TITLE:

Evaluation of Neurocognitive Changes in Parkinson'Ss Disease Patients with Deep Brain Stimulation

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1.0 BACKGROUND AND HYPOTHESES

Multiple lines of evidence support the role of the subthlalamic nucleus (STN) in the motor circuitry, evidenced by its role as a primary target for deep brain stimulation (DBS) in patients with Parkinson's disease (PD). Parkinson's disease can result in progressive deficits in memory, attention, and executive as well as visual-spatial abilities[1]. While STN DBS is associated with a clear motor benefit, its role in cognition has been equivocal with some evidence suggesting cognitive decline in verbal fluency[2,3].

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[4]. The STN is thought to have three distinct components: motor (dorsolateral STN), associative (ventral) and limbic (ventromedial)[5]. While typical DBS stimulation targeting is in the motor (dorsolateral) STN, there is increasing evidence that STN DBS may also affect cognitive domains. For instance, PET studies have demonstrated that DBS of the STN activates the dorsolateral prefrontal cortex, a brain region involved in working memory and executive function[6]., as well as other cortical regions such as the supplementary motor area and the anterior cingulate[7]. Furthermore, prior studies have demonstrated that PD patients with bilateral STN DBS exhibited significant improvements in cognitive functions with stimulation turned "on" versus "off."

Interestingly, these previous studies have all utilized the typical DBS stimulation parameters (high frequency gamma oscillations (100-180 Hz stimulation)). However, there is growing evidence that low frequency (theta: 5-12 Hz) STN stimulation preferentially improves executive function compared to gamma stimulation (100-150 Hz)[8]. Such findings are consistent with literature suggesting that theta frequency oscillations in the STN are associated with higher cognitive functions such as conflict resolution[9]. Together, these findings suggest that the STN plays a previously underappreciated role in cognitive functioning. We hypothesize that acute low frequency STN DBS will improve performance on cognitive testing.

This study first aims to confirm previous findings that suggest improvement in cognitive tasks with STN high frequency DBS. Specifically, improvements have been found on the Paced Visual Serial Addition Task (PVSAT), and the Random Number Generation Test (RNGT), which evaluate attention, concentration, task switching, working memory, cognitive processing speed, and executive function[10-12]. We will also validate the acute effects of DBS on verbal fluency.

To our knowledge, prior studies have not examined the influence of "on" versus "off" stimulation on impulse control. We also propose to examine impulse control, as increased impulsivity is associated with reduced frontal-striatal connectivity in PD patients[13]. Impulsivity will be measured with the Quotient Test, which has been previously used to assess patients with attention-deficit/hyperactivity disorder.

The second aim of this study is to determine if low frequency (theta) stimulation will improve performance on various cognitive tasks more than high frequency stimulation.
Recent findings that suggest theta stimulation improves executive function compared to gamma stimulation raises the possibility that a mix of stimulation frequencies may be required to optimize motor and neurocognitive benefits. This study will directly compare theta versus gamma stimulation to provide further insight into this intriguing possibility.

PD patients with STN DBS electrodes represent a unique opportunity to study this circuitry in humans. Such studies would increase our understanding of role of the basal ganglia in executive and higher cognitive functioning. Confirmation of a direct influence of STN DBS on cognitive function in our patient population would serve as the basis for additional studies that identify the underlying neurophysiological correlates. Our current study has two specific aims: (1) evaluate the acute effects of high frequency (gamma) STN stimulation on cognitive tasks and (2) compare the outcomes to acute effects of low frequency (theta) STN stimulation.

If there is an effect of either stimulation paradigm, future studies would need establish if chronic stimulation would have similar effects. Currently, high frequency stimulation (>100 Hz) is necessary to improve motor outcomes; however, there are known deficits (verbal fluency) after deep brain stimulation. Preliminary data from the PI's previous work as well as published literature demonstrates that various cognitive domains may improve with low frequency (theta; 5-12 Hz) stimulation. Current technology can allow for interleaving stimulation paradigms. Therefore, if low frequency stimulation can improve certain aspects of cognition, it may be possible to interleave high and low frequency stimulation paradigms to improve both the motor and cognitive aspects of Parkinson's Disease with DBS.

2.0 OBJECTIVES AND PURPOSE

The first aim of this study is to validate previous neurocognitive changes demonstrated in PD patients with DBS stimulation "on" versus "off"[10,11,14] utilizing standard DBS stimulation paradigms. The second aims is to determine if low frequency (theta) stimulation results in improved cognitive performance compared to gamma stimulation. Specifically, we will perform tests that evaluate cognitive processing efficiency, executive function and impulsivity, including the Random Number Generation Test (RNGT), Delis Kaplan Executive Function System (including verbal fluency), Color Word Interference Test (D-KEFS CWIT), and the Quotient Test, respectively. Validation of cognitive improvements at specific stimulation frequencies may lead to identification of stimulation parameters that improve executive function in PD patients. These findings will also serve as the basis for future studies investigating the neurophysiological basis for STN-mediated influences on cognition.

3.0 STUDY DESIGN

In this single-center pilot study, we will investigate possible short-term neurocognitive changes induced by deep brain stimulation (DBS) in patients with Parkinson's disease between the "on" and off" state. During the "on" phase, bilateral monopolar stimulation of the electrode contact associated with the ventral STN will be turned on; testing in the "on" state will be tested at both theta (5-10 Hz) and gamma (100-180 Hz) stimulation. In order to improve blinding to "on" versus "off" states and increase the uniformity of stimulation parameters, the intensity will be adjusted to 2.5 V for all patients. Patients with baseline settings at less than 1.5 V will be excluded from the study. During the "off" phase, both DBS electrodes will be turned off. Since turning the stimulation "on" vs "off" may induce motor effects that could influence testing performance, we will examine if the order in which settings are applied impacts the results of cognitive testing.

During a single outpatient visit, a baseline assessment (baseline stimulation parameters, including frequency, pulse width and voltage) of each neuropsychological task will first be performed in order to accommodate patients to the given task and reduce practice effect. Patients will then perform a battery of tests with the stimulator "on" at the theta frequency, "on" at the gamma frequency, and off; the sequence of these three settings will be changed for each patient in a single-blind fashion. Thus, patients will complete this battery of tasks a total of four times. Duration of testing will be approximately three hours.

The first task to be performed will be the RNGT, which evaluates executive functions such as updating and monitoring of information and inhibition of automatic responses[16]. During this task, participants will be asked to say a sequence of 100 numbers (each number ranging from one to nine) as randomly as possible timed with an auditory pacing stimulus (1 kHz, 200 ms duration) at a rate of 1 Hz. Subjects will be instructed to listen to the first few pacing tones without responding. The loudness of the tone will be adjusted to a comfortable level for each individual. Randomness will be described as picking a piece of paper (numbered one through nine) out of a hat and subsequently replaced. We will analyze previously used measures to quantify deviation from randomness, including repetition measures (repetition of the same digit within a specific time frame), cycling measures (attempt to use all alternative digits before repeating a digit), and seriation measures (tendency to use natural order of numbers)[16].

Executive functioning was also measured with the Delis Kaplan Executive Function System Color Word Interference Test (D-KEFS CWIT)[17]. The D-KEFS CWIT test consists of five subtests (verbal fluency, color naming, word reading, color-word interference, and color-word interference switching) subtests. For each subtest the total score consists of the total time in seconds to complete the test as well as the total number of commission and omission errors. The D-KEFS CWIT test has been suggested as a reliable and valid measure of the inhibition and switching aspect of executive functioning in patients with PD [18].

The Quotient System will be used to measure hyperactivity, attention and impulsivity. It is a noninvasive device designed to capture micro movements of the head using an infrared motion detector in conjunction with a reflector worn on the test subject's head while the patient completes a 15-20 minute computerized test. The device produces 4 measures of neurocognitive performance: motion analysis, attention analysis, shift in attention state and Quotient composite scores. These tasks are generally used to assess frontal lobe function. After the test is completed, patterns of motion, accuracy of the responses, and fluctuations in attention state are analyzed and scored using proprietary algorithms based on 19 or more parameters. The motion detection includes 6 movement metrics. The Attention Response Analysis includes measures of accuracy, omission errors, commission errors, latency, variability, and response time variability. Baseline movement data will be collected during "on" versus "off" stimulation to ensure that differences in tremor and/or dyskinesia does not

confound interpretation of hyperactivity, attention, or impulsivity. Data for each patient is compared to age and gender matched cohorts.

Data collected from the patients' medical charts will include age, gender, handedness, age at onset of epilepsy, highest level of education, primary language, language laterality, age at surgery, time from diagnosis to surgery medications, other medical conditions, imaging, symptoms, clinical rating scales for Parkinson's disease and previous neuropsychological scores.

4.0 DEVICE INFORMATION

Quotient ADHD system

The following devices hae already been implanted in patients. We will only temporarily be changing the settings.

Activa PC 37601
Activa SC 37602
Activa SC 37603
BS lead 3387 and 3389

Please see Investigators Device Brochures for more information.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

Participants with idiopathic Parkinson's disease with motor fluctuations and/or dyskinesias that have received bilateral electrode implantation in the subthalamic nucleus are candidates for this study. Recruitment will take place during routine outpatient follow up clinic visits and by telephone or email, using a patient database from the deep brain stimulation case conference to identify suitable patients. Volunteers that are candidates for the study will be screened with neuropsychological assessment to exclude patients with dementia or clinical depression. For those patients that meet enrollment criteria and complete informed consent, testing will occur as a separately scheduled visit. Patients must be able to sit and participate for the duration of the testing period. Any condition in which the judgment of the investigator would prevent the subject from completion of the study will be excluded.

Inclusion Criteria:

1. Male or female patients who had previously undergone bilateral STN deep brain stimulation implantation
2. Age >18 years old
3. Stable medication regimen for at least 3 months.
4. Patient informed and able to give written consent
5. Able to comply with all testing, follow-ups and study appointments and protocols

Exclusion Criteria:

1. History of epilepsy or seizure
2. History of major substance abuse
3. Patients with baseline settings at less than 1.5 V will be excluded from the study

Subjects have the right to withdraw from the study at any time, for any reason, without jeopardizing their medical care

6.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME

The order of stimulation parameters after baseline will be changed for each patient by moving the order by one step. E.g. patient 1: gamma, theta off; patient 2: theta, off, gamma; patient 3: off, gamma theta. The subject will not be told which setting is being used.

7.0 STUDY AGENT ADMINISTRATION OR INTERVENTION AND TOXICITY MANAGEMENT PLAN

During the "on" phase, bilateral monopolar stimulation of the electrode contact associated with the ventral STN will be turned on; testing in the "on" state will be tested at both theta (5-10 Hz) and gamma (100-180 Hz) stimulation. In order to

improve blinding to “on” versus “off” states and increase the uniformity of stimulation parameters, the intensity will be adjusted to 2.5 V for all patients. During the “off” phase, both DBS electrodes will be turned off.

Parkinson’s disease patients routinely have their settings changed to optimize their therapy if they hare not having adequate response to their current treatment, especially in their first few programming sessions. Patients also have a controller to turn it off and on. Stimulation is routinely turned off in clinic to check for symptoms, or by the patients, who have a controller. Many patients turn their stimulation off at night or for other reasons. The length of time (45 minutes) and adjustments that we are performing would only be for research. Theta stimulation is not routinely used clinically and would only be for research.

There are no risks of turning the stimulation off or lowering the frequency, but it is possible that during this they will not have the motor benefits of DBS (tremor, bradykinesia may return); however, once normal stimulation is turned back on this will resolve. Patients will be monitored during the testing and can stop participating at any point and we will return their stimulation settings back to baseline.

The CTSI Scientific Committee reviewed this study

8.0 ASSESSMENT OF EFFICACY AND SAFETY

Patients will be monitored during the testing. We will ask the patient to inform us if they are feeling uncomfortable and want to stop participating or take a break. If patients want to stop participating, we will return the patients stimulation settings to baseline. Any adverse side effects will be reported to the IRB.

9.0 CLINICAL AND LABORATORY EVALUATIONS AND STUDY CALENDAR

Baseline (Session 1)	Session 2	Session 3	Session 4
RNGT (5 minutes) Verbal Fluency (5 minutes) D-KEFS CWIT (10 minutes) Quotient Task (20 minutes)	RNGT (5 minutes) Verbal Fluency (5 minutes) D-KEFS CWIT (10 minutes) Quotient Task (20 minutes)	RNGT (5 minutes) Verbal Fluency (5 minutes) D-KEFS CWIT (10 minutes) Quotient Task (20 minutes)	RNGT (5 minutes) Verbal Fluency (5 minutes) D-KEFS CWIT (10 minutes) Quotient Task (20 minutes)

(All during one day)

12.0 DATA COLLECTION AND MONITORING

RNGT, Verbal Fluency, D-KEFS CWIT task results will be de-identified using a key and collected on paper. They will be stored in a locked cupboard in a locked office. MRNs and the key will be kept on a password protected Excel 2016 (Microsoft) spreadsheet on an encrypted and secure computer. No one except the study personnel will have access to the spreadsheets or papers. The behavioral data collection process is built into the Quotient ADHD System, details of which are described on their website (http://www.quotient-adhd.com).

Data collected from patients electronic medical records will be coded and kept on a password protected Excel 2016 (Microsoft) spreadsheet on an encrypted and secure computer separate from the key. No one except the study personnel will have access to the spreadsheets or papers.

13.0 STATISTICAL CONSIDERATIONS

Based upon our power analyses, our sample sizes for each of the tasks range from 20-29 patients[10,11,15]. Therefore, we will enroll 30 patients to detect significant differences in cognitive function for the first phase of the study.

Power analyses

Study	Projected Sample Size	Mean Result ± SD	Absolute Change (Percent Change)
RNGT	20	43±14	+8.6 (20%)
Delis Kaplan Executive Function	26	9.1±3.3	±1.8 (20%)
Verbal Fluency (preliminary data)	29	47±17	+9.4 (20%)
Quotient	Exploratory		

Non-parametric data analysis will be performed for each of the tasks, including RNGT, D-KEFS CWIT and the Quotient tasks. Each task will be analyzed using within-subjects ANOVA.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in adherence to ICH Good Clinical Practice.

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