Real-time classification of target borders during deep brain stimulation surgery

**Thesis for the degree of
“Doctor of Philosophy”**

**By
Dan Valsky**

Submitted to the Senate of the Hebrew University of Jerusalem

February 2021

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**This work was carried out under the supervision of
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ABSTRACT

Human patients with advanced Parkinson's disease (PD) and dystonia are often treated by Deep Brain Stimulation (DBS), which can alleviate the clinical symptoms of the disease. The most common brain targets are the subthalamic nucleus (STN) and the globus pallidus internus (GPi). These targets have been proven to be surgically safe and beneficial over time.

Achieving a positive therapeutic response without adverse side effects depends to a large extent on the DBS lead location. Many medical centers use electrophysiological mapping techniques; i.e., multiple (1-5) track microelectrode recordings (MER) to optimize target selection during the implantation of DBS leads. The three MER criteria for implantation into the STN and GPi are the length of the recorded trajectory in the nucleus, the presence of movement-responsive neurons, and the span of the therapeutic window which is usually defined as the distance from the borders of the adjacent axonal tracts. Currently, the demarcation of the borders and subdomains of DBS targets must be done manually by a neurophysiologist. The process of delineation of the STN-substantia nigra pars reticulata (SNr) and the striato-pallidal transitions along pre-planned trajectories is time-consuming and may be biased, leading to a sub-optimal location of the DBS lead. Several previous studies developed detection procedure to discriminate the STN from the white matter (Moran et al., 2006; Zaidel et al., 2009). Part one of my PhD reports the development of a real-time machine learning algorithm for the classification of both the uninterrupted STN-SNr transition (Valsky et al., 2017) and striato-pallidal borders (Valsky et al., 2020).

Striatal dysfunctions play a key role in the pathophysiology of PD and dystonia, but current understanding of the changes in the discharge rate and pattern of striatal projection neurons (SPNs) remains limited. The basal ganglia (BG) are often divided into low versus high frequency discharge nuclei; i.e., the striatum versus the STN, globus pallidus externus (GPe), GPi, and the SNr. Circuitry models of PD are based on striatal dopamine loss and aberrant striatal inputs to the BG network. To date, striatal activity has not been extensively studied during electrophysiology-guided mapping in patients undergoing DBS procedures primarily because of unsuitable mapping techniques or surgical time restrictions on recordings in the striatum.

By analyzing the spatial and spectral characteristics of the striatum, GPe and GPi MERs, we discovered that pathological beta-oscillations comprised a continuous stretch within the GPi in PD (Valsky et al., 2020). This contrasts with the GPe in PD that forms gradient beta-oscillations as a function of the distance from the ventral border. We then observed that the spatial distribution of low-frequency activity for both the GPe and GPi was nearly identical across genetic and non-genetic dystonia patients. In contrast, the GPe and GPi in PD exhibited both tremor (4-5 Hz) and beta frequency oscillations. We discovered a similar striatal spatial oscillatory distribution across the PD, genetic and non-genetic dystonia patients.

After pooling data across all subjects and averaging across electrode trajectories, we found a unique signature in the striatum of both the non-genetic and genetic dystonia classes under light anesthesia consisting of an alpha (8-12 Hz) oscillation (Valsky et al., 2020). In contrast, the striatum in awake genetic and awake non-genetic dystonia patients displayed no oscillations. We then observed a peak in the high beta range (20-30 Hz) of the GPi in the non-genetic awake dystonia patients. In contrast, the power spectra of the GPi in the genetic dystonia patients in

both the lightly anesthetized and awake patients displayed decreased beta-oscillatory activity. These properties contribute to the goal of identifying the accurate DBS lead placement in an automatic and unbiased way.

There is an ongoing debate in the literature as to whether the spiking activity of SPNs is grossly abnormal, as reported by Singh et al., (2016) in humans and monkeys, or not, as reported by several groups in mice and monkeys (Deffains et al., 2016a; Ketzef et al., 2017; Maltese et al., 2019b). To better understand striatal firing abnormalities, in part two of my research, I recorded and examined striatal firing abnormalities in PD and dystonic patients undergoing DBS surgeries (Valsky et al., 2020). I utilized a machine learning algorithm to automatically detect the striato-GPe border, and applied objective methods for the identification of striatal units and the quantification of their isolation quality and stationarity. Contrary to long-standing assumptions, I found no evidence for SPNs dysfunction, and that spike sorting errors were the likely cause of the perceived changes in neuronal firing rates in previous studies. The results showed that the firing rates and firing patterns of striatal neurons in PD patients did not differ significantly from those in patients with dystonia. Although some disease-dependent differences were initially observed in firing rate and burst firing, these disappeared when the analysis was restricted to well-isolated stationary recordings (Valsky et al., 2020).

Overall, the findings from this PhD thesis reveal that machine learning methods can provide an accurate confirmation of the STN-ventral and striato-pallidal borders without requiring input from an expert physiologist. These algorithms can thus minimize operating time and lead to outcome optimization in both STN and GPi DBS surgery. This machine learning method also helps resolve the long-standing controversy over the nature of striatal dysfunction in PD and suggests that changes in BG pathophysiology likely arise from structures outside the striatum.

Letter of contribution

This dissertation is made up of three publications that summarize research carried out primarily by Dan Valsky, under the supervision of Prof. Hagai Bergman. The three articles were published in peer-reviewed journals. Dan Valsky is the lead author in all the three, which are listed below.

- I. Designing a method for the automatic, fast and reliable detection of the subthalamic borders

Valsky, D., Marmor-Levin, O., Deffains, M., Eitan, R., Blackwell, K. T., Bergman, H., & Israel, Z. (2017). Stop! border ahead: Automatic detection of subthalamic exit during deep brain stimulation surgery. *Movement disorders : official journal of the Movement Disorder Society*, 32(1), 70–79. <https://doi.org/10.1002/mds.26806>

- II. Designing a real-time striato-pallidal border detection method

Valsky, D., Blackwell, K. T., Tamir, I., Eitan, R., Bergman, H., & Israel, Z. (2020). Real-time machine learning classification of pallidal borders during deep brain stimulation surgery. *Journal of neural engineering*, 17(1), 016021. <https://doi.org/10.1088/1741-2552/ab53ac>

- III. Determining the true discharge rate and pattern of the striatal projection neurons in Parkinson's disease and dystonia

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INTRODUCTION

I. Pathophysiology of Parkinson's disease and dystonia

Parkinson's disease (PD) and dystonia are two of the most common movement disorders, and have a wide spectrum of etiologies and clinical presentations. To date, the pathophysiology of PD and dystonia is still unclear. Traditionally, PD is attributed to the degeneration of the midbrain dopaminergic neurons which also disrupts other neuromodulatory systems, including the cholinergic, serotonergic and histaminergic systems (Bolam and Ellender, 2016; Fox et al., 2009). Although there is no degeneration of the midbrain dopaminergic neurons in dystonia, an imbalance between the midbrain dopaminergic and striatal cholinergic systems (Aosaki et al., 2010; Benarroch, 2012; Bonsi et al., 2011), as well as cerebellar dysfunction (Fremont et al., 2017; Helmich, 2018; Tewari et al., 2017) are present in both PD and dystonia. Nevertheless, BG dysfunction is still regarded as the source of the cardinal symptoms of both diseases (Mink, 1996; Wichmann, 2018).

II. Clinical symptoms and treatments for Parkinson's disease

Parkinson's disease (PD) is the most common basal ganglia (BG) movement disorder, affecting more than 1% of the elderly population (Bennett et al., 1996). Four motor symptoms constitute the main deficits in PD: slowness of movement (bradykinesia and akinesia), tremor, rigidity, postural instability and gait deficits. Other deficits (e.g., cognitive and emotional) also frequently accompany the motor symptoms of PD and its treatment (Dubois and Pillon, 1997; Murray, 1996). The conventional treatment of PD consists of dopamine replacement therapy, which includes dopamine precursors (e.g., levodopa), dopamine agonists as well as dopamine reuptake and catabolic inhibitors. However, after several years, severe side effects caused by this medical treatment usually develop (such as on-off fluctuation and levodopa induced dyskinesia), and patients become candidates for treatment with an invasive surgical procedure.

III. Deep brain stimulation for treating motor symptoms of PD and dystonia

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and the internal segment of the globus pallidus (GPi) is currently the most widespread and effective surgical procedure for advanced PD (Anderson et al., 2005; Odekerken et al., 2016; Okun et al., 2009; Weaver et al., 2012) and dystonia (Coubes et al., 2004; Krause et al., 2004; Ostrem and Starr, 2008; Vidailhet et al., 2005; Volkmann et al., 2012), with over 150,000 patients treated worldwide (Saenger et al., 2017). Implanting the DBS lead in the optimal location is critical, in that recent data from North American databases suggest that the rate of revision and removal of DBS leads is between 15.2 and 34.0%, whereas up to 48.5% of revisions are due to sub-optimally placed electrodes (Rolston et al., 2016).

IV. Process for locating the DBS target borders and nearby structures

Mis-localization of the electrodes in the structures surrounding the DBS target may cause unacceptable side effects (Benabid et al., 2009; Castrioto et al., 2014). Therefore, the current approved methods to locate the DBS target borders in the brain (both the STN and GPi for PD) involve the use of a combination of stereotactic imaging protocols and measurements of the electrical activity of brain cells, the assessment of the therapeutic impact of stimulation and adverse effects. Although recent imaging protocols have been able to improve targeting

(Thompson et al., 2017), electrophysiology is still considered by many experts to be necessary to identify and verify the target's functional borders intraoperatively (Lozano et al., 2018). This is due to the inherent resolution limitations of neuroimaging, possible anatomic brain shifts during DBS surgery (Choi et al., 2018; Halpern et al., 2008; Khan et al., 2008), as well as differences in the connectivity and physiology of subdomains of the same anatomical nucleus.

As part of the standard clinical protocol, electrical data are collected from spike range (e.g., 300-6000 Hz) recordings, in a procedure called microelectrode recordings (MERs). MER is done today in discrete steps (i.e., 100, 500 and 1000 micrometers) along the route to the target. Usually, the demarcation of the STN and GPi borders is performed manually by a neurophysiologist. The exact detection of the STN-exit and striato-pallidal borders is considered difficult by many experts. Since DBS is carried out today in more than 1000 centers world-wide, there is a lack of electrophysiological expertise in many centers.

The detection of the *dorsolateral* region of the STN (STN entry) is based on clear-cut changes in electrical activity in the form of a sharp increase in MER activity (Moran et al., 2006; Zaidel et al., 2010). In contrast, several factors can make the electrophysiological determination of the *ventral* STN border more difficult. For example, an uninterrupted STN- substantia nigra pars reticulata (SNr) transition is less easy to detect because in this case there is no decrease in MER activity. In addition, the cells in the STN ventral domain have firing characteristics (reduced beta band and tremor frequency oscillations) resembling SNr cells (Bejjani et al., 2000; Benazzouz et al., 2002; Hutchison et al., 1998; Rodriguez-Oroz et al., 2001; Sterio et al., 2002). Finally, the electrophysiological determination of the STN exit can be challenging because white matter gaps in the STN may lead to erroneous early detection of STN exit (Moran et al., 2006).

Similarly, several factors can make the electrophysiological determination of the striato-pallidal borders challenging, in particular the case of an uninterrupted GPe-GPi transition (Schiff et al., 2002), since there is no decrease in neural activity. In addition, the cells in the striatum may have transient episodes of high-frequency action potentials (injury potentials, provoked by movements of the microelectrode) resembling GPe cells (DeLong, 1971; Lozano and Hutchison, 2002; Vitek et al., 1998). Finally, in patients under general deep anesthesia there may be a significant suppression of both spontaneous and evoked neuronal discharges from pallidal neurons (Hutchison et al., 2003; Venkatraghavan et al., 2016). Therefore, electrophysiological determination of the STN and striato-pallidal borders can be ambiguous, leading to suboptimal location of the DBS lead and inadequate clinical outcomes.

V. Striatal recordings in humans, primates, and rodents

The striatum (i.e., the main input structure of the BG network) is the main recipient of midbrain dopaminergic neurons (Menegas et al., 2015) and also receives di-synaptic cerebellar projections (Bostan et al., 2013; Hoshi et al., 2005). Most [~95% and ~70-80% in rodents and primates, respectively (Graveland et al., 1985; Petryszyn et al., 2018, 2014)] striatal neurons are medium spiny projection neurons (SPNs) that receive afferents from the cortex and the thalamus, and together with the STN neurons, innervate the central (i.e., GPe) and output (i.e., GPi and SNr) BG structures (Albin et al., 1989; Gerfen et al., 1990). Therefore, alterations in striatal signaling disrupt normal BG activity and may lead to the manifestation of the motor and non-motor symptoms of PD and dystonia (Albin et al., 1989; Bergman et al., 1990; Gerfen et al., 1990).

Dysregulation of BG activity may consist of changes in discharge rate (Albin et al., 1989; Gerfen et al., 1990). Unlike in all other BG structures, extracellular recordings of spiking activity in non-human primates (NHPs) reveal that SPNs have a very low discharge rate (~1-2Hz at rest) and are phasically active (i.e. they emit short bursts) around relevant behavioral events (Crutcher and DeLong, 1984; Kimura et al., 1990). However, previous studies of the BG in the NHP model of PD have mainly focused on the STN, GPe and GPi which are structures with a high frequency tonic discharge (i.e. 25-70Hz at rest) (Deffains et al., 2016a; Fillion and Tremblay, 1991; Wichmann and DeLong, 2003). These studies have reported excessive GPi/SNr discharge rates in PD that lead to an increase in BG inhibitory outputs to the thalamus and the frontal cortex motor areas (Wichmann and DeLong, 2003). Conversely, it is assumed that dystonia (and other hyper-kinetic states) are characterized by reduced GPi/SNr activity (Guehl et al., 2009).

More recent studies of the BG in animal (rodent and NHP) models of PD and human patients (undergoing DBS procedures) have dealt with changes in discharge patterns and synchronization. Parkinsonism-related β oscillations have been observed in local field potentials (LFPs) recorded in all BG structures, including the striatum (Deffains et al., 2016a; Kondabolu et al., 2016; Lemaire et al., 2012; Singh and Papa, 2019). Similarly, low frequency (4-12Hz) LFP oscillations have been recorded in the BG network of dystonic patients (Piña-Fuentes et al., 2018; Silberstein et al., 2003). Finally, β oscillations are commonly observed in the spiking activity of the STN, GPe and GPi of MPTP-treated monkeys (Deffains et al., 2016a; Soares et al., 2004) and PD patients (Kühn et al., 2005; Moshel et al., 2013; Silberstein et al., 2003; Valsky et al., 2020a; Zaidel et al., 2010).

Nevertheless, direct evidence of abnormal activity of the striatal SPNs is still elusive. Previous studies utilizing the NHP model of PD reported striking increases (~15-fold increase from the normal discharge rate of ~1-2Hz) in the firing rate of the SPNs subsequent to striatal dopamine depletion and the induction of parkinsonism (Singh et al., 2016). The same research group also reported a high discharge rate of SPNs recorded in PD and dystonic patients (~30Hz and 9Hz, respectively) (Singh et al., 2016). They also found a significant change in the firing pattern of striatal neurons, with many SPNs exhibiting bursting activity in PD patients and MPTP monkeys as compared to a smaller fraction in patients with dystonia. Finally, the SPNs of patients with an essential tremor (ET, regarded as a non-BG disorder) have a very low discharge rate (~2Hz) and no tendency to burst, as reported in normal NHPs (Liang et al., 2008; Singh et al., 2016).

These spectacular changes in the discharge rate and pattern of SPNs in the NHP model of PD run counter results obtained in our research group. Deffains et al. recorded the activity of SPNs and other BG neurons in Vervet monkeys before and after systemic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment and the induction of severe parkinsonian symptoms. Although Deffains et al. found robust changes in the discharge properties (rate, pattern and synchronization) of the STN, GPe and BG output structures, they did not observe any difference in the discharge rate (~2-3Hz) or pattern of SPNs in the MPTP-treated monkeys in comparison to the recordings in the same monkeys before MPTP treatment (Deffains et al., 2016a; Deffains and Bergman, 2019).

Extracellular recordings of SPN spiking activity of anesthetized (Mallet et al., 2006; Sharott et al., 2017) and awake (Chen et al., 2006; Kish et al., 1999) rats before and after striatal dopamine

depletion by 6-hydroxydopamine (6-OHDA) treatment have revealed a significant, but very slight increase in the SPN discharge rate. Rodent studies make it possible to differentiate between SPNs expressing D1 and D2 dopamine receptors. A significant imbalance in the discharge rate and calcium dynamics of D1 and D2 SPNs was observed in the dopamine-depleted striatum (Mallet et al., 2006; Parker et al., 2018; Sharott et al., 2017). In particular, D2 SPNs increased their discharge (Mallet et al., 2006; Sharott et al., 2017) and were also prone to being entrained to parkinsonian β oscillations (Sharott et al., 2017). Nevertheless, the absolute increase in the discharge rate even of the D2 SPNs was still modest (from ~ 0.5 to ~ 2.8 Hz) (Sharott et al., 2017). Moreover, recent studies have reported no significant increase in the low discharge rate of either SPN subpopulation in striatal dopamine-depleted mice (Ketzev et al., 2017; Maltese et al., 2019b).

Since only one research group has recorded drastic increases in the spontaneous spiking activity in the striatum of PD patients in comparison to either dystonic patients or the normal levels of striatal activity reported in healthy animals (Singh et al., 2016), we examined our human patient data to determine whether we could report similar changes.

RESEARCH GOALS

Designing a method for the automatic, fast and reliable detection of the subthalamic borders

In Part I of my PhD thesis, I designed an automatic method for the detection of the STN-substantia nigra pars reticulata (SNr) transition, based on a characterization of their electrical activity. Existing methods (Danish et al., 2008; Falkenberg et al., 2006; Zaidel et al., 2009), are successful in identifying the STN-white matter transitions, but are not as reliable in identifying the STN-SNr transition. To improve the detection of STN-SNr transition as well as the lower border of the STN, I developed a computational analysis method that utilizes MER power spectra and allows for real-time, high accuracy discrimination between STN and SNr (Valsky et al., 2017).

Designing a real-time striato-pallidal border detection method

In Part II, I addressed the current need for improved MER analysis during GPi targeting. I developed a classification system to enable neurosurgeons to actively track the delineation of the pallidal borders along pre-planned trajectories. Recent work in pallidal physiological mapping (Alam et al., 2016; Neumann et al., 2017; Wang et al., 2018) has underscored the potential value of intraoperative computer-aided classification of the borders. I utilized a dataset covering five classes of disease to train the classification algorithm composed of awake Parkinson's disease patients, as well as awake and lightly anesthetized both genetic and non-genetic dystonia patients. I designed a machine learning algorithm to provide predictions of the pallidal borders, based on hidden Markov models and the L_1 -distance measure in RMS and power spectra of the MER. I tested the machine learning algorithm's performance prospectively against the judgment of three electrophysiologists in the operating rooms of three hospitals (Hadassah-Hebrew University Medical Center, Sourasky Medical Center, and Rabin Medical Center) using newly collected data (Valsky et al., 2020).

Determining the true discharge rate and pattern of the striatal projection neurons in Parkinson's disease and dystonia

There is an ongoing debate in the literature as to whether the spiking activity of SPNs is grossly abnormal, as reported by Singh et al., (2016) in humans and monkeys, or not, as reported by several groups in mice and monkeys (Deffains et al., 2016a; Ketzef et al., 2017; Maltese et al., 2019b). To date, striatal activity has not been extensively studied during electrophysiology-guided mapping in patients undergoing DBS procedures primarily because of unsuitable mapping techniques or surgical time restrictions on recordings in the striatum. To better understand striatal firing abnormalities, in part III of my PhD thesis, I recorded and examined striatal firing abnormalities in PD and dystonic patients undergoing DBS surgeries (Valsky et al., 2020). I utilized a machine learning algorithm to automatically detect the striato-GPe border, and applied objective methods for the identification of striatal units and the quantification of their isolation quality and stationarity (Valsky et al., 2020).

METHOD

Patients and surgery

In total, 7,204 (131 trajectories, 81 patients) and 11,774 (148 trajectories, 52 patients) MER segments of background spiking activity undergoing STN and GPi DBS surgery were analyzed in this thesis. For the STN-exit detection study (Results I), the neuronal database was split into two parts. The training dataset was composed of 58 trajectories (obtained from 30 PD patients) containing 2678 stable MER segments. Seventy-three additional trajectories recorded from 51 other patients, yielding 4526 stable MER segments (test dataset) used solely to test the robustness of the HMM detection. For the striato-GPe-GPi detection study (Results II), a total of 116 microelectrode trajectories (42 PD and dystonia patients) aimed at the GPi in five classes of disease were analyzed, yielding a total of 11,774 MER segments. The five classes included: awake PD patients, awake and lightly anesthetized genetic and non-genetic dystonia patients. For the striatum study (Results III), a total of 93 microelectrode trajectories aimed at the GPi were analyzed (48 in PD and 45 in dystonia), yielding a total of 933 and 718 MER segments within the posterior putamen of patients suffering from PD and dystonia, respectively. A total of 16 PD and 13 dystonic (non-genetic and genetic dystonia) patients were involved.

All patients met the criteria for DBS and signed written informed consent for surgery that involved microelectrode recordings. The studies were authorized and approved by the Institutional Review Board of Hadassah Hospital in accordance with the Helsinki Declaration (reference code: 0168-10-HMO).

Surgery was performed using a CRW stereotactic frame (Radionics, Burlington, MA, USA). BG target coordinates were chosen as a composite of the indirect anterior commissure-posterior commissure (AC-PC) atlas-based location and direct (1.5 or 3Tesla) T2 magnetic resonance imaging, using Framelink 4 or 5 software (Medtronic, Minneapolis, USA).

Data acquisition

The data were acquired using two systems: MicroGuide (prior to 2015, previously described in (Castrito et al., 2016)) and Neuro Omega (from 2015, Alpha Omega, Nazareth, Israel). In the Neuro Omega system, raw and spiking signals were amplified by 20, and sampled at 44 kHz by a 16-bit A/D converter (using ± 1.25 V input range; i.e., ~ 2 - μ V amplitude resolution).

The raw signal was bandpass filtered from 0.075 to 10k Hz, using a hardware 2 and 3 pole Butterworth filter, respectively. The spiking signal was bandpass filtered from 300 to 9000 Hz, using a hardware 4-pole Butterworth filter.

In the MicroGuide system (Alpha Omega Engineering, Nazareth, Israel), neurophysiological activity was recorded via polyamide coated tungsten microelectrodes (Alpha Omega) with an impedance mean $\pm$ the standard deviation (SD): $0.63 \pm 0.16 \text{ M}\Omega$ (measured at 1 kHz at the beginning of each trajectory). The signal was amplified by 10,000 or 25,000, band-passed from 250 to 6,000 Hz, using a hardware four-pole Butterworth filter, and sampled at 24 or 48 kHz by a 12 bit A/D converter (using $\pm 5 \text{ V}$ input range).

Microelectrode recordings

For each recording session in the STN DBS, for both the left and right hemispheres, a MER trajectory using one or two parallel microelectrodes (2 mm apart) was made, starting 10 mm above the pre-operative T2 MRI image-based calculated target (center of the dorsolateral STN). Trajectories followed a double-oblique approach towards the dorsolateral STN target, which was designed to avoid the cortical sulci, the ventricles and major blood vessels. Therefore, although primarily in a dorsal-ventral direction, the trajectories also took an anterior-posterior and lateral-medial course. A typical trajectory was approximately 60 degrees from the axial AC-PC plane and 15 degrees from the mid-sagittal plane.

On each recording session in the GPi DBS, a MER exploration was made starting 15 mm above the calculated target. Our trajectories followed a double-oblique approach (50 to 80° from the axial AC-PC plane and 0 to 10° degrees from the midsagittal plane) through the posterior putamen and the GPe and towards the ventral border of the posterior-lateral portion of the GPi target. The "central" electrode was directed at the ventral border of the posterior-lateral portion of the GPi and the "anterior" electrode was located 2mm anterior/ventral to the central electrode in the parasagittal plane. Some of these recordings were made by a single microelectrode trajectory (instead of two) to accommodate cortical anatomy under the burr hole and brain blood vessels.

MER segments were regularly sampled in space to avoid recording bias towards particular striatal units. For all the DBS surgeries, the step size between two MER segments ranged from 100 to 200 μm and was controlled by the neurophysiologist to achieve optimal identification of the borders. At each step, MER segments were recorded from 4 to 140s (after a 2-s signal stabilization period).

Software and Statistics

In this thesis, the striatal, GPe, GPi and STN MERs were subjected to root mean square (RMS), power spectral density (PSD) analysis, offline spike sorting, support vector machine (SVM) and cluster analysis, as well as advanced methods such as a hidden Markov model (HMM). These techniques are presented in the method sections of the respective articles (Results I- III).

RESULTS

- I. Designing a method for the automatic and reliable detection of the subthalamic borders
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Stop! Border Ahead: Automatic Detection of Subthalamic Exit During Deep Brain Stimulation Surgery

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ABSTRACT: Background: Microelectrode recordings along preplanned trajectories are often used for accurate definition of the subthalamic nucleus (STN) borders during deep brain stimulation (DBS) surgery for Parkinson's disease. Usually, the demarcation of the STN borders is performed manually by a neurophysiologist. The exact detection of the borders is difficult, especially detecting the transition between the STN and the substantia nigra pars reticulata. Consequently, demarcation may be inaccurate, leading to suboptimal location of the DBS lead and inadequate clinical outcomes.

Methods: We present machine-learning classification procedures that use microelectrode recording power spectra and allow for real-time, high-accuracy discrimination between the STN and substantia nigra pars reticulata.

Results: A support vector machine procedure was tested on microelectrode recordings from 58 trajectories that included both STN and substantia nigra pars reticulata that achieved a 97.6% consistency with

human expert classification (evaluated by 10-fold cross-validation). We used the same data set as a training set to find the optimal parameters for a hidden Markov model using both microelectrode recording features and trajectory history to enable real-time classification of the ventral STN border (STN exit). Seventy-three additional trajectories were used to test the reliability of the learned statistical model in identifying the exit from the STN. The hidden Markov model procedure identified the STN exit with an error of 0.04 ± 0.18 mm and detection reliability (error < 1 mm) of 94%.

Conclusions: The results indicate that robust, accurate, and automatic real-time electrophysiological detection of the ventral STN border is feasible. © 2016 International Parkinson and Movement Disorder Society.

Key Words: subthalamic nucleus; substantia nigra; deep brain stimulation; Parkinson's disease; microelectrode recording

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Surgical treatment for advanced Parkinson's disease (PD) includes high-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN), which has proved to be surgically safe and beneficial over time.^{1–4}

In some patients, mood disorders such as depression⁵ or manic symptoms^{6–11} may be observed after stimulation as a result of suboptimally placed DBS leads. By contrast, the combined stimulation of the substantia nigra pars reticulata (SNr) and STN may improve freezing of gait in patients with advanced PD.^{10,11} Therefore, accurate differentiation of the STN from the SNr is essential for achieving optimal therapeutic benefit while avoiding psychiatric complications.

Microelectrode recordings (MERs) along preplanned trajectories are often used for improved delineation of the location of the STN during DBS surgery for Parkinson's disease. The detection of the *dorsolateral* region of the STN is based on clear-cut changes in electrical activity in the form of a sharp rise in the total power of the MER (as measured by the root mean square [RMS]),¹² the tremor frequency, and the β -oscillatory activity (13-30 Hz).¹³ In contrast, several factors can make electrophysiological determination of the *ventral* STN border more difficult, in particular, an uninterrupted STN-SNr transition, because in this case there is no drop in activity (or RMS). In addition, the cells in the STN ventral domain have firing characteristics (reduced β -band and tremor-frequency oscillations) resembling SNr cells.¹⁴⁻¹⁸ Finally, electrophysiological determination of the STN exit can be challenging because white matter gaps in the STN may lead to erroneous early detection of STN exit.¹² Therefore, the electrophysiological determination of the STN ventral border can be ambiguous and occasionally difficult to define.

Although recent imaging studies have been able to improve the differentiation between the STN and the SNr,¹⁹ electrophysiology is still necessary to identify and verify the STN-SNr transition intraoperatively. To facilitate detection of the transition, this article describes a new automatic, reliable procedure for locating the STN exit. Earlier automatic methods that use RMS values^{12,20-23} were successful in identifying STN-white matter (STN-WM) transitions, but were not as good for the direct STN-SNr transition. To improve the STN-SNr transition and STN lower border detection, we developed a computational analysis procedure that capitalizes on several features from the power spectra of the MER and allows for high accuracy discrimination between the STN and the SNr.

Patients and Methods

Patients and Surgery

MERs were analyzed from 131 microelectrode trajectories that passed through both the STN and the SNr of 81 Parkinson's disease patients undergoing bilateral STN DBS implantation. The patients' demography and clinical state were as follows: mean age, 62.1 years; mean disease duration, 10.3 years; 36% female, mean Unified Parkinson's Disease Rating Scale — part III (UPDRS III) score OFF/ON therapy before surgery, 51.1/19.4; and mean levodopa equivalent dosage before surgery, 849.6 mg/day. Patient demographic information appears in Supporting Information Table S4. This study was authorized and approved by the Institutional Review Board of Hadassah Hospital in accordance with the Helsinki Declaration (reference code HMO-0064-12). All patients were awake during surgery. Further

details on the surgical procedure and data acquisition can be found in our previous reports.^{12,23}

Microelectrode Recordings

For both the left and right hemispheres, 1 or 2 parallel microelectrodes were inserted, and the recording started 10 mm above the calculated target. Our trajectories followed a double-oblique approach toward the dorsolateral STN target. In most cases, 2 microelectrodes were used (Fig. 1A). A “central” electrode was directed at the center of the dorsolateral STN target (as per imaging) and often traversed the STN and entered the SNr without passing through the white matter. An “anterior” electrode was advanced 2 mm anterior to the central electrode (in the parasagittal plane) and therefore crossed the STN-SNr area in a more ventral plane. In contrast to the central electrode, the anterior electrode often passed through the white matter before it entered the SNr. Analysis was not based on continuous recordings during the entire advance toward the dorsolateral STN target, but rather on segments of data recorded at specific points (without electrode movement; Fig. 1B). Segments of data were recorded for at least 4 seconds after 0.5 seconds of lowering the electrode. Further details on the microelectrode recordings and the intervals of the depths are presented as Supporting Information.

Neural Data Sets

We divided our neuronal database into 2 parts. The training data set was composed of 58 trajectories (obtained from 30 PD patients) containing 2678 stable MERs recorded in the white matter before the STN, STN dorsolateral oscillatory region (DLOR), STN ventromedial nonoscillatory region (VMNR), and white matter after STN and SNr. A subset of this data set, containing 1720 MERs from the dorsal and ventral STN as well as the SNr, was used for the support vector machine (SVM) procedure. The training data set of 58 trajectories was also used to find the optimal parameters for the hidden Markov model (HMM). Seventy-three additional trajectories recorded from 51 other patients, and yielding 4526 stable MERs (test data set), were used solely to test the robustness of the HMM detection.

Root Mean Square

The RMS estimate was calculated from the multi-unit activity recorded by the microelectrode at each electrode depth. RMS values are susceptible to electrode properties (eg, electrode impedance)¹²; hence, the RMS was normalized by the pre-STN (white matter) baseline RMS,^{12,23} creating what we term the normalized RMS (NRMS).

FIG. 1. Overview of STN targeting. (A) Schematic diagram of a typical trajectory of two parallel microelectrodes showing subcortical structures. STN- Subthalamic nucleus, SNr- Substantia nigra reticulata, ZI - zona incerta (B) One-second example of 14 representative raw signal traces (in descending order) out of the 82 recorded signal traces at various depths along the trajectory (a single DBS track) from a Parkinson's disease patient. The signal at each position was recorded for at least 4 seconds. The segment at 2.55 mm estimated distance to target (EDT) was recorded for a longer period of time than the others because responses to active and passive limb movements are tested. The traces indicate regions of internal capsule (white matter), dorsolateral oscillatory region (DLOR) STN, ventral medial non oscillatory region (VMNR) STN, white matter between STN and SNr; vertical bar indicates 256 μ V, horizontal bar indicates 100 ms. (C) Functional state model represents the anatomy which is sequentially encountered during micro-electrode recording of the STN detection. At all depths along the trajectory the electrode is in one of a finite set of states. Arrows between the states represent the possible state transitions. Solid lines depict a typical trajectory state sequence that proceeds through the first three states consecutively and then to the white matter between STN and SNr. Dotted lines depict: 1) a trajectory that enters the SNr immediately after the STN, 2) a trajectory that starts in the white matter and enters the VMNR, 3) one that goes directly into the SNr without passing through the STN.

Power Spectral Density (PSD)

Visual inspection of the average STN and SNr power spectra revealed significant differences in the 5-300 Hz domain. To identify the frequency band that contained the largest difference between the STN and the SNr, we divided the 5-300 Hz range of the power spectra into 10 approximately logarithmically spaced bands. For each band, we calculated the mean power for each MER and then evaluated the difference in the mean power between the STN and the SNr. Using this method, we identified which frequency bands had the largest difference between the STN and the SNr. Additional details are presented in the Supporting Information.

SVM Discrimination of STN and SNr MERs

In machine learning, SVMs are supervised learning models that are specifically designed to solve a classification problem off-line, after all the data have been collected. For our SVM analysis, measurements in both time and frequency domains (based on the NRMS and power spectra of the MERs) were used as features for the SVM classification. The classification procedure used the NRMS and the "100-150 Hz/5-25 Hz power ratio" features, as well as their class label (STN or SNr) for each of the 1720 MERs in the training data set. The performance of the SVM classifier was

evaluated by 10-fold cross-validation. Additional details are presented in the supporting information.

The SVM requires labeling the MERs of each region, which is not amenable to real-time use. Here we used the SVM to identify which features had the most information in terms of discriminating regions. However, once the optimal features had been selected, the SVM was no longer needed or used.

The Hidden Markov Model

The HMM takes the set of features extracted from the raw data as input and provides the output clustering in real time. In previous reports,^{23,24} the HMM procedure was used to discriminate the STN from the white matter. This study goes beyond these previous works by designing a HMM procedure with improved ability to detect the STN exit by delineating the borders between STN and SNr (even for cases without a WM gap between the STN and the SNr). Details on the HMM are provided in the supporting information.

All statistical analyses were performed using custom-made MATLAB 7.5 routines (Mathworks, Natick, MA). The statistics presented in this report, if not specified otherwise, are the mean $\pm$ standard error of the mean; the criterion for statistical significance was set at $P < 0.05$ for all statistical tests.

FIG. 2. STN-white matter transition versus STN-SNr transition. (A) Clearly defined STN-white matter (STN-WM) transition in three example trajectories (from three patients). The top three graphs represent the normalized root mean square (NRMS) analysis as a function of EDT. The bottom three graphs represent the power spectral distribution (PSD) spectrogram of the data, in relation to EDT on the x-axis. The arrow on each trajectory points to the transition between the STN and the WM (determined by an expert neurophysiologist). The green dashed lines represent the baseline of the NRMS (i.e., WM). (B) The same as in A, but for the STN-SNr transition. The power spectral density color-scale represents $10 \log_{10}$ (power spectral density / average power spectral density). The arrow on each trajectory points to the transition between the STN and the SNr (determined by an expert neurophysiologist). EDT = estimated distance to target (defined as the dorsolateral STN target according to preoperative imaging).

Results

Power Spectra Features Help to Discriminate STN From SNr Recordings

The NRMS values calculated from the MERs were very effective in detecting the STN border with the white matter. As presented in the 3 examples in Figure 2A (top), the STN-entry and STN-exit borders

appear as a sharp increase and decrease in the NRMS, respectively.^{12,23} In these “easy” cases the electrode traversed the STN and entered the SNr after passing through the white matter. The power spectra of these SNr (Fig. 2A, bottom) depict a unique signature: blue vertical lines indicating a reduction in relative power at lower frequencies. However, some trajectories lacked a clearly defined

FIG. 3. “100-150 Hz / 5-25 Hz Power Ratio” separates STN from SNr better than NRMS. (A) The left hand figure illustrates the NRMS distribution for dorsal STN (red), ventral STN (blue), SNr (green), white matter before STN (white), white matter after STN (gray). Right hand figure same as left, but three subcortical structures are superimposed on the x-axis, and show the overlap in NRMS distribution of the STN and the SNr. (B) The left hand figure illustrates the power spectral density as a function of the frequency, with a linear scale plot in the DLOR STN (red), VMNR STN (blue), SNr (green). The right hand figure is the same as left, but with a logarithmic scale plot of the x-axis. The shaded regions mark SEMs. (C) The left hand figure illustrates “100-150 Hz / 5-25 Hz Power Ratio” distribution in five regions. Right hand figure same as left, but has the three subcortical structures superimposed on the x-axes.

STN exit (eg, Fig. 2B). These are the “hard” cases in which there is no clear transient reduction in the NRMS (NRMS gap), most probably because the electrode traversed the STN and entered the SNr without passing through the white matter after the STN. Although the SNr cannot be identified by the NRMS in these cases, the SNr was identified by the electrophysiologist and can be seen in the power spectra (Fig. 2B, bottom), as depicted by the vertical blue lines. These examples suggest that power spectra

characteristics can be used to assist in detection of the STN exit, especially for cases without an STN-WM transition and NRMS gap.

To evaluate the ability of the NRMS to distinguish the STN from the SNr, we calculated the distribution of their NRMS values. Figure 3A shows the overlap in the NRMS distribution of 660 MERs in the STN DLOR, 990 MERs in the STN VMNR, and 155 MERs in the SNr (training data set). The significant overlap between the different distributions suggests

FIG. 4. A linear support vector machine classifier provides high performance discrimination between the STN and SNr populations. A support vector machine (SVM) classifier was trained and tested on 155 randomly selected samples from the STN and all 155 samples from the SNr, using NRMS and the “100-150 Hz / 5-25 Hz Power Ratio” features. The linear-kernel decision boundary is used to classify the trained data for the SNr (hollow square; green) and the STN (hollow triangle; blue); then new data points are classified as SNr (solid square; green) or STN (solid triangle; blue). Yellow circles (within the hollow squares and triangles) represent the support vectors defining the decision boundary between the STN and SNr samples.

that there is no clear separation between the STN and the SNr using NRMS. In contrast, Figure 3B, illustrating the mean PSD of the STN and SNr recordings, suggests that features from the PSD could be used to discriminate the STN from the SNr. In line with the characteristic signature of the STN and SNr in the spectrograms (Fig. 2), the average PSDs of the 2 STN domains and the SNr revealed different nonoverlapping features. The mean SNr PSD (Fig. 3B, green trace) presented decreased activity in the 5- to 25-Hz band compared with the mean PSD of the STN DLOR and VMNR (Fig. 3B, red and blue traces). In addition, the mean PSD in the SNr displayed increased activity in the 85- to 300-Hz band (Fig. 3B, green trace).

To determine quantitatively which part of the power spectra enables the best discrimination of the STN from the SNr, we examined 10 (approximately logarithmically distributed) bands along the frequency axis in the power spectra. The mean power in 2 frequency bands — high frequency (100-150 Hz) and low frequency (5-25 Hz) — provided the greatest discrimination between the STN and the SNr (discrimination matrix of 10 bands presented in Supporting Information Table S1). We therefore calculated the ratio of the power of these 2 frequency bands and termed this new feature the 100-150 Hz/5-25 Hz power ratio. Figure 3C shows very little overlap in the distributions of STN and SNr power ratio values.

Support Vector Machine Analysis Confirms the Utility of the Power Ratio for STN-SNr Discrimination

An SVM classifier was used to examine the ability of the 100-150 Hz/5-25 Hz power ratio to provide robust discrimination between the SNr and the STN. Figure 4 shows the result of an SVM classifier that was trained and tested on 155 randomly selected samples from the STN and all 155 samples from the SNr. A linear-kernel decision boundary was used to classify the training set as SNr (hollow square; green) or STN (hollow triangle; blue), and then new data points were classified as SNr (solid square; green) or STN (solid triangle; blue). Yellow circles represent the support vectors defining the decision boundary between the STN and SNr samples. Figure 4 further demonstrates the absence of correlation between NRMS and the 100-150 Hz/5-25 Hz power ratio. Both these characteristics reinforce the utility of the power ratio feature as an additional attribute for classifying MERs. The discrimination performance of the SVM classifier for the entire training data set using 2 features, NRMS and 100-150 Hz/5-25 Hz power ratio, was evaluated by 10-fold cross-validation and is presented as an error matrix in Supporting Information Table S2. The overall classification accuracy rate was 97.6%.

Hidden Markov Model Analysis Enables Reliable Detection of STN Exit

The hidden Markov model (HMM) procedure uses MER features and trajectory history to enable real-time decisions about electrode placement. The use of trajectory history in addition to the MER features enables the HMM procedure to “neglect” recording glitches that a classification method (eg, SVM) would classify incorrectly. Our previous HMM procedures²³ did not include the SNr as a possible state and did not use the high frequencies (100-150 Hz) of the power spectrum. Here we extended the HMM procedure to discriminate between the STN and SNr using the 100-150 Hz/5-25 Hz power ratio and NRMS features, together with the depth of the trajectory (ie, estimated distance to the target). The distribution of STN-exit borders was evaluated and revealed that 77 of 131 trajectories (59%) had STN-WM transitions and that 54 of 131 trajectories (41%) had STN-SNr transitions.

Figure 5 presents 3 examples of a typical trajectory’s NRMS and PSD as well as the 100-150 Hz/5-25 Hz power ratio feature. At each depth along the trajectory during the implant process the NRMS and power spectra features of the MERs are continually calculated and updated. Based on these calculations a new assessment by the HMM is made automatically in real time. An expert physiologist lowers the electrode along the trajectory until the red line appears (ie, as

FIG. 5. Robust detection of the STN-SNr transition by the “100-150 Hz / 5-25 Hz Power Ratio” feature. Top and middle panels illustrate a typical trajectory's NRMS and PSD, respectively. Bottom panel represents the “100-150 Hz / 5-25 Hz Power Ratio” feature as a function of the estimated distance to target (EDT). The three sample trajectories illustrate the direct transition from the STN to SNr. The red line in the top panel illustrates the STN-SNr transition defined by the real time HMM analysis. The dashed green lines represent the baseline of the NRMS (i.e., WM). Each segment along the trajectory was recorded for at least 4 seconds, except for a few segments where responses to active and passive limb movements were tested. The data acquisition arrow marks the real duration of a single track of the example trajectories as a function of EDT. The total recording time of a single DBS track of the example trajectories from the left to the right column: 992 seconds, 622 seconds and 608 seconds. The HMM running time arrow shows the duration of the HMM processing as a function of the number of MERs (lower arrow). MERs = micro-electrode recordings.

determined by the real-time HMM analysis). This indicates that the STN ventral border has been reached, followed by either the SNr or white matter. The 3 example trajectories illustrate the direct transition from the STN to the SNr. The red line in the top panel illustrates the direct STN-SNr transition defined by the real-time HMM analysis. It takes 99 milliseconds in real time to process a new trajectory and

determine whether it is STN or not, as illustrated by the HMM running time in Figure 5. The time to analyze each subsequent MER is less than a millisecond per MER, making this a practical method for use during DBS surgery.

For each of the 58 trajectories in the training data set, the HMM parameters (transition and emission matrices) were estimated from the other 57 trajectories

(leave-one-out cross-validation). The resulting mean (of all 58 trajectories) HMM transition and emission matrices are presented in Supporting Information Table S3.

The performance of the HMM was assessed with 2 measures. The first is the mean OUT location error. It is defined as the difference between the *location* (*Human Expert's Classification*), which is the location of the transition defined by the neurophysiologist, and *location*(HMM), which is the HMM inferred location of the transition, both measured in millimeters of estimated distance to the target. The second measure is the OUT transition error, which is defined as an OUT location error greater than 1 mm. Hits were the number of correctly detected OUT transitions. Misses were the number of OUT transitions (according to the human expert's decision) that the HMM procedure did not detect.

The OUT location error for both STN-SNr and STN-WM demonstrated better mean and standard deviation than that found by previous methods.^{12,23} The performance of the OUT location error on the training data set had an error of 0.1 ± 0.34 mm (mean $\pm$ standard deviation), with 2 misses of 58 trajectories (97% hits).

The HMM procedure has to deal with a heterogeneous variation of trajectories, as some transitions are from VMNR STN to SNr and others from white matter before STN to SNr. Because an automatic detection algorithm that can be used in the operating room needs to function on novel data without being continually adjusted, it is important to demonstrate that the HMM procedure can work with completely novel data. Therefore, 73 other trajectories (from 51 patients, all trajectories included both the STN and SNr) were evaluated by the HMM procedure. The HMM procedure identified the STN exit with an error of 0.04 ± 0.18 mm. Using the 1-mm threshold, the OUT transition error of the novel data set committed 4 misses of 73 trajectories (94% hits), which is better than that found when applying the previous HMM procedure²³ and Bayesian method¹² (12 misses of 73 trajectories, 83% hits, and error = 0.50 ± 0.59 mm, respectively). The performance of the new HMM procedure was shown to be robust to the specified threshold because threshold values of 0.5 and 0.15 mm produced similar quantitative results (4 and 7 misses of 73 trajectories, respectively).

Discussion

We described a computational machine-learning procedure with a new feature, namely, the ratio of high-frequency (100-150 Hz) power to low-frequency (5-25 Hz) power, which enables high accuracy discrimination of the STN from the SNr. We used an SVM

procedure to verify that the 100-150 Hz/5-25 Hz power ratio is a reliable feature for discriminating the STN and SNr populations. Then, we utilized an HMM procedure using the MER features together with the trajectory history to detect the STN exit either to the white matter or SNr.

The MERs along preplanned trajectories are commonly used to confirm the STN territory during DBS surgery for Parkinson's disease; however, there is a lack of consensus on whether the MER allows for reliable separation between the STN exit point and the SNr entry point. Across the ventral region of the STN, there are fewer kinesthetic neurons,²² and the STN VMNR neurons are characterized by consistently reduced β -band and increased gamma (30-100 Hz) activity.¹³ Similarly, the discharge pattern of the neurons in the SNr (below the STN target) lacks the β -band and tremor-frequency oscillations, but has increased gamma activity.¹⁴⁻¹⁸ In addition, islands of cells have been observed with firing characteristics of both SNr and STN cells.²² Therefore, the electrophysiological determination of the transition from the STN to the SNr is ambiguous and difficult to evaluate.

Several studies have developed automatic detection and visualization not only for the STN, but also for the SNr based on objective and quantitative MER features.^{12,20,22,25-27} Some of these studies have used features that require spike detection algorithms to identify the firing pattern.²⁵⁻²⁷ Although these features may aid in detecting the STN ventral border near the SNr, it is still computationally challenging to calculate neuronal spike characteristics in a real-time intraoperative scenario.¹² Moreover, the ideal isolation of single units requires 5- to 10- μ m steps of electrodes and is very time consuming. In contrast, NRMS values that are based on unsorted multiunit activity are easy to measure. The STN entry and STN exit often manifest as a sharp increase and decrease in the NRMS, respectively.^{12,23} Some studies have used the NRMS together with spectral features of the analog signal, which are computationally efficient to calculate.^{20,22,27} However, these spectral features do not lead to reliable or robust identification of the transition between the STN and the SNr. Here, we divided the 5- to 300-Hz range power spectra into frequency bands. This division allowed us to determine which frequency bands contained the largest difference between the STN and the SNr and to accurately detect the STN ventral border.

When implementing the NRMS and features from the power spectra, there are several ways to differentiate the STN from the SNr using automatic detection methods. Some studies have proposed rule-based detection methods^{22,27}; however, they are unable to detect the direct STN-SNr transitions. For example, despite that Cagnan et al²⁷ used the power spectra of tremor and the alpha band (3-12 Hz), beta band (13-30 Hz), and

gamma band (31–100 Hz) as features, their algorithm still required a white matter gap in the trajectory between the STN and the SNr to detect the SNr. Furthermore, rule-based detection systems tend to be overly complex and may not generalize to other surgical centers. Other studies^{12,23,25} have used machine-learning techniques to automatically extract the “rules” or decision boundaries to discriminate between the STN and the SNr. These machine-learning procedures are either unsupervised and involve extracting patterns using unlabeled training data (that still require labeling of the output)²⁵ or supervised, which require the labeling of the electrophysiological signals used for training.^{12,23} For example, Wong et al²⁵ used a clustering algorithm (unsupervised machine learning) that returns a prespecified number of clusters, but then requires the human observer to label the clusters. The main drawback of these techniques is that they do not take the previous location of the MERs into account when determining the electrode’s current location. A supervised technique that uses the electrode’s location is HMM. For example, Zaidel et al²³ combined the power spectra of β -band features and NRMS to locate the STN and its subterritories. The 2 advantages of the HMM procedure are the short recording time needed for location analysis and low computational cost. Our approach goes beyond this previous work by delineating the borders between STN and SNr which thus enables intraoperative application with greater accuracy.

Accurate discrimination between the STN and the SNr is of crucial importance for achieving optimal therapeutic benefits while avoiding psychiatric complications for PD DBS procedures. The beneficial effects of bilateral STN DBS on motor symptoms and quality of life have been repeatedly confirmed in patients with advanced PD²⁸; however, psychiatric complications induced by STN DBS have also been reported.^{29,30} In some patients with PD with impulse control disorders, their abnormal behavior may be provoked by stimulation with a ventral contact of the DBS lead and suppressed by switching off this contact.^{6–9} It also has been reported that manic^{31,32} and depressive⁵ symptoms are induced by stimulation of active contacts located in the SNr. On the other hand, the SNr is thought to be particularly involved in balance control during gait.³³ The combined stimulation of the SNr and the STN has been reported to improve axial symptoms (including freezing of gait, balance, and posture) compared with standard STN stimulation.^{10,11} In summary, automatic and reliable localization of the direct STN–SNr transition and STN lower-border detection could lead to improved localization of DBS leads and better DBS clinical outcomes. It takes 99 milliseconds in real time to process a new trajectory and decide whether it is STN or not, making this a practical method for use during DBS surgery. This analysis tool can be easily learned

and employed in the DBS operating room. Future studies might incorporate MER data from multiple centers to test the applicability of these algorithms for automatic navigation in DBS surgery. ■

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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.

II. Designing a real-time striato-pallidal border detection method

- a. Valsky, D., Blackwell, K. T., Tamir, I., Eitan, R., Bergman, H., & Israel, Z. (2020). Real-time machine learning classification of pallidal borders during deep brain stimulation surgery. *Journal of neural engineering*, 17(1), 016021. <https://doi.org/10.1088/1741-2552/ab53ac>

PAPER

Real-time machine learning classification of pallidal borders during deep brain stimulation surgery

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PAPER

Real-time machine learning classification of pallidal borders during deep brain stimulation surgery

Dan Valsky^{1,9} , Kim T Blackwell², Idit Tamir³, Renana Eitan^{4,5,6}, Hagai Bergman^{1,7,8} and Zvi Israel⁸¹ The Edmond and Lily Safra Center for Brain Research (ELSC), The Hebrew University, Jerusalem, Israel² Department of Bioengineering, George Mason University, Fairfax, VA, United States of America³ Department of Neurosurgery, Rabin Medical Center, Petach Tikva, Israel⁴ Faculty of Medicine, Department of Medical Neurobiology, Hebrew University of Jerusalem⁵ Jerusalem Mental Health Center, Hebrew University Medical School, Jerusalem, Israel⁶ Functional Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States of America⁷ Department of Medical Neurobiology (Physiology), Institute of Medical Research—Israel-Canada (IMRIC), The Hebrew University-Hadassah Medical School, Jerusalem, Israel⁸ Department of Neurosurgery, Center for Functional and Restorative Neurosurgery, Hadassah-Hebrew University Medical Center, Jerusalem, Israel⁹ Author to whom any correspondence should be addressed.E-mail: dan.valsky@mail.huji.ac.il**Keywords:** Deep brain stimulation, Parkinson's disease, machine learning, striatum, dystonia, pallidum, light general anesthesiaSupplementary material for this article is available [online](#)**Abstract**

Objective. Deep brain stimulation (DBS) of the internal segment of the globus pallidus (GPi) in patients with Parkinson's disease and dystonia improves motor symptoms and quality of life. Traditionally, pallidal borders have been demarcated by electrophysiological microelectrode recordings (MERs) during DBS surgery. However, detection of pallidal borders can be challenging due to the variability of the firing characteristics of neurons encountered along the trajectory. MER can also be time-consuming and therefore costly. Here we show the feasibility of real-time machine learning classification of striato-pallidal borders to assist neurosurgeons during DBS surgery. **Approach.** An electrophysiological dataset from 116 trajectories of 42 patients consisting of 11 774 MER segments of background spiking activity in five classes of disease was used to train the classification algorithm. The five classes included awake Parkinson's disease patients, as well as awake and lightly anesthetized genetic and non-genetic dystonia patients. A machine learning algorithm was designed to provide prediction of the striato-pallidal borders, based on hidden Markov models (HMMs) and the L_1 -distance measure in normalized root mean square (NRMS) and power spectra of the MER. We tested its performance prospectively against the judgment of three electrophysiologists in the operating rooms of three hospitals using newly collected data. **Main results.** The awake and the light anesthesia dystonia classes could be merged. Using MER NRMS and spectra, the machine learning algorithm was on par with the performance of the three electrophysiologists across the striatum-GPe, GPe-GPi, and GPi-exit transitions for all disease classes. **Significance.** Machine learning algorithms enable real-time GPi navigation systems to potentially shorten the duration of electrophysiological mapping of pallidal borders, while ensuring correct pallidal border detection.

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and the internal segment of the globus pallidus (GPi) is the most common and effective surgical procedure for advanced Parkinson's disease (PD) [1–4] and dystonia [5–9], with over 150 000

patients treated worldwide [10]. Implanting the DBS lead in the optimal location is critical for optimal outcome. Recent data from North American databases suggest that in intracranial neurostimulation therapies up to 48.5% of revisions are due to suboptimally placed electrodes [11, 12]. Many studies of human intraoperative localization of DBS targets have focused

on the STN alone [13, 14]. However, there is increasing interest in identifying pallidal physiomarkers [15–17]. The GPi is the primary target for dystonia, and it is increasingly used for PD, based on the finding of equivalent motor benefits in three out of four randomized trials of STN versus GPi-DBS [1–4]. Two recent studies have reported that an inappropriate lead placement is the most common cause for the observed therapeutic failures of GPi-DBS in dystonia patients [18, 19].

Successful implantation of the DBS lead within the GPi may be facilitated by microelectrode recording (MER), which affords accurate spatial demarcation of the external segment of the globus pallidus (GPe) and GPi borders [20]. However, MER can be time-consuming and therefore costly. Here, we describe a computational method that enables neurosurgeons to actively track the delineation of the striato-GPe–GPi transitions along pre-planned trajectories. Recent work in pallidal physiological mapping [15–17] has not included intraoperative computer-aided classification of the striato-pallidal borders, or has not compared the spatial oscillatory distribution of the neuronal activity within striatum, GPe and GPi across different classes of the disease in awake and lightly anesthetized patients.

Several factors can make electrophysiological determination of the striato-pallidal borders challenging, in particular an uninterrupted GPe–GPi transition [21], since there is no decrease in neural activity. In addition, the cells in the striatum may have transient episodes of high-frequency discharge (due to injury potentials, provoked by movements of the microelectrode) resembling GPe cells [22–24]. Finally, in patients under light anesthesia there may be a significant suppression of both spontaneous and evoked neuronal discharges from pallidal neurons [25, 26].

Although recent imaging protocols have been able to improve GPi targeting [27], many experts still consider that electrophysiology is necessary to identify and verify target borders intraoperatively [28]. This is due to the inherent resolution limitations of neuro-imaging and co-registration techniques, and possible brain shifts during DBS surgery [29–31]. Shorter surgery times can also help limit the cerebrospinal fluid leak [32], and therefore brain shifts [29–31]. Because the method described here does not require spike detection algorithms or electrophysiology expertise to perform and interpret the findings, the duration of the electrophysiological mapping of the target is likely to be significantly shortened.

Methods

Patients

Patients with PD and isolated dystonia were recruited from the movement disorders clinics at the Hadassah Medical Center in Jerusalem. All patients were scheduled to undergo implantation of DBS electrodes

into the GPi and underwent MR imaging, and evaluation for motor and non-motor impairment within the 30 d prior to surgery. We recorded the neuronal extracellular activity from 32 patients with dystonia and ten patients with PD. In 13 patients with dystonia, recordings were performed in the awake state, without any sedation or anesthesia. In the other 19 dystonic patients, recordings were performed under light general anesthesia. Recordings in all PD patients were performed in the awake state, at least 12 h following withdrawal of dopaminergic medication. Ten additional patients were used to test the robustness of the algorithm, as explained in *Validation*. Patient demographic information appears in supplementary table S1 (stacks.iop.org/JNE/17/016021/mmedia). Written informed consent was obtained from all patients and the study was approved by the Institutional Review Board of Hadassah Hospital in accordance with the Helsinki Declaration (reference code: 0168-10-HMO).

Anesthesia

General anesthesia was induced with intravenous propofol ($1.5\text{--}2\text{ mg kg}^{-1}$) and alfentanil ($10\text{ }\mu\text{g kg}^{-1}$). Neuromuscular blockade was achieved with vecuronium (0.1 mg kg^{-1}) to facilitate endotracheal intubation. Anesthesia was then maintained with nitrous oxide in oxygen (70%:30%) and isoflurane (prior to 2016, 0.9%–1.2%) or sevoflurane (from 2016; 0.9%–2%). Before fixing the frame and the skin incision, local anesthetic (0.5% bupivacaine, 2% lidocaine 50:50) was injected. Pallidal spiking activity is highly dependent on the level of anesthesia. The deeper the anesthesia, the less spiking activity can be detected in the pallidum [25, 26]. To achieve light anesthesia, at least 10 min prior to MER, the nitrous oxide, isoflurane and sevoflurane dose were reduced to the point where single neuronal units could be observed (in the range of 0.1–0.3 minimum alveolar concentration (MAC) of nitrous oxide plus 0.2–0.3 MAC of isoflurane or sevoflurane; total MAC achieved 0.3–0.6 MAC). This level was not further adjusted during the course of MER, and was similar across all patients (with dystonia) operated under light general anesthesia included in this study. During the light anesthesia, neuromuscular blockade was continued, ambient light and noise in the operating room were reduced, and the heart rate and blood pressure were closely monitored. Subsequent to MER, anesthesia was restored to the range prior to MER. For surgeries that were performed without general anesthesia, the patients' fully aroused state was continuously confirmed by a team member.

Data acquisition

The data were acquired using two systems: MicroGuide (prior to 2015, previously described [33]) and Neuro Omega (from 2015, Alpha Omega, Nazareth, Israel). In the Neuro Omega system, raw and spiking signals were

amplified by 20, and sampled at 44 kHz by a 16-bit A/D converter (using ± 1.25 V input range; i.e. ~ 2 μ V amplitude resolution). The raw signal was bandpass filtered from 0.075 to 10 kHz, using a hardware 2 and 3 poles Butterworth filter, respectively. The spiking signal was bandpass filtered from 300 to 9000 Hz, using a hardware 4-poles Butterworth filter.

Microelectrode recordings (MERs)

For each hemisphere and for every recording session, an exploratory MER using one or two microelectrode trajectories (2 mm apart) was determined starting at 15 mm above the image-based calculated target. Our trajectories followed a double-oblique approach through the striatum and the GPe towards the ventral border of the posterior-lateral portion of the GPi target. The electrophysiological characteristics of these neighboring structures have been published elsewhere [22–24] and were used in the operating room to manually tag the borders of the structures. Some of these recordings were made by a single microelectrode trajectory (instead of two) to accommodate for cortical anatomy under the burr hole and brain blood vessels. The trajectory recordings were not continuous, but in steps as detailed below.

A total of 84 exploratory MERs (from one or two microelectrodes on each recording) were analyzed, yielding a total of 116 microelectrode trajectories aiming at the GPi. The analysis was based on portions of data recorded at specific points (i.e. different spatial locations) along the trajectory with the electrode stationary. We term these data MER segments because they are not totally independent from each other in the sense that in each microelectrode trajectory the data were recorded from the same electrode (same impedance) and the same hemisphere. We recorded a total of 1174 MER segments within the Str, GPe and GPi.

MER segments were regularly sampled in space. For all our GPi-DBS surgeries, the depth steps of the recorded signals ranged from 200 μ m to 100 μ m and were controlled by the neurophysiologist to achieve optimal identification of the pallidal borders. Shorter steps (~ 100 μ m) were used when the electrode was advanced closer to and within the presumed location of the GPi. At each step, MER segments were recorded for at least 4 s, after the 2 s signal stabilization period. All MER segments were subjected to stability analysis using a custom-made algorithm and only those meeting these stability criteria were included [34]. A few MER segments were recorded for longer durations than others because the responses to active and passive limb movement were tested. The length of the MER segments were not homogenous and varied between 4 and 90 s. We excluded MER segments when active and passive limb movements were tested in the learning phase.

Neural datasets

Two independent datasets were prepared for the training and validation of the machine learning

models. The training dataset was composed of 116 microelectrode trajectories that passed through the striatum, GPe and GPi of 42 PD and dystonia patients undergoing bilateral GPi-DBS implantation. The training dataset of 116 trajectories was also used to find the optimal parameters for the hidden Markov model (HMM).

The testing dataset was composed of 32 trajectories, in ten patients from three medical centers (Hadassah-Hebrew University Medical Center $n = 5$, Sourasky Medical Center $n = 3$, Rabin Medical Center $n = 2$) and was used to test the robustness of the algorithm. Subsequently, five trajectories were excluded because single neuronal units were not observed at 0.4–0.6 of MAC. Thus, 27 trajectories were included in the independent test dataset (6 Parkinson's disease patients, two genetic dystonia and two non-genetic dystonia patients). Additional details on the neuronal and MER dataset appear in the supplementary material and table S2 and S3.

Root mean square (RMS)

The RMS estimate was calculated from the multi-unit activity recorded by the microelectrode at each electrode depth. During the surgery we did not attempt to optimize the signal-to-noise ratio or the isolation of single units. RMS values are susceptible to electrode properties (e.g. electrode impedance) and other artifacts related to the operating room [34]. To enable comparisons of the RMS values between trajectories and patients we normalized the RMS values. Each session's RMS in a trajectory was divided by the mean RMS of the first ten stable sessions in the same trajectory (pre-pallidum baseline RMS). This normalized RMS (NRMS) was found to be an effective measure as it reflects the relative change in the total power of the signal, which rises dramatically entering the pallidum [35,36]. For example, entry and exit from the GPe and GPi are marked primarily by a dramatic increase and decrease in NRMS (figure 6, top panels), respectively. Additional details are presented in the supplementary material.

Power spectral density (PSD)

The PSD was calculated from the mean-subtracted absolute value of the analog (multi-unit activity) signal [37, 38]. The mean-subtracted signal was used to expose the frequency band of interest (below 300 Hz) since the original analog data were bandpass filtered at 300–9000 Hz (the 300 Hz cutoff was used to exclude the effects of field potentials and because of operating room constraints). The average power spectral density was calculated for each trace using Welch's method, with a 3 s Hamming window (50% overlap) and a spectral resolution of 1/3 Hz (sampling frequency 44 kHz, number of discrete Fourier transform points = 132 000). To normalize the PSD we divided the PSD by the total power of the signal from 0 to 22 KHz (excluding PSD values within 2

Hz of the 50 Hz power supply artifacts and their 100 and 150 Hz harmonics) creating a relative PSD [34]. This normalization revealed the relative power across frequencies and minimized the overlap between the measures of the NRMS and the PSD. Additional details are presented in the supplementary material.

The distance in power spectral density and RMS

The distances between regions and classes were calculated as the L1-distance (sometimes referred to as the ‘Manhattan distance’—the sum of absolute differences) of the mean PSD and NRMS. Additional details are presented in the supplementary material.

The HMM

HMMs are advantageous for general and highly variable tasks across many sequence analysis classifications [39, 40]. The HMM takes the set of features extracted from the raw data as input and provides the output clustering in real-time. In previous reports [14, 41], the HMM procedure has successfully been used to discriminate the STN from the white matter or substantia nigra pars reticulata. This study extends our previous work by designing an online HMM algorithm that can detect the striato-pallidal borders (i.e. estimate the inference states of the electrode at each depth along the trajectory). Figure 1 shows the machine learning working system.

Estimating the HMM

For purposes of the HMM procedure, a trajectