connectivity between the mesolimbic reward system and cortical regions involved in decision making and executive function (e.g., ventromedial prefrontal cortex, dorsolateral prefrontal cortex)(19–27). In particular, altered rsFC between the dorsal and ventral mesial prefrontal cortex (d/vMPFC), anterior cingulate cortex (ACC) and ventral striatum (VS) is most consistently observed across disorders of addiction such as cocaine (28), heroin (29), nicotine (30–33), and even internet addiction (32–35), but also in obsessive-compulsive disorder (OCD) (34). Furthermore, vMPFC activity seems to be tightly linked to dMPFC activity (36, 37). Thus, understanding whether and how deep rTMS targeting the MPFC influences the connected networks is critical to its potential clinical efficacy.

In Study 1, we first assess rsFC between MPFC and striatum in a relatively large sample of healthy controls. In Study 2, we then ask whether inhibitory deep wide-field stimulation with an H7-coil positioned over the MPFC [which, given the non-focal nature of the H7-coil (38, 39), we have defined here as supplementary motor area (SMA), preSMA, and dMPFC] influences rsFC with VS in a separate group of healthy controls. We focused on VS given its aberrant rsFC observed in pathological disorders as well as in our findings in Study 1 of negative connectivity of MPFC with VS and positive connectivity of mid-cingulate with VS. We hypothesize that low-frequency inhibitory rTMS will decrease rsFC of the MPFC with VS.

METHODS AND MATERIALS

Protocol Design and Participants

In Study 1, seed to whole brain intrinsic rsFC was examined for the mesial PFC (SMA, pre-SMA and dMPFC) and the mid-cingulate. For intrinsic baseline mapping, blood-oxygenation level dependent (BOLD) fMRI data was collected during rest (10 min, eyes open, watching white fixation cross on black screen) from 154 healthy volunteers (71 females; age 31 ± 13 years) at the Wolfson Brain Imaging Center, University of Cambridge, UK, with a Siemens Tim Trio 3T scanner and 32-channel head coil.

In Study 2, we used inhibitory, 1 Hz rTMS deep wide-field stimulation with an H7-coil targeting the mesial PFC. In order to examine the effects of rTMS on neural fluctuations, we used both ROI-to-ROI analyses and confirmed findings with independent component analysis (ICA). Resting state fMRI data (10 min, eyes open, watching white fixation cross) was collected immediately before and after rTMS (average time between rTMS end and EPI sequence was 285 ± 27 s) in a separate group of 20 healthy volunteers (15 females; age 36 ± 12 years) at the National Institutes of Health (Bethesda, MD, USA) core fMRI Facility, with a Siemens Skyra 3T scanner and 32-channel head coil.

All subjects provided informed written consent. This study was approved by the Research Ethics Committee of the University of Cambridge and the Institutional Review Board of the National Institutes of Health.

Transcranial Magnetic Stimulation With the H-coil (Study 2)

To modulate the excitability of deep frontal areas in Study 2, we used a Hesed coil type 7 (H7-coil). Its design aims at stimulating frontal brain regions (i.e., the PFC) and reaching deep brain regions without increasing the electric field levels in the more superficial cortical regions (6, 40). Deep TMS using other coils (e.g., classical double-cone coil) can be uncomfortable due to excessive stimulation of superficial structures and painful muscular contractions. The frames of the inner rim of H7-coil are also flexible to accommodate a variety of human skull shapes and allow a comfortable and closer fit of the coils to the scalp (**Supplementary Figure S1**).

We first found the hotspot and determined the active motor threshold (AMT) of the *Tibialis anterior muscle*, as an area situated medially at a depth similar to our regions of interest (**Figure 1A**). The AMT was defined as the lowest intensity able to evoke a motor potential with an amplitude at least 200 μV above the background EMG activity of a 10% maximal voluntary contraction of the left Tibialis anterior in 5 out of 10 consecutive trials. The coil was always maintained in the midline to avoid the problem of left-right anatomical and functional asymmetry, on top of the unknown exact geometrical location of the maximum field intensity of the H7-coil. In this way, the threshold determined for the left TA corresponded to an intensity strong enough to evoke action potentials in the pyramidal neurons on the mesial cortex at that depth in each individual. Repetitive

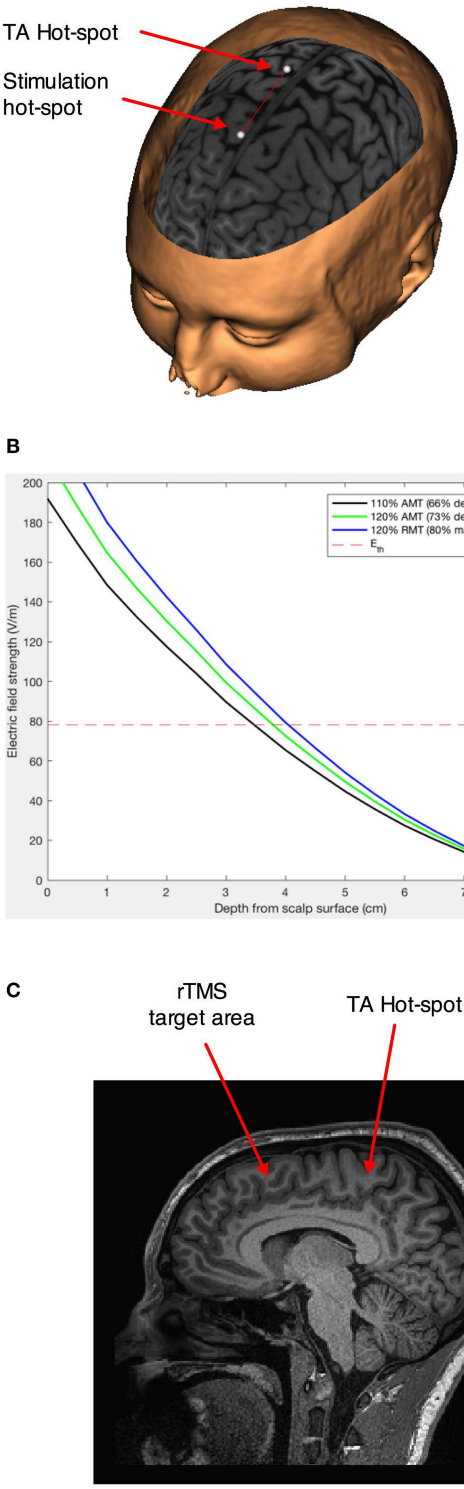

FIGURE 1 | Stimulation paradigm. **(A)** Schematic representation of the movement of the projection of the geometric center of the H7 coil 5 cm in front of the empirically found hot-spot for the left *Tibialis anterior* muscle (41, 42). The points represent an ideal (not neuronavigated) center of the interior of the H7 helmet. **(B)** Estimation of the induced electrical field intensity with distance from the coil for stimulation at 110% of the active motor threshold (AMT)—our *(Continued)*

FIGURE 1 | intensity of choice, and 120% AMT and 110% resting motor threshold—higher intensities distribution modeled for comparison. The dotted line represents the theoretical intensity of the induced electrical field for AMT. **(C)** Sagittal section showing the area in the dorso-mesial prefrontal cortex found at an equivalent depth to the *Tibialis anterior* motor representation.

TMS was delivered with a biphasic magnetic stimulator (Magstim Rapid2; The Magstim Company, Whitland, South West Wales, UK) with a frequency of 1 Hz and at 110% AMT intensity. Nine hundred pulses were administered over the MPFC, 5 cm anterior to the Tibialis anterior hot-spot, for 15 min. By choosing this location, we assured that the maximum field would cross areas BA 8/9, which are located in front of the peSMA (41, 42). When administered in accordance with current international guidelines, transcranial magnetic stimulation has been shown to be safe (43, 44), with few mild adverse effects, although we acknowledge that these safety guidelines are derived primarily from studies using conventional figure-8 coils.

We used medium intensity stimulation (i.e., 110% of the active motor threshold; average effective intensity 66 ± 8% of the maximum stimulator output) of the H7-coil, which would have penetrated effectively up to a depth of 3.5 cm from the surface of the scalp (**Figure 1B**), corresponding to the mesial PFC region (**Figure 1C**).

Resting State Functional MRI

The following describes the resting state acquisitions and analyses used for Study 1 and 2.

Acquisition Study 1: Functional images were acquired with a multi-echo echo planar imaging sequence with online reconstruction (repetition time (TR), 2.47 s; flip angle, 78°; matrix size 64 × 64; resolution 3.0 × 3.0 × 3.0 mm; FOV, 240 mm; 32 oblique slices, alternating slice acquisition slice thickness 3.75 mm with 10% gap; iPAT factor, 3; bandwidth (BW) = 1,698 Hz/pixel; echo time (TE) = 12, 28, 44 and 60 ms).

Study 2: Functional images were acquired with a multi-echo echo planar imaging sequence (TR, 2.47s; flip angle, 70°; matrix size 70 × 60; in-plane resolution, 3.0 mm; FOV, 210 mm; 34 oblique slices, alternating slice acquisition slice thickness 3.0 mm with 0% gap; iPAT factor, 3; bandwidth (BW) = 2,552 Hz/pixel; TE = 12, 28, 44, and 60 ms).

For both studies, anatomical images were acquired using a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence (76 × 240 field of view (FOV); resolution 1.0 × 1.0 × 1.0 mm; inversion time, 1,100 ms).

Preprocessing

The following processing and analyses apply to both resting state fMRI data unless stated otherwise. To enhance signal-to-noise ratio, we used multi-echo EPI sequence and independent component analysis (ICA), which allows data to be denoised for motion, physiological, and scanner artifacts in a robust manner based on physical principles (45).

Multi-echo independent component analysis (ME-ICA v2.5 beta6; http://afni.nimh.nih.gov) was used for data analysis and denoising. ME-ICA decomposes the functional data into independent components using FastICA. BOLD percent signal changes are linearly dependent on echo time (TE), a characteristic of the T2* decay. TE dependence of BOLD signal is measured using the pseudo-F-statistic, Kappa, with components that scale strongly with TE having high Kappa scores (46). Non-BOLD components are TE independent and measured by the pseudo-F-statistic, Rho. Components are thus categorized as BOLD or non-BOLD based on their Kappa and Rho weightings, respectively. Non-BOLD components are removed by projection, robustly denoising data. Each individual's denoised echo planar images were coregistered to their MPRAGE and normalized to the Montreal Neurological Institute (MNI) template. Spatial smoothing of the functional data was performed with a Gaussian kernel (full width half-maximum = 6 mm).

Region of Interest (ROI)-Driven Analysis

We performed ROI-driven functional connectivity analysis using CONN-fMRI Functional Connectivity toolbox (47) for Statistical Parametric Mapping SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), using denoised, coregistered, smoothed functional data. The time course for each voxel was temporally band-pass filtered ($0.008 < f < 0.09$ Hz). Each individual's anatomical scan was segmented into gray matter, white matter and cerebrospinal fluid. Significant principle components of the signals from white matter and cerebrospinal fluid were removed.

Study 1: Intrinsic functional connectivity mapping

For intrinsic rsFC mapping in 154 healthy volunteers, ROI-to-whole brain connectivity was computed for mesial PFC and mid cingulate ROI's. Connectivity maps were thresholded at FWE $p < 0.05$ whole brain corrected. Both positive and negative functional connectivity was examined across the whole brain. Anatomically-defined ROIs were manually created or altered using MarsBaR ROI toolbox (48) for SPM (see **Supplementary Methods** for seed definitions).

Study 2: Effects of rTMS: ROI-based

To address the *a priori* hypothesis, ROI-to-ROI functional connectivity was first computed using Pearson's correlation between BOLD time courses for mesial PFC with ventral striatum, both pre- and post-TMS. These were entered into a paired samples *t*-test to compare between pre- and post-TMS. For the *a priori* ROI-to-ROI functional connectivity analysis between the mesial PFC and VS, $p<0.05$ was considered significant. On an exploratory basis, to assess the impact of rTMS on rsFC of deeper structures such as the mid-cingulate which lies immediately below the mesial PFC, ROI-to-ROI functional connectivity of mesial PFC to mid cingulate and mid cingulate to VS were examined pre- and post-TMS. $P<0.025$ was considered significant (Bonferonni corrected for multiple comparisons). The VS anatomical ROI has previously been used (49) and hand drawn using MRIcro (http://www.cabiatl.com/mricro/mricro/) based on a published definition of VS (50).

Effects of rTMS: Independent Component Analysis (Study 2)

To confirm the ROI-to-ROI findings, we then conducted ICA. While ICA has been shown to engender statistically similar results as seed based approaches in healthy volunteers (51), ICA is a multivariate data-driven approach that requires fewer *a priori* assumptions and takes into account interacting networks. Therefore, if TMS affects larger scale neural networks, ICA should succeed in highlighting this. Denoised, coregistered, and smoothed functional data was entered into ICA analysis using FSL MELODIC 3.14 software (FMRIB, University of Oxford, UK; www.fmrib.ox.ac.uk/fsl/melodic2/index.html) that performs probabilistic ICA to decompose data into independently distributed spatial maps and associated time courses to identify independent component variables (52). A high model order of 40 was used as a fair compromise between under- and over-fitting (53). Multi-session temporal concatenation was used to allow computation of unique temporal responses per subject/session. Comparisons between pre- and post-TMS was performed using FSL dual regression for reliable and robust (54) voxel-wise comparisons using non-parametric permutation testing with 5,000 permutations and using threshold free cluster enhancement (TFCE) controlling for multiple comparisons (55). Group differences of components that include MPFC were calculated with $p < 0.05$ thresholds.

RESULTS

Baseline Mapping

Intrinsic resting state whole brain connectivity maps for mesial PFC and mid cingulate are displayed in **Figure 2** and reported in **Supplementary Tables S1, S2**. Both positive and negative functional connectivity are displayed. Mesial PFC and mid cingulate showed opposite patterns of connectivity with ventral striatum: mesial PFC had negative but mid cingulate had positive functional connectivity with VS.

Effects of TMS

Focusing on our *a priori* hypothesis, we show that after rTMS, mesial PFC had reduced functional connectivity with ventral striatum ($t = 2.201$, $p = 0.043$) (**Figure 3**). We then show an effect on mid-cingulate functional connectivity with reduced functional connectivity following rTMS between the mesial PFC and mid-cingulate ($t = 4.325$, $p = 0.001$) and enhanced functional connectivity between mid-cingulate and VS ($t = -2.495$ $p = 0.024$).

We conducted ICA on the resting state data pre- and post-rTMS to confirm our *a priori* hypothesis and analysis. Out of 40 components, three included prominent mesial frontal cortex (**Figure 4**). Of the three mesial frontal network components, dual regression revealed that one of these components (IC11) was significantly decreased post-rTMS (TFCE $p = 0.0360$). The IC00 included prominent dmPFC; the IC11 included dmPFC, preSMA, and SMA; the IC38 included prominent anterior and mid cingulate, and dmPFC. The dmPFC/ACC can be considered part of the dorsal attention network.

