RESEARCH ARTICLE

Accelerated Transcranial Ultrasound Neuromodulation in Parkinson's Disease: A Pilot Study

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ABSTRACT: Objective: Low-intensity transcranial focused ultrasound (TUS) is a novel method for neuromodulation. We aimed to study the feasibility of stimulating the bilateral primary motor cortices (M1) with accelerated theta-burst TUS (a-tbTUS) on neurophysiologic and clinical outcomes in Parkinson's disease (PD).
Methods: Patients were randomly assigned to receive active or sham a-tbTUS for the first visit and the alternate condition on the second visit, at least 10 days apart. a-tbTUS was administered in three consecutive sonications at 30-minute intervals. We used an accelerated protocol to produce an additive effect of stimulation. Patients were studied in the OFF-medication state. Transcranial magnetic stimulation (TMS)-elicited motor-evoked potentials (MEPs) were used to assess motor cortical excitability before and after TUS. Clinical outcomes after a-tbTUS administration were assessed using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-III.
Results: A total of 20 visits were conducted in 10 PD patients. Compared to the baseline, TMS-elicited MEP amplitudes significantly increased following active but not sham sonication ($P = 0.0057$). MEP amplitudes were also higher following a-tbTUS than sham sonication ($P = 0.0064$). There were no statistically significant changes in MDS-UPDRS-III scores with active or sham a-tbTUS.
Conclusions: a-tbTUS increases motor cortex excitability and is a feasible non-invasive neuromodulation strategy in PD. Future studies should determine optimal dosing parameters and the durability of neurophysiologic and clinical outcomes in PD patients. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: low-intensity focused ultrasound; Parkinson's disease; transcranial magnetic stimulation; non-invasive brain stimulation

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Parkinson's disease (PD) is a life-altering neurodegenerative disorder, with an estimated annual incidence rate ranging from 5 to over 35 new cases per 100,000 individuals worldwide.[1,2] Current treatments for PD involve dopaminergic pharmacotherapy, surgical intervention including deep brain stimulation (DBS), and non-pharmacologic supportive measures.[1] Although these treatments can alleviate motor symptoms such as bradykinesia, tremor, and rigidity, pharmacological therapies become less effective with disease progression and may cause adverse effects.[1,3] Surgical procedures such as DBS pose risks of peri- and post-operative complications, including infection, hemorrhage, and hardware failure. DBS also requires frequent patient visits

for device programming.[4] Moreover, accessibility to DBS is limited to highly specialized centers. As such, novel non-invasive and accessible therapies for PD are needed.

Non-invasive brain stimulation (NIBS) techniques, such as repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation, hold promise as potential interventions for PD, particularly in patients with refractory symptoms or who are not surgical candidates.[5-7] rTMS has shown therapeutic efficacy in mitigating motor symptoms and depression in patients with PD.[7,8] Despite these promising results, conventional NIBS techniques for PD are limited by low spatial resolution and superficial targeting. Transcranial-focused ultrasound stimulation (TUS) is an emerging NIBS technique that can reach superficial and deep brain targets with high spatial resolution in the order of cubic millimeters.[9,10] This resolution is comparable to the electromagnetic field generated by a DBS lead. Neuromodulation using TUS has been studied in humans, specifically for depressed mood, pain control, dementia, epilepsy, and traumatic brain injury.[10] However, studies of TUS in the context of PD remain scarce.[11-13]

Our group has previously shown that theta-burst TUS (tbTUS) of the primary motor cortex (M1) produces longer and more consistent motor-evoked potentials (MEPs) than sham and conventional TUS protocols in healthy subjects.[14] In our subsequent experiments, we assessed the single tbTUS protocol in PD patients, and the results showed increased M1 excitability in both the medication-ON state and the control group, whereas no such changes were observed in the medication-OFF state.[11-13] In this article, we applied a novel accelerated tb-TUS (a-tbTUS) paradigm to PD patients to determine its feasibility and whether a-tbTUS has any neurophysiologic or potential clinical impacts in the medication-OFF state PD. a-tbTUS draws on principles of accelerated rTMS protocols[15,16] to deliver multiple stimulation sessions in a single day. Such an approach can reduce the duration of treatment, reduce the burden of standard treatment schedules, and may enhance treatment efficacy by evoking non-homeostatic additive metaplasticity.[17-19]

Patients and Methods

Study Subjects and Experimental Procedure

A total of 10 patients were studied. Inclusion criteria included age between 18 and 80 years, PD diagnosis of at least 1-year duration confirmed by a movement disorder neurologist using the Movement Disorder Society (MDS) Clinical Diagnostic Criteria,[20] and stable dopaminergic medication dose for a minimum of 4 weeks. Patients were excluded if they had a history of stroke or seizure, comorbid dementia, previous surgical intervention to treat PD, contraindications for TMS (eg, cardiac pacemaker, transcranial implants, and metal implants), significant psychiatric disorders such as depression or psychosis, inability to understand the study procedures, use of antipsychotics or recreational drugs usage, or were pregnant.

Subjects were studied in the OFF-medication condition, with all PD-related medications withdrawn for at least 12 h before the start of each study visit. Participants underwent two visits with either sham or active a-tbTUS, randomly assigned and separated by at least 10 days (Fig. 1). Each study visit took 2 to 3 hours in duration. The intervention consisted of three sets of a-tbTUS sonications delivered to bilateral M1s at 30-minute intervals. For each visit, the hemisphere (left vs. right M1) sonicated first was randomly assigned. Before and after the intervention, PD motor signs were assessed using the MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-III. Cortical excitability and intrinsic motor cortical circuits were assessed using TMS immediately following the last sonication. The rater for MDS-UPDRS-III was blinded to the intervention. Written informed consent was obtained from each subject, and all experimental procedures were performed in accordance with the Declaration of Helsinki. The study was approved by the University Health Network Research Ethics Board (#20-5740, Toronto, Canada). The primary outcomes of the study were feasibility and safe delivery of a-tbTUS as assessed by the occurrence of adverse events reported by study subjects within 1 week of the stimulation session and those observed by the examiner during the study visit. Secondary outcomes included treatment efficacy measured by MDS-UPDRS-III scores and TMS measures (MEP amplitude, short-interval intracortical inhibition [SICI], and short-interval intracortical facilitation [SICF]).

Transcranial Magnetic Stimulation and Electromyography Recording

TMS was applied to bilateral M1s using a 70 mm figure-eight coil connected to four Magstim 200^2 stimulators via a "four-to-one" connection box (Magstim, Whitland, Dyfed, UK). The coil was held tangentially to the skull with the handle pointing backward and laterally at a 45° angle to the sagittal plane. TMS was used to determine the left and right motor representations (hotspot) for the first dorsal interosseous (FDI) muscles, defined as the areas over M1 evoking the largest and most consistent muscle-evoked potentials (MuEPs) in the FDI muscles. The areas were marked on the scalp to ensure consistent TMS coil repositioning and to center the ultrasound transducer. TMS measures of MEP amplitude, SICI, and SICF were recorded on the more affected side only. A wrist rest was used to

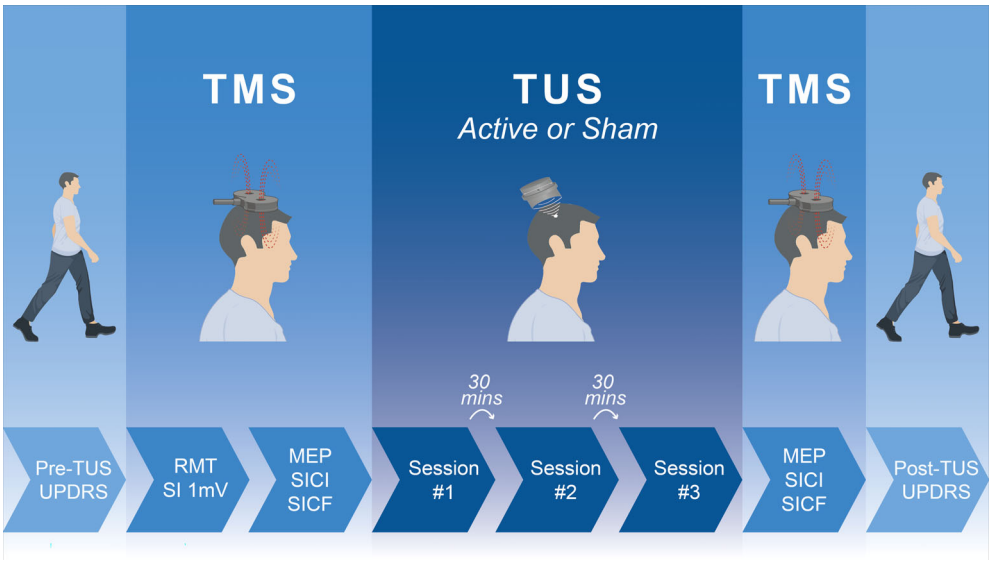

FIG. 1. Overview of study visits. Each participant underwent two study visits separated by a minimum of 10 days. At the initial visit, subjects were randomly assigned to receive sham or active accelerated-theta burst transcranial ultrasound stimulation (a-tbTUS), and subsequently underwent the alternate condition at the second study visit. During the intervention, three sets of a-tbTUS sonications were delivered to bilateral primary motor cortices (M1s,) with 30-minute intervals between each set. The side sonicated first was also randomly assigned for each visit. Before and after the intervention, Parkinson's disease (PD) motor signs were assessed using the Movement Disorder Society (MDS)-Unified Parkinson's Disease Rating Scale (UPDRS)-Part III, whereas cortical excitability and intrinsic motor cortical circuits were assessed using transcranial magnetic stimulation (TMS) immediately following the last of three sonications. [Color figure can be viewed at wileyonlinelibrary.com]

reduce interference by rest tremors with TMS-elicited measures. Resting motor threshold (RMT) was defined as the lowest stimulator intensity required to elicit MEPs of at least 50 μV in the relaxed FDI muscle in at least 5 of 10 consecutive pulses. TMS pulses were triggered using Signal 4.07 software (Cambridge Electronic Design, Cambridge, UK).

M1 excitability before and after ultrasound stimulation was assessed using single-pulse TMS-elicited MEPs. TMS pulses were delivered at an inter-trial interval of 5 s and used the stimulator intensity inducing MEPs of ~1 mV peak-to-peak amplitude (SI_{1mV}) at baseline (mean ± SD: 59.2 ± 10.6% maximum stimulator output [MSO]). Fifteen MEPs were recorded at each time point. SICI and SICF were probed using paired-pulse TMS at M1. For SICI, a conditioning stimulus (CS) was delivered 2 ms before a test stimulus (TS). The CS was set at 80% RMT, and the TS used the stimulator intensity, which induced MEPs of ~1 mV peak-to-peak amplitude (SI_{1mV}) at that time point. For SICF, two stimuli were delivered at an interstimulus interval (ISI) of 1.3 ms. The first stimulus (S1) was at $SI_{1mV,}$ and the second stimulus (S2) was at RMT. RMT and SI_{1mV} were estimated at each time point because RMT and SI_{1mV} may change after a-tbTUS. A total of 15 trials of SICI, SICF, and TS alone were collected in one block in a random order for a total of 45 trials. Paired-pulse MEP amplitudes were expressed as a ratio to the mean amplitude of the unconditioned MEP amplitudes from the TS-only trials. Ratios larger than one indicated facilitation.

Surface electromyography (EMG) was recorded from the left and right FDI muscles using pairs of 9-mm diameter Ag-AgCl electrodes in a belly-tendon montage. EMG signals were amplified at 1 K (Intronix Technologies Corporation Model 2024F, Bolton, Ontario, Canada), bandpass filtered between 20 and 2500 Hz, and digitized at 5 kHz (Micro 1401, Cambridge Electronics Design, Cambridge, United Kingdom). Recordings were stored in a laboratory computer for offline analyses.

Transcranial Ultrasound Stimulation of the Motor Cortex

Ultrasound stimulation was delivered using a custom two-element annular array ultrasound transducer (H246, Sonic Concepts Inc., Bothell, Washington) with a fundamental frequency of 0.5 MHz, diameter of 38 mm, and thickness of 10 mm. A programmable radiofrequency amplifier (Transducer Power Output System TPO201-80, Sonic Concepts Inc., Bothell, Washington) delivered the required power to the transducer via a 50 Ω impedance matching module. The sonication depth was set as 30 mm according to the scalp-cortex distance to the hand motor area[21] as reported in our previous study.[14] The tbTUS paradigm consisted of an 80 s train of pulses with a pulse repetition frequency of 5 Hz, pulse duration of 20 ms, ultrasonic stimulus duration of 200 ms, and duty cycle of 10%, for a total of 400 pulses (Supplementary Table S1). The power of ultrasound was set as 20 W. The acoustic focus of the ultrasound waveform was measured in our previous

study.[14] The estimated spatial-peak pulse-average intensity (I_{SPPA}) was 2.26 W/cm^2, and the spatial-peak time-average intensity (I_{SPTA}) was 0.23 W/cm^2 at the M1 target, both well below the United States Food and Drug Administration safety standards.[14]

Ultrasound stimulation was targeted to the FDI hotspots for TMS. Conductive gel (Wavelength® MP Blue Multi-Purpose Ultrasound Gel) was applied before ultrasound transducer placement on the scalp. For sham a-tbTUS, the transducer was flipped so that the inactive face of the transducer was in contact with the scalp. Temporary fatigue was noted in four patients following the experiments. No significant adverse effects were noted during, or following a-tbTUS administration, supporting the safety profile of a-tbTUS pulsing schemes.

Statistical Analysis

Descriptive statistics were reported as the mean ± standard deviation for continuous variables. Single-trial EMG background was estimated as the EMG area from 1 to 200 ms before the TMS pulse. Trials with EMG backgrounds above 2.5 standard deviations from the mean were excluded from analyses. The Shapiro–Wilk test was used to assess normality. Measures with a normal distribution were analyzed using Student's paired two-tailed *t*-tests. Measures that deviated significantly from normal distribution were analyzed using paired two-tailed Wilcoxon signed-rank tests. Tests compared measures before and after sonication and baseline measures between conditions. Post-sonication TMS measures were also expressed as a ratio to baseline measures, and tests were done to compare the ratios between conditions. Pearson's coefficient was calculated to assess correlations between changes in MEP amplitude from baseline and the change in MDS-UPDRS-III scores for each condition. The significance was set at $\alpha = 0.05$ for all tests. Statistical analyses were performed using R Studio (2022.02.3 + 492, "Prairie Trillium" https://www.rstudio.com).

Results

Subject Characteristics

The 10-subject cohort comprised two women and eight men, with a mean age of 63.8 ± 7.15 years (range: 54–76 years). Characteristics of subjects and pre-procedural MDS-UPDRS-III scores are given in Table 1 and Supplementary Tables S2 and Table S3, respectively. The mean disease duration was 6.3 ± 4.1 years. Most patients (n = 6/10, 60%) exhibited tremor-dominant signs at the time of diagnosis. Nearly all patients (n = 9/10, 90%) were taking medications for PD (Table 1). No moderate or severe adverse events were reported in any study participants either during or after the sonications. Although 4 out of 10 patients reported temporary fatigue after study visits, patients did not report any headache, neck pain, scalp heating, or muscle twitches.

a-tbTUS Modulates Motor Cortical Excitability

In each condition (active and sham), an average of 0.8 trials for MEP amplitude, 0.73 trials for SICI, and 0.40 trials for SICF were rejected in each patient due to pre-stimulus EMG artifacts. Post-sonication measures of SICI for the active condition ($W = 0.79$, $P = 0.010$) and SICF for the sham condition ($W = 0.80$, $P = 0.015$) were not normally distributed.

Baseline RMT and SI_{1mV} were comparable between the two study visits (RMT: 48.7 ± 6.5% MSO for the active condition, 49.2 ± 7.3% MSO for the sham condition; SI_{1mV}: 59.3 ± 10.5% MSO for the active condition, 59.4 ± 11.0% MSO for the sham condition) (Supplementary Fig. S1A,B). Post-sonication RMT was 49.2 ± 6.6% MSO in the active condition and 48.8 ± 7.8% MSO in the sham condition. RMT and SI_{1mV} were not significantly altered by active (RMT: $t(9) = -0.6$, $P = 0.6$; SI_{1mV}: $t(9) = 0.7$, $P = 0.5$) and sham (RMT: $t(9) = 0.6$, $P = 0.5$; SI_{1mV}: $t(9) = -1.0$, $P = 0.3$) sonications (Supplementary Fig. S1A,B). MEP amplitudes significantly increased from 1.08 ± 0.22 mV at baseline to 1.72 ± 0.67 mV after active sonication ($t(9) = -3.61$, $P < 0.01$) (Fig. 2A). In contrast, there was no significant change in MEP amplitudes before (1.12 ± 0.20 mV) and after (0.99 ± 0.17 mV) sham sonication ($t(9) = 1.91$, $P = 0.089$) (Fig. 2A). MEP ratio was also significantly different between active (1.58 ± 0.5 folds) and sham (0.90 ± 0.20 folds) conditions ($t(9) = 3.54$, $P < 0.01$) collectively supporting cortical facilitation by active a-tbTUS. Compared to baseline, there was no significant change in SICI or SICF after active [SICI: $z = 0.76$, $P = 0.49$; SICF: $t(9) = -1.41$, $P = 0.19$] or sham [SICI: $t(9) = -0.18$, $P = 0.86$; SICF: $z = 1.27$, $P = 0.23$] sonications (Fig. 2B,C). There was also no significant difference in SICI and SICF ratios between conditions, although SICF was increased after active (2.71 ± 1.27 to 3.39 ± 1.59) but decreased with sham (4.09 ± 2.15 to 3.09 ± 1.67) a-tbTUS. Baseline measures of MEP amplitude [$t(9) = 0.55$, $P = 0.59$], SICI [$t(9) = 1.60$, $P = 0.14$], and SICF [$t(9) = 2.09$, $P = 0.06$] between conditions were not statistically different.

a-tbTUS Does Not Significantly Affect MDS-UPDRS-III Scores but May Impact Upper Extremity Rigidity

There was no statistically significant difference in MDS-UPDRS-III scores before and after the a-tbTUS procedure in the active ($t(9) = 1.8$, $P = 0.1$) and sham ($t(9) = 1.6$, $P = 0.1$) conditions (Fig. 3A). Similarly, the

TABLE 1 *Characteristics of study subjects*

Patient ID	Age (y)	Sex	Disease duration (y)	Handedness	Side of worse symptoms	Presenting symptom at diagnosis	PD medications	LEDD* (mg)
1	76	M	9	R	L	LUE tremor	Levodopa-carbidopa, pramipexole	1375
2	70	F	2	R	L	LUE tremor	Levodopa-carbidopa, selegiline	400
3	66	F	7	R	R	Reduced arm swing on the R	Levodopa-carbidopa, amantadine	500
4	65	M	2	R	R	RLE tremor	Levodopa-carbidopa	600
5	55	M	2	R	R	RUE tremor	No medications	0
6	62	M	1	R	L	LLE tremor	No medications	0
7	69	M	8	R	R	RUE tremor	Levodopa-carbidopa	525
8	65	M	12	R	R	Dyskinesia, gait imbalance	Levodopa-carbidopa, pramipexole, amantadine	1425
9	54	M	10	L	L	Gait disturbance	Levodopa-carbidopa	450
10	56	M	10	R	L	Generalized rigidity	Levodopa-carbidopa, pramipexole	700

Abbreviations: PD, Parkinson's Disease; LEDD, levodopa equivalent daily dose; M, male; R, right; L, left; LUE, left upper extremity; F, female; RLE, right lower extremity; RUE, right upper extremity; LLE, left lower extremity.
*Calculated using formula and conversion factors from http://www.parkinsonsmeasurement.org/toolBox/levodopaEquivalentDose.htm.

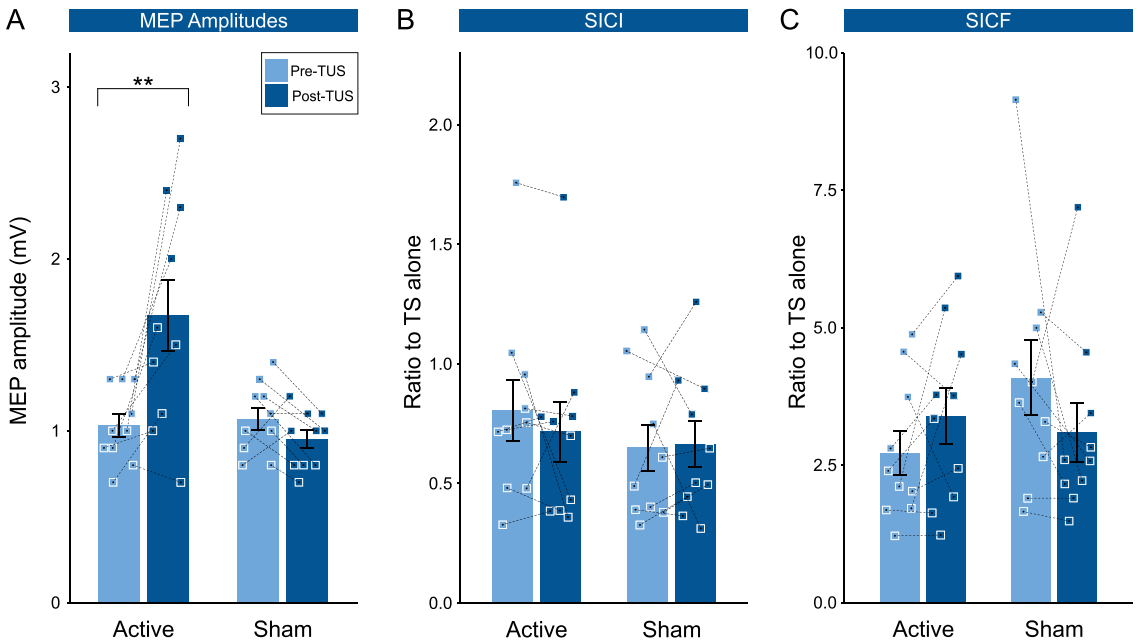

FIG. 2. Effects of accelerated theta-burst transcranial ultrasound stimulation (a-tbTUS) on motor cortical excitability and intracortical circuits. (**A**) Motor-evoked potential (MEP). (**B**) Short-interval intracortical inhibition (SICI). (**C**) Short-interval intracortical facilitation (SICF). Bars with associated standard error of the mean are shown for each measure (on the vertical axis). Bars in light blue show the active condition. Bars in dark blue show the sham condition. Each condition is shown with before a-tbTUS (pre-TUS) and after a-tbTUS (post-TUS). [Color figure can be viewed at wileyonlinelibrary.com]

subgroup analysis of MDS-UPDRS-III sub-scores did not reveal significant changes. However, in the active condition, there was a non-significant trend toward improvement in the upper extremity (UE) rigidity scores [$t(9) = 2.1$, $P = 0.06$] compared with the sham condition [$t(9) = 0.7$, $P = 0.5$] (Fig. 3B). Notably, all three

patients with a baseline total UE rigidity score of ≤2 did not experience any changes in their scores in the active condition, whereas five out of seven patients with a baseline score of ≥3 had at least a one-point improvement (Supplementary Table S2). Changes in MEP amplitude did not show significant correlation with baseline MDS-UPDRS-III scores and changes in MDS-UPDRS-III scores.

Discussion

We applied a novel accelerated TUS protocol for neuromodulation in patients with PD. To our knowledge, this is the first study utilizing a-tbTUS to investigate the impact of this intervention on neurophysiologic and clinical outcomes in PD. With regard to our primary outcome measures, the procedure was well tolerated by all patients, and no safety issues occurred. Furthermore, our results demonstrate that active sonications induced changes in cortical excitability, as evidenced by a 1.6-fold relative increase in MEP amplitudes. The clinical impact of this modulation on cortical excitability, as measured by MDS-UPDRS-III, was not immediately apparent.

Our previous studies have demonstrated that tbTUS enhances M1 excitability in healthy individuals.[14,22] TMS studies have shown that M1 excitability, as assessed by the MEP input–output curve while at rest, was higher in patients with PD in the medication-OFF state than in healthy controls,[23] and the slope of the curve correlated with the severity of bradykinesia.[24] However, MEP amplitude and input–output curve decreased in PD patients compared to controls during muscle contraction.[23] The increased rest MEP amplitude in PD is generally considered a compensatory response.[24] Moreover, the majority of rTMS studies that showed improvement in motor functions in PD used excitatory high-frequency rTMS.[25] An evidence-based review concluded that bilateral high-frequency rTMS to M1 has probably efficacy in improving motor functions in PD.[6] Therefore, we tested the excitatory tbTUS protocol to bilateral M1. Our current study revealed increased MEP amplitudes in medication-OFF PD patients following three consecutive a-tbTUS sessions, similar to levels in healthy subjects following a single tbTUS session,[14] suggesting a potential additive metaplastic effect of accelerated ultrasound sessions.

The impact of TUS on SICI in healthy individuals depends on the specific sonication parameters employed, with studies demonstrating either potentiation[26] or no change[27] with online protocols. Our previous studies using a single session of tbTUS led to a reduction in SICI in healthy individuals.[14,22] In PD patients, SICI is reduced and can be normalized by dopaminergic medications or subthalamic DBS,[2,24,28] whereas SICF is increased in PD.[29] We did not detect changes in SICI or SICF measured at single ISIs of 1.3 and 2 ms, respectively, following both active and sham a-tbTUS conditions. We tested only one ISI for SICI and SICF to limit the duration of study visits, as patients may experience significant discomfort in the OFF-medication state. We cannot exclude the

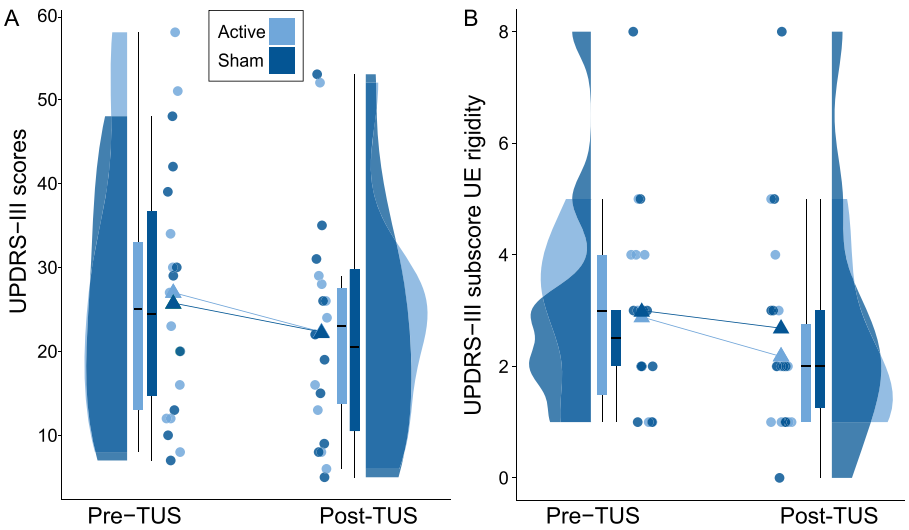

FIG. 3. Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-III and upper extremity (UE) scores. Rain plots depict changes in motor symptoms in subjects with Parkinson's disease before and after accelerated theta-burst transcranial focused ultrasound (a-tbTUS). The plot highlights significant changes and facilitates the identification of key findings related to MDS-UPDRS-III scores and UE rigidity in response to a-tbTUS. (**A**) Rain plot depicting MDS-UPDRS-III scores, a measure of overall motor symptoms, in subjects with Parkinson's disease. Each data point represents an individual subject, with the *x*-axis indicating the baseline (pre-TUS) versus post-treatment (post-TUS) measures and the *y*-axis representing MDS-UPDRS-III scores. Data points are colored based on the stimulation condition (active vs. sham), with light blue indicating active TUS and dark blue indicating sham TUS. The "smear" effect is applied to prevent overlap of data points, improving visual clarity. (**B**) Same as in (**A**) but for UE rigidity scores of the MDS-UPDRS-III, in the same subjects. [Color figure can be viewed at wileyonlinelibrary.com]

possibility that changes in intracortical circuits could occur at other ISI.

The administration of a-tbTUS did not yield a statistically significant improvement in global MDS-UPDRS-III scores in this study. This may be due to insufficient power in this pilot study to detect small effect sizes. Moreover, the intervention only targeted the hand region of M1, potentially limiting its impact on lower extremity scores. Disease heterogeneity also occurred in our patient cohort, with symptoms ranging from mild to severe and three patients with a baseline MDS-UPDRS-III score of 12 or below. Because demonstrating treatment efficacy in patients with mild symptoms can be statistically challenging, it is not surprising that the study did not find a significant effect. Importantly, extrapolating from the literature on rTMS, we anticipate that three treatment sessions alone are likely insufficient to induce durable effects.[30]

Other study limitations should be noted. One such limitation is the extended duration of the study visits, which lasted more than 2 h. This prolonged duration may have contributed to patient fatigue toward the end of the visits, which in turn may have impacted the MDS-UPDRS-III scores. Patient fatigue and discomfort in the OFF-medication condition also constrained our capacity to test multiple outcome measures. We only tested one ISI for each intracortical circuit. In addition, we did not test the less affected side. Therefore, whether the response to a-tbTUS differs between the more and less affected sides remains unknown. However, physiological changes in PD, including reduced SICI, are more prominent on the more affected side than the less affected side.[2] We did not investigate the neuropsychiatric effects of a-tbTUS. However, we excluded patients with prominent mood symptoms, and M1 stimulation is not expected to have a significant effect on mood. Furthermore, although tbTUS has been tested in healthy subjects,[14,22] a-tbTUS has not yet been evaluated in healthy subjects. Because we did not include a healthy control group in the study, we cannot determine whether the physiological responses to a-tbTUS in PD-OFF patients were normal. This would be an important direction for future studies. However, this was not the aim of the present study, which was to establish the feasibility and safety of a-tbTUS in PD patients to provide foundational knowledge for future phase II and III trials.

Although the small sample size of this study may have limited the ability to draw definitive conclusions regarding clinical outcomes, the results provide valuable information to inform power analyses for future studies. Focusing on patients with moderate to severe symptoms rather than patients with mild symptoms may increase the likelihood of detecting a significant effect. Overall, our findings offer valuable insight that can guide the design of future research in this area.

Conclusion

This pilot study represents a novel approach to NIBS in PD, utilizing an a-tbTUS protocol. Our findings demonstrate that this approach is feasible and well tolerated by patients across the spectrum of disease severity. a-tbTUS was associated with increased M1 excitability, which may suggest that changes in cortical circuits occur with a-tbTUS sonications, although it did not correlate with clinical motor outcomes. Future studies with larger cohorts should be aimed at determining optimal a-tbTUS dosing schedules, as well as the durability of neurophysiologic and clinical outcomes in PD patients.

Author Contributions

Conception of the work: NS, MYRD, CS, GD, RC, AML; Acquisition of the data: NS, MYRD, CS, TCG; Data interpretation: NS, MYRD, CS, IEH; Statistical analysis: NS, MYRD, CS; Writing the first draft: NS, MYRD, CS; Critical revision and approval of the manuscript: All authors.

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Conflicts of Interest

NS, MYRD, CS, GD, IEH, TCG, XC, KZ, AY, and RC report no disclosures relevant to the manuscript. CS has been receiving fellowship grants from Michael and Amira Dan Foundation and the Turkish Neurosurgical Society. AML is the scientific director for Functional Neuromodulation and a consultant to Medtronic, Abbott, Boston Scientific, Insightec, and the Focused Ultrasound Foundation.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.