BRIEF REPORT

Theta-Gamma Subthalamic Stimulation for Verbal Fluency in Parkinson's Disease: A Randomized, Crossover Trial

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ABSTRACT: Background: High-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) improves Parkinson's disease (PD) motor symptoms but may deteriorate verbal fluency (VF). Theta stimulation showed potential cognitive benefits associated with motor worsening.

Objectives: This randomized, double-blind, crossover study evaluated the efficacy and safety of combined theta-gamma frequency stimulation on VF in PD patients with STN-DBS.

Methods: Patients were randomized 1:1 for standard or theta-gamma stimulation. VF, motor, and non-motor symptoms were assessed at baseline, 1 h, and 1 month after each period. Data were analyzed using a linear mixed-effects model.

Results: Twelve patients completed the study. Non-episodic ($P = 0.038$) and episodic VF ($P = 0.030$) improved after 1 month of theta-gamma stimulation, while phonemic and switching fluency were unchanged. Motor and non-motor outcomes were unaffected by the stimulation, with mild adverse events.

Conclusion: Combined theta-gamma stimulation may enhance VF in PD patients with STN-DBS without worsening motor symptoms or safety concerns. © 2025 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; deep brain stimulation; theta-gamma frequency; verbal fluency

Background

High-frequency (130–180 Hz) deep brain stimulation (DBS) targeting the subthalamic nucleus (STN) is an effective and relatively safe therapy for Parkinson's disease (PD) patients experiencing levodopa-related motor complications despite optimal medical therapy.[1-4] However, evidence suggests gradual cognitive decline after STN-DBS, particularly in verbal fluency (VF), possibly related to the surgery or the stimulation itself.[5]

VF, considered both an executive function and a language task, primarily involves the frontal and temporal cortical regions, including the hippocampus, differently engaged based on language-specific or domain-general VF tasks.[6-10]

Theta rhythms (4–10 Hz) have been associated with cognitive tasks, especially of memory processing.[11,12] STN theta oscillations have also been linked to tasks involving VF, working memory and conflict situations.[4,13] Pilot studies indicate that theta stimulation may improve

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VF, particularly episodic retrieval, but only in acute settings.[14-16] However, a deterioration of motor performance was observed when stimulating at 10 Hz compared with no stimulation.[17]

New DBS systems allow for multiple, independent current sources and/or frequency settings within a single lead, enabling the application of different stimulation frequencies simultaneously. This 2-month, randomized, double-blind, crossover trial aimed to assess the efficacy and safety of combining standard high-frequency (gamma) and very low-frequency (theta) stimulation for VF in PD, in both acute and chronic settings.

Methods

Participants

PD patients implanted with bilateral STN-DBS Vercise Cartesia™ Directional Leads (Boston Scientific, Valencia, CA, USA) for at least 6 months were recruited from the Movement Disorder Center at AOU Città della Salute e della Scienza, Turin, Italy. Additional inclusion/exclusion criteria are detailed in the Supplementary Data. The study, conducted from November 2023 to September 2024, was approved by the Institutional Review Board (Protocol No. 0112357), registered on clinicaltrials.gov (NCT06509048), and written according to the CONSORT (Consolidated Standards of Reporting Trails) extension to randomized crossover trials.[18]

Study Design

This randomized, double-blind, crossover study involved two periods of 1 month (Fig. S1). Patients were randomly assigned 1:1 to start with either standard or theta-gamma STN stimulation, with randomization and parameter settings managed by an unblinded investigator (M.Z.), while two blinded investigators conducted clinical (G.I.) and neuropsychological (E.M.) assessments.

Before randomization, the unblinded investigator evaluated the tolerance for adding theta frequency (6 Hz) stimulation at the most ventral contact (targeting the ventromedial STN zone, confirmed by volume of tissue activation [VTA] analysis) to the standard gamma stimulation (100–180 Hz).[15,19] Theta was set at a pulse width of 60 μs and an intensity between 2 and 3 mA, ensuring no worsening of rigidity or immediate side effects. Details are available in the Supplementary Data.

Outcome Measures

Patients were evaluated during daily-ON to avoid potential cognitive worsening associated with wearing OFF,[20] at baseline, and after each 1-month randomization period (Fig. S2).

The primary endpoint was the mean difference in VF scores between the two stimulation settings. VF tasks were based on previous similar studies,[14,15] including phonemic fluency (generating words starting with three letters), category fluency (naming items within a specific category), and switching between two categories (switching fluency). Category fluency was further divided into episodic categories (items with high autobiographical or spatial context such as 'names of your friends') and non-episodic categories (items with low autobiographical or spatial context such as 'units of measurement'). To minimize retest bias, different versions were administered at each session.

Secondary endpoints included adverse events (AEs), motor and non-motor symptoms and their complications assessed by the Movement Disorder Society-sponsored revision of the Unified Parkinson Disease Rating Scale (MDS-UPDRS) Parts I–IV, the Beck Depression Inventory-Short Form (BDI-SF), the Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS), and the Patient Global Impression of Change (PGI-C). MDS-UPDRS-III and VF assessments were also collected 1 h after the stimulation change.

Statistical Analysis

Based on a previous pilot study with similar design and outcome measures,[14] reporting a significant effect size ($f = 0.54$) for non-episodic category VF scores favoring theta frequency stimulation, a sample size of 9 was calculated for 80% power at a 5% significance level for the crossover design using G*power software.[21] Analyses included the intention-to-treat population (patients completing at least one post-stimulation evaluation).

A linear mixed-effects regression model was used to compare scores, with fixed effects for visit time, stimulation setting, and their interaction. In the absence of significant interactions, final models excluded the interaction term in order to evaluate the main effect of stimulation setting across time points. The model incorporated random effects for individual patients and baseline scores as covariates to control for initial differences. Bonferroni's correction was applied for post-hoc pairwise comparisons. Data analysis was performed with SPSS Version 29 (IBM Corp., Armonk, NY, USA), with two-tailed P-values and $\alpha = 0.05$.

Results

Fourteen PD patients were recruited and randomized. Table 1 reports baseline demographic and stimulation data. Two patients (one in each group) experienced AEs including worsening of anxiety and motor fluctuations within the first week leading to withdrawal. Both were included in the acute effect analysis but not in the chronic effect analysis, which included 12 patients (10 men, 2 women), with a mean age of 56.7 ± 8.0 years and average PD duration of 14.1 ± 3.7 years.

TABLE 1 *Demographic and stimulation characteristics of randomized patients at baseline*

Patient ID	Age (years)	Sex	Education (years)	Months from surgery	Electrode contacts		Intensity (mA)		Pulse width (μs)		Frequency (Hz)	
					R	L	R	L	R	L	R	L
001	47	M	13	36	5,6,7	5,6,7	2.4	3	60	60	130	130
002	52	M	13	12	6,7	7	2.8	1.6	60	60	180	180
003	64	F	11	50	5,6,7	5,6,7	2.9	2.4	60	60	130	130
004	71	M	5	55	5 (25%) 7 (75%)	2,3,4	4.5	3.7	60	60	100	100
005	43	M	16	51	5 (26%) 6 (3%) 7 (71%)	5 (23%) 6 (23%) 7 (54%)	2.6	2.8	60	60	180	180
006	64	M	13	50	2,3,4	2,3	4.2	4.2	60	60	130	130
007	60	M	13	18	5,6,7	5,6,7	2.8	2.9	60	60	130	130
008	55	M	8	30	5,6,7	5,6,7	1.6	2.7	60	60	130	130
009	64	M	17	27	Bipolar 5 (45%) 6 (10%) 7 (45%) 8+	Bipolar (2,3,4)− (5,6,7)+	3.4	2.9	60	60	130	130
010	58	M	13	19	6,7	6,7	2	3.9	60	60	130	130
011	62	M	8	33	2,3,4	2,3,4	2.1	2.8	60	60	130	130
012	58	F	12	60	2 (19%) 3 (40%) 4 (41%)	5 (5%) 6 (47%) 7 (48%)	3.8	3	40	50	180	180
013	51	M	13	52	5,6	5,6,7	3.5	2.7	60	60	130	130
014	54	F	8	42	5 (14%) 6 (13%) 7 (13%) 8 (60%)	5 (14%) 6 (16%) 7 (16%) 8 (54%)	2.8	2.8	60	60	180	180

Note: Electrode contacts bilaterally ranged from the omnidirectional contact 1 (deep) to contact 8 (superficial), with tri-segmented contacts at second (2–3-4) and third (5–6-7) levels. If no percentage is reported, stimulation was equally distributed among contacts. If not specified, patients were on monopolar stimulation (with IPG as anode).
Abbreviations: R, right; L, left; M, male; F, female; IPG, implantable pulse generator.

Effect of Theta-Gamma Frequency Stimulation on VF

For the acute effect analysis, there were no significant effects of the stimulation setting on any VF task, including phonemic fluency ($P = 0.260$), episodic category ($P = 0.863$) non-episodic category ($P = 0.141$), and switching ($P = 0.341$).

For the chronic effect analysis, since there was no significant interaction between stimulation setting and visit time for any VF task (all $P > 0.2$), we focused on the main effect of stimulation setting. Theta-gamma stimulation significantly improved non-episodic category VF scores ($F(1,20) = 4.937$, $P = 0.038$) over standard stimulation (corrected mean ± standard error: 7.42 ± 0.64 vs. 5.42 ± 0.64).

