



Cognitive effects of theta frequency bilateral subthalamic nucleus stimulation in Parkinson's disease: A pilot study

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ABSTRACT

Background: There is significant evidence for cognitive decline following deep brain stimulation (DBS). Current stimulation paradigms utilize gamma frequency stimulation for optimal motor benefits; however, little has been done to optimize stimulation parameters for cognition. Recent evidence implicates subthalamic nucleus (STN) theta oscillations in executive function, and theta oscillations are well-known to relate to episodic memory, suggesting that theta frequency stimulation could potentially improve cognition in Parkinson's disease (PD).

Objective: To evaluate the acute effects of theta frequency bilateral STN stimulation on executive function in PD versus gamma frequency and off, as well as investigate the differential effects on episodic versus nonepisodic verbal fluency.

Methods: Twelve patients (all males, mean age 60.8) with bilateral STN DBS for PD underwent a double-blinded, randomized cognitive testing during stimulation at (1) 130–135 Hz (gamma), (2) 10 Hz (theta) and (3) off. Executive functions and processing speed were evaluated using verbal fluency tasks (letter, episodic category, nonepisodic category, and category switching), color-word interference task, and random number generation task. Performance at each stimulation frequency was compared within subjects.

Results: Theta frequency significantly improved episodic category fluency compared to gamma, but not compared to off. There were no significant differences between stimulation frequencies in other tests.

Conclusion: In this pilot trial, our results corroborate the role of theta oscillations in episodic retrieval, although it is unclear whether this reflects direct modulation of the medial temporal lobe and whether similar effects can be found with more canonical memory paradigms. Further work is necessary to corroborate our findings and investigate the possibility of interleaving theta and gamma frequency stimulation for concomitant motor and cognitive effects.

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Introduction

Parkinson's disease (PD) is a movement disorder characterized by bradykinesia, resting tremor, and rigidity [1]. However, the prevalence and severity of nonmotor effects of PD, which may precede motor symptoms, has been increasingly recognized [1–5]. In particular, PD disease progression has been associated with

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cognitive decline in a number of domains including executive function, processing speed, language, episodic memory, and visuospatial processing [2–6]. While conventional pharmacological and surgical treatments of PD are effective in improving motor symptoms of PD, they do not improve cognitive deficits and may even have deleterious effects on cognition [7–11].

Chronic high frequency deep brain stimulation (DBS) in the subthalamic nucleus (STN) and internal segment of the globus pallidus (GPi) through implanted electrodes has demonstrated efficacy for improving motor symptoms of PD, as well as reducing levodopa-induced dyskinesias [12]. However, an abundance of data has demonstrated long-term declines in cognitive performance in PD patients with DBS compared to those without DBS, notably in executive functions including verbal fluency [8–11,13]. This has been shown particularly for STN DBS, with worse cognitive outcomes compared to GPi DBS [13–15]. Conversely, a limited number of studies have investigated the acute effects of on versus off stimulation, showing improvements or no change in color-word interference (Stroop) and verbal fluency, and worsening of random number generation [16–21]. These tasks involve multiple facets of executive function, including working memory, response inhibition, monitoring, and task switching [22–24]. Similarly, these processes implicate theta oscillations and are impaired in PD patients, raising the possibility of improving these processes through theta frequency stimulation [25–30]. However, results of these studies are mixed and have not been consistently replicated.

Current stimulation parameters are optimized for motor benefit, with frequencies in the high gamma (100–180 Hz) range. On the other hand, increased theta rhythms (5–12 Hz) have been implicated in a range of cognitive functions, including spatial and episodic learning and memory [31–34]. The role of hippocampal theta oscillations have been well established in spatial and episodic memory encoding and retrieval, hence termed hippocampal-dependent [34–38]. More recently, STN theta oscillations have been implicated in executive function, including verbal fluency, working memory, response inhibition and sensorimotor conflict [21,28,29,39–43]. Furthermore, there is evidence that theta frequency stimulation may improve verbal fluency and color-word interference (Stroop) compared to no stimulation [21,39]. Such findings have implications for optimizing cognitive outcomes following DBS for PD in clinical practice.

While verbal fluency has classically been considered an executive function and language task involving frontal and lateral temporal cortical regions, recent work has identified involvement of the hippocampus and related medial temporal structures in category verbal fluency, particularly when cues draws on retrieval of autobiographical or spatial content [44–48]. These findings may be related to the role of hippocampal theta oscillations in episodic memory processes and raise the possibility of enhancing these processes through theta frequency DBS.

In our study, we aimed to evaluate the acute effects of bilateral theta frequency STN stimulation on verbal fluency and other executive functions in PD compared to that of gamma frequency stimulation and no stimulation. We hypothesized that (1) acute theta frequency stimulation would improve executive functions, including verbal fluency, color-word interference, and random number generation, compared to gamma frequency and off

stimulation; (2) theta frequency stimulation would differentially improve episodic category verbal fluency compared to nonepisodic category or letter fluency; and (3) gamma frequency STN stimulation would improve executive function compared to off stimulation in patients with PD.

Materials and methods

Participants

This study was a prospective double-blinded randomized crossover pilot trial performed at Keck Hospital of the University of Southern California. It was conducted with study approval from the Institutional Review Board (IRB) in accordance with the Health Insurance Portability and Accountability Act and registered on clinicaltrials.gov (NCT04383665). Informed consent was obtained for all patients according to the Declaration of Helsinki.

Twelve adult patients were recruited who had previously been implanted with bilateral STN DBS for Parkinson's disease and had their DBS stimulation parameters optimized for motor benefit (gamma frequency). Patients were included if they were >18 years old, had been optimized on DBS therapy, were on stable medication regimen for >3 months, able to provide informed consent, fluent in English, able to complete cognitive testing, and able to tolerate DBS turned off. Patients were excluded if they had a history of dementia, seizures, major substance abuse, a baseline DBS voltage of <1.5 V, or were unable to tolerate their DBS system off due to motor symptoms.

Stimulation parameters

Three stimulation paradigms were utilized: (a) off (no stimulation), (b) theta (10 Hz) and (c) gamma (patients' baseline settings of 130–135 Hz). First, patients underwent cognitive testing at their baseline gamma frequency for comparison with preoperative scores. Testing was then repeated double-blind at (a) off, (b) theta and (c) gamma frequency in a block randomized order using a sequentially ordered key. Randomization of stimulation frequency order was counterbalanced across all six possible order combinations to control for stimulation order. An unblinded investigator (CM) independent from cognitive testing was responsible for the stimulation frequency parameters and had exclusive access to the frequency order key, ensuring double blinding. Electrode selection, voltage and pulse width were not modified. A 5-min delay between frequency changes and testing was held for acclimatization, based on the results of previous data and work by the investigators [49–51]. Patients took their PD medications during their scheduled regimen throughout the session. Stimulation parameters were returned to baseline at the end of the session. A timeline of the testing session is outlined in Fig. 1.

Cognitive testing

Verbal fluency was evaluated by instructing patients to name as many words beginning with a specific letter (letter fluency), in a specific category (category fluency), and switching between two categories (switching) as they could in 1 min. Probe categories were taken from the updated and expanded version of the Battig and

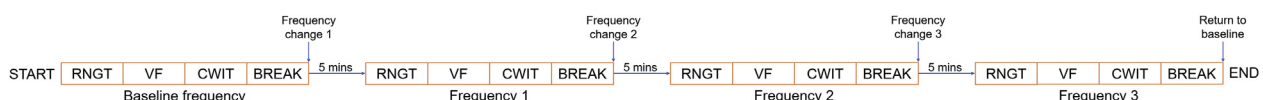


Fig. 1. Timeline of the testing session.

Table 1

Patient demographics, clinical information, and deep brain stimulation settings.

Patient	Age	Sex	Ethnicity	Native language ^a	Education	Handedness	Months since surgery	Preoperative UPDRS		Postoperative UPDRS ^b		Electrode contacts ^c		Voltage (V)		Pulse width (μs)		Frequency (Hz)	
								Off	On	Off	On	R	L	R	L	R	L	R	L
1	61	M	Asian	Mandarin Chinese	College	R	6.4	36	14	23.5	7.5	8	2	2.1	2	60	60	135	135
2	62	M	Caucasian	English	Graduate degree	L	17	38	13	27	15	10	1	1.8	2.4	60	70	135	135
3	48	M	Hispanic	Spanish	11th grade	R	18					11	3,2	2.3	2.5	70	60	130	130
4	70	M	Caucasian	English	Graduate degree	R	19	16	9.5	12.5	3.5	9	0	1.7	1.9	70	70	135	135
5	71	M	Caucasian	English	College	R	6.2	14	3.5	12	2	8	2	1.7	1.6	70	70	135	135
6	54	M	Caucasian	English	College	R	11	32	3	21.5	8.5	11	3	2.2	2.5	60	60	135	135
7	63	M	Hispanic	Spanish	College	R	12	42	24	28	13	10	3	2	2.2	60	60	130	130
8	62	M	Caucasian	English	College	R	42	26.5	12	35.5	5.5	8,9	3	1.8	1.8	60	60	120	120
9	62	M	Caucasian	English	College	R	32	34	12	14	3.5	8	2	1.5	2.4	70	70	135	135
10	45	M	Caucasian	English	Graduate degree	R	52	28.5	9	40.5	12	9,8	0,1	2.6	3.2	120	105	125	125
11	73	M	Caucasian	English	Graduate degree	R	8.2	35	20	26	10	9	1	2.2	2.6	70	70	130	130
12	58	M	Caucasian	English	Graduate degree	R	28	36	5	39.5	20	10	3	2.5	2.5	60	70	130	130
Mean ± SD ^d							60.8 ± 8.2	21 ± 14	30.7 ± 8.86	11.4 ± 6.53	25.5 ± 10.2	9.14 ± 5.40		2.03 ± 0.33	2.3 ± 0.41	69.2 ± 16.1	68.8 ± 11.9	131 ± 5	131 ± 5

^a all patients were fluent in English.^b UPDRS: Unified Parkinson's Disease Rating Scale^c electrode contacts ranged from 11 (superficial) to 8 (deep) on the right, and from 3 (superficial) to 0 (deep) on the left^d SD: standard deviation

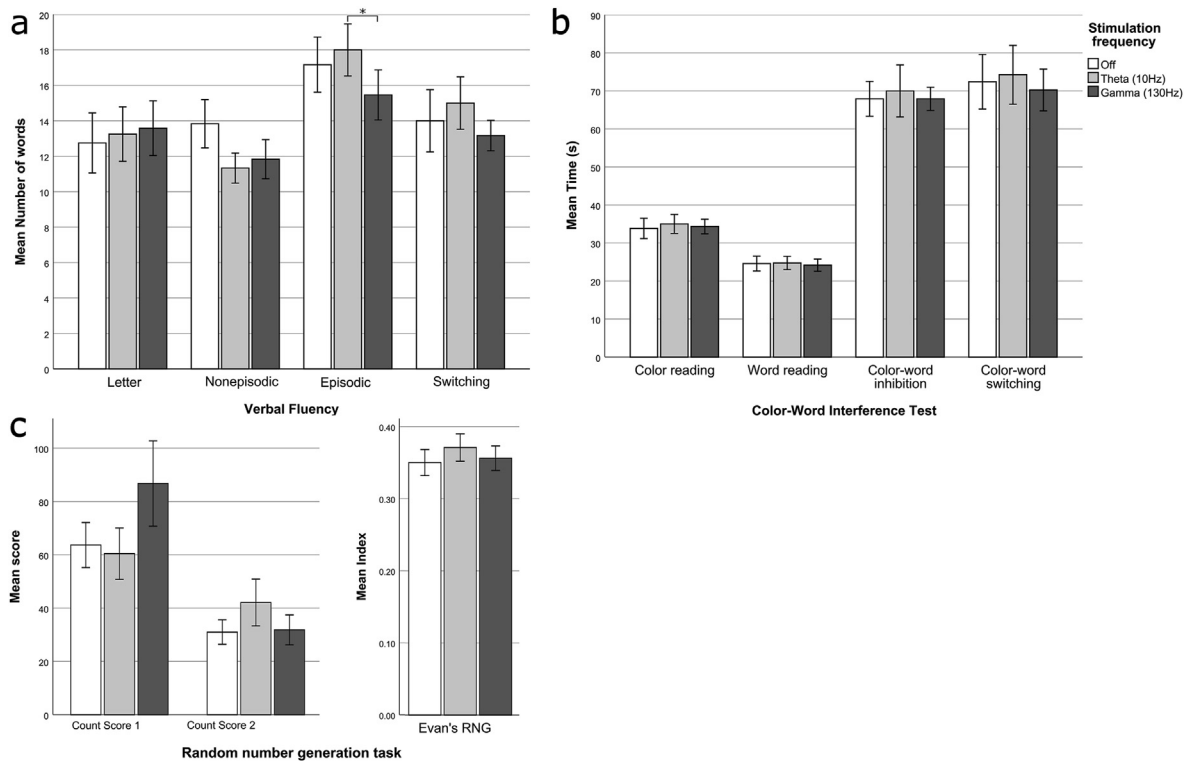


Fig. 2. Neuropsychological scores by stimulation frequency for (a) verbal fluency, (b) color-word interference task, and (c) random number generation. Error bars represent one standard error of the mean. * denotes $p < 0.05$.

Montague (1969) norms [52,53] and divided into episodic and nonepisodic categories based on and validated by previous work (see discussion) [45–48]. Episodic categories contained high autobiographical or spatial context (for example, ‘names of your friends’, ‘kitchen utensils’) and nonepisodic categories contained less autobiographical or spatial context (for example, ‘modes of transportation’) [45–48]. Switching categories were nonepisodic. Probes by category are listed in Supplementary information 1. Patients completed all of the same tests in the same order, but probe types were varied between rounds and stimulation order was counterbalanced to control for probe difficulty. Total number of words verbalized in each 1-min category were counted, excluding repeated or incorrect words.

Processing speed, inhibition and switching components of executive function were evaluated using the Delis-Kaplan Executive Function System Color Word Interference Test (Pearson), consisting of color naming, word reading, color-word interference, and color-word interference switching subsets [54]. Time to completion in seconds was recorded.

Working memory, inhibition, monitoring, and switching components of executive function were evaluated using the random number generation task, where patients were instructed to verbalize a sequence of 100 random numbers between 1 and 10 in synchrony with a 1 Hz metronome [23,24]. The concept of randomness was explained to subjects as analogous to picking a piece of paper numbered 1–10 out of a hat and then replacing it [22]. Responses were analyzed for measures of randomness including sequential response bias (RNG index, described by Evans, 1978) and inhibition of counting in steps of 1 or 2 (count scores 1 and 2, described by Spatt and Goldenberg, 1993) using RGCALC [55–57].

Patients first underwent one round of each test at their baseline settings before repeating all tests in the same order for each of the three stimulation frequencies. Testing commenced at 8:30am and lasted for approximately 3 h. All patients were tested in the neurosurgery outpatient clinic by a single investigator (JL, MBBS).

Statistical analysis

Sample size was calculated at 12 patients for a power of 0.8 and an alpha of 0.05 using G*Power (Heinrich Heine University of Düsseldorf) [58]. Effect sizes were calculated using data from previous studies and our own previous data [16–21,39].

Statistics were performed and graphics generated by SPSS 26 (IBM). Scores for the three frequency groups were compared using separate repeated-measures analysis of variance (rmANOVA) for each cognitive task with stimulation frequency as the within-subject variable. Mauchly's Test was used to assess sphericity and the Greenhouse-Geisser correction was used to correct for violations. Normality of data was assessed using histogram plots, skewness and kurtosis statistics, and the Shapiro-Wilk test. Although proven robust to deviations of normality, the Type I error rate for the F-test of ANOVA was evaluated for variables that did not meet the assumption of normality with the Kruskal-Wallis test and the Type I error rate for the F-test was found robust in 100% of the variables evaluated [59]. Post-hoc analyses between the three groups were performed using the protected Fisher's least square differences (LSD), known to preserve the experiment-wise type I error rate for three groups [60]. Significance was assigned to $p < 0.05$. Standard errors were reported to portray the precision of means and group differences.

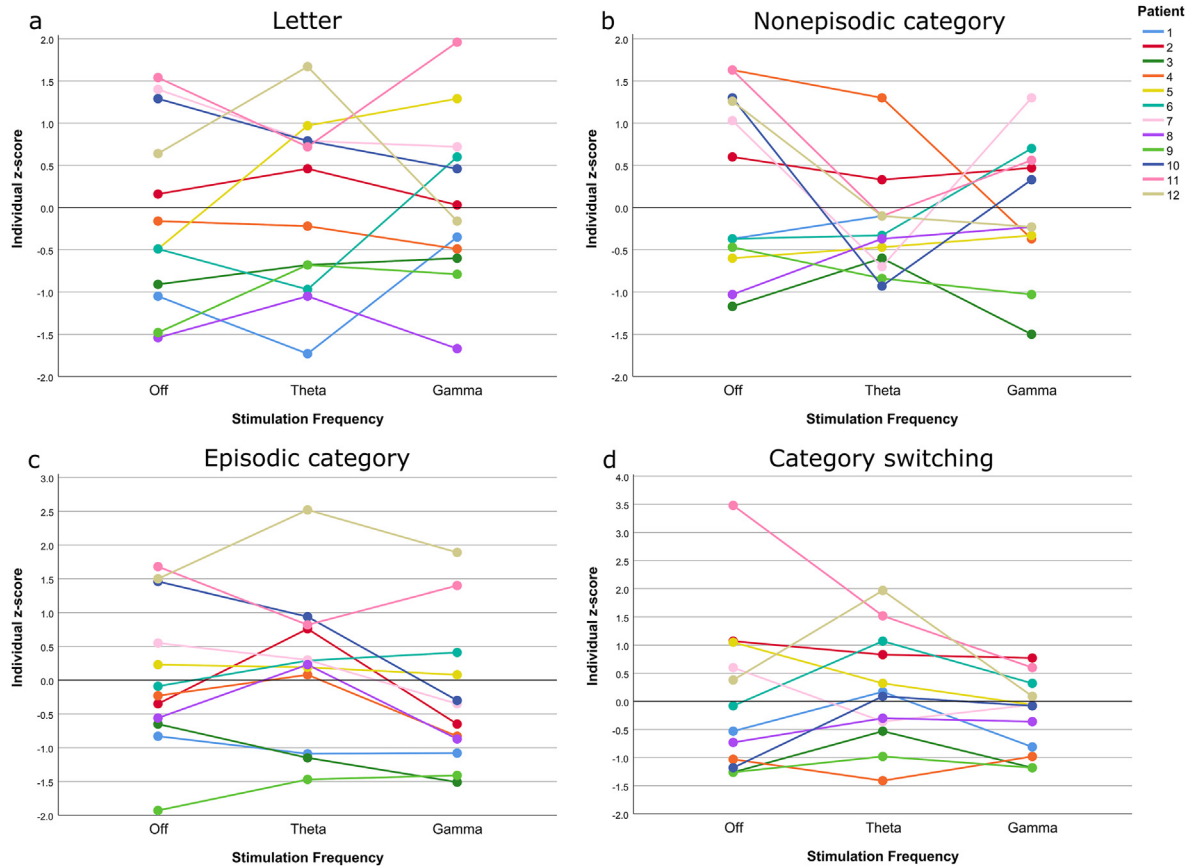


Fig. 3. Individual changes in verbal fluency scores by stimulation frequency, normalized within the sample population. (a) letter, (b) nonepisodic category, (c) episodic category, (d) category switching.

Results

Participants

Twelve patients (all males, mean age 60.8, range 45–73) with PD participated in the study. The mean number of months since DBS insertion was 21.4 (range 7–52). All participants were on a 2–3

hourly regime of carbidopa-levodopa. None of the patients had been previously diagnosed with cognitive impairment. Demographics, Unified Parkinson's Disease Rating Scale (UPDRS) scores, and DBS settings for each patient is outlined in Table 1. All 12 participants completed testing, and all results were analyzed. Pre-operative cognitive test scores were unavailable.

Table 2

Neuropsychological scores per stimulation frequency. Mean scores standard error of the mean (SEM), and repeated measures analysis of variance (rmANOVA) omnibus test statistics shown. Episodic verbal fluency scores were significantly higher during theta versus gamma stimulation (Fisher's least significant differences $p = 0.02$). There were no other significant differences in scores between stimulation frequencies ($p > 0.05$).

Neuropsychological test	Off		Theta		Gamma		rmANOVA		
	Mean	SEM	Mean	SEM	Mean	SEM	F	dF	p
Verbal Fluency									
Letter	12.75	1.70	13.25	1.54	13.58	1.54	0.21	2	0.81
Nonepisodic category	13.83	1.36	11.33	2.93	11.83	1.11	1.72	2	0.19
Episodic category	17.17	1.56	18.00	1.47	15.46	1.47	3.69	2	0.04*
Category switching	14.00	1.76	15.00	5.12	13.17	0.86	0.94	2	0.41
Color-Word Interference									
Color reading	33.83	2.68	35.00	2.51	34.33	6.61	0.39	2	0.69
Word reading	24.58	1.96	24.75	1.74	24.17	5.62	0.57	2	0.57
Color-word interference	67.92	4.58	70.00	6.84	67.92	10.54	0.22	2	0.81
Color-word switching	72.42	7.17	74.25	7.74	70.25	18.98	1.05	2	0.37
Random Number Generation									
Evan's RNG	0.35	0.02	0.35	0.02	0.37	0.01	0.81	2	0.46
Count score 1	−3.10	0.41	−3.21	0.38	−2.90	0.34	0.75	2	0.49
Count score 2	−3.27	0.29	−2.65	0.40	−2.32	0.25	2.62	2	0.10

* denotes $p < 0.05$.

Table 3

Literature review of studies comparing the on-off effect of subthalamic nucleus stimulation. CANTAB: Cambridge Neuropsychological Test Automated Battery; TMT: Trail Making Test; WCST: Wisconsin Card Sorting Test; RNG: Random number generation; VCALT Visual Conditional Associative Learning Task; MDRS: Mattis Dementia Rating Scale.

Study	Year	N	Stimulation duration	Chronic effects	Acute effects	Reference
Pillon et al.	2000	48	12 months	Decline in category verbal fluency	Improvement in psychomotor speed (word and color reading) and spatial working memory (CANTAB); no differences in color-word interference (Stroop)	[20]
Jahanshahi et al.	2000	7	8 months	Not reported	Improvement in processing speed (color naming) and executive function (TMT, WCST and RNG); no differences in letter or semantic verbal fluency, color-word interference (Stroop) or visual learning (VCALT)	[18]
Morrison et al.	2004	17	3 months	Decline in attention, mental tracking, letter and semantic fluency	No differences	[19]
Witt et al.	2004	23	12 months	No differences in MDRS	Improvement in RNG; declines in color-word interference (Stroop); no differences in digit span, verbal fluency or dual-tasking performance	[69]
Fraraccio et al.	2008	15	20 months	Decline in processing speed and color-word interference (Stroop)	No differences	[17]
Okun et al.	2009	22	7 months	Decline in verbal fluency	No differences	[15]
Ehlen et al.	2014	14	41 months	Not reported	Improvement in letter, but not semantic, verbal fluency	[16]
Scangos et al.	2018	15	2 days	Not reported	Decline in conflict adaptation; no difference in color-word interference (Stroop)	[21]

Verbal fluency

Episodic category verbal fluency scores were 16% higher during theta versus gamma frequency stimulation (rmANOVA: $F(2,22) = 3.69$, $p = 0.04$; LSD: $p = 0.02$; Cohen's $d = 0.76$), with no difference during theta versus off (LSD: $p = 0.41$) or gamma versus off (LSD: $p = 0.09$) (Fig. 2a). There were no significant differences between frequencies for letter (rmANOVA: $F(2,22) = 0.21$, $p = 0.81$), nonepisodic category (rmANOVA: $F(2,22) = 1.71$, $p = 0.20$), or switching ($F(2,22) = 0.94$, $p = 0.41$) scores. There was heterogeneity in response to frequencies as shown in Fig. 3. Neuropsychology scores by stimulation setting and rmANOVA test statistics are outlined in Table 2. Distribution statistics and histograms are shown in Supplementary information 2 and 3.

Color-word interference

There were no significant differences in completion time or errors across any of the conditions, including color processing (time: $F(2,22) = 0.39$, $p = 0.69$; errors: $F(2,22) = 0.79$, $p = 0.47$), word processing (time: $F(2,22) = 0.57$, $p = 0.57$; errors: $F(2,22) = 0.41$, $p = 0.67$), color-word interference (time: $F(2,22) = 0.22$, $p = 0.81$; errors: $F(2,22) = 0.24$, $p = 0.79$) or color-word switching (time: $F(2,22) = 1.05$, $p = 0.37$; errors: $F(2,22) = 0.03$, $p = 0.97$) (Fig. 2b).

Random number generation

There were no significant differences in any indices of random number generation including Evan's RNG ($F(2,22) = 0.81$, $p = 0.46$), count score 1 ($F(2,22) = 1.99$, $p = 0.16$), or count score 2 ($F(2,22) = 1.61$, $p = 0.22$) (Fig. 2c).

Discussion

Our study investigated verbal fluency and executive function in PD patients. We found improved episodic category verbal fluency

during theta versus gamma frequency (baseline) stimulation, but not in either frequency versus DBS off. There were no differences in executive function as measured by other verbal fluency tasks, the color-word interference and random number generation tasks between any of the stimulation settings.

STN and cognition

The role of the STN in the inhibition of motor output from the basal ganglia is well established [61,62]. However, it has been increasingly recognized that the STN may contribute to cognitive functions outside the motor circuitry, such as inhibition of automatic or habitual responses [41,61–63]. The STN is thought to have three distinct components: motor (dorsolateral), associative (ventral), and limbic (ventromedial) [64]. While DBS for PD targets the motor (dorsolateral) STN, there is increasing evidence that STN DBS may also affect cognitive domains. Positron emission tomography studies examining glucose metabolism have demonstrated that STN DBS activates the dorsolateral prefrontal cortex, a brain region involved in working memory and executive function, as well as other cortical regions such as the supplementary motor area, anterior cingulate cortex, and temporal lobe [65–68].

Cognitive impacts of STN DBS

Meta-analyses of cohort studies with and without control groups have consistently shown small but significant deteriorations in verbal learning, memory, and executive function following STN DBS in PD patients; larger declines have been reported in letter and semantic fluency [8–11]. STN DBS has also been found to have poorer verbal fluency compared to GPi [13–15].

On-off effects of DBS

Several studies have compared the acute on-off effects of STN stimulation at postoperative timepoints ranging from the time of

DBS stimulation onset to 4.3 years postoperatively, and yielded very mixed findings [15–21,69]. The findings of these studies are outlined in Table 3. Interestingly, studies reporting cognitive changes pre versus postoperatively but not on versus off highlight the relative contribution of the lesional effect of DBS surgery compared to the effect of electrical stimulation [15,17,19]. Indeed, a number of studies have shown postoperative declines in verbal fluency at timepoints ranging from three days to several months [15,70]. This is corroborated by data showing comparable verbal fluency PD patients with DBS before versus after activation [71].

In our study, there were no significant differences in verbal fluency during on versus off, although mean scores in every verbal fluency category decreased numerically, and total verbal fluency scores decreased in all but two patients and the group mean decreased by 10% during gamma frequency stimulation versus off. These results contradict the results of previous on-off studies that reported increased verbal fluency during gamma frequency stimulation [16]. Such discrepancies may be related to differences in anatomic location of electrodes and volume of stimulation. Declines in verbal fluency have been correlated with ventral electrode position and volume of STN activation from electrodes providing optimal motor benefit [15,72,73]. Increases in verbal fluency have been correlated with anterolateral electrode location, stimulation amplitude, and volume of STN activation from electrodes ventral to those providing optimal motor benefit [16,73]. However, electrode position does not fully account for the great heterogeneity in response to stimulation, and our results support that a subset of responders underlie the observed changes, with other studies reporting reliable change indices of 23–40% [74–76]. Further work is required to explore the differences between patients showing cognitive change after DBS and those who do not.

In view of mixed data in the literature, our results replicate previous findings of no effect of acute DBS on processing speed and executive function (color-word interference, random number generation) [17,20].

Theta frequency oscillations and cognition

The majority of studies investigating the longitudinal or acute on-off effects of DBS utilize clinically used stimulation parameters with frequencies in the 100–180 Hz gamma range. While gamma frequencies are thought to reflect broadband asynchronous activity, narrowband oscillatory activity in the theta frequency band (5–12 Hz) has been proposed to underlie long-distance communication between distant brain regions during cognitive processes. During successful memory encoding and retrieval, time-dependent increases in synchrony have been demonstrated in theta frequencies, but desynchronization has been shown in gamma frequencies [31–33]. In particular, theta oscillations in the hippocampus, medial temporal lobe, and prefrontal cortex have been substantially implicated in spatial and episodic learning and memory [35–38].

Although the majority of research into theta rhythms in cognition has centered on the hippocampus and limbic pathways, there is evidence that theta frequency oscillations in the STN are associated with higher cognitive functions such as response inhibition and conflict resolution [25–29]. Such actions have been shown to increase theta phase synchrony within the medial prefrontal cortex [29]. Moreover, increased theta activity in the ventral STN has been associated with impulsivity in PD and inhibition of compulsivity in

obsessive-compulsive disorder [77]. Together, these findings suggest that the STN plays an underappreciated role in cognitive functioning.

Effect of theta frequency stimulation on verbal fluency

Two previous studies have investigated the effects of theta frequency STN stimulation. Wojtecki et al. showed that 10 Hz stimulation of the bilateral STN significantly improves overall verbal fluency (letter, category, letter switching, category switching) versus 130 Hz stimulation, although there was no significant difference between either frequency versus off [39]. The same authors demonstrated increased 6–12 Hz oscillations in frontal regions, and 6–7 Hz STN-frontal coherence during a letter fluency task, corroborating the role of theta oscillations in frontostriatal circuits [40]. Interestingly, gamma frequency STN stimulation has been found to decrease glucose metabolism in frontal networks during verbal fluency, although these functional changes do not reflect the lack of impairment – and even improvement – in verbal fluency in on versus off studies of gamma frequency STN stimulation [16,18–20,78].

Letter fluency is thought to rely more heavily on frontostriatal circuits involving the left inferior frontal lobe. While category fluency also involves these executive pathways, it also relies on the left temporal lobe to support retrieval from semantic memory [40,79,80]. While semantic and episodic memory are often considered distinct, with semantic memory involving the frontal and lateral temporal lobes, and episodic memory involving medial temporal structures [34–38,47], recent evidence suggests that semantic categories often draw on episodic (autobiographical and spatial) memory processes as a recall strategy [44–48]. In these studies, specific probes assignment was based on the pattern of performance and reported strategies commonly used by healthy control participants across these studies (for example, visualizing themselves walking in the kitchen for utensils). The distinction between episodic and nonepisodic noted in terms of common strategies were further supported by findings showing greater impairments on episodic probes than nonepisodic probes in patients with amnesia and mesial temporal lobe damage and greater hippocampal activation in healthy individuals for autobiographical and spatial probes relative to nonepisodic trials (Ryan et al., 2008; Sheldon et al., 2012, 2016) [45–48]. This may help resolve previous discrepancies in the fMRI literature regarding the role of medial temporal structures in semantic fluency [45,80].

Our study found a 16% improvement in categories with autobiographical or spatial context (episodic), but not in letter or categories lacking context (nonepisodic) after acute theta compared to gamma frequency STN stimulation. These results may relate to the role of hippocampal theta oscillations in episodic encoding and recall [34–38]. There is fMRI and diffusion tensor imaging evidence for STN connections with medial temporal regions, including the hippocampus [68,81–84]. In one study of patients with traumatic brain injury, deficits in verbal recall was correlated with reduced hippocampal connectivity with the STN [68]. In another study utilizing simultaneous magnetoencephalography combined with local field potentials from externalized STN DBS leads in PD patients, coherence in the 7–12 Hz band was found between the STN and ipsilateral temporal regions [67].

In view of the well-described impact of STN DBS on verbal fluency – reported by one study as a 14% decline at one year and

18% at three years – our findings along with those of Wojtecki et al. suggest the potential for a new paradigm to improve cognitive outcomes following STN DBS [8–11,85]. As our study did not demonstrate an effect of stimulation frequency on nonepisodic or letter verbal fluency, further work is required to elucidate the role of the STN within functional circuits and explain the differential response to STN stimulation of different verbal fluency sub-domains. The role of the hippocampus in verbal fluency remains to be fully understood, and future research investigating the effect of theta frequency STN stimulation on more canonical measures of hippocampal-dependent episodic memory would provide valuable insight into STN modulation of hippocampal function. It must be noted that along with the results of Wojtecki et al. our study did not demonstrate a significant improvement in verbal fluency during acute theta frequency stimulation versus off, possibly due to statistical underpowering [40]. Therefore, it is uncertain whether our results reflect a direct improvement in verbal fluency versus mitigation of negative gamma frequency stimulation effects.

Effect of theta frequency stimulation on color-word interference

Scangos et al. showed improved color-word interference (Stroop) during theta frequency versus no stimulation, however they did not directly compare theta versus gamma frequency stimulation [21]. Our study found no difference in color-word interference during theta versus either gamma frequency or no stimulation. Other metrics of executive functions were also unaffected by stimulation frequency in our study, including updating processes (color-word switching); random number generation, working memory, response inhibition and updating processes (random number generation); and suppression of semantic and associated words (letter-semantic fluency contrast scores) [86,87]. This discrepancy may be related to differences in study design. Firstly, whereas Scangos et al. tested patients before activating DBS for the first time, the mean time since DBS in our patients was 21 months, during which patients may have adapted to functioning with gamma frequency stimulation. Secondly, while our patients completed the color-word interference task approximately 15 min after setting the stimulation frequency, the authors did not specify the length of this period. On the other hand, they showed no effect of habituation to two days of theta frequency stimulation, and previous animal data suggests that cognitive improvements during theta frequency stimulation may be immediate [50,51]. Differences in patient demographics may have further contributed to a potential lower sensitivity of subjects to changes in test performance, including relatively high education levels and younger age in our patients.

Study limitations and other considerations

A number of measures were taken to reduce confounding variables in our study, including completing testing in a single session, at the same time of day, administered by a single investigator double-blinded to stimulation frequency. All patients continued their prescribed medications during testing in order to reduce confounding from worsening motor symptoms and to assess cognition under clinically relevant conditions. Although PD medications are known to impact cognition in a variety of manners, randomization of stimulation order reduced the impact of this on our analyses [7].

Our study did not control for motor state during testing, which is likely to have differentially impacted stimulation frequencies. Improved motor symptoms during 'on' states compared to 'off' states has been associated with improved cognition, albeit confounded by levodopa therapy and with discrepancies between

cognitive domains [88,89]. Therefore, 'off' states in our patients during DBS off or theta frequency, often discerned by patients, may have negatively impacted neuropsychological performance.

All of our patients were male, fluent in English, aged 45–73, able to complete all neuropsychological testing, and able to tolerate DBS turned off. Our study was not designed nor powered to investigate inter-subject differences such as age, time from DBS implantation, education, first language, or motor function. Although the impacts of these characteristics are unknown, this may limit the external validity of our results to different patient populations. For example, patients speaking English as a first language may be more sensitive to the effects of stimulation frequency in verbal fluency measures, compared to those speaking English fluently, but as a second language. Also unknown is the adequacy of a 5-min period of stimulation prior to each round of neuropsychological testing, however, based on previous animal data, there is evidence for immediate behavioral effects of theta frequency stimulation [50,51]. Moreover, human data demonstrates the adequacy of a 5-min washout period for motor benefits of DBS [49]. Of note, other studies reported periods of between 30 min and two days [16–19,21].

Future directions

Current evidence for the on-off and frequency effects of DBS on cognition is limited to few and small studies with large heterogeneity in design, neuropsychological tests and results. Therefore, larger studies are needed to confirm these findings and explain the variability in response.

Despite positive cognitive results reported by ours and previous studies, theta frequency stimulation does not provide control of motor symptoms, for which gamma frequency stimulation remains the gold standard. Therefore, an important next step would be to explore how theta and gamma frequencies can be integrated. Interleaving stimulation voltage and/or pulse width between multiple electrode contacts is commonly used to control distinct symptoms while reducing side effects from stimulation of each contact [90,91]. Accordingly, it may be possible to interleave theta frequency stimulation with gamma stimulation to unconfound cognitive effects from the motor state as in the present study [88,89]. Based on the effect of electrode placement and on cognitive outcomes, directional leads provide an added opportunity for anatomically directed theta and gamma frequency stimulation to further investigate differential anatomical considerations for motor and cognitive effects. Additionally, no studies have examined the impact of other parameters including voltage and pulse-width for theta frequency, which must be established.

Conclusions

DBS implantation for PD represents a unique opportunity to study the electrophysiology of cognitive circuitry in humans. Our study is the first to show improvements in episodic category verbal fluency during theta versus gamma frequency STN stimulation, corroborating a role of theta oscillations in hippocampal-dependent memory processes. While our results raise the intriguing possibility of novel DBS paradigms utilizing interleaving frequencies, additional studies are necessary to identify the underlying neurophysiological correlates of theta frequency stimulation of the STN and confirm its effects on cognition.

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CRediT authorship contribution statement

Jordan Lam: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Justin Lee:** Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Marcus Williams:** Formal analysis, Writing - original draft, Writing - review & editing, Visualization. **Melanie Cohn:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Writing - review & editing, Visualization. **Melissa Wilson:** Formal analysis, Writing - review & editing, Visualization. **Catherine Mark:** Methodology, Investigation, Resources, Data curation, Writing - review & editing, Project administration. **Nasrin Esnaashari:** Methodology, Investigation, Resources, Writing - review & editing, Project administration. **Andrew Petkus:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing - review & editing. **Jennifer Hui:** Conceptualization, Writing - review & editing. **Danielle Feigenbaum:** Conceptualization, Writing - review & editing. **Mark Liker:** Conceptualization, Writing - review & editing. **Charles Y. Liu:** Conceptualization, Writing - review & editing. **Brian Lee:** Conceptualization, Writing - review & editing. **Darrin J. Lee:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration.

Declaration of competing interest

There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2020.12.014>.

Author declaration

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial

Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from (darrin.lee@med.usc.edu).

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