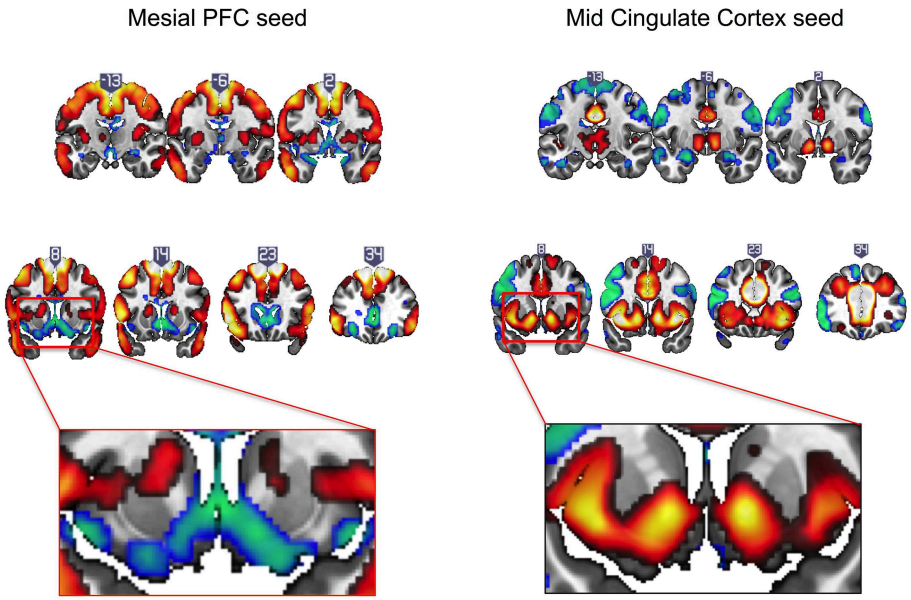

FIGURE 2 | Intrinsic resting state connectivity maps for mesial prefrontal cortex (PFC) and mid cingulate cortex seeds to whole brain in healthy controls. Positive (yellow-red) and negative (green-blue) functional connectivity are displayed. The rectangular insets at y = 8 highlighting differences in direction of connectivity of the striatum are shown for the mesial PFC (bottom row, left) and mid cingulate (bottom row, right). Coronal images (y-values shown above image) are thresholded at whole brain family-wise error, corrected $p < 0.05$ on a standard MNI template.

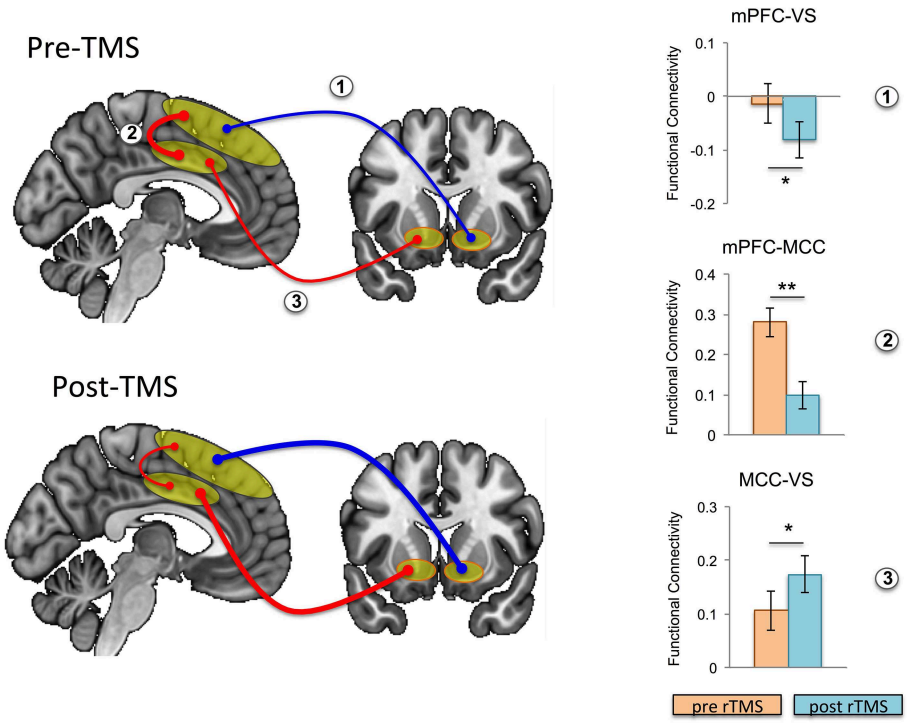

FIGURE 3 | Effects of repetitive transcranial magnetic stimulation (rTMS) on intrinsic functional connectivity in healthy controls. Functional connectivity is schematically illustrated at baseline (i.e., pre-rTMS; top left) and post-rTMS (bottom left); pre- and post-rTMS effects on seed-to-seed functional connectivity are shown in the bar graphs. After rTMS, functional connectivity between mesial prefrontal cortex (mPFC) and ventral striatum (VS), and between mPFC and mid cingulate cortex (MCC) was reduced, while functional connectivity between MCC and VS was increased (the thickness of the arrows correspond to strength, and color to direction: red, positive connectivity; blue, negative connectivity). Error bars are shown as standard error of the mean. *$p < 0.05$, **$p = 0.001$.

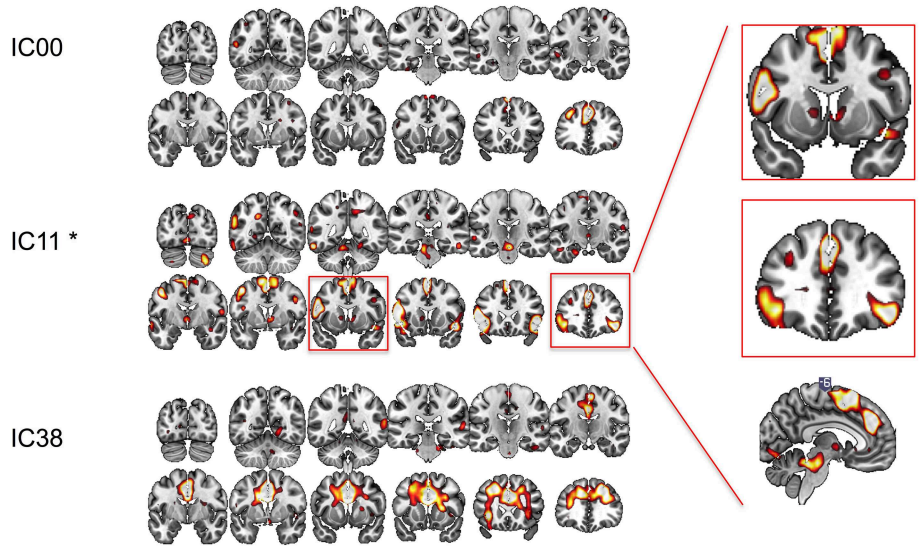

FIGURE 4 | Functional connectivity at rest between different regions of interest explored with independent component analysis pre- and post-rTMS. Three components included prominent mesial-frontal cortex (IC00, IC11, and IC38). The insert shows IC11, which included supplementary motor area (SMA), pre-SMA, dorsomedial prefrontal cortex/dorsal cingulate, and ventral caudate/striatum, and bilateral inferior frontal cortices was significantly decreased post-rTMS. *$p < 0.05$.

DISCUSSION

We characterized the effects of deep wide-field mesial prefrontal rTMS on the resting-state functional network in healthy individuals. We first mapped intrinsic functional connectivity of mesial prefrontal and mid-cingulate cortical regions in a large sample of healthy volunteers. We found that intrinsic functional connectivity of the mesial PFC region of interest with ventral striatum was negative, whereas the intrinsic functional connectivity of mid-cingulate connectivity with ventral striatum was positive. Then, we show that deep wide-field inhibitory rTMS targeting the mesial PFC decreases rsFC between this broad mesial PFC region and the ventral striatum. These findings were further confirmed with ICA analysis, a data-driven approach. Based on the modeling of the magnetic field distribution, induced-electrical field decay, and the depth of the target region stimulated, we likely also inhibited directly the dorsal posterior regions of Brodmann Area 32, corresponding to dorsal anterior cingulate—a fact subsequently confirmed by the ICA analysis. Inhibitory rTMS also decreased functional connectivity of the "stopping" network including pre-SMA, right inferior frontal cortex, and ventral caudate. This is in line with previous reports, in which inhibitory rTMS (including continuous theta burst stimulation) targeting the pre-SMA with standard figure-of-eight coil has been shown to enhance motor response inhibition (56).

We also found effects of deep rTMS on connectivity between deeper structures such as the mid-cingulate cortex, which was unlikely to be directly stimulated with our stimulation parameters: decreased rsFC between the broad mesial PFC and mid-cingulate cortex, and, unexpectedly, enhanced rsFC between mid-cingulate cortex and ventral striatum. These findings suggest that while deep wide-field mesial prefrontal inhibitory rTMS might directly decrease the functional connectivity between the stimulated and the connected structures, the decreased influence from superficial cortical regions might indirectly enhance the intrinsic connectivity between remote structures (i.e., the mid-cingulate cortex and ventral striatum).

Application of rTMS to superficial cortical regions with the strongest negative functional connectivity with subgenual ACC has already been shown to be most clinically efficacious in reducing depression (57). Thus, based on the deep cortical or subcortical structure of interest for a given disorder, appropriate superficial sites for rTMS can be selected based on intrinsic functional connectivity strengths and patterns. Since we demonstrate in our second study that there is an exaggeration of intrinsic functional connectivity strengths with deep inhibitory rTMS, detailed mapping of baseline connectivity patterns will inform the selection of rTMS targets with the aim to "normalize" aberrant underlying functional connectivity in disease states. The outcome of this modulation could be of interest in the treatment of disorders relying on the mesioprefrontal-cingulo-striatal circuit.

The H-coil series was originally designed to have a significant impact on deep structures, like the anterior cingulate cortex (6, 7). It has been used with different degrees of success to treat depression (58, 59), alcohol use disorders (60), nicotine addiction (61), and even as adjunctive therapy in Parkinson's disease (62), blepharospasm (63), and chronic migraine (64). Due to the quick drop in TMS efficacy with increasing target depth (65), it has been proposed that any stimulation outside the primary motor cortex should be referenced to motor cortex excitability and adjusted to the target depth (66, 67). The original assertion that the H-coil can modulate the activity of deep structures has been based mainly on calculating the intensity of the induced electrical

field at different depths for a given stimulation intensity (40). However, other factors can significantly influence the efficacy of rTMS, including the orientation of the coil (68–70) and the configuration of the subjacent and/or target cortex (71–75), as well as the secondary electrical fields generated at the boundary between the cerebrospinal fluid and the gray matter (76). Subsequent studies of the distribution of the magnetic field generated by the H-coil revealed that the largest field intensity variation and hence, the functional effect covers first the mesial neuronal structures in close proximity to the coil, i.e., superior MF areas, like dMPFC, pre-SMA, SMA (40, 77–79), and only secondarily deeper structures such as the cingulate cortex if stimulation intensity is high enough (7, 40). In order to reach the stimulation threshold of neurons, a total field of 30–100 V/m is needed, depending on the neurons (80). Since focal coils, like flat 8-shaped or double-cone coils, produce very strong fields that decay fast as a function of distance, 500 V/m would be induced at 1 cm depth (i.e., scalp) for 50 V/m at 5 cm, which would be very uncomfortable due to superficial muscle contraction under the stimulated site (6). According to our simulations (**Figure 1B**) using a spherical head model, the structure of the H7-coil induces only 150 V/m at 1 cm in the same conditions, albeit at the cost of focality, making it more tolerable. In this study, we used medium intensity stimulation (i.e., 110% of the active motor threshold; average effective intensity 66 ± 8% of the maximum stimulator output), which would have stimulated a region of interest corresponding to the mesial PFC. This allowed us to influence directly the output of these areas and indirectly the activity of functionally linked structures (81–86). Based on the simulated model of the target and depth reached using our stimulation parameters, we likely directly stimulated down to dorsal posterior regions of Brodmann Area 32 corresponding to dorsal anterior cingulate. However, it is unlikely that we directly stimulated the mid-cingulate; thus any change in connectivity observed in the mid-cingulate would likely be an indirect effect via changing the functional output of connected areas. Here, we extend the understanding of the effects of magnetic stimulation over the middle frontal areas, following previous TMS studies investigating more superficial stimulation of the lateral frontal areas (57, 87–89). Subsequent studies are indicated to investigate the influence of higher intensities and higher frequencies (90) on rsFC of frontal superficial and deep structures, when applied with coils designed to reach broader regions. The magnetic field generated by an H7-coil is covering a much wider area of the frontal lobe, but as with the classical double-cone coil, which has a similar shape but smaller, the magnetic field generated at the edges of the coil is assumed to be non-focal and weak enough as not to induce a meaningful neuronal depolarization.

We delivered magnetic pulses at 1 Hz for 15 min. This frequency can induce a long term depression (LTD)-like effect in the targeted neuronal networks that outlasts the stimulation for a sufficient duration to assess the influence on resting-state fMRI (91–94). By using low stimulation intensities, we effectively depressed the excitability of the superior mesial prefrontal areas and possibly also the dorsal posterior region of Brodmann Area 32 corresponding to dorsal anterior cingulate cortex. An LTD-like effect would thus decrease neuronal excitability in the mesial PFC, rendering it less responsive to incoming information. Decreased responsiveness would functionally decouple this region from both neighboring and deeper structures. Indeed, we found reduced functional connectivity of the broad mesial PFC with mid-cingulate, and between the broad mesial PFC and ventral striatum, with ICA confirming decreases in the network including mesial PFC, dorsal anterior cingulate and ventral caudate/ventral striatum. Since the fronto-striatal network relies on a dynamic equilibrium between its different parts (11, 95, 96), functionally "nudging" one part should entrain a reconfiguration of all functional connections, including functional connectivity between remote regions receiving projections from the stimulated region. This seems to be the case in our study: we found increased functional connectivity between the mid-cingulate area and ventral striatum after inhibiting the mesial PFC.

The outcome of this modulation could be of interest in treatment of disorders relying on the mesioprefrontal-cingulo-striatal circuit. In healthy humans, this circuit is involved in cognitive and emotional control, error and conflict monitoring (97–99), response inhibition (100), and positive and negative prediction error and anticipation (101–103). Abnormal cortico-ventro striatal hyperconnectivity has been OCD (104–106) and addictions [for a review see (107)]. In disorders of addiction, decreased functional connectivity between the ventral striatum and the cingulate cortex bilaterally is commonly observed (29, 32), with enhanced dorsal cingulate and ventral striatal activity in the context of drug cues (108). Numerous targets had been proposed for invasive deep brain stimulation aimed at correcting these imbalances, including the anterior limb of the internal capsule (109), subthalamic nucleus (110), and ventral striatum/nucleus accumbens (111). In order to avoid the risks of an invasive procedure, studies have explored stimulating other nodes of these networks that are accessible to TMS at the surface of the brain. Stimulation of the dorsolateral prefrontal cortex, is [arguably (58, 59)] successful in treatment-resistant major depressive disorder (4, 112), with modest results in OCD (113). On the other hand, stimulation of the dorso-medial prefrontal cortex (114) or preSMA/SMA complex (115–117) seems slightly more encouraging. Notably, there is no gold standard yet for the frequencies to be used. The stimulation frequencies used thus far in most studies cover a wide range including continuous delivery at 1 Hz, or intermittently at 10 or 18 Hz in 5 s trains separated by breaks of 10 s. While 1 Hz stimulation is known to induce LTD-like effects, the mechanism of action and the eventual outcome of other multiple medium-frequency trains is still open to debate and investigation (118, 119).

Wide inhibitory stimulation of the dorso-mesial areas of the frontal lobe might have both clinical and mechanistic benefit. Wider superficial stimulation has a clear clinical benefit allowing a reduction in the intensity of the stimulation with deeper stimulation, thus increasing patients' comfort and adherence by decreasing superficial muscle contraction, and minimizing risks. Aberrant activity in networks in psychiatric disorders may affect broader regions that can be targeted via wide inhibitory stimulation. We show that stimulation that is both wide and deep is associated with decreased connectivity between the mesial

prefrontal areas and deeper structures (like the mid-cingulate areas and ventral striatum), with possibly a secondary effect of increasing connectivity between cingulate and ventral striatum. Wider stimulation will also have a broader effect on multiple neural regions, impacting a wide range of cognitive functions. Using the H7-coil with inhibitory rTMS is thus consistent with both inhibition of the pre-SMA shown to enhance motor response inhibition (56) and decreased dorsal cingulate activity associated with drug cue reactivity (108). Therefore, the H7-coil has the capacity to both enhance the response inhibition associated with the stopping network in disorders of addiction, and decrease drug cue reactivity associated with the dorsal cingulate and ventral striatum. However, it is unclear whether decreasing dorsal cingulate activity across all conditions would be the optimal approach, as resting state functional connectivity between cingulate and ventral striatal regions are commonly decreased in disorders of addiction. Further studies investigating a state-specific effect of rTMS may be relevant with pairing H-coil stimulation with drug cues with or without concurrent response inhibition. It also remains to be established whether our findings are specific to wide-field deep rTMS or whether focal deep rTMS (which is be more difficult to tolerate) would show similar rsFC pattern changes within cingulate regions.

This study is not without limitations. While we did not have a sham control, we note that our findings revealed both increases and decreases in connectivity—suggesting that an order effect is unlikely to account for these observations. It is also technically impossible to achieve a realistic sham with the H-coil, since the real stimulation evokes a specific, unconfoundable small contraction of the anterior belly of the occipitofrontal muscle. The localization of the peak stimulus effect is also more difficult with the H-coil, since the coils' positions inside the helmet are flexible and the precise technical characteristics of the coils are proprietary to the company. We do present, however, an X-ray of the coil structure and the geometrical approximation of the coil used in the modeling of the magnetic field penetration depth **(Supplementary Figure S1)**. Subsequent studies testing higher frequencies and/or intensities are indicated, as well as repeated stimulation sessions (over minimum 4 weeks) in preparation for clinical trials.

We highlight that non-invasive wide and deep inhibitory brain stimulation appears to decrease the underlying functional connectivity of regions immediately within the stimulation zone while enhancing functional connectivity of deeper structures such as mid-cingulate to ventral striatum. This unexpected finding might be related to the decreased influence from superficial cortical regions via decreased cortico-cortical connectivity. A deep wide-field coil allows both greater tolerability and the capacity to influence multiple relevant neural regions and cognitive functions. These dissociable findings may be relevant particularly to disorders of addiction and OCD, and have implications for designing interventional deep rTMS studies.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Institutional Review Board (IRB) of the National Institutes of Health (NIH) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the NIH IRB.

AUTHOR CONTRIBUTIONS

TP, LM, MH, and VV contributed conception and design of the study. TP, LM, RH, Z-DD, SH, and KM analyzed the data. LM and KB performed the statistical analysis. TP and LM wrote the first draft of the manuscript. Z-DD and SH wrote sections of the manuscript. All authors contributed to manuscript revision, read 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.2019.00587/full#supplementary-material

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REVIEW
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Transcranial Focused Ultrasound (tFUS) and Transcranial Unfocused Ultrasound (tUS) Neuromodulation: From Theoretical Principles to Stimulation Practices

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Transcranial focused ultrasound is an emerging technique for non-invasive neurostimulation. Compared to magnetic or electric non-invasive brain stimulation, this technique has a higher spatial resolution and can reach deep structures. In addition, both animal and human studies suggest that, potentially, different sites of the central and peripheral nervous system can be targeted by this technique. Depending on stimulation parameters, transcranial focused ultrasound is able to determine a wide spectrum of effects, ranging from suppression or facilitation of neural activity to tissue ablation. The aim is to review the state of the art of the human transcranial focused ultrasound neuromodulation literature, including the theoretical principles which underlie the explanation of the bioeffects on neural tissues, and showing the stimulation techniques and parameters used and their outcomes in terms of clinical, neurophysiological or neuroimaging results and safety.

Keywords: focused ultrasound, transcranial stimulation, non-invasive brain stimulation (NIBS), transcranial focused ultrasound (tFUS), transcranial ultrasound (tUS)

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INTRODUCTION

Preliminary animal studies suggest that, potentially, different sites in the peripheral nervous system, from nerves (1) to spinal roots (2), and in the central nervous system, from superficial regions like primary motor cortex (3) or frontal eye field (4), to more deep areas like hippocampus (3), amygdala (5), or thalamus (6) can be targeted by focused ultrasound stimulation technique. In addition, animal studies showed that this technique has a high spatial resolution, useful also for mapping small brain areas, as shown by Fry (7) for the mapping of lateral geniculate nucleus, or by Ballantine et al. (2) for the stimulation of Edinger-Westphal nucleus.

Furthermore, a recent fMRI resting-state functional connectivity animal study (8), showed that the effect of tFUS neuromodulation can last for up to 2 h after stimulation, opening a new way to explore not only the online effect but also the long lasting effect of neuromodulation. The first human transcranial application of ultrasounds for neuromodulation was described by Hameroff et al. (9), with an unfocused transcranial ultrasound (tUS) continuous stimulation of posterior frontal cortex, applied on 31 patients affected by chronic pain. The first human application of focused transcranial ultrasound (tFUS) technique was described by Legon et al. (10). They targeted

the primary somatosensory cortex of healthy volunteers, in a within-subjects, sham-controlled study. One of the most interesting results of tFUS applications was a case report of emergence from minimally conscious state, after low intensity non-invasive ultrasonic thalamic stimulation in a patient after acute brain injury (11). Following this first single evidence, a clinical trial is ongoing to explore the effect of thalamic low intensity focused ultrasound in acute brain injury patients (12).

Regarding peripheral nervous system neuromodulation, Bailey et al. (13) explored the ability of continuous US at 1.5 MHz in modulating the ulnar nerve stimulation response to magnetic stimulation (MS). This study showed no significant change in electromyographic response during magnetic plus US ulnar nerve stimulation. However, further studies are needed in order to explore different parameter of stimulation.

In recent years, the scientific community showed a progressive increasing interest on FUS neuromodulation, and some reviews have been published in order to summarize the state of the art on this topic (14–18).

Mechanisms of Actions of US Neuromodulation

Focused ultrasound is a non-invasive, non-ionizing technique. In order to target a brain region, the first challenge is to let ultrasounds single waves to reach the target at the same time, without different acoustic reflection, refraction, and distortion due to the inhomogeneity of skull bone. This problem can be solved by time shifting each single ultrasound wave, according to the related skull bone acoustical properties, in order to let all the waves to reach the target at the same time (19–22).

The mechanical interaction between US and neuronal membranes can modify the membrane gating kinetics through the action on mechanosensitive voltage-gated ion channels or neurotransmitter receptors (23–25). The study of Tyler et al. (25) supports this hypothesis. Their study showed, on *ex vivo* mouse brains and hippocampal slice cultures, that low-intensity, low-frequency ultrasound (LILFU) is able to activate voltage-gated sodium and calcium channels. However, this can't be the only mechanism of action, explaining the action potential induction, since in simulations, considering the role of membrane tension on activation of mechanically sensitive voltage gated channels, the resulting effect was too low to induce an excitation (26, 27).

In addition, the mechanical action of US is able to induce cavitation into the cellular membrane, by means of membrane pore formation, which changes the membrane permeability.

The bilayer sonophore model (28) was introduced to better explain the bioeffects of US, taking into consideration the biomechanical proprieties of US and of cell membranes. According to this model (28), the mechanical energy of US leads to periodic expansions and contractions of the membrane. In this model, the US bioeffect is dependent on the tension applied to the membrane. With a progressive increase in membrane stretch intensity, the bioeffect is mediated by different mechanisms. First by the activation of mechanosensitive proteins. Then, with an increase of intensity, there is a pore formation and with the maximum stretch that can be achieved with the technique a membrane rupture and irreversible lesion is obtained (28) (**Figure 1**).

Considering the electrical properties of the cell membrane at rest, which can be approximated with a parallel plate capacitor, a hypothesis is that the dynamic fluctuation of the membrane bilayer changes the instantaneous membrane capacitance and leads to a capacitive current, which can potentially activate voltage-dependent sodium and potassium channels (27) (**Figure 2**). The neuronal bilayer sonophore model (27) combines, in a complementary way, all the biomechanical and bioelectrical proprieties of the cell membrane described, and predicts the stimulation parameter needed to reach a successful motor cortex stimulation. It explains, for example, the higher efficacy of long US stimulation pulses (3, 29, 30), and how the action potential can be elicited after the end of the US stimulus (27, 31), with a good overlap with the experimental results obtained using real stimulation on the mouse motor cortex (30).

Stimulation Parameters

An acoustic wave can be defined by two fundamental parameters: the intensity, defined as the amplitude of the wave, and the instantaneous period (T), defined as the time needed to complete

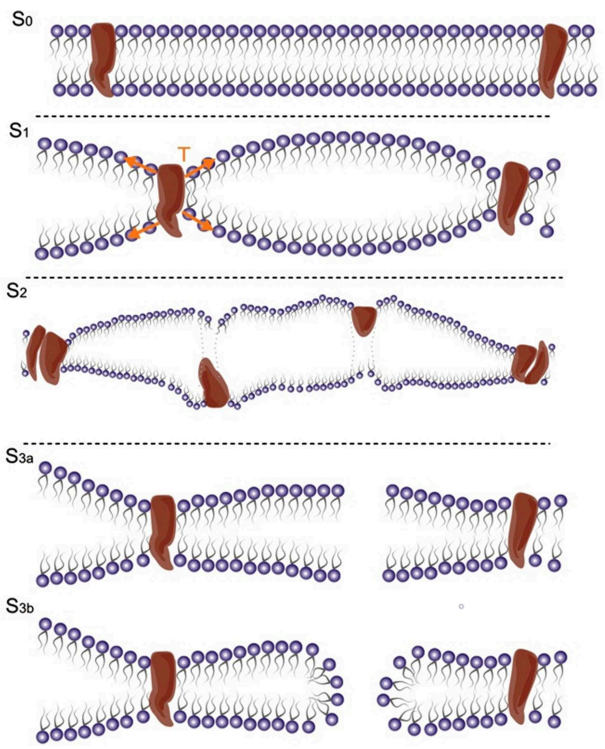

FIGURE 1 | Ultrasound gradually increases tension in the membrane. From the reference stage (S0), the stretch first activates mechanosensitive proteins (S1); growing tension might damage membrane proteins (S2) and then might induce pore formation (S3a, S3b) or cause membrane rupture [modified, with permission, from Krasovitski et al. (28)].

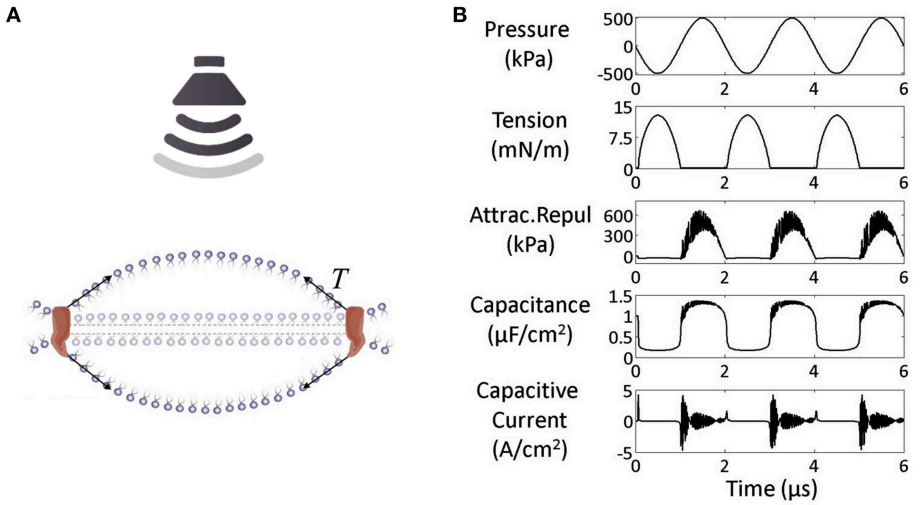

FIGURE 2 | (A) Under US effect the membrane starts fluctuating around a steady state. **(B)** Mechano-electrical dynamics of the model membrane to US (pressure amplitude 500 kPa and frequency 0.5 MHz): The increase in Acoustic pressure induces an increase in attraction/repulsion force, which increases the capacitance leading finally to a capacitive current. Acoustic pressure (kPa), tension (mN/m), combined attraction/repulsion force per area between the leaflets (sum of molecular and electrostatic forces, kPa), membrane capacitance ($\mu F/cm^2$), and capacitive displacement current (A/cm^2) [modified, under the terms of the Creative Commons Attribution 3.0 License, from Plaksin et al. (27)].

one single oscillation cycle, which is used to calculate the Acoustic frequency (Af) (**Figure 3**, Equation 1). In addition to these two parameters, the stimulus duration (StimD) is the total duration of one single sonication.

During the stimulus duration two paradigms of sonication are used: continuous or pulsed. Some of these protocols resemble those used for non-invasive brain stimulation based on repetitive transcranial magnetic stimulation [see Di Lazzaro and Rothwell (32) for a review]. The most used one for neuromodulation is the pulsed paradigm.

For the pulsed paradigm, two additional periods need to be defined: the pulse duration (PD), which is the period of acoustic sonication from the starting point of oscillation to the ending point, before the pause and the pulse repetition period (PRP), which is the period between the starting point of two consecutive sonications, or, in other terms, the sum of the pulse duration (PD) and the pause between two consecutive sonications. This period is used to calculate the pulse repetition frequency (PRF) (**Figure 3**, Equation 2). For the pulsed paradigm, the duty cycle (DC) (**Figure 3**, Equation 3) is the fraction of the pulsed repetition period (PRP) covered by the pulse duration (PD). The cycles per pulse (c/p) are the number of cycles during a single pulse (**Figure 3**, Equation 4); instead, the number of pulses (Np) is the number of pulses throughout the stimulus duration (**Figure 3**, Equation 5).

The sonication delivered during the stimulus duration period can be repeated, without pauses, for the continuous stimulation protocol. Instead, intermittent protocols are characterized by pauses between the sonications, defined as inter stimulation intervals (ISIs). The intermittent protocol is the most used for FUS neurostimulation, instead the continuous one is the most used for the unfocused stimulation (**Table 1**).

For safety reasons the indexes that describe the thermal and biomechanical effects of the sonication need to be defined. These parameters are related to the instantaneous intensity of stimulation and its instantaneous acoustic pressure. The two main mechanisms that can induce tissue damage are: local heating, which through proteins denaturation leads to cell death, and inertial cavitation. The latter is thought to be mediated by the collapse of gas bubbles due to the pressure exerted by ultrasonic field sufficiently strong to allow tissue damage.

Both, animal histological studies (8, 41, 42) and human neuroimaging studies (37, 38), showed that it is possible to neuromodulate brain circuits without inducing tissue damage. The thermal index (TI) is the ratio of total acoustic power to the acoustic power required to raise tissue temperature by 1°C under defined assumptions. Finally, the non-thermal, mechanical bioeffect is described by the mechanical index (MI), which is directly proportional to the ultrasound beam's peak negative pressure and inversely proportional to the frequency of the beam.

The intensity, spatial-peak pulse-average (I_{SPPA}) is the value of the pulse-average intensity at the point in the acoustic field where the pulse-average intensity is a maximum or is a local maximum within a specified region. The intensity, spatial-peak temporal-average (I_{SPTA}) is the value of the temporal-average intensity at the point in the acoustic field where the temporal-average intensity is a maximum, or is a local maximum within a specified region.

The FDA guidelines defined the safety threshold for diagnostic usage of US for adult cephalic ultrasound, which can be applied to neuromodulation. These parameters are Isspa $\leq$ 190 W/cm^2, Ispta $\leq$ 94 mW/cm^2 and a mechanical index $\leq$ 1.9 (43).

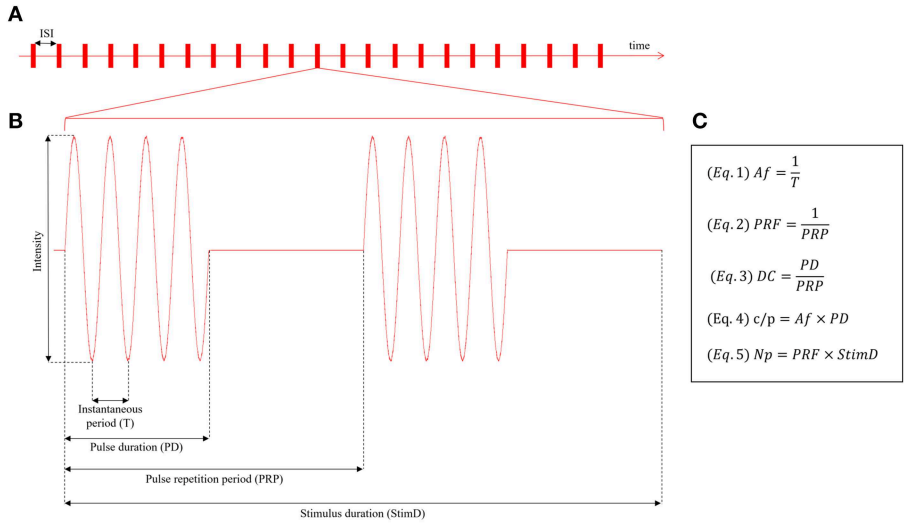

FIGURE 3 | (A) Intermittent protocol stimulation. The single sonications are followed by pauses, defined inter stimulation interval (ISI). **(B)** Pulsed paradigm of stimulation, defined by the following parameters: Intensity of stimulation, instantaneous period (T), pulse duration (PD), pulse repetition period (PRP), stimulus duration (StimD). **(C)** Fundamental equations for the stimulation protocol description: Equation (1) = Acoustic frequency (Af), Equation (2) = pulse repetition frequency (PRF), Equation (3) = duty cycle (DC), Equation (4) = cycles per pulse (c/p), Equation (5) = number of pulses (Np).

Focused Ultrasound for Targeted Drug Delivery

Focused ultrasound technique can be used also to facilitate drugs delivery in a specific brain area. Until now the most explored application is chemotherapy delivering. However, this versatile technique could be applied for neuromodulation purposes, with different mechanisms.

The first mechanism is a focal blood–brain barrier (BBB) opening, through a transient opening of endothelial tight junctions. Indeed, both animal (44, 45) and human (46) studies showed that FUS in combination with microbubbles administered intravenously can open the BBB, in a targeted, non-invasive, safe, and reversible manner. This technique could be used for targeted neuromodulation, with therapy which doesn't cross the BBB. For example Wang et al. (47) showed that it is possible to facilitate gene therapy delivery with recombinant adeno-associated virus, in a non-invasive way, through focused ultrasound targeted BBB opening, with potential applications for optogenetics (48) neuromodulation.

The second system is the local release of drugs, minimizing the effect on other brain areas. Indeed, focused ultrasound can be used to locally release drugs which are administered into the bloodstream through a vehicle (e.g., microbubble, liposome) sensitive to local temperature or pressure changes (49).

METHODS

The literature search methods included the PubMed/MEDLINE databases with the following research string, in Nov 2018: ("Neuromodulation" OR "Brain Stimulation") AND ("focused ultrasound" OR HIFU OR LIFU OR Low-intensity focused ultrasound). After abstract reading and screening, only human studies which described focused ultrasound neuromodulation approaches were included in the present review. In addition to the search protocol described, further articles suggested by experts in the field where read and screened (**Table 1**).

RESULTS

Physiological Effects in Normal Subjects

Legon et al. (10) used tFUS to target the human primary somatosensory cortex (S1), showing that tFUS significantly decreased the amplitudes of somatosensory evoked potentials elicited by median nerve stimulation. Furthermore, tFUS significantly modulated the spectral content of sensory-evoked brain oscillations and enhanced the performance on sensory discrimination tasks. The neurophysiologic effects had a spatial resolution of about 1 cm or less.

In another study, tFUS altered EEG intrinsic oscillatory dynamics, preferentially affecting the phase distribution of beta band and modulated the phase rate across beta and gamma frequencies. Furthermore, tFUS affected the phase distributions in the beta band of the early but not of the late components of somatosensory evoked potentials, suggesting a spatial specificity. This hypothesis was supported by the loss of neuromodulatory effects after the displacement of the transducer 1 cm laterally from the original cortical target (39).

Primary (SI) and secondary (SII) somatosensory cortical areas of the hand were targeted in a study by Lee et al. (50), in which two transducers were used. The areas were stimulated separately or simultaneously, under neuronavigation guide. tFUS elicited various types of tactile sensations in the contralateral hand/arm regions. The effects were transient and reversible, and the stimulation resulted safe, as assessed by repeated clinical and neuroradiological evaluations. In addition this study showed, the

TABLE 1 | tFUS and tUS neuromodulation studies.

References	Device	N. of subjects	Disease type/healthy subjects	Study design	Stimulation target	Protocol duration	Ultrasound parameters	Energy	Results	Adverse events
Ai et al. (33)	Custom-made, single-element FUS transducer; A_f: 0.50 MHz Diameter 30 mm, focal length 30 mm, 7T MRI compatible Focused, Pulsed	5	Healthy volunteers	Within-subjects, sham-controlled study	**Primary motor cortex** (tFUS paired with high field 7T fMRI targeted on the dominant thumb BOLD representation)	54 stimuli, ISI 5.5 s	A_f: 0.50 MHz; PD: 0.36 ms; PRF: 1 kHz; Np: 500; DC: 36%; c/p: 180; StimD: 500 ms	I_{SPPA}: 16.95 W/cm^2; MI: 0.97	tFUS increased BOLD activation volumes generated during a cued tapping task. The effect was spatially confined to the sonicated area. No detectable effects on SMA and PMd.	No auditory or tactile sensation
Legon et al. (34)	Custom- designed, single-element FUS transducer; A_f: 0.50 MHz Height 1.25 cm, aperture 30 mm, focal length 22 mm, Attached at the center of a TMS 8-coil (Magstim Inc., UK) for concurrent and concentric tFUS/TMS delivery Focused, Pulsed	12 (exp. 1) 10 (exp. 2) 28 (exp. 3)	Healthy volunteers	Within-subjects, sham-controlled study	**Primary motor cortex** (Exp 1–2: dominant FDI hotspot; Exp 3: dominant APB hotspot)	Exp1: 10 tFUS/TMS stimuli from RMT-20% to 100% stimulator output, in increments of 5%, ISI of 10 seconds) Exp2: 10 tFUS/TMS stimulations every 10 s for each TMS paired-pulse ISI from 1 to 15 ms. Exp3: 100 stimuli at random time intervals between 3 and 6 s	A_f: 0.50 MHz; PD: 0.36 ms; PRF: 1 kHz; Np: 500; DC: 36%; c/p: 180; StimD: 500 ms tFUS 100 ms prior to: the TMS pulse (exp. 1), to the CS (exp. 2) and to the visual stimulus (exp. 3)	I_{SPPA}: 17.12 W/cm^2; I_{SPTA}: 6.16 W/cm^2; MI: 0.9	Concentric and concurrent tFUS/TMS on M1 inhibited the amplitude of single-pulse MEPs, attenuated intracortical facilitation, did not affect intracortical inhibition and significantly reduced reaction time in a motor task.	Mild and moderate symptoms such as neck pain, sleepiness, muscle twitches, itchiness and headache (assessed by questionnaire). No severe symptoms reported.
Legon et al. (35)	Custom-designed, single-element FUS transducer (*Ultran Group, Inc., State College, PA*); A_f: 0.50 MHz Aperture 63 mm, focal length 70.92 mm (55 mm from exit plane), f# 1.13 Focused, Pulsed	20 (exp. 1) 20 (exp. 2)	Healthy volunteers	Within-subjects, sham-controlled study	**Unilateral sensory thalamus** targeted through a neuronavigation system from the individual MRI	Exp1: 300 stimuli, ISI 4 s Exp2: 90 stimuli	A_f: 0.50 MHz; PD: 0.36 ms; PRF: 1 kHz; Np: 500; DC: 36%; c/p: 180; StimD: 500 ms Median nerve stimuli time-locked to occur 100 ms after the onset of tFUS waveforms	I_{SPPA}: 14.56 W/cm^2; MI: 0.89 After bone transmission: I_{SPPA}: 7.03; W/cm^2; MI: 0.56	tFUS decreased P14 SEP amplitude. Decrease in ability in a tactile judgement task. Effect upon cortical oscillatory dynamics	Not available

(Continued)

TABLE 1 | Continued

References	Device	N. of subjects	Disease type/healthy subjects	Study design	Stimulation target	Protocol duration	Ultrasound parameters	Energy	Results	Adverse events
Leo et al. (36)	2 transducers: 1) *3T experiment:* A_f: 0.50 MHz Active diameter 60 mm, focal length 55 mm, focal FWHM intensity volume 48.64 mm^3 2) 7T experiment: A_f: 0.86 MHz Active diameter 64 mm, focal length 54 mm, focal FWHM intensity volume 35.77 mm^3 Both: Focused, Pulsed	6 (3T exp.) 1 (7T exp.)	Healthy volunteers	Pre-post interventional study	3T experiment: **Primary motor cortex** hand knob of the dominant hemisphere 7T experiment: **Left head of the caudate**	3T experiment: 90 stimuli, ISI 12-14 s 7T experiment: 5 off/on cycles, stimulation delivered at ISI ≅ 12 s during on cycles	3T experiment: A_f: 0.50 MHz; PRF: 1 kHz; Np: 500; DC: 36%; c/p: 180; StimD: 500 ms 7T experiment: A_f: 0.86 MHz; PRF: 1 kHz; DC: 50%; c/p: 420; StimD: 500 ms	I_{SPPA}: 6W/cm^2 (after bone transmission)	tFUS induced BOLD fMRI signals in the targeted cortical regions (in 3 of 6 subjects) and in the targeted subcortical region	Not available
Lee et al. (37)	MRI-compatible FUS transducer Af: 0.27 MHz Focal length 3 cm, acoustic focus 3 mm (diameter) and 17 mm (length) Focused, Pulsed	19 (exp. 1) 10 (exp. 2)	Healthy volunteers	Within-subjects, single-blind, sham-controlled study	**Primary visual cortex**, under 3T MRI guidance	Exp.1: 50 stimuli, ISI 13 s Exp.2: 50 stimuli, ISI 2.5 s	Af: 0.27 MHz; PRF: 500 Hz; PD: 1 ms; DC: 50%; StimD: 300 ms	I_{SPPA}: 16.6 W/cm2 Estimates at the target location: I_{SPPA}: mean 3 W/cm2; MI: mean 0.6	tFUS induced BOLD fMRI signals in V1 and other visual areas, elicited phosphenes and elicited cortical evoked EEG potentials similar to the classical VEP generated by photic stimulation	No adverse effects, as assessed by neurological examination, anatomical MRI (at 3 time points) and follow-up telephone interviews (after 2 months)
Lee et al. (37)	Two sets of single-element FUS transducers (*Ultran Group Ltd, State College, PA*) Af: 0.21 MHz Shape: segmented-spheres Outer diameter (OD):30 mm Focal distance: 25 mm. Each transducer was affixed to an applicator (*Zamerican, Zacuto, Chicago, IL*) mounted on a helmet (*modified from Giro Section Helmet, Santa Cruz, CA*) Focused, Pulsed	10	Healthy volunteers	Within-subjects, double blind,sham-controlled study	**Left primary and secondary somatosensory cortex** (areas of the hand, separately or simultaneously stimulated under multi-modal neuroimage-guidance)	20 stimuli for each session (4 sessions)	Af: 0.21 MHz; PRF: 500 Hz; PD: 1 ms; DC: 50%; StimD: 500 ms	I_{SPPA}: 35.0 W/cm^2; I_{SPTA}: 17.5 W/cm^2 Estimates at the target location: I_{SPPA}: 7.0–8.8 W/cm^2 I_{SPTA}: 3.5–4.4 W/cm^2	tFUS of either primary and secondary somatosensory cortex, stimulated separately or simultaneously, eliciited tactile sensations from the contralateral hand/arm areas	No abnormal findings post-tFUS (assessed by neurological examination, MMSE, anatomical MRI on the same day, at 2 weeks and 4 weeks, and by telephone interview at 2 months after the sonications)

(Continued)

TABLE 1 | Continued

References	Device	N. of subjects	Disease type/healthy subjects	Study design	Stimulation target	Protocol duration	Ultrasound parameters	Energy	Results	Adverse events
Monti et al. (11)	BXPulsar 1001, Brainsonix Inc. Single-element spherical transducer; A_f: 0.65 MHz Diameter and radius of curvature 71.5 mm Focused, Pulsed	1	Post-traumatic disorder of consciousness (minimally conscious state) 19 days post-injury	Case report, part of an ongoing clinical trial (12)	**Thalamus** (MRI-guided by a 3 Tesla Magnetom Tim Trio MR scanner)	10 sonications, 30 s each, separated by 30 s pause intervals	A_f: 0.65 MHz; PD: 0.5 ms; PRF: 100 Hz	I_{SPTA}: 720 mW/cm^2	Emergence from minimally conscious state	Clinical improvement suggested that the procedure was safe and well-tolerated
Lee et al. (38)	Ceramic piezoelectric FUS transducer (*Channel Industries, Santa Barbara, CA*) Outer diameter 6 cm, radius-of- curvature 7 cm A_f: 0.25 MHz Low Intensity Focused Ultrasound Pulsation	12 (exp. 1) 6 (exp. 2)	Healthy volunteers	Within-subjects, sham-controlled study	**Primary somatosensory cortex** (hand area) under subject-specific image-guidance	(Exp. 1): 200 stimuli, ISI 3 s (Exp. 2): 100 stimuli, ISI ≅2 s	A_f: 0.25 MHz; PRF: 500 Hz; Tone-burst-duration: 1 ms; DC: 50%; StimD: 300 ms	I_{SPPA}: 3W/cm^2 Estimated I_{SPPA} at the target: 0.7 ± 0.5 W/cm^2	tFUS elicited transient tactile sensations on the hand and arm area contralateral to the sonicated hemisphere, with anatomical specificity of up to a finger. EEG showed sonication-specific evoked potentials.	No adverse effects, as assessed by neurological examination, anatomical MRI (at 3 time points) and follow-up telephone interviews (after 2 months)
Mueller et al. (39)	Two-channel, 2 MHz function generator (*BK Precision Instruments*) delivered at 0.5 MHz Focused, pulsed	18 (exp. 1) 7 (exp. 2)	Healthy volunteers	Within-subjects, sham-controlled study	Exp.1 **Somatosensory cortex** (CP3) Exp.2 1cm laterally	120 stimuli, ISI 6 s	A_f: 0.50 MHz; PD: 0.36 ms; PRF: 1 kHz; Np: 500; c/p: 180; StimD: 500 ms	I_{SPPA}: 23.87 W/cm^2; MI: 1.13	tFUS altered EEG beta phase and modulated the phase rate across beta and gamma frequencies. tFUS affected phase distributions in the beta band of early SEP components. Neuromodulatory effects were lost when the transducer was displaced 1 cm laterally from the original cortical target.	Not available

(Continued)

TABLE 1 | Continued

References	Device	N. of subjects	Disease type/healthy subjects	Study design	Stimulation target	Protocol duration	Ultrasound parameters	Energy	Results	Adverse events
Legon et al. (10)	Custom-made, single-element FUS transducer; A_f: 0.50 MHz Diameter 30 mm, focal length 30 mm Focused, Pulsed	10 (exp. 1) 8 (exp. 2) 12 (exp. 3) 12 (exp. 4)	Healthy volunteers	Within-subjects, sham-controlled study	**Primary somatosensory cortex** (crown of the postcentral gyrus and posterior wall of the central sulcus, encephalographic electrode CP3)	Exp 1 and 2: 120 stimuli, ISI 6 s Exp 3: 90 stimuli 100 ms before each task Exp4: 120, ISI 6 s	A_f: 0.50 MHz; PD: 0.36 ms; PRF: 1 kHz; Np: 500; DC: 36%; c/p: 180; StimD: 500 ms Median nerve stimuli time-locked to occur 100 ms after the onset of tFUS waveforms	I_{SPPA}: 23.87 W/cm^2 (≅4-fold lower through the skull); MI: 1.13 Peak rarefactional pressure: 0.80 MPa	Exp1. A: tFUS significantly attenuated the amplitudes of somatosensory evoked potentials B: tFUS significantly modulated the spectral content of sensory-evoked brain oscillations Exp2. tFUS modulation of brain activity is spatially restricted (≅1 cm or less) Exp3 and 4. tFUS significantly enhanced performance on sensory discrimination tasks without affecting task attention or response bias.	No thermal or mechanical sensation
Gibson et al. (40)	tUS: Phillips CX50 Diagnostic System, with a Phillips S5-1 broadband plane sector transducer array; aperture 20.3cm, frequency range 1–5 MHz. TMS: neuronavigation-assisted eXemia TMS system (*Nextstim Ltd., Helsinki, Finland*) with a 70 mm 8-coil. Unfocused, Continuous	21 (active stim) 22 (sham stim)	Healthy volunteers	Between-subjects, single-blind, sham-controlled study	**Primary motor cortex** (abductor pollicis brevis motor hotspot)	2 min	Af: 2.32 MHz; HGen, B-mode; Harmonics: on; DC: <1%; Focal depth: 10 cm	Isppa: 34.96 W/cm^2; Ispta: 132.85 mW/cm^2; MI: 0.67 Peak negative pressure: 1.02 MPa (in degassed water)	tUS increased cortical excitability (average increase in MEPs amplitude of 33.7% at 1 min and of 32.2% at 6 min post stimulation. No significant differences at 11 and 16 min post stimulation). No differences in mood (assessed by a brief questionnaire on subject well-being)	No significant differences in sensations linked tingling, itching etc. (assessed by questionnaires) between active and sham group

(Continued)

TABLE 1 | Continued

References	Device	N. of subjects	Disease type/healthy subjects	Study design	Stimulation target	Protocol duration	Ultrasound parameters	Energy	Results	Adverse events
Hameroff et al. (3)	General Electric LOGIQe, 12L-RS probe A_f: 8 MHz Unfocused, Continuous	31	Chronic pain	Double blind, sham-controlled, crossover study	**Posterior frontal cortex,** contralateral to the maximal pain	15 s stimulation	A_f: 8 MHz; B Mode; Power: 100%; Depth: 3.5 cm; Harmonics: on; Cross- Xbeam: on	MI = 0.7 Max Intensity = 152 mW/cm^2 TIs = 0.5 TIc = 0.2 (values at the posterior frontal scalp)	tUS significantly improved measures of global affect derived from subjective reports, at 10 and 40 min following stimulation.	Transient headache exacerbation following stimulation (1 subj)

In gray background: unfocused stimulation protocols, in white background: focused stimulation protocols. Af, acoustic frequency; c/p, cycles per pulse; DC, duty cycle; Exp, experiment; ISI, inter stimulus interval; ISPPA, Intensity Spatial Peak Pulse Average; ISPTA, Intensity spatial peak temporal average; MEPs, motor evoked potentials; MI, mechanical index; Na, not available; Np, number of pulses; PD, pulse duration (width); PMd, dorsal premotor cortex; PRF, pulse repetition frequency; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; SD, Sonication Duration; SMA, supplementary motor area; StimD, stimulus duration; TI, Thermal Index; TIb, Thermal Index of bone; TIc, Thermal Index of Skull/Cranium; TIs, Thermal Index of soft tissue; TMS, transcranial magnetic stimulation. Note: where not specified, I_{SPPA} is the incident acoustic intensity estimated before transcutaneous and transcranial transmission, e.g., In free water.

feasibility of the simultaneous stimulation of different human brain areas.

In Lee et al. (38), tFUS stimulation of the human somatosensory cortex elicited somatosensory sensations with anatomical specificity up to a finger, and evoked EEG potentials.

fMRI studies showed the effects of tFUS on cortical and subcortical brain areas, with the ability of high-resolution non-invasive functional brain mapping (33, 36, 37).

Indeed, Leo et al. (36), demonstrated that tFUS stimulation of cortical (primary motor cortex) and subcortical (head of the caudate) areas can induce blood oxygen level dependent (BOLD) signals in 3T and 7T fMRI, respectively. More recently, pairing tFUS on human primary motor cortex (M1) with 7T BOLD fMRI signals in a cued finger tapping task study, Ai et al. (33) showed that tFUS selectively increases BOLD activation volumes of the target finger representation. These effects did not spatially overcome the sonicated area, and therefore did not involve other motor regions, such as supplementary motor area (SMA) and dorsal premotor cortex (PMd).

tFUS has been used also to target the human primary visual cortex (V1) Lee et al. (37) showed, on BOLD fMRI signals, that tFUS stimulation elicited the activation of a network of brain regions, including V1 and other areas involved in visual and higher-order cognitive processes. Furthermore, stimulation elicited perception of phosphenes and EEG evoked responses.

The effects of tFUS on corticospinal excitability have also been studied through transcranial magnetic stimulation (TMS). Combining a custom-made FUS transducer and a 8-shaped TMS coil, Legon et al. (34) assessed for the first time in humans the effect of concentric and concurrent tFUS/TMS stimulation on M1. The stimulation had an inhibitory effect on single-pulse MEPs and intracortical facilitation, and significantly decreased the reaction time in a motor task.

Legon et al. (35) tested the effects tFUS stimulation on sensory thalamus, that was targeted by a single-element focused ultrasound through a neuronavigation system based on the individual subject anatomical MRI. tFUS stimulation inhibited the P14 SEP, and was associated with a change in EEG oscillatory dynamics and to a reduced ability in a tactile judgement task. In addition, this study outlined the value of taking into account the individual skull morphology to produce safe and accurate stimulations.

In a recent single-blind, sham-controlled study (40), tUS was targeted to the motor cortex through a diagnostic imaging ultrasound system. The unfocused stimulation increased MEPs amplitude by 34% compared to baseline, and the increase was recorded up to 6 min after the stimulation. This short-term increase of motor cortex excitability contrasts with a previous findings of MEP inhibition during concurrent tFUS/TMS (34). As discussed by the authors, stimulation parameters and other methodological factors might explain the different findings.

Therapeutic Application

Despite several studies showed the neurological therapeutic applications of lesional FUS and FUS mediated BBB opening in different diseases like essential tremor (51–54), Parkinson's disease (55–57), depression (58, 59), obsessive-compulsive

disorder (60, 61), neuropatic pain (62, 63), Alzheimer disease (46, 64), only two studies explored in humans the therapeutic efficacy of tUS (9) and tFUS (11) bioelectrical neuromodulation (**Table 1**).

Hameroff et al. (9) used a 8 MHz unfocused transducer to study the effects of transcranial ultrasound stimulation (tUS) on mood, and global affect in 31 patients with chronic pain, in a double-blind, sham-controlled crossover study. Stimulation was targeted to the posterior frontal cortex, contralateral to the most severe pain. After the stimulation, a significant improvement in subjective parameters of global affect derived from the Visual Analog Mood Scale was found.

As part of an ongoing clinical trial on low intensity focused ultrasound in acute brain injury (12), Monti et al. (11) reported a case of emergence from minimally conscious state after low intensity non-invasive ultrasonic thalamic stimulation.

Transcranial Focused vs. Unfocused Ultrasound Neuromodulation

Despite transcranial focused ultrasound (tFUS) and transcranial unfocused ultrasound (tUS) neuromodulation techniques share the same basic mechanisms of action, when applied on the same target they can lead to quite different results.

These results are related to the intrinsic differences between the two techniques. The most important, one is the volume of the brain involved in the ultrasound field. It is intuitive that the volume of the brain involved in the focused or unfocused neuromodulation, and the underlying neural circuits, are crucial to determine the output of the tFUS or tUS neuromodulation. This has been supported also by experimental results, where tFUS and tUS were applied on the same target, the primary motor cortex: tUS increased MEPs amplitude (40) instead tFUS induced a MEP inhibition (34). In addition, the sonication delivered during the stimulus duration period, is generally continuous, without pauses, for tUS, and pulsed, characterized by pauses between the sonications, for tFUS. Low-intensity pulsed FUS is the most effective FUS technique for neuromodulation in both animal model (5, 6) and humans (**Table 1**). Instead, high intensity continuous FUS is widely used for therapeutic irreversible lesioning (51, 55, 58, 60).

DISCUSSION

Transcranial focused ultrasound is an emerging technique for non-invasive neurostimulation, with direct action on bioelettrical neural activity, and in addition could be used for targeted drug delivery.

Compared to magnetic or electric non-invasive brain stimulation, this technique has a higher spatial resolution and can reach deep structures. In addition, animal studies suggest that, potentially, different sites of the central and peripheral nervous system can be targeted by this technique.

Even if still in a small number, the increasing interest in this technique, led to encouraging results in human studies. These preliminary human studies focused their attention on classic non-invasive neurostimulation targets, like the primary motor cortex, somatosensory area or primary visual cortex, with some studies that explored deep structures like thalamus (11, 35) or basal ganglia (36). All showed neurostimulation efficacy in terms of clinical, neurophysiological or functional neuroradiological outcomes (**Table 1**).

The data collected since now shows that this technique is safe and well-tolerated, when the stimulation parameters and protocol follow the available guidelines. In addition, tFUS can be also conducted without hair shaving (65). The majority of the studies reported no severe adverse effects. Mild and moderate symptoms are reported such as neck pain, sleepiness, muscle twitches, itchiness, and headache (9, 34) (**Table 1**). In future studies, proper assessments, aimed to define the safety parameters for tUS and tFUS, are needed. Finally, every tUS or tFUS protocol should explore the role of auditory confounding factors on the neural responses, in order to show that the effect of stimulation is the consequence only of the targeted area neuromodulation, and not due to an indirect auditory impact (66, 67).

Overall, the results up to now encourage the study of tUS and tFUS as non-invasive neuromodulatory techniques in humans. The high spatial resolution of tFUS and the possibility of stimulating cortical and deep brain regions suggest many potential applications, such as cortical and subcortical mapping, the study of functional connectivity, the modulation of neurotransmission. Regarding tUS as a potential neuromodulatory tool, noteworthy is the high accessibility of the devices, which are routinely used in health care settings. Further research is needed to clarify tUS and tFUS efficacy and underlying mechanisms, and to optimize stimulation parameters and targeting accuracy. The initial safety profiles seem promising. A rigorous approach must be maintained in order to ensure safe sonications.

AUTHOR CONTRIBUTIONS

LB: conception, organization, execution, and writing of the first draft. EF: execution, writing of the first draft, and review and critique. VD: conception, organization, and review and critique.

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REVIEW
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Spinal Cord Stimulation for Freezing of Gait: From Bench to Bedside

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Spinal cord stimulation (SCS) has been used for the treatment of chronic pain for nearly five decades. With a high degree of efficacy and a low incidence of adverse events, it is now considered to be a suitable therapeutic alternative in most guidelines. Experimental studies suggest that SCS may also be used as a therapy for motor and gait dysfunction in parkinsonian states. The most common and disabling gait dysfunction in patients with Parkinson's disease (PD) is freezing of gait (FoG). We review the evolution of SCS for gait disorders from bench to bedside and discuss potential mechanisms of action, neural substrates, and clinical outcomes.

Keywords: spinal cord stimulation, gait, Parkinson's disease, pain, freezing of gait

INTRODUCTION

Spinal cord stimulation (SCS) has been used for several decades as a minimally invasive neuromodulation strategy for the treatment of patients with chronic pain (1). With a good efficacy profile and a relatively low incidence of side effects, SCS comprises one of the proposed therapeutic modalities in guidelines for the management of refractory neuropathic pain (2). In recent experimental work, SCS has also been suggested to improve motor and gait dysfunction in parkinsonian states (3, 4). In Parkinson's disease (PD), a common and disabling problem is freezing of gait (FoG). Although in its infancy, recent studies using SCS for the treatment of FoG have shown promising results (5–8).

In this review, we first describe particular aspects of FoG that pose challenges for the development of therapeutic interventions and the interpretation of post-treatment results, including its complex mechanisms, episodic nature, and multifactorial pathophysiology. We then summarize experimental and clinical data. Finally, we analyze anatomical and physiological concepts that may assist in the development and or improvement of SCS strategies to treat gait dysfunction and FoG. The search strategy on PubMed included the following terms: SCS OR dorsal column stimulation AND Parkinson, which retrieved 126 abstracts. Twenty one were directly related to the topic. Those articles were used as a starting point for the search of additional, related articles that would bring relevant clinical data, cases, and series reports.

FREEZING OF GAIT: A PUZZLING PHENOMENON

Of all motor and non-motor symptoms in PD, FoG is one of the most incapacitating and enigmatic. It affects nearly 50% of moderate idiopathic PD patients and 80% of subjects in more advanced stages of the disease (9). In general, FoG may be defined as a transitory impossibility to keep the progression of gait despite the intention to walk (10). FoG is a major risk factor for falls (11), significantly contributes to functional incapacity (12), and frequently leads to a reduction in quality of life (13). Factors that trigger and relieve FoG suggest that this is a complex entity with multiple interconnected mechanisms. FoG mostly occurs during walking through narrow passages (14), situations of cognitive overload (e.g., dual tasks) (15), anxiety (16), and turning movements (17). Factors that alleviate freezing are certain visual patterns (e.g., stripes on the floor) (18), auditory cues (19), proprioceptive and haptic stimuli (20), and other compensation strategies (21). The pathophysiology of FoG comprises an interplay of heterogeneous sensory, motor, and cognitive aspects and remains poorly understood. Compared to non-freezers, PD patients with FoG experience more pronounced postural instability and impaired gait (22). In FoG patients, gait features are significantly impaired compared with control patients without FoG (nFoG), representing a global pattern of gait impairment. Changes in motor patterns prior to freezing include a higher cadence, a smaller stride length (23, 24), and dysfunctional anticipatory postural adjustments (APA) (25) (**Figure 1A**). APA dysfunction occurs especially in patients with start hesitation, characterized by a difficulty in step initiation. The transition between the upright stance to movement that occurs during step initiation is challenging, given that forward movements are a source of body disequilibrium. APA is required to counterbalance the internal forces generated to move the center of mass forward, allowing for a controlled step initiation. Prior to step initiation, APA is usually characterized by a sequence of events beginning with a backward displacement of the center of pressure toward the moving leg. Thereafter, the center of pressure is displaced toward the supporting foot. The mediolateral component is thought to be involved in balance control, while the sagittal component enables the forward acceleration of the center of mass (26). Although mechanisms of APA are not completely understood, adjustments are modulated by higher brain centers, such as the supplementary motor area (SMA) (27, 28). APA abnormalities restrain the body weight shift, leading to shorter steps with smaller amplitudes. Patients with start hesitation have multiple (29) and impaired APAs (30), which could lead to a hesitant ineffective initiation of gait (**Figure 1B**).

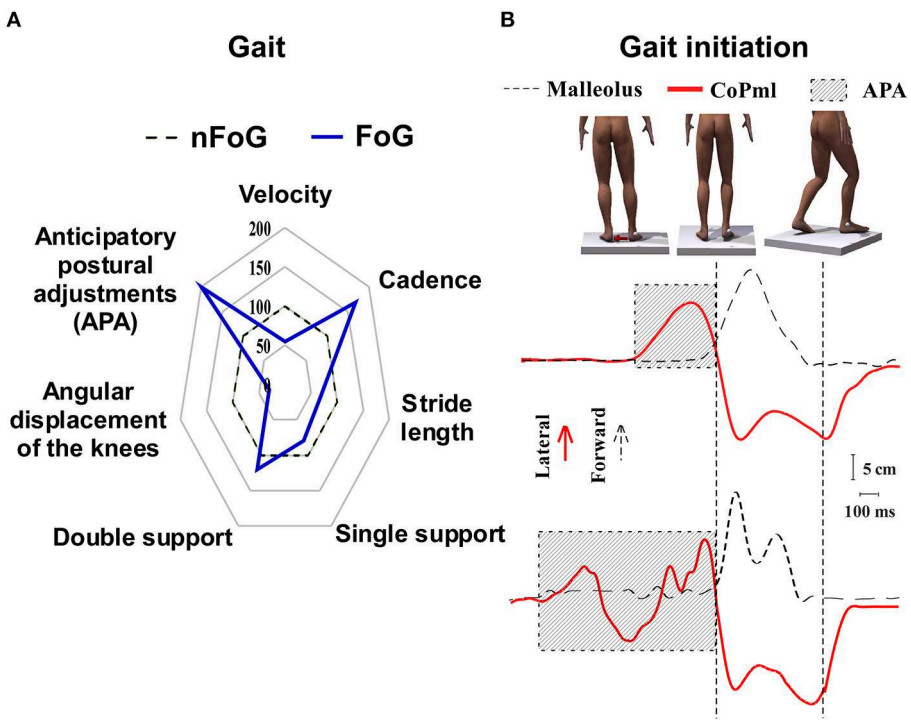

FIGURE 1 | Characteristic motor patterns associated with freezing of gait in Parkinson's disease. **(A)** Patients exhibit dysfunction prior to or during freezing of gait. Note that these variables are recorded in different tasks: impairment of APA occurs prior to step initiation; altered cadence and stride length during gait, and disorders of angular displacement of the knee during the so-called trembling knees. The central dotted line of the satellite plot represents patients without freezing of gait (nFoG) data. Deviations along the axes radiating from the center of the plot represent the percentage in which patients with freezing of gait (FoG) differ from nFoG (blue line). **(B)** Representation of the step initiation task. The panel on the top represents the sequence of the events during step initiation. The red arrow shows the shifting of body weight before moving the opposite foot forward. The curves on the middle and bottom show the CoPml (red curve) and malleolus displacement (dotted line). The upper curves represent a normal stepping eliciting one APA before the leg movement. The lower curves represent multiple and longer APAs usually seen during FoG episodes. The hatched area are APAs (time from the increasing of mediolateral force to the step onset).

Pre-clinical studies investigating mechanisms of freezing and gait dysfunction highlight changes in subcortical and brainstem circuits, including the mesencephalic locomotor region (MLR) and the pedunculopontine nucleus (PPN) (31, 32). Following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration, ∼50% of non-human primates developed FoG (33). In naïve animals, deficits produced by MLR lesions mimic those observed in parkinsonian states (34). Stimulation of the MLR exerts complex effects. Depending on the stimulation site within the PPN and frequency, it may augment or reduce FoG (35). From a translational perspective, observations from non-humans primates must be considered with caution. Postural adjustments are pivotal for an efficient biped gait in humans, while non-human primates often express quadruped locomotion. In order to keep balance during bipedal stance, humans require more intricate postural adjustments that probably involve a more complex neural circuitry. This may help to elucidate discrepancies between clinical and pre-clinical models and explain why studies aiming to clarify mechanisms of FoG are often more elucidative than studies in experimental models.

In PD patients, comparative functional studies using positron emission tomography, single-photon emission computed tomography, functional magnetic resonance imaging, and functional near infrared spectroscopy have been conducted at rest and when functional tasks were performed in the absence or presence of freezing with intriguing results (**Figure 2**). At rest, patients with FoG (FoG+) showed decreased activation of the orbitofrontal cortex, premotor cortex (36, 37), and basal ganglia (38) compared to patients who did not experience FoG (FoG-). Patients with FOG+ had increased functional connectivity (FC) between frontal areas, particularly the SMA, the cerebellar locomotor region (CLR) and MLR. In contrast, these patients had decreased FC between the prefrontal cortex and basal ganglia (39). Interestingly, freezers showed decreased structural and functional connectivity between SMA and subthalamic nucleus (STN), known to be involved in the inhibition control (40). The cerebellum, more specifically the dentate nucleus, had decreased connectivity with brainstem, basal ganglia, frontal, and parieto-occipital cortices in FoG+ compared to FoG- (41). Additional findings in FOG+ were increased FC between the putamen and amygdala (42), and between the MLR and middle temporal gyrus (MTG) (43). It is noteworthy the increased interaction between areas that process movement planning (SMA), emotion (amygdala), and sensory integration (MTG) with subcortical regions associated with the processing of movement initiation (CLR and MLR). This highlights the contribution of subcortical structures that process emotional and sensory information, probably activating regions involved in motor planning and gait initiation.

Distinct brain activity has been found on imaging studies depending on whether freezing episodes were present during task performance. In the absence of freezing, a decrease in frontal activity has been demonstrated along with an inconsistent activation of subcortical regions (44–47).

During the occurrence of freezing, studies have shown less subcortical and sensorimotor cortical activity (48, 49), but higher activation of frontal regions (50, 51) and insula (50). A decrease in functional connectivity between the cognitive network (DLPFC and posterior parietal cortex) and basal ganglia (49) was correlated with increased frequency of FoG episodes during a virtual pedaling task.

These findings point to a dynamic profile of brain correlates of freezing, evidencing a contribution of frontal areas and the reduced participation of sensorimotor cortex, basal ganglia, and brainstem during motor arrests. However, caution is needed when interpreting the above-mentioned studies due to the use of distinct approaches (e.g., imagined gait, cycling, and manual tasks). Also, in most neuroimaging studies patients were lying in the scanner without the requirements of bipedal postural control. Another important limitation is the incomplete information provided by such studies on the characteristics of freezing (start hesitation, turning, during gait), which may have different pathophysiological mechanisms. This substantially increases variability.

In addition to imaging studies, brain networks involved in freezing have also been investigated with *in vivo* electrophysiology and non-invasive wireless scalp EEG. Tard et al. (52) recorded abnormal beta band oscillations in central and frontal areas associated with a disruption in the integration between attention patterns frequently found during auditory task and motor preparation in FoG+ patients. As scalp EEG renders access mostly to convexity neocortical areas, it has been used to study the correlation between this episodic phenomenon and cognitive networks. Butler et al. (53) showed an excessive recruitment of lateral premotor areas and the loss of automatic motor control related to attentional deficits associated with FoG. Other studies have shown that specific patterns of scalp EEG may be used to identify and even predict FoG episodes (54).

In addition to brain circuits, those in the spinal cord have also been associated with disrupted gait control in FoG+. The normal gait should integrate feed-forward information processed in cortical control centers, basal ganglia, cerebellum, and brainstem and feedback input derived from the periphery to modulate spinal patterns generation centers (CPG) (55). Although CPGs are capable of generating complex patterns, such as autonomous gait, they receive extensive connections from higher brain centers that generate motor engrams for volitional or reactive behavior. Gait as a complex behavior is generated by the interaction between brain circuits and CPGs mediated by intricate mechanisms of descending feed-forward control and feedback loops. These comprise pathways that control sensory information, posture, and balance, including cerebellar, vestibular, and reticular systems. FoG may occur when brain circuits that should integrate multifactorial stimuli in higher brain circuits are not capable of processing sufficient information for a timely convergence into the complex behavior of walking. Gait initiation requires processing and coordination of updated environmental information with exact coupling of postural adjustment in advance of steps forward (56). This mechanism seems to be disrupted in PD patients with FoG (57). For example, during step initiation there must be an efficient pairing between the preparation phase and voluntary step, which is modulated by the SMA (27). Defective APAs

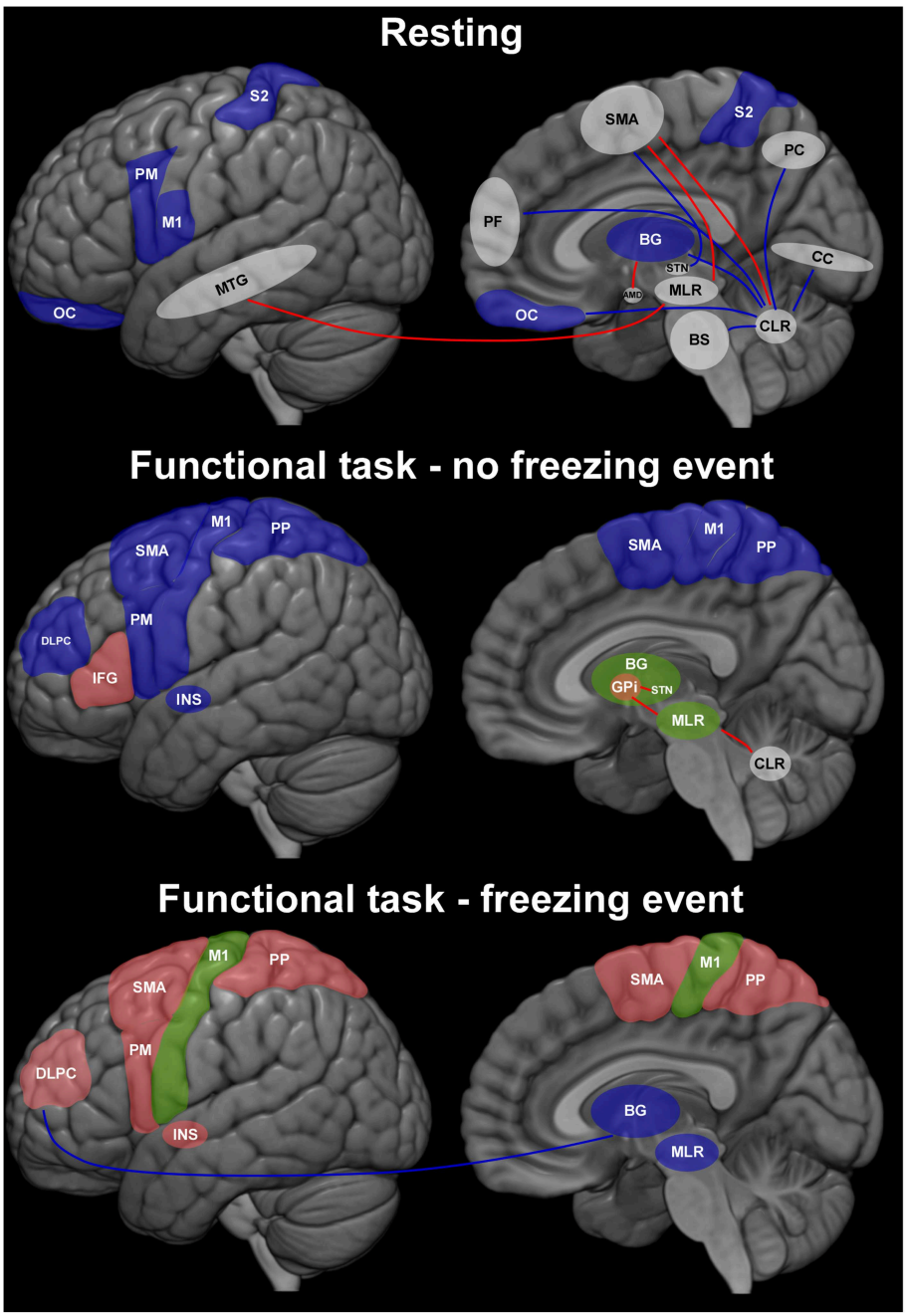

FIGURE 2 | Representation of brain dynamics in three conditions during which patients with Parkinson's disease (PD) were assessed. The results describe the contrast between patients with or without freezing of gait (FoG+ > FoG–). Blue regions are those for which available evidence shows less activity in FoG+ than in FoG–; green indicates regions with higher and lower activity in FoG+; red represents regions in which activity was higher in FoG+ than FoG–. Traces indicate connections between two regions (red: higher; blue: lower in FoG+). White regions are those involved in brain circuits (connectivity studies) without representation of level of the activity between FoG+ and FoG–. AMD, amygdala; BG, basal ganglia; BS, brainstem; CC, calcarine cortex; DLPFC, dorsolateral prefrontal cortex; GPi, internal globus pallidus; IFG, inferior frontal gyrus; INS, insula; M1, primary motor cortex; MLR, mesencephalic locomotor region; MTG, middle temporal gyrus; OC, orbitofrontal cortex; PC, precuneus; PF, prefrontal cortex; PM, premotor cortex; PP, posterior parietal cortex; S2, secondary somatosensory cortex; SMA, supplementary motor area; STN, subthalamic nucleus.

or disengaged postural corrections of steps have been directly related to the occurrence of FoG (29). Our group has recently found that SCS was able to decrease the duration of FoG and the timing between APA and step initiation in severe freezers (58). One hypothesis is that, by activating ascending spinal pathways that reach the SMA, high frequency SCS (300 Hz) might have

corrected dysfunctional postural adjustments, improving gait and FoG (59). This is in agreement with clinical neuroimaging data and pre-clinical electrophysiology studies suggesting that SCS modulates sensorimotor, prefrontal, cingulate, and insular cortices (3, 4, 60, 61), all regions considered to play a role in mechanisms of FoG (3, 4, 60–62).

TRANSLATIONAL HELIX: CONCEPTS FROM THE BENCH TO THE BEDSIDE

Although SCS has been used in the past for the treatment of various movement disorders (63), its popularity in the last two decades have faded. Potential reasons include the lack of consistent and reproducible results, limited knowledge on its mechanism of action and technological restrictions. This began to change in 2009, when Fuentes et al. showed that SCS applied to dopamine-depleted mice resulted in a remarkable improvement in locomotion (4). Possible explanations for this finding were the modulation of oscillatory brain activity and the fact that the spinal cord is a major channel of afferent information to the brain (59). Strikingly, locomotive behavior initiated a few seconds after stimulation onset and proceeded by instantaneous changes in local field potentials (LFP) in the motor cortex and striatum (4). The proposed mechanism to mediate this effect was the inhibition of pathological synchronized slow wave oscillations often found in motor circuit related structures of PD patients and animal models (3–5). While stimulation induced a prompt shift from lower to higher frequencies in motor circuits, this tended to outlast SCS discontinuation by up to 50 s, suggesting a significant carry-over effect. In non-human primates, stimulation parameters that induced changes in kinematic measures were also able to effectively change oscillatory patterns in thalamo-cortical-basal ganglia networks (**Figure 3**) (3). Similar to the benefits described above, gait dysfunction in PD was shown to be improved in patients treated with upper thoracic cord SCS at high frequencies (e.g., 300 Hz), with a carry-over effect being clearly noted (6, 58). Regarding electrochemical interactions, in dopamine transporter knockout mice (DAT-KO) the dose of L-dopa required to induce locomotion was decreased to one fifth following SCS (4). In contrast, synergistic effects between dopaminergic medications and SCS have not been clinically documented.

Relevant Anatomical Aspects of the Spinal Cord in the Context of SCS

Spinal cord stimulation (SCS) has been used for many years with a relatively low profile of adverse events. This is probably due to the fact that electrodes are implanted in the epidural space underneath the laminae and spinous processes. As electrical stimulation is routinely delivered to the posterior aspect of the cord in therapeutic SCS protocols, most of the current invariably spreads to the dorsal columns and occasionally posterior radiculi. These elements are mainly composed by thick myelinated axons that are excited at low thresholds and may detour electrical current due to reduced impedance of its fibers. However, in different spinal cord levels there are also different fiber content which vary in diameter and consequently in electrical excitation threshold. Within the cervical spine enlargement, there are vast numbers of sensory fibers coming from the upper limbs, as well as internuncial and second order neurons. On the other hand, at mid and upper thoracic levels, the cord is considerably thinner for two main reasons: (i) a smaller contingent of segmental afferents coming from less densely innervated dermatomes in the torso and (ii) long projection axons that tend to progressively decrease in diameter after entering the cord in the dorsal root entry zone (64). At theses levels, the propagation velocity is decreased while the stimulation threshold in the dorsal column is increased (65). In addition, ascending fibers from lower limbs course medially in these spinal levels, occupying a deeper position in the dorsal columns. Thus, SCS applied in high thoracic cord is more likely to modulate deeper fiber layers and dorsal horn before generating intense lower limb paresthesias (66). As an example, at spinal thoracic levels the posterior thoracic nucleus (Clarke's column) located in the depth of gray matter of the dorsal horn (lamina VII of Rexed) gives origin to important ascending fibers. This nucleus is a major relay center for unconscious proprioception with cells that collateralize and send afferents within the dorsal column and spinocerebellar tracts (67) directly reaching various structures in the brainstem, diencephalon and deep cerebellar nuclei. In upper thoracic levels, where the cord is thinner, most long projection fibers are composed of small diameter fibers when compared to those at the spinal enlargements (**Figure 4**). Apparently, the practical result of this is that SCS at this level can reach a wider range of ascending tracts with similar stimulating thresholds.

Mechanistic Hypotheses

At a first glance, it may seem somewhat evident that SCS would improve gait directly by facilitating local spinal circuits directly in charge of limb muscle control. Although there might be a local component, as SCS induces improvement in gait performance (e.g., stride length, velocity) the improvement in FoG, which is mediated mainly by brain circuit dysfunctions, suggests that the effect of SCS is more likely to occur on suprasegmental circuits though the stimulation of ascending fibers. In support of this hypothesis, robust inhibition of parkinsonism-related slow wave brain oscillations has been demonstrated in rodent and primate PD models (3–5, 59). However, the percentage of fibers or which ascending systems should be excited to induce this effect remain unclear. Unfortunately, none of the pre-clinical studies discussed this topic in detail, probably because epidural SCS applied to small animals is rather unselective due to diminutive dimensions of the cord. So far, the dorsal columns were picked as natural candidates to be involved in this effect. They are the most superficial and probably have the lowest threshold for epidural SCS. However, data from recent clinical studies suggest that the most efficient stimulation parameters reach deeper sites in the spinal cord (6) or are more comprehensive (less selective). For instance, when SCS was applied deeper into the upper thoracic cord due to the steering of electrical field (see technological and technical issues), it excites the dorsal columns but probably also a greater variety of ascending afferents and long propriospinal

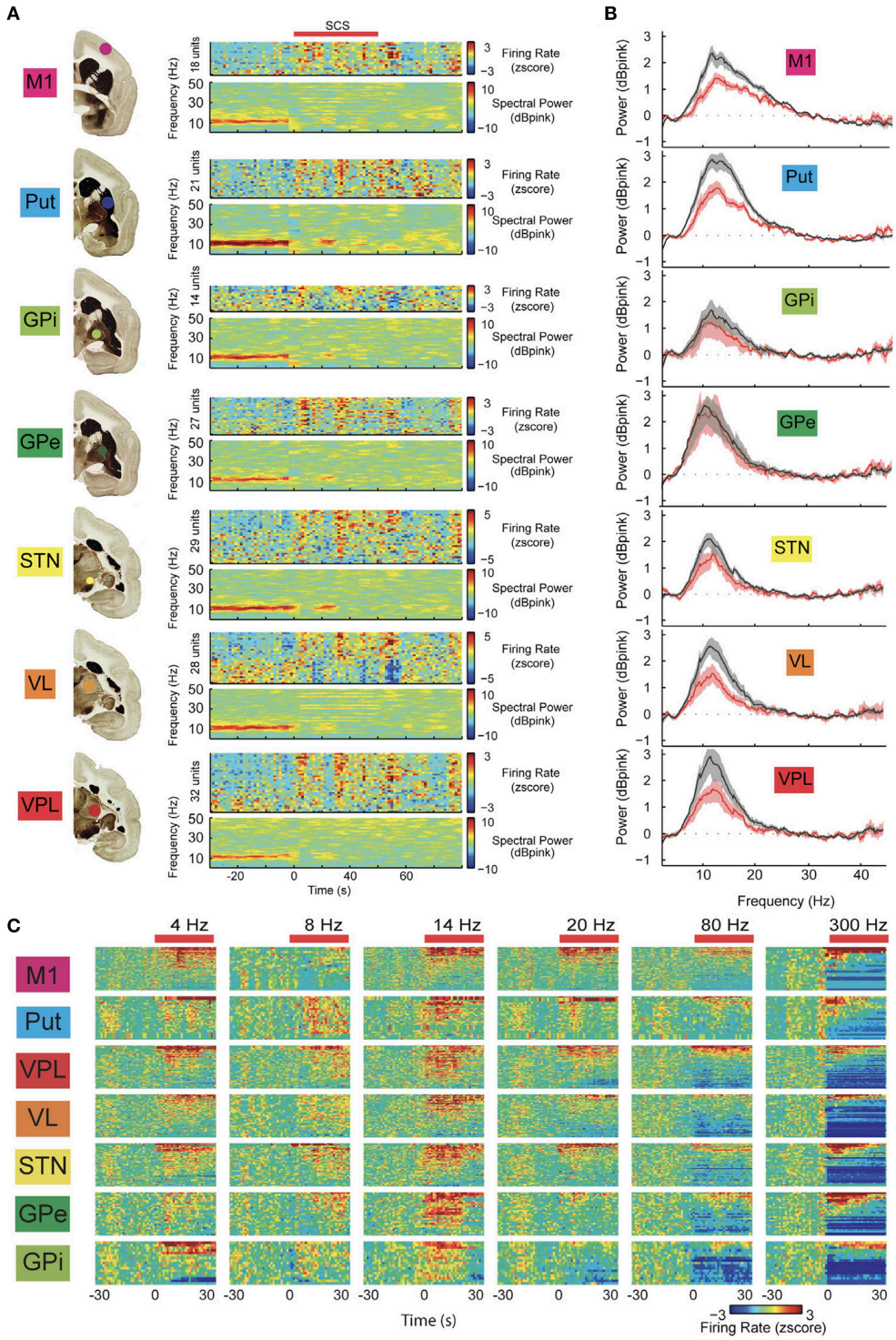

FIGURE 3 | (A) Example of parallel changes in local field potential (LFP) power and neuronal firing rate in multiple structures of the cortico-basal ganglia-thalamic loop during high frequency spinal cord stimulation (SCS). Note the immediate reduction of low-frequency oscillations (beta band) in response to SCS (red bar, stimulation frequency: 4 Hz; color codes denote decibels above pink noise background for LFPs). **(B)** Average LFP spectra for all recording sessions normalized to pink noise showing a significant SCS-induced reduction in LFP beta-power in all structures, except the globus pallidus externus (GPe). Shaded area denotes 95% CI with 100 bootstraps. **(C)** Standardized neuronal firing rate response to different SCS frequencies in multiple structures of the basal ganglia circuits (neurons rank ordered according to responses). Note that most significant changes in neuron firing were achieved at higher frequencies. M1, primary motor cortex; Put, putamen; VPL, thalamus ventroposterior nucleus; VL, thalamus ventrolateral nucleus; STN, subthalamic nucleus; Gpi, globus pallidus internus. Adapted with permission from Santana et al. (3) (**Figures 2A,B**, **3A**).

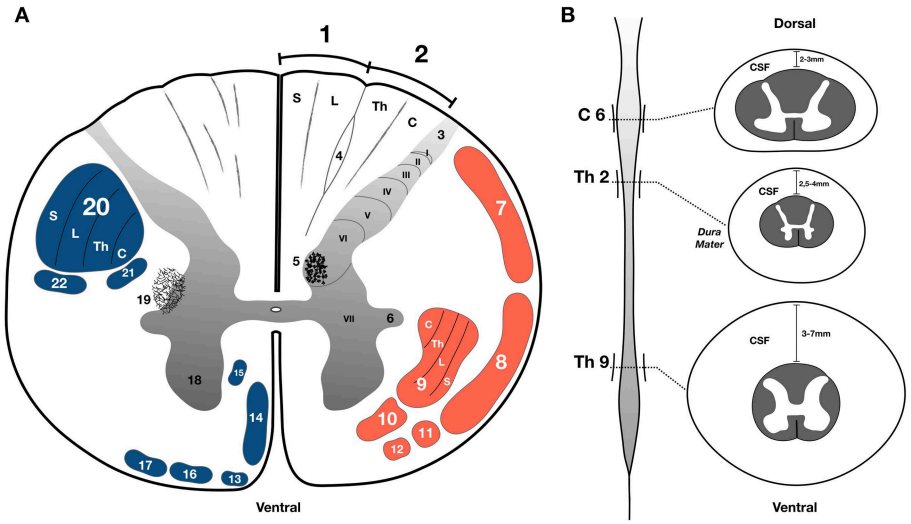

FIGURE 4 | (A) Schematic illustration of a transverse section of the thoracic spinal cord; the upper part of the figure shows the position of structures in white (white background) and gray matter (gray gradient); 1. Gracile fasciculus of Goll; 2 Cuneate fasciculus of Burdarch (dorsal column); 3. Lissauer's tract; 4. Semilunar tract (Schultz's comma); 5. Thoracic nucleus of Clarke; 6. Intermediate column; 7. Posterior spinocerebellar tract; 8. Anterior spinocerebellar tract; 9. Lateral spinothalamic tract; 10. Anterior spinothalamic tract; 11. Spino-olivary tract; 12. Spinotectal tract; 13. Tectospinal tract; 14. Anterior corticospinal tract; 15. Reticulospinal tract; 16. Anterior vestibulospinal tract; 17. Olivo-spinal tract; 18. Anterior column (Gray matter); 19. Reticular formation of the spinal cord; 20. Lateral corticospinal tract; 21. Lateral vestibulospinal tract; 22. Rubro spinal tract; Lamina of Rexed (I to X–gray matter). **(B)** Representation of the spinal cord in longitudinal axis showing the cervical and lumbar enlargements and the respective transverse sections and the distance from the dura to the surface of the cord at different levels. Somatotopy abbreviations; C, cervical; Th, thoracic; L, lumbar; S, sacral; C6, sixth cervical level; Th2, second thoracic level; Th9, ninth thoracic level; CSF, cerebrospinal fluid. Adapted with permission from de Souza et al. (68).

fibers located adjacent to the gray matter of the dorsal horn. Additionally, when SCS is applied to the lower thoracic spinal cord, the most efficient parameters include long pulse widths, with lower frequencies tested so far (7). These are in line with the current hypothesis that therapeutic SCS for gait should include multiple projection bundles to brainstem, cerebellum, basal ganglia, thalamus, and cortical areas, besides acting on local and integrated spinal circuits. Among various cortical areas that probably mediate SCS effects on gait, dysfunctions in SMA are directly involved in the pathophysiology of FoG. It has been found that SCS may influence neuronal firing in the SMA, a key hub for controlling gait initiation (27, 64). The SMA does not receive direct thalamic projections but it does receive inputs from somatosensory regions (SI, SII, and area 5) (65). In fact, our recent study showed that SCS improved the timing of APAs during gait initiation (58), a behavior found to be modulated by SMA (27). As mentioned above, frontal activity (e.g., SMA) is increased, whereas subcortical and sensorimotor cortex activity is decreased during motor arrests (48, 50). Altered activity of SMA could intensify its influence over the subthalamic nuclei (STN) via the hyper-direct pathway (66). The increased STN firing in PD states could influence the globus pallidus internus, inhibiting thalamo-cortico-basal circuit activity (66), while reducing activity in the mesencephalic motor area and PPN (67). By inhibiting pathological synchronized slow brainwave oscillations in the SMA, SCS could restore physiological aspects of neuronal circuits known to be involved in gait initiation.

Technological and Technical Issues

Bearing the anatomical and electrodynamic features of spinal cord elements in mind, electrode configuration and stimulation field become important variables. Electrodes that provide two or more parallel columns of stimulation contacts and allow multiple combinations of settings are more versatile. Paddle electrodes with three columns of contacts may offer some advantages, since they allow the correction of lateral shift and facilitate the appraisal of the physiological midline. Although, this montage may also be achieved with percutaneous electrodes, at least three leads have to be implanted in order to provide similar coverage. Also useful is the transverse tripolar montage with a middle cathode sided by a pair of anodes. This configuration prevents afferent radiculi from unwanted stimulation, while steering the electrical field further into deep spinal cord elements (69). Transverse stimulation also tends to be more selective than monopolar or longitudinal bipolar stimulation (70) and has been associated with promising clinical results (6).

Percutaneous leads are quite popular among pain physicians because they allow electrode implants to be performed through a puncture. Also, they can be inserted into just about any spinal level and travel longitudinally to the first segments of cervical (71). Those leads are mainly implanted in lower thoracic levels for the treatment of pain in the lower limbs and low back (72–77). The method was applied in most anecdotal reports serendipitously describing improvement in PD symptoms. The larger series reported to date followed this classical method, implanting percutaneous leads over the lumbar spinal cord

enlargement (7, 8, 78). The best parameters for treating PD symptoms in that study included a relatively long pulse width (PW). Although this does not necessarily deliver more energy, currents applied for a longer time allow slow depolarizing ion channels in dendrites, cell bodies, and in lesser diameter and poorly myelinated axons to be excited (79). Also, a denser stimulation will recruit elements located deeper in the spinal cord (80), possibly including gray matter regions and projection fibers located in quadrants of the cord other than the dorsal columns (**Figure 4A**). Conversely, these parameters increase the chance of direct stimulation of nerve rootlets, which may cause discomfort in adjacent dermatomes or muscle contractions in correspondent myotomes (81).

The frequency of stimulation may also change responses from the neural tissue. In the spinal cord, low frequency stimulation often induces intermittent paresthesias or a sense of vibration, while frequencies >60 Hz tend to elicit a continuous sensation. According to pre-clinical studies (3, 4), 300 Hz stimulation even with low PW inhibits pathological slow wave brain oscillations (**Figure 3C**) and provides good for clinical implementation (6, 58). This may be noticed when stimulation is delivered to higher thoracic levels, where the cord has a small diameter and is relatively close to the dural membrane (**Figure 4B**). A drawback of continuous stimulation at higher frequencies is high-energy consumption, which makes the generator recharge intervals quite short.

More recently, the technological progress in electrode construction provided a larger number of contacts (up to 32) with intelligent programming software. To date, percutaneous paddle leads have not been tested for PD symptoms and gait problems. Novel implantable pulse generators provide SCS systems with multiple programming platforms, such as frequencies of up to 10 KHz and burst waveforms intermingled with pauses that allow paresthesia free stimulation. This type of stimulation will be very useful in blinded studies.

Relevant Data From Clinical Studies

Spinal cord stimulation (SCS) has been used to treat refractory pain for over 50 years. Since the 1970s, several reports have been published showing the motor benefits of this technique (82–84). The pioneer paper by Cook using SCS in patients without pain was published in 1973 (85). He described five patients with multiple sclerosis treated with high frequency SCS at the upper thoracic cord who had a major improvement on disability caused by pyramidal, cerebellar, and brain stem symptoms (85). Subsequent reports have then been published using SCS to treat a wide range of motor disorders, including spasticity (86), spasmodic torticollis (84, 87), and orthostatic tremor (88, 89). In 1997, Waltz published a review of 1,336 cases with multiple sclerosis, cerebral palsy, spinal cord injury, dystonia, spasmodic torticollis, spinocerebellar ataxia, and post-traumatic brain injury who had marked or moderate amelioration after SCS (63). Particular improvements in balance, stability, gait and posture were noted.

After the initial experience described above, SCS for movement disorders has reemerged in the past decade following the spark generated by preclinical reports (3, 4).

Anecdotal Reports

At first, investigators described the effects of SCS in patients with PD that also had refractory pain and postural inclination (5). Although we recognize the importance of the following reports, the absolute results should be analyzed with caution due to the fact that the overall improvement in gait may also be related to an improvement of other conditions (e.g., pain) and also that none of them included placebo arm or trial. Those studies showed no significant improvement in FOG but gait and balance were not considered as primary outcome measures (90). Fénelon et al. presented the case of a 74 years old patient who developed PD 8 years after T9–T10 SCS for failed back syndrome (72). The authors objectively demonstrated improvements in tremor, bradykinesia, and rigidity with stimulation at 130 Hz. No benefit was found on gait, as measured by time to walk 7 m, turn, and walk back (72). In contrast, Landi et al. described an improvement in gait and postural instability after T9–T10 stimulation in a chronic pain patient with PD previously treated with STN-DBS (73). Hassan et al. described a 43-year-old PD patient with progressive improvement in the timed 10-m walk test and UPDRS part III 2 years after SCS implanted in the C2 region for neck and upper extremity pain (74). Akiyama et al. showed improvement on timed up and go test and camptocormia 29 days after SCS implantation at the level of T8 in a 65-year-old PD patient previously treated with bilateral STN-DBS (75). Soltani and Lalkhen presented serendipity results of improvement in leg tremor and other unrated parkinsonian symptoms (76). A common feature of these open label reports is that stimulation parameters and the spinal level of electrode implantation were apparently defined based on routine SCS protocols for pain. As such, percutaneous leads were largely implanted in lower thoracic levels and stimulation delivered at wide pulse width and frequencies that ranged from 7 to 130 Hz. An improvement in parkinsonian features was unexpectedly observed in those patients, but fortunately reported. No specific tests were done to establish optimal parameters to treat motor symptoms. More recently, Kobayashi et al. (77) described a PD patient with intractable pain treated with thoracic SCS (T6–T8) who had substantial improvements in motor scores (70%), posture and gait measures (25% sagittal vertical axis; 25% time, and 28% number of steps in the 20 m walking test). An interesting aspect of that study is that, in addition to tonic stimulation, the patient received burst SCS with no associated paresthesias. While both therapies were found to be effective, less amplitude was required for a good post-operative outcome when burst stimulation was delivered (40 Hz burst with five spikes of 500 Hz). Although those reports suggested a benefit on walking, the improvement in pain was still a major confounder, as stated by Thiriez et al. (91).

Clinical Studies Primarily Focusing on SCS for Axial Symptoms and Gait

The series of studies described above encouraged further trials using SCS in PD and the development of protocols to specifically assess motor outcomes (**Table 1**). Thevathasan et al. (92) investigated the effect of high cervical SCS in two PD patients who were blindly evaluated while receiving suprathreshold and

TABLE 1 | Studies approaching SCS as a treatment of motor symptoms and gait disorders in Parkinson's disease.

References	No. of patients	Mean disease duration (years)	DBS prior to SCS	Electrode type	SCS level	Freq	PW	Kind of stimulation	Dopa condition at evaluation	Evaluations/ Follow up (months)	Study design	UPDRS motor score: improvement (%)	Gait Analyses	Other outcomes: Improvement (%)
Thevathasan et al. (92)	2	NA	No	Quadripolar and octopolar; cylindrical	High cervical	130 and 300 Hz	240 and 200 μs	Tonic Supra threshold and sub threshold for each patient	Night withdrawal	10 day PO/None	Acute double blind crossover between two conditions (supra and sub threshold) with a washout of 20 min.	0% 0%	Timed 10 m walk: no improvement	Timed hand arm movements: 0% Timed lower limb tapping:0%
Agari et al. (78)	15	17.2	Seven cases	Quadripolar and octopolar; cylindrical	T7–T12	5–20 Hz	210–330 μs	NA	On med	Baseline, 3 and 12 months/12 months	Case series (prospective)	19.5% at 3 months 9% at 12 months	Timed 10 m walk: improvement of 9.2% at 3 and 2.1% at 12 months. TUG: improvement of 25.7% at 3 and 13.3% at 12 months.	Postural improvement at 3 months 25%; at 12 months 9%
Pinto de Souza et al. (6)	4	21.2	Four cases (mean 7.8 years before SCS)	Three columns (5-6-5); paddle	T2–T4	300 Hz	90 μs	Tonic 105% of the threshold for paraesthesia	12 h withdrawal	Baseline, 1, 3, and 6 months/6 months	Case series (prospective)/ Blinded randomized evaluation with 60 × 300 Hz at the 4 month with a washout of 2 h between conditions.	36.8% at 1 month 48.7% at 3 months 38.3% at 6 months	20 m walk: improvement of 58% on time and 65.7% on steps numbers at 6 months. TUG: improvement of 63.2% at 6 months. TUG with double task: improvement of 54% at 6 months. Stride length: increase of 170% at 6 months.	PDQ 39: improvement of 44.7% at 6 months. FOG: improvement of 56.4% at 6 months.
Samotus et al. (7)	5		No	Double octopolar; cylindrical	T8–T10	30–60 Hz	200–500 μs	Tonic Supra threshold for paraesthesia	On med	Baseline, 4, 6 months/6 months	Case series (prospective)/11 frequencies and pulse width different combinations for each patient.	33.4% at 6 months	Stride length: increase of 38.9% at 6 months. Steps velocity: increase 29.4% at 6 months. Swing improved 21% at 6 months.	FOG: improvement in 26.8%. at 6 months. ABC (daily activities): improvement of 65% at 6 months.

(Continued)

TABLE 1 | Continued

References	No. of patients	Mean disease duration (years)	DBS prior to SCS	Electrode type	SCS level	Freq	PW	Kind of stimulation	Dopa condition at evaluation	Evaluations/ Follow up (months)	Study design	UPDRS motor score: improvement (%)	Gait Analyses	Other outcomes: Improvement (%)
Kobayashi et al. (77)	1	3	No	Double octopolar; cylindrical	Th6–Th8	Burst DR high frequency		Burst No paraesthesia	NA	14 days after Burst SCS/None	Case report	70% after 14 days	20 m walk: improvement of 25% on time and 28% on steps numbers.	Sagittal vertical axis improvement of 25%.
de Lima-Pardini et al. (58)*									12 h withdrawal	Three conditions (blinded randomized): SCS 300 Hz frequency; SCS 60 Hz frequency; 3) SCS off				300 Hz SCS improved APA (time and amplitude) and reduced time of Fog.
Hubsch et al. (8)	5	14.8	1 patient (no details)	Octopolar; cylindrical	Th 10-Th 11	100 Hz	300 μs	Tonic Supra threshold for paraesthesia	On /Off Med	60 days	Case series (prospective)/ Short Follow up	On SCS 23% On Med +On SCS 36.8% After 60 days	Stand-walk-sit test On SCS 23.6% On Med +On SCS 29.8%	FoG-Q–no improvement PDQ39–small improvement

This study was an extension of study 3.

subthreshold stimulation at frequencies as high as 130 Hz. Overall, no improvements in UPDRS motor score and gait assessment were noticed.

Agari et al. (78) implanted thoracic SCS electrodes (T7–T12) in a series of 15 patients with moderate to advanced PD suffering from refractory back and leg pain. At 3 months, UPDRS motor scores improved by 19.5%, measures of daily life activity by 21%, timed 10 m-walk by 9.5%, timed up and go test by 25.7%, and postural scores by 25%. However, the magnitude of these beneficial effects declined by 12 months with significant results still being detected only for TUG (13.3% compared to baseline). No control group was proposed in this study and, as stated above, the presence of pain and especially its improvement may be pointed as bias.

Pinto de Souza at al. (6) have implanted high thoracic SCS electrodes (T2-4) in four DBS-treated PD patients with prominent gait dysfunction. Implant site, electrode geometry (paddle leads) and stimulation settings (300 Hz/90 μs) were similar to those used in animals models. At 6 months, UPDRS motor scores improved by 38.3% while various gait parameters were improved by 54–65%. There were also improvements in quality of life (PDQ 39 by 44.7%) and FoG (FoG-Q questionnaire by 56.4%), suggesting steady clinical progress. To test the possibility of a placebo effect and bias associated with SCS-induced paraesthesias, a blinded randomized crossover evaluation was conducted comparing off stimulation, 60 and 300 Hz on the fourth month of treatment. While 300 Hz significantly improved gait measures, in average SCS at 60 Hz was not as effective. This is of particular importance in times of skepticism as to whether SCS is effective, especially when FoG is considered. The same group of patients was studied in a gait laboratory (1) to address the effects of SCS on FoG and distinct domains of postural control, including APA. The gait behavior was assessed through kinematics and kinetics, which allowed for objective outcomes, mainly for the assessment of the occurrence and duration of FoG, and amplitude and time of APA. For the first time FoG was objectively evaluated during SCS using a recent frequency domain approach to determine FoG events (93).

As for clinical observations, although both SCS at 300 and 60 Hz improved APA and the duration of FoG episodes in relation to the OFF-SCS condition, SCS at 300 Hz showed significantly higher benefits than 60 Hz. The duration of FoG after 60 Hz SCS improved by 73% compared to 91% after 300 Hz. The time of APA improved by 4.35% after 60 Hz SCS and 17% following 300 Hz stimulation. In contrast, reactive postural control was not affected by SCS.

Samotus et al. (7) studied five male PD patients treated with SCS delivered through percutaneous electrodes implanted in lower thoracic levels. Although patients were followed overtime, no double-blind trial was described in this report. Optimal stimulation parameters were selected over different frequencies (range 30–60 Hz) and broad pulse widths (200–500 μs). The authors observed acute decreases in FoG episodes during at least two evaluation sessions in the laboratory to objectively assess gait parameters (velocity, stride length, swing), always under the effect of levodopa. Improvements in UPDRS motor scores (33%), Activities-specific Balance Confidence (ABC) daily activities (65%), swing (21%), stride length (38.9%), velocity (29.4%), and FoG (26.8%) were observed during acute evaluation sessions at 6 months. Of note, the best reported results were observed when high pulse widths were used. This fact is quite interesting because it corroborates the concept that larger pulse widths tend to be less selective, as less excitable neuronal elements also tend to depolarize. In the same direction, electrical current has also been considered to reach further deep into the spinal cord. In the lumbar spinal cord enlargement, stimulation would theoretically require larger pulse widths to reach a wider range of ascending systems, as the cord diameter is considerably wider. On the frequency side, data from this series does not specify if SCS at 300 Hz was tested, as described in the pre-clinical study by Fuentes et al. (4) and clinical data from the study by Pinto de Souza et al. (6). One possible explanation might be related to the different stimulation site in the lower cord. This apparent diversion needs to be further studied.

More recently Hubsch et al. (8) have studied five PD patients with prominent axial symptoms who received monopolar stimulation (100 Hz/300 μs) from a single midline percutaneous epidural lead at the level of T10–T11. Patients were assessed OFF and ON levodopa at short term (60 days). Though a blinded evaluation of videos was conducted for the stand-walk-sit test, patients could still feel the paresthesias when SCS was ON. In average, patients performed better during gait assessments with ON-SCS + ON-Ldopa. Improvements with SCS (23.6%) or levodopa (19.3%) were similar with a synergistic effect recorded when both therapies were administered in conjunction (29.8%). Similar effects were observed in the MDS-UPDRSIII; While the improvement with ON-SCS (23.22%) did not differ from ON-Ldopa's, ON-SCS + ON-Ldopa led to a 36.8% improvement. No significant changes were observed in FOG-Q but PDQ39 improved slightly, especially in the mobility scores at 60 days. The positive effects observed in this series were accomplished with 130 Hz stimulation and a large pulse width (300 μs). The remaining parameters and stimulation site were similar to Samotus at al. (7).

Freezing of gait (FoG) and gait disturbance are not exclusively observed in PD but also in atypical parkinsonism. Rohani et al. described two patients with primary progressive FoG treated with SCS at T10–T11. Gait analyses revealed an improvement in FOG and gait at 5 and 24 months, respectively (93). Unrelated to FoG or PD, a recent series of studies have shown promising results with the use of SCS to treat motor deficits in patients with spinal cord injury (94, 95).

The above-reviewed reports suggest that cardinal symptoms of PD can improve following SCS. Of particular interest, however, would be locomotion improvements in patients with gait problems, especially FoG. Most PD symptoms respond well to medication alone and additional deep brain stimulation (DBS) (96). Even FoG may improve chronically with DBS when this symptom responds acutely during the levodopa challenge test (97). So, FoG subtype unresponsive to medication or DBS may in the future be one of the indications to SCS in PD. According to the report of de Souza et al. (6), patients with advanced PD chronically treated with DBS who develop unresponsive FoG despite effective treatment to other symptoms, also benefit from

SCS. Yet, PD patients who somehow cannot receive DBS may be another indication for SCS, once cardinal symptoms and gait problems respond (7, 8, 78). On the other hand, SCS does not seem to potentiate levodopa, as observed with subthalamic nucleus DBS, or to block dyskinesias, as commonly described following internal pallidum stimulation (6, 7). A word of caution should be added to the comments above because most of the data disclose in the literature does not include control arms (6) and are considered low class evidence. Well-designed trials including double blind and placebo control arms with a large sample size and specific stimulation protocols are still needed for SCS to be considered as a potential treatment.

FINAL REMARKS

The therapeutic use of SCS in patients with movement disorders is not novel. However, the field was recently rekindled by preclinical experiments providing a stronger rationale, optimized stimulation settings, and better appraisal of potential mechanisms (3, 4). Clinical trials following some aspects described in those studies have recently been conducted with promising results. With accumulation of experience and based in a more comprehensive amount of data, the importance of a few aspects became clear. *Choice of electrode*. The electrical field created by single cylindrical and paddle electrodes is fairly different. Paddle electrodes require a surgical approach while cylindrical electrodes can be implanted percutaneously. The former, however, covers a wider portion of the spinal cord and allows several configurations that may modulate different tracts and neural elements. *Choice of generator*. Currently, generators that provide stable energy delivery by automatic positional control and new generators that allow burst and kHz stimulation could facilitate the design of blinded studies, since no paresthesias are felt. *Spinal level*. While benefits were shown following cervical and low thoracic stimulation, a more comprehensive analysis with data from animal studies and translational clinical implementation suggests that the upper thoracic cord may be the hot spot for SCS. Stimulation of the cervical and lumbar spinal cord enlargements has also been described. *Stimulation parameters*. The most effective electrical wave type may be different for each spinal cord level, but apparently they all point to the need of recruiting less excitable elements, including those deep-seated in the spinal cord. In addition to electrode configuration, defining appropriate pulse width, and the frequency most suited to treat different PD symptoms would be important to optimize the therapy and standardize studies. *Clinical characteristics of the treated population*. It is important to define the clinical phenotype and symptoms that better respond to SCS, as well as stimulation interactions with medication regimens, including L-DOPA.

Based on the information gathered and summarized above, we expect the future development of well-designed trials including specific disease phenotypes. If FoG is the intended condition to be treated, experienced clinical staff should be involved, since this is an episodic phenomenon highly influenced by internal and external factors. In one hand, gait lab evaluations are important to calculate the metrics of gait change. However, lab settings can cause biases in the determination of outcomes. Only part of the outcome measures should take place in gait labs. Data should also be generated in conditions as close as possible from every day life conditions. In addition, measurements capable of identifying changes in locomotion, the occurrence and severity of FoG episodes and other disabilities, such as falls, should be included. Other methods to obtain information in longer periods as functional scales, diaries or actigraphic monitoring should also be considered, since they provide additional information to the ones obtained in gait labs. Visits should be short to avoid testing too many experimental conditions at the same time because patients can get tired in long sessions and recorded information may not be accurate. The design of trials should include few test conditions and sufficient time for the wash out between interventions, including the surgical procedure itself; all patients should endure this period after implantation. Surgical procedures can induce a strong placebo effect, which in FoG should be seriously considered. If possible, a method for blinding patients and observers should also be included in order to reach the highest level of evidence. Adapting the technology and procedures for each particular neurological condition and severity will hopefully provide stronger data and establish indications for the used of SCS in conditions associated with FoG.

AUTHOR CONTRIBUTIONS

AdL-P, DC, BMo, and CP wrote the first draft of the article. EF, CH and AdL-P wrote the final draft of the article. MdS, CH, and EF provided the contextual frame of the review. All authors critically revised the manuscript. EF, AdL-P, and DC designed the figures.

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