Eight patients performed better with theta-gamma stimulation, three with standard stimulation, and one showed no difference.

For the episodic category VF, the theta-gamma stimulation setting also led to higher scores ($F(1,20) = 5.466$, $P = 0.030$) (corrected mean ± standard error: 12.25 ± 0.83 vs. 9.5 ± 0.83), with 10 patients showing improvement, while two performed better with standard stimulation.

In contrast, no significant effect of stimulation setting was observed for phonemic fluency ($F(1,20) = 1.681$, $P = 0.210$) and switching ($F(1,20) = 1.324$, $P = 0.272$).

Table S1 and Fig. S3 report individualized raw scores.

Secondary Outcomes: Safety, Motor, and Non-Motor Assessment

Excluding the two dropouts, a total of 19 mild AEs occurred. All AEs resolved spontaneously within a few days and were similarly distributed between the two groups (details in Table S2).

For the acute effect analysis, there was no difference in the MDS-UPDRS-III score between the two stimulation settings ($F(1,21) = 0.040$, $P = 0.843$).

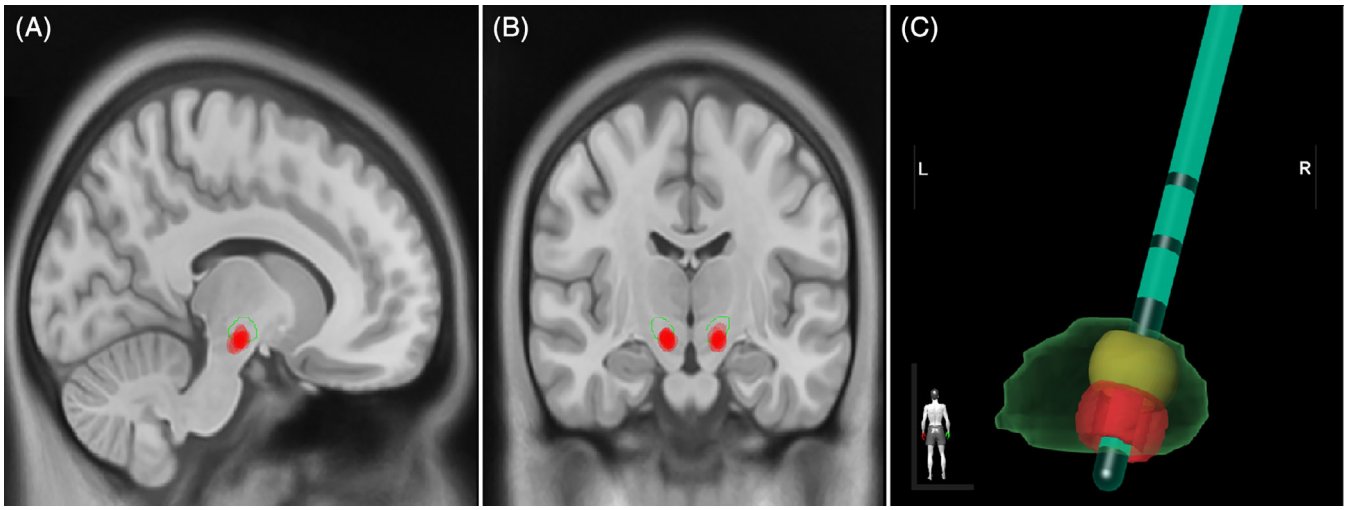

FIG. 1. Volume of tissue activated (VTA) with the stimulation of the most ventral contact and tridimensional representation of the theta-gamma stimulation of the subthalamic nucleus. Sum maps representing the number of overlapping VTAs (red circles) when stimulating the most ventral electrode contact are shown overlaid on sagittal (A) and coronal (B) slices of a T1 standard magnetic resonance imaging brain template. The STN are represented with green outlines. (C) A tridimensional sample of the VTA obtained with simultaneous stimulation of the right STN in two contacts of the same lead (1- with red sphere, and 567- with yellow sphere) from one patient in our cohort, obtained through the software Stimview XT (Boston Scientific, Valencia, CA, USA). L, left; R, right. [Color figure can be viewed at wileyonlinelibrary.com]

Similarly, for the chronic effect analysis, there was no interaction between stimulation setting and visit time for the MDS-UPDRS-III score ($P = 0.675$) and no main effect of the stimulation settings ($F(1,20) = 0.196$, $P = 0.663$). Furthermore, both stimulation settings did not lead to any changes in MDS-UPDRS-I ($P = 0.639$), UPDRS-II ($P = 0.956$), and UPDRS-IV ($P = 0.355$). No significant changes were observed for other subscales, as reported in Supplementary Data and Table S2.

The VTA sum map, available for 11 patients, confirmed the ventromedial STN target of the most ventral contact (Fig. 1).

Discussion

This study demonstrated that combined theta-gamma frequency STN stimulation can improve VF in PD patients with STN-DBS safely and without worsening cardinal motor symptoms. The lack of motor deterioration or significant AEs, both immediately and after 1 month, suggests that this approach may be suitable for long-term use. Improvements were observed in both episodic and non-episodic VF categories, with no negative impacts on mood or impulsivity. The two dropouts were evenly distributed between the groups and attributed their withdrawal to emotional factors, while other AEs were mild and self-limiting.

We observed VF improvement after 1 month of theta-gamma stimulation, but not immediately, contrasting with previous trials.[14-16] As no significant interaction was found between stimulation setting and time in any VF outcome, we focused on the main effect of stimulation in our statistical models, in line with standard practice in crossover designs. Moreover, two previous studies found improvements only in episodic VF when comparing theta stimulation to OFF-stimulation or gamma alone.[14,15] This delay and wider effect on VF suggest that sustained theta-gamma stimulation may promote neuroplastic changes requiring additional time to contribute to cognitive enhancement.[22-24] Regarding the chosen experimental frequency, while two of these studies explored the effect of alpha-theta stimulation (10 Hz) on verbal fluency,[14,16] Lee et al.,[15] during similar VF tasks, found the peak left theta frequency in the STN at around 6 Hz, and increased STN-frontal coherence in the 6–7 Hz range was found during a different letter fluency task in a second study by Wojtecki et al.[19] Technical constraints also influenced our choice, as manufacturer-imposed safety limits prevented simultaneous stimulation at certain frequencies.

The VF network is complex, with episodic memory primarily supported by hippocampal structures and semantic memory by frontal and lateral temporal lobes, which may overlap in the retrieval processes required for VF tasks.[8-10] Functional MRI studies indicate shared activation sites across these networks, potentially explaining the simultaneous improvements in both VF categories.[6,7] Moreover, recent research suggests that theta stimulation at 6 Hz enhances higher-order cognitive functions, including working memory, by increasing the connectivity between the STN and the right middle frontal gyrus, aligning with our findings, as VF partly depends on working memory processes.[25]

Our findings offer insights into STN functional topography. Stimulation of the ventromedial STN, linked with associative and limbic functions, appeared to improve VF, which differed from previous studies

that targeted the dorsal STN and proposed a functional gradient within the STN, rather than activation of distinct subregions.[14,15] We support this hypothesis, though we targeted the ventromedial STN to maintain gamma frequency stimulation at the dorsolateral STN, a 'sweet spot' for motor benefits.[26,27]

While our findings are promising, several limitations must be acknowledged. The small sample size limits generalizability, and the relatively short follow-up may not fully capture the chronic effects of theta-gamma stimulation. Although significant, VF improvements may not translate into meaningful clinical benefits, which are difficult to quantify objectively.[28] Additionally, without an OFF-stimulation condition, it is challenging to determine whether the observed improvements were derived directly from theta-gamma stimulation or the mitigation of any potential negative effects of gamma stimulation alone.

Future studies should investigate the long-term effects of theta-gamma stimulation on other cognitive domains, such as working memory. Targeted left ventral STN stimulation could provide insights into lateralized cognitive processing, helping to refine stimulation protocols. Tailoring stimulation based on each patient's peak theta power frequency during VF tasks could enhance efficacy and enable more personalized treatment approaches. Exploring combined frequency stimulation in PD patients developing mild cognitive impairment or VF impairments after STN-DBS, or applying it earlier in DBS treatment, could further optimize long-term outcomes.

In conclusion, this study provides preliminary evidence that combined theta-gamma frequency stimulation may improve VF in PD patients treated with STN-DBS safely and without worsening motor symptoms. This approach could potentially be integrated into existing stimulation paradigms, but further research is needed to validate these results and explore their broader clinical implications.

Author Roles: (1) Research Project: A. Design, B. Organization, C. Clinical Data Collection, D. VTA Analysis; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique, C. Final Manuscript Approval.
G.I.: 1C, 2A, 2B, 3A, 3C.
E.M.: 1C, 3B, 3C.
C.L.: 1C, 3B, 3C.
F.D.: 1C, 3B, 3C.
F.D'A.: 1C, 3B, 3C.
C.C.: 1D, 3B, 3C.
C.A.A.: 2C, 3B, 3C.
A.R.: 2B, 3B, 3C.
M.G.R.: 3B, 3C.
M.B.: 3B, 3C.
L.L.: 3B, 3C.
M.Z.: 1A, 1B, 2A, 2C, 3A, 3C.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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.