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Subthalamic Nucleus Neuronal Firing Rate Increases with Parkinson's Disease Progression

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive loss of dopaminergic cells in the central nervous system, in particular the substantia nigra, resulting in an unrelenting loss of motor and non-motor function. Animal models of PD reveal hyperactive neurons in the subthalamic nucleus (STN) that have increased firing rates and bursting activity compared to controls. Although STN activity has been characterized in advanced stage PD patients, it has not been described in early stage PD patients. Here we present the results of STN neuronal recordings from early stage PD patients (Hoehn and Yahr stage II) enrolled in an ongoing clinical trial compared to recordings from age and sex matched advanced PD patients. STN neurons had a significantly lower firing rate in early versus advanced PD (28.7Hz vs. 36.3Hz; $p < 0.01$). The overall activity of the STN was also significantly lower in early versus late PD, as measured by background neuronal noise (12.4mV vs. 14.0mV; $p < 0.05$). No significant difference was identified between groups in the bursting or variability of neuronal firing in the STN, as measured by a burst index or the interspike interval coefficient of variability. The results suggest that neuronal firing in STN increases with PD progression.

Keywords

Neurophysiology; Neurodegeneration; Parkinson's Disease; pathophysiology; Subthalamic nucleus; rate model

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that is characterized by a progressive loss of motor control resulting in resting tremor, muscle rigidity, bradykinesia, and postural instability¹. These symptoms are the result of disordered function in the motor circuitry of the basal ganglia caused by the loss dopaminergic signaling from the substantia nigra compacta (SNc)^{2, 3}. Although dopaminergic medications are effective in treating the symptoms of PD in the early stages of the disease, they become less effective over time, requiring increasingly higher doses that often result in disabling motor fluctuations and dyskinesias. At this medically refractory stage of the disease, deep brain stimulation (DBS) is an FDA approved, commonly used therapy that electrically modulates the activity of the basal ganglia⁴.

The subthalamic nucleus (STN) is a commonly selected target for DBS and evidence from non-human primate models of PD suggests it may play a role in the pathophysiology of PD^{4, 5}. Non-human primates given 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that destroys dopaminergic neurons in the SNc and causes parkinsonian symptoms^{6, 7}, exhibit abnormal STN activity, characterized by increased neuronal firing, and more irregular and bursting patterns of activity^{8–12}. In these animal models, altering the influence of the STN by lesioning^{13–15}, or by high-frequency stimulation¹⁴ results in improvement in parkinsonian symptoms. Thus, increased STN activity is suspected to be central to development of parkinsonian symptoms and is associated with increased inhibitory drive to the motor thalamus via the output nuclei of the basal ganglia (globus pallidus internus; GPi, and the substantia nigra reticulata; SNr)⁵.

Despite considerable evidence implicating abnormal STN activity in animal models of PD, it is still unclear whether this is a feature of human Parkinson's disease, due to the lack of a true control group for comparison. Neuronal recordings in human STN have been primarily limited to advanced stage PD patients undergoing microelectrode recording to guide the placement of DBS leads^{16–20}. These findings are typically reported in comparison to animal models, and it unclear how these results compare to normal patients or patients with early stage PD.

We are currently conducting a pilot clinical trial testing deep brain stimulation of the bilateral STN in subjects with early stage PD²¹. The purpose of this trial is to obtain preliminary safety and tolerability data necessary to launch a large-scale multicenter trial evaluating DBS in early stage PD. Our ongoing trial provides a unique opportunity to gather neuronal recordings from the STN and surrounding structures in subjects at a very early disease state. We report here the results of microelectrode recordings from the STN of eight early stage PD patients prospectively implanted with bilateral STN DBS, compared to eight gender and age matched advanced stage PD patients undergoing the same procedure as standard of care.

Methods

Subjects

Bilateral STN recordings were compared between two groups of eight patients implanted with DBS leads at Vanderbilt University Medical Center. Subjects in the early PD group (7 males, 1 female; 57.4 ± 1.1 years) are part of an ongoing, prospective, randomized clinical trial designed to gather safety and tolerability data in early stage PD patients treated with STN DBS (NCT00282152). Early stage patients were required to meet the following criteria at the time of enrollment: Hoehn and Yahr Stage II off medication,²² on PD medications greater than 6 months and less than 4 years without motor fluctuations or dyskinesias, and

demonstrate a 30% improvement on the motor exam of the Unified Parkinson's Disease Rating Scale (UPDRS-III) scores on PD medication. A total levodopa equivalent dose (LED) was calculated for each patient as the follows: $LED = \text{levodopa dose} + 0.75 \times \text{levodopa CR dose} + 16.7 \times \text{rotigotine dose} + 65 \times \text{pramipexole dose} + 16.7 \times \text{ropinirole dose} + 0.5 \times \text{amantadine dose} + [0.25 \times (\text{levodopa dose} + 0.75 \times \text{levodopa CR dose})]$ if the patient was taking entacapone or tolcapone)^{23–25}. At the time of surgery, subjects in the early group had been treated for PD an average of 3.1 ± 0.8 years, at a LED of 360 ± 150 mg/day, and had UPDRS-III scores of 27.0 ± 3.1 off medication and 11.9 ± 2.3 on medication (Table 1).

Subjects in the advanced PD group were eight age and gender matched patients that received bilateral STN DBS implants within the same 2 year period for advanced PD (Hoehn and Yahr Stage III–IV) not adequately controlled by medication. Seven of these patients had medication related motor fluctuations and dyskinesias, and one patient had a significant response to apomorphine, but could not tolerate levodopa therapy due to nausea. Subjects in the advanced group were treated with PD medications an average of 10.3 ± 0.3 years at a LED of 1210 ± 183 mg/day, and had UPDRS-III scores of 42.3 ± 4.0 and 17.1 ± 4.9 , off and on medication, respectively (Table 1).

Subjects in both groups were evaluated by a neuropsychologist and neurologist prior to surgery to ensure they were appropriate candidates for DBS therapy. Patients with clinically significant dementia or cognitive impairment, major psychiatric illness, severe gait symptoms, or serious non-motor medication side effects (hallucinations, delirium, or abnormal impulsivity), were not offered surgery. The early PD clinical trial was granted an investigational device exemption by the U.S. Food and Drug Administration (g050016), and is approved by the Vanderbilt University Institutional Review Board (040797). All participants provided informed consent prior to all study procedures. Additional details of the design of the clinical trial can be found at the clinicaltrials.gov website using the NCT00282152 identifier.

Surgery

Surgical methods were the same between groups. A week prior to surgery, patients had fiducial bone markers implanted under general anesthesia, and CT and MRI scans were obtained. Surgical planning software (Waypoint® planner, FHC) was used to merge imaging sequences and allow the surgeon to define a safe trajectory to the STN based on a combination of direct and indirect targeting methods²⁶ and a customized stereotactic platform (mT Platform®; StarFix, FHC) was manufactured^{27, 28}. Patients discontinued dopamine agonists and all remaining Parkinson's medications prior to surgery (48 and 24 hours, respectively).

For implantation of the DBS lead, patients were brought to the operating room and placed in a semi-recumbent position. The scalp was prepared and injected with local anesthetic, a burr hole was created, and a durotomy was performed to expose the brain surface. Additional analgesia was provided by low dose dexmedetomidine and remifentanyl, which was titrated to maintain patient comfort. The stereotactic platform was attached to bone anchors, and electrode microdrives (microTargeting, FHC) were attached to each side of the platform. Arrays of 2–4 tungsten microelectrodes ($0.3 - 1 \text{ M}\Omega @ 1 \text{ kHz}$, FHC) were placed into each hemisphere via guide tubes spaced 2mm apart in a “Ben-gun” configuration²⁹. Anesthesia was then discontinued at least 20 minutes prior to STN recordings, so that patients would be alert and responsive throughout microelectrode mapping.

Microelectrode mapping

Microelectrode signals were band pass filtered (0.5–5 kHz), amplified, displayed, and digitally stored (24 kHz sampling rate) using a 4 channel Leadpoint® recording system (Medtronic, Inc.). Ten second microelectrode recordings were made at regular intervals (~0.5mm) along a predefined trajectory to the STN starting at 10mm above target and finishing at 5mm below target or at the dorsal border of the SNr. Recordings within STN and SNr were classified by a neurophysiologist based on accepted criteria; namely increased background activity (neuronal noise), and high rate irregularly firing neuronal units^{16–18, 29–31}. The depth of STN and SNr borders were recorded in a spreadsheet. Macrostimulation mapping was then performed under the supervision of a movement disorders neurologist to characterize the stimulation thresholds for symptom relief and side effects. Stimulation was delivered via a 1mm reference contact on the microelectrode canula, with a Grass S88 stimulator (Astro-Med, Inc) used as a constant voltage source (150µs cathodal pulses at 150 Hz). Once the most favorable track and depth for stimulation was identified, the test electrode was replaced with a permanent DBS lead, which was tested for functionality, affixed to the skull, coiled under the scalp, and prepared for connection to a pulse generator during a follow-up procedure within ten days. The same procedure was repeated for the opposite hemisphere.

Microelectrode recording analysis

All patient data was randomized and analyzed offline by a blinded investigator. Tracks with less than 1.5mm of STN recordings were excluded from analysis. A custom MATLAB (The MathWorks) routine was used to measure the root mean square (RMS) of each recorded trace as an index of neuronal background activity. Individual units were extracted from STN recordings with Spike Sorter 2 (Plexon), using an automated cluster analysis of principal components (PC), and further refined with template matching upon visual inspection. Poorly isolated units, or multiple units with overlapping clusters in 2d PC space (MANCOVA p-value >0.05) were excluded from further analysis. Neuroexplorer 4 (Nex Technologies) was used to characterize single unit firing patterns, including firing frequency, interspike interval (ISI) statistics (mean, mode, and coefficient of variance; 3ms bins) and to generate a burst index with a correction for firing rate (mode ISI⁻¹/mean firing frequency)³².

Statistical analysis

Statistical analysis was performed using PASW Statistics 17 (SPSS). Normally distributed data were compared using Student's one- or two-tailed t-test ($\alpha=0.05$) and are reported as mean $\pm$ standard error of the mean. Data with non-normal distributions (firing frequency, burst index and CV) were compared using nonparametric Mann-Whitney tests (one-tail, $\alpha=0.05$) and are reported as median values with the 25th to 75th percentile range.

Results

STN was identified in 90 separate microelectrode tracks across patients: 45 in the early stage group and 45 in the advanced group. The groups did not differ significantly in the number of STN penetrations identified per hemisphere (early: 2.8 ± 0.3 ; advanced 2.8 ± 0.2), the recording time spent in each track (early: 31.4 ± 2.4 ; advanced 31.0 ± 2.8 mins), or the interval between anesthetic discontinuation and STN recordings (early 81 ± 14 mins; advanced 67 ± 10 mins). The groups did differ in the amount of anesthesia given prior to electrode recordings, insofar as the advanced PD group required higher doses of dexmedetomidine to be kept comfortable prior to electrode recording (early 1.1 ± 0.2 mcg/kg-1hr-1 advanced: 1.7 ± 0.2 mcg/kg-1hr-1; $t(30) = -2.60$, $p<0.05$). Remifentanyl dosages were not statistically different between groups (early PD: 0.4 ± 0.1 mg/kg-1hr-1; advanced PD: 0.3 ± 0.1 mg/kg-1hr-1). No difference was found between the early and advanced

groups in STN length as measured by the longest recorded STN pass per hemisphere (4.6 ± 0.3 mm vs. 4.4 ± 0.3 mm, respectively), or mean STN length across tracks (3.7 ± 0.3 mm vs. 3.5 ± 0.2 mm, respectively).

Recordings within STN were characterized by high amplitude background noise, reflecting the summed activity of large densely packed neurons in the nucleus. We measured the root mean square of STN recordings and found the background activity in the early stage PD group was 12.4 ± 0.8 mV, which was significantly lower than the 14.0 ± 0.5 mV measured in the advanced stage group ($t(30) = -1.48$, $p < 0.05$; Fig. 1).

A total of 190 units were isolated from 168 STN neuronal recordings: 113 units in the early group, and 77 units in the advanced group. The median firing rate of STN units in early group was 28.7 Hz with most units firing between 19.7 – 38.7 Hz (25th to 75th percentile). The firing rate of STN units in the advanced group was significantly higher with a median value of 36.3 Hz and a range of 25.8 – 48.5 Hz (25th to 75th percentile: $U=3240$, $P=0.002$; Fig. 2A.).

Using a burst index (BI)¹⁶, and interspike interval coefficient of variability (CV),³³ we characterized the bursting and variability of STN unit firing. No significant difference was found between groups for either measure. The early group had a median BI of 3.1 (25th to 75th percentile: 2.3– 5.1) versus a BI of 2.9 (25th to 75th percentile: 2.3– 4.1) in the advanced group (Fig 3B; $p > 0.05$). The median CV of the early group was 1.2 (25th to 75th percentile: 1.0– 1.5.) versus a CV of 1.1 (25th to 75th percentile: 0.9– 1.4) in the advanced group (Fig 3C; $p > 0.05$).

Discussion

This analysis represents the first comparison of STN neurophysiology between patients with early stage PD to those with advanced PD. The primary finding is that STN neurons in early PD fire at a significantly lower rate than in advanced PD. This suggests that STN neuronal firing rates likely increase with disease progression. If further investigation confirms this, it would support a rate model of PD pathophysiology^{8, 34}. A secondary, but related finding is that early stage PD is associated with a lower overall level of STN background activity when compared to advanced disease. In contrast, no significant differences were identified between groups in terms of STN size, or overall bursting activity.

Study limitations

One limitation of this analysis is that fewer STN units were isolated in the advanced PD group compared to the early group. This difference does not appear to be related to sampling density, because the number of STN penetrations per hemisphere and length of the nucleus were nearly identical between groups. The average recording time was also very similar between groups, suggesting that the mapping protocol was the same between groups. A more likely interpretation is that the lower background activity in the STN of the early stage group made units easier to isolate during intraoperative recording and offline extraction.

Another limitation of this study is that the groups received different levels of anesthetic prior to microelectrode mapping. In particular, patients in the advanced PD group required higher levels of dexmedetomidine to be kept comfortable before microelectrode recordings, presumably due to the greater severity of their symptoms off PD medication. It could be argued that the higher dose of dexmedetomidine in the advanced group resulted in increased neuronal activity in the STN. Several lines of evidence argue against this interpretation, however. First, the firing rates observed in the STN of the advanced PD group are similar to

those published for advanced PD patients in studies that used local anesthesia only^{16, 20}. Second, dexmedetomidine is favored as an anesthetic for microelectrode mapping for DBS, because it has minimal effect on STN neurophysiology, even when continuous dosing regimens are used^{35–37}. Finally, at higher doses dexmedetomidine has been shown to suppress neuronal activity in the STN³⁵. Consequently, the higher average dose of dexmedetomidine in our advanced PD group would be expected to *lower* neuronal background activity and firing rates, not *increase* it.

Neuronal bursting

The lack of difference in STN bursting activity in our groups (measured by a burst index and the coefficient of ISI variability) is unexpected, given that changes in neuronal firing patterns are consistently reported in the STN in animal models of PD^{8–10, 12}. A difference in bursting may have not been detected due to technical factors such as sedation levels or relatively short recording epochs, but the burst index and CV of our groups are very similar to the values reported in previous studies with more restrictive anesthetic regimens, and longer recording periods^{16, 18}. An alternative interpretation is that an increase in bursting activity may occur in the STN at an earlier time point in the disease, prior to Hoehn and Yahr stage II. This explanation is consistent with the results of animal models of PD, which indicate that bursting activity increases soon after dopamine depletion, and may precede changes in firing rate^{9, 38}.

Firing rate

Our finding of elevated STN firing rates in advanced versus early patients parallels the findings in animal models of PD that consistently report increased discharge rates in the STN following the application of compounds toxic to the substantia nigra^{8–12}. Our finding of a 26.4% increase STN firing rate between early and advanced groups (28.7 Hz vs 36.3 Hz) is particularly close to the relative change in STN firing rate reported in non-human primate models of PD. For example, monkeys exhibit a 36.8% increase in mean firing rate (19 Hz vs 26 Hz) when given a dose of MPTP sufficient to create severe parkinsonian symptoms⁸.

Although the firing rate of our advanced group is higher than that reported for monkey models, it is similar to previous reports in PD patients undergoing microelectrode mapping for DBS implantation. The median STN firing rate of 36.3 Hz identified here falls within the 33 – 42 Hz range typically reported^{16–18, 20, 30}. In contrast, the median firing rate identified in our early group (28.8 Hz) is the lowest yet reported in any human PD study. Recently, Stiegerwald, et al. reported a mean discharge rate of 19.3 Hz in the STN of essential tremor patients undergoing DBS implantation²⁰. Assuming the neurophysiology of STN in essential tremor patients is similar to normal, this finding suggests that subthalamic neurons in our early PD group may have already undergone a marked increase in relative discharge frequency. Accordingly, STN firing frequency appears to be elevated at a very early clinical stage of disease when patients have very mild symptoms, and becomes more elevated as the disease progresses and symptoms worsen. If future investigations confirm this hypothesis, it would support a rate model of PD pathophysiology^{2, 3}. According to this theory, degeneration of the substantia nigra compacta (SNc) leads to disinhibition of the STN, causing it to overdrive the output nuclei of the basal ganglia (GPi and SNr) generating increased inhibition of motor cortical areas via the motor thalamus, thereby leading to the emergence of the cardinal symptoms of PD. This interpretation should be made with caution, however, as the long-term effects of levodopa treatment on the neurophysiology of the STN are unknown. Chronic levodopa therapy is associated with enduring pharmacodynamic changes^{39, 40}, that may influence the firing rate of STN neurons differently in advanced PD patients compared to those at an earlier stage of the disease.

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Figure 1. Neuronal background noise in the subthalamic nucleus, measured by the root mean square of STN recordings, was significantly lower in the early PD group compared to the advanced PD group ($p < 0.05$).

Figure 2. Distribution of (a) firing frequency, (b) burst index values, and (c) interspike interval coefficient of variability of single units in the subthalamic nucleus of early and advanced PD groups. The median firing frequency was significantly lower in early PD versus late PD ($p < 0.01$). Burst index and interspike interval coefficient of variability values were not significantly different between groups ($p > 0.05$).

Table 1

Clinical characteristics of subjects*

	Early PD	Advanced PD
Gender	1F 7M	1F 7M
Age (years)	57.5 ± 1.6 [52 – 67]	57.4 ± 1.7 [52 – 66]
Years on PD medication	3.1 ± 0.8 [0.6 – 7.4]	10.3 ± 1.2 [6.4 – 17.3]
Levodopa equivalent dose (mg/day)	360 ± 150 [50 – 1250]	1210 ± 183 [350 – 1750]
UPDRS-III⁺ Off medication	27.0 ± 3.1 [15 – 41]	42.3 ± 4.0 [25 – 60]
UPDRS-III⁺ On medication	11.9 ± 2.3 [2 – 21]	17.1 ± 4.9 [2 – 49]
UPDRS-III⁺ Improvement (On vs Off)	61% ± 24% [18% – 96%]	55% ± 22% [43% – 87%]

* mean ± standard error [range]

⁺ Unified Parkinson's Disease Rating Scale part III (motor subscale)