BRIEF REPORT

A New Stimulation Mode for Deep Brain Stimulation in Parkinson's Disease: Theta Burst Stimulation

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ABSTRACT: Background and Objectives: The purpose of this study was to assess efficacy and safety of a new patterned theta burst stimulation algorithm of DBS with the aim of expanding the therapeutic window and clinical benefit in PD.

Methods: In this single-center, randomized, double-blind, clinical short-term trial, unilateral conventional subthalamic DBS was compared with unilateral patterned stimulation algorithms with intraburst high- or low-frequency theta burst stimulation in 17 PD patients.

Results: There were no serious adverse events with theta burst stimulation. During monopolar review, conventional subthalamic DBS and high-frequency theta burst stimulation were comparable, but low-frequency theta burst stimulation differed by requiring higher stimulation amplitudes for symptom reduction, but a larger therapeutic window. High- and low-frequency theta burst stimulation with adapted stimulation amplitude were effective in PD symptom reduction with differential effects on akinesia and tremor, depending on the theta burst stimulation mode.

Conclusions: Theta burst stimulation is a safe and effective stimulation mode with potential future application opportunities. © 2020 International Parkinson and Movement Disorder Society

Key Words: deep brain stimulation; Parkinson's disease; subthalamic nucleus; therapeutic window width; theta burst stimulation

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DBS of the STN (STN-DBS) is a clinically effective therapy in Parkinson's disease (PD).[1-4] DBS is usually applied by continuous delivery of high-frequency rectangular pulses at 130 Hz through bilateral electrodes in the STN. However, with usage of this conventional DBS mode, there remain postoperative issues particularly in the long-term follow-up of increasing numbers of operated PD patients, which require DBS reprogramming in the course of the time.[5,6] For specific troubleshooting or prevention of DBS-induced side effects in the long term, the new focus of interest has become the development of new algorithms of DBS.

The purpose of this project was to assess new DBS algorithms by using patterned stimulation techniques. In this pilot trial, we first aimed to assess efficacy and safety of theta burst stimulation (TBS) algorithm of DBS.

Materials and Methods

The study was approved by the local Ethics Committee of the Medical Council in Hamburg (reference number: PV5281). All participants gave written informed consent.

Design

The study was a single-center, randomized, double-blind, clinical short-term trial to compare the effect of unilateral conventional STN-DBS (c-DBS) versus three different unilateral patterned stimulation algorithms of STN-DBS on symptoms of the more affected, contralateral body side. We tested: (1) high-frequency TBS with an intraburst frequency of 200 Hz (HF-TBS); (2) low-frequency TBS with an intraburst frequency of 50 Hz (LF-TBS); and (3) low-frequency TBS with adapted, increased stimulation amplitude (aLF-TBS; Fig. 1).

All three patterned stimulation forms consisted of stimulation bursts of 0.1-second duration repeated at 5 Hz with an impulse width of 60 μs. Stimulation amplitude was kept constant during c-DBS, HF-TBS, and LF-TBS, but increased during aLF-TBS along the

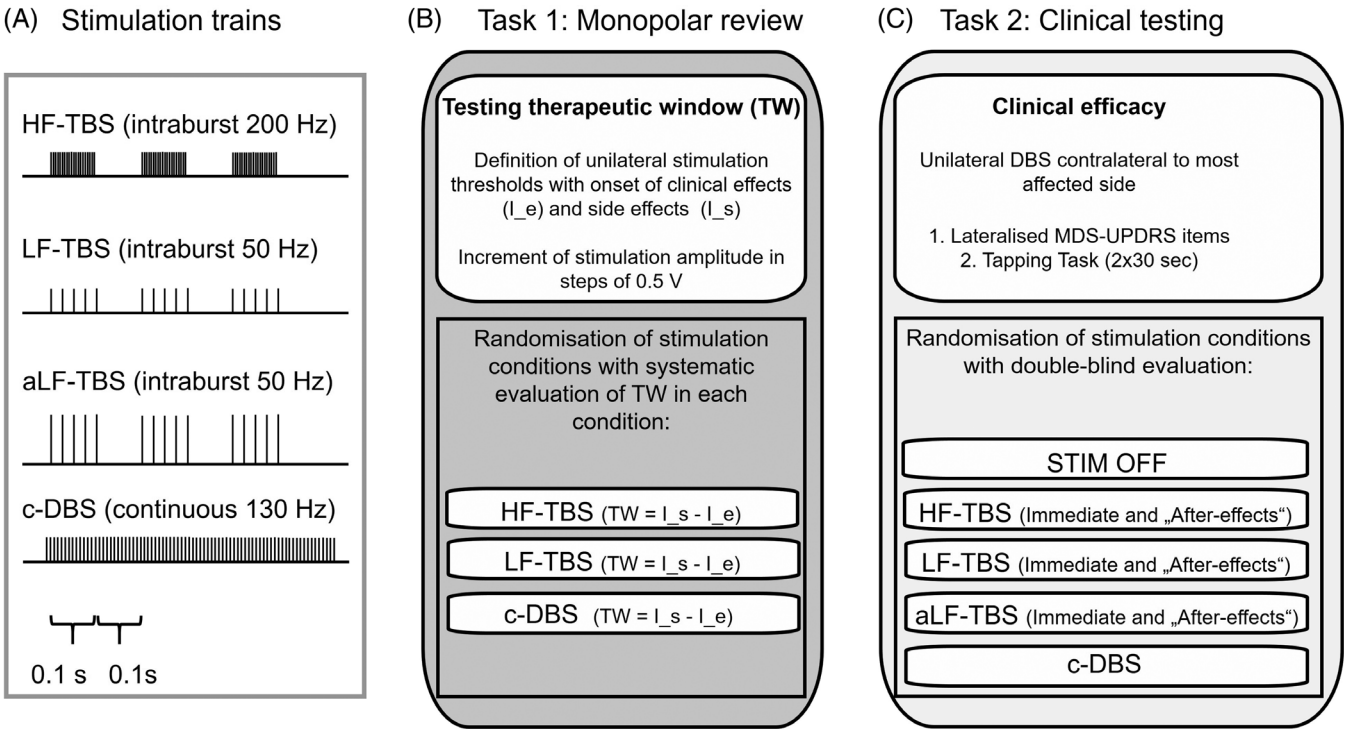

FIG. 1. Experimental setup. (A) Stimulation trains of the experimental sessions. c-DBS was applied with 130 Hz (lowest row). TBS was applied in a cycling mode with intervals of 0.1 second, switching stimulation OFF and ON. Intraburst frequency varied from 200 Hz, resulting in an overall frequency of 100 stimuli per second (HF-TBS, upper row) to 50 Hz with total numbers of 25 stimuli per second (LF-TBS and aLF-TBS, middle rows). (B) Task 1 consisted of a monopolar review to determine the therapeutic window width of each stimulation mode. (C) Task 2 included assessments of the clinical efficacy of the different stimulation modes by using the MDS-UPDRS and objective tapping task. MDS-UPDRS, International Parkinson and Movement Disorder Society–sponsored revision of the UPDRS.

TEED[7] (total energy delivered: amplitude^2 × impulse duration × frequency / impedance), resulting in comparable TEED of HF-TBS and aLF-TBS.

Because of limited programming options of the Medtronic system (Medtronic, Minneapolis, MN), we stimulated in a constant-voltage mode, which implies some limitations on reproducibility of the delivered microcoulombs at the cathode and replicability of the pulse form in the tissue attributable to capacitive reactance.

The TBS stimulation modes were applied by usage of the cyclic mode of the chronically implanted Medtronic devices, periodically switching DBS ON and OFF for 0.1 second. Stimulation artifacts were recorded by surface electromyography electrodes applied to the pacemaker. All patients were tested after overnight withdrawal of dopaminergic medication (MED OFF). Stimulation conditions were randomized in each task with an intertrial interval between stimulation conditions of 30 minutes (Fig. 1).

Participants

Seventeen patients (5 female; age, 64 ± 2 years) suffering from advanced idiopathic PD (disease duration: 13.82 ± 1.42 years; H & Y stage: 2.7 ± 0.11 in the MED-ON and STN-DBS-ON condition) participated in the study. PD patients were studied if: (1) idiopathic PD in H & Y 2 to 4 was present; (2) patients were implanted with the Medtronic Activa PC/RC pacemaker; (3) stable postoperative condition (40.64 ± 6.78 months postoperatively); and (4) unchanged dopaminergic medication in the preceding 4 weeks were present. The postoperative daily levodopa-equivalent dose was 624.12 ± 66.75 mg (45% of preoperative dosage).

Tasks

Task 1: Assessment of Therapeutic Window by Monopolar Review

Unilateral stimulation was applied at the clinically most effective electrode contact in the different stimulation modes with pulse width 60 μs. The therapeutic window was determined by gradually increasing voltage in steps of 0.5 V until 5 to 6 V. Stimulation amplitude was extracted at which the first and full clinical effect on rigidity and the first side effect occurred (Fig. 1).

Task 2: Clinical Assessment of PD Motor Symptoms

The aim of task 2 was to (1) assess the safety and tolerability of unilateral TBS in PD patients, (2) investigate the immediate effect of conventional STN-DBS and three different TBS modes with different intraburst

frequencies on clinical PD motor symptoms, and (3) assess potential short- and long-term outlasting after effects on clinical motor symptoms. Stimulation parameters in the different stimulation conditions were 2.74 ± 0.12 V, 60 μs, and 130 Hz during c-DBS; 2.74 ± 0.12 V, 60 μs, and intraburst 200 Hz during HF-TBS; 2.74 ± 0.12 V, 60 μs, and intraburst 50 Hz during LF-TBS; and 5.48 ± 0.24 V, 60 μs, and intraburst 50 Hz during aLF-TBS. Video-taped assessments of lateralized International Parkinson and Movement Disorder Society–sponsored revision of the UPDRS (MDS-UPDRS) items were performed (items 3.3–3.8, 3.15–3.18). A quantitative tapping task on a tapping board of the more affected hand was performed (2× 30 seconds) along the CAPSIT (Core Assessment Program for Surgical Interventional Therapies) protocol.[8]

Statistical Analysis

Descriptive statistics in Table 1 include mean ± standard error of mean. Repeated general linear model analysis of variance (ANOVA) with the intrasubject factor stimulation condition (STIM OFF, c-DBS, HF-TBS, LF-TBS, and aLF-TBS) was performed for the lateralized total UPDRS and the subitems rigidity, akinesia, and tremor and tapping performance. Post-hoc Wilcoxon signed-ranks tests were performed to compare effects of the different stimulation conditions (IBM SPSS Statistics version 20.0; SPSS, Inc., Chicago, IL).

Results

All stimulation modes were safe and did not induce serious adverse events. In the aLF-TBS conditions, 1 patient complained of severe akinesia, so that this stimulation mode was stopped prematurely.

Task 1: Monopolar Review and Therapeutic Window

The three stimulation modes—c-DBS, HF-TBS, and LF-TBS—differed during monopolar review (Table 1, upper rows). Although the stimulation strength with first meaningful effect on rigidity was not significantly different between the three stimulation modes, there was a tendency of lower required stimulation strength during HF-TBS. Full resolution of rigidity (80–100%) was not achieved in 5 PD patients during LF-TBS, but in all patients during HF-TBS and c-DBS. ANOVA testing revealed significant differences for the required stimulation amplitude for full rigidity resolution ($F = 9.42$; $P = 0.002$), with significantly higher stimulation strength required during LF-TBS compared to c-DBS or HF-TBS. Side-effect thresholds differed significantly between stimulation conditions (ANOVA, $F = 8.97$; $P = 0.003$) with a disproportionately highest threshold during LF-TBS, resulting in an increased therapeutic window width with LF-TBS compared to the other stimulation modes (ANOVA, $F = 5.13$; $P = 0.021$).

TABLE 1. Results of the monopolar review in task 1 (upper rows) and effects of the different stimulation modes on clinical symptomatology in task 2 (lower rows)

	STIM OFF	c-DBS	LF-TBS	aLF-TBS	HF-TBS	ANOVA
Task 1: monopolar review/stimulation amplitude (V)						
Onset of rigidity reduction	Not applicable	0.93 ± 0.09	1.00 ± 0.13	Not applicable	0.76 ± 0.06	n.s.
Full rigidity resolution	Not applicable	2.74 ± 0.35	4.18 ± 0.53[a] P = 0.013	Not applicable	2.47 ± 0.27	F = 9.42 P = 0.002
Onset side effects	Not applicable	4.93 ± 0.30	5.74 ± 0.24[a] P = 0.003	Not applicable	4.78 ± 0.37	F = 8.97 P = 0.003
Therapeutic window	Not applicable	4.00 ± 0.30	4.74 ± 0.27[a] P = 0.008	Not applicable	4.01 ± 0.38	F = 5.13 P = 0.021
Task 2: clinical effects/MDS-UPDRS						
Total lateralized score	16.35 ± 1.31	10.47 ± 1.08	14.47 ± 1.38[a] P < 0.001	12.29 ± 1.15[a] P = 0.015	12.53 ± 1.17[a] P = 0.007	F = 8.95 P < 0.001
Akinesia	8.25 ± 1.08	5.25 ± 0.69	7.81 ± 0.90[a] P = 0.001	6.08 ± 0.73[a] P = 0.02	6.81 ± 0.82[a] P = 0.009	F = 5.35 P = 0.008
Tremor	4.06 ± 0.78	2.65 ± 0.65	3.82 ± 0.73[a] P = 0.028	3.21 ± 0.74	2.76 ± 0.63	F = 3.25 P = 0.05
Rigidity	3.94 ± 0.33	2.53 ± 0.33	2.94 ± 0.29	3.14 ± 0.27	2.97 ± 0.26	F = 7.19 P < 0.001

Task 1: Stimulation strengths were recorded at which the first meaningful effect on rigidity, the full effect on rigidity (80–100%), and first observable side effects were observed. The therapeutic window width was calculated from side-effect (l_s) and effect thresholds (l_e). Task 2: Total lateralized MDS-UPDRS-III, tremor items rigidity items, and akinesia items of lateralized MDS-UPDRS-III were recorded. Significant *P* values of post-hoc Wilcoxon tests comparing different TBS conditions with c-DBS are shown. Of note, clinical scores were significantly improved in post-hoc *t* tests during c-DBS, aLF-TBS, and HF-TBS compared to STIM OFF; those *P* values are not shown.
[a]Compared to c-DBS.
n.s., not significant.

Task 2: Clinical Assessment of PD Motor Symptoms

Unilateral application of the four stimulation algorithms—c-DBS, HF-TBS, LF-TBS, and aLF-TBS—revealed differential effects on contralateral, clinical PD symptoms (Table 1, lower rows).

The total lateralized MDS-UPDRS score was improved by all stimulation conditions in STIM ON compared to STIM OFF (ANOVA, $F = 8.95$; $P < 0.001$) apart from LF-TBS without amplitude adjustment. In a second step, we differentiated the motor symptoms into the three domains rigidity, tremor, and akinesia. ANOVA testing revealed an overall effect of all stimulation modes for all three domains (rigidity, $F = 7.19$; $P < 0.001$; tremor, $F = 3.25$; $P = 0.05$; akinesia, $F = 5.35$; $P = 0.008$). However, the TBS stimulation forms varied in their efficacy in regard of the different PD symptoms. Rigidity was equally improved by all stimulation conditions with no significant differences between c-DBS and all three TBS stimulation forms. Akinesia was only significantly improved by c-DBS and aLF-TBS compared to STIM OFF, but not by HF-TBS or LF-TBS. On the contrary, tremor was equally improved by c-DBS and HF-TBS compared to STIM OFF, but not by LF-TBS or aLF-TBS. Therefore, akinesia and tremor seemed to be differentially modulated by TBS depending on the intraburst frequency of the respective TBS mode.

Quantification of akinesia by a standardized tapping task confirmed the pattern of the observed stimulation effects. ANOVA revealed a significant effect of stimulation condition on tapping scores ($F = 4.4$; $P = 0.009$) with a more pronounced stimulation effect with HF-TBS and c-DBS.

We could not observe stimulation outlasting after effects of HF-TBS, LF-TBS, and aLF-TBS. After application of the specific, new patterned stimulation mode for 20 to 30 minutes, TBS was switched off and motor symptoms were reevaluated 30 minutes later in the experimental OFF state. There was no significant difference between the initial OFF condition and the after effect OFF condition in terms of UPDRS and tapping scores.

Discussion

The purpose of this project was to assess new patterned DBS algorithms with the aim of maximizing clinical stimulation effects in PD by enlarging therapeutic window width.

There are some limitations of the study. First, comparison of TBS modes is difficult given the complexity of the neurophysiological mechanisms. Operationally, TEED was used in an attempt to facilitate comparisons between stimulation patterns, recognizing the difficulty of drawing firm inferences from comparisons.

Second, we applied TBS only unilaterally. The next planned step is to assess the safety profile of bilateral TBS stimulation and evaluate also axial symptoms. The third limitation is the relatively short time of application of the different TBS modes with ~20 to 30 minutes to ensure feasibility of the study within 1 day. However, this short stimulation duration may be at the cost of the observed lack of neuroplastic after effects compared to other studies assessing stimulation-outlasting effects in MPTP-treated nonhuman primates[9] and PD patients.[10] Last, the observed "acute effects" of TBS need to be replicated in long-term observations during chronic stimulation and under medication to ensure the feasibility of TBS as a suitable stimulation mode in the clinical routine.

Although the mechanisms of action of DBS are still under discussion, there was recent evidence of frequency-dependent inhibitory synaptic plasticity as putative mechanism of DBS.[11] In respect of the necessity of long-term treatment of DBS patients, it would be a desirable goal to induce "beneficial plasticity" in the STN. Principles of the understanding and mechanisms of induction of neuronal synaptic plasticity can be drawn from studies using transcranial magnetic stimulation (TMS) at the motor cortex in humans.[12,13] TBS by TMS has been demonstrated to be highly effective in the induction of stimulation outlasting cortical modulation.[14,15] Although there are limitations on the transfer of a cortical stimulation pattern to a subcortical DBS lead because of specific neuroanatomical and functional differences, there are promising TMS features that could account for STN-DBS. TBS-TMS is supposed to modulate expression of brain-derived neurotrophic factor or cFOS, increase GABAergic activity,[15] and modulate N-methyl-D-aspartate receptor activity[14]; however, the transfer of these mechanisms to STN-DBS remains hypothetical at this time.

Findings from a previous study indicate that DBS pattern variations might result in similar clinical results within interburst time ranges of 0.1 to 0.5 seconds.[16] LF-TBS with low intraburst frequencies might have dropped outside the efficacious window, resulting in higher required dosages.

In summary, this short-term, randomized, double-blind, clinical trial represents the first step in the development of new, patterned DBS stimulation forms by demonstrating safety, efficiency, and partial enhancement of therapeutic window width depending on TBS intraburst frequency.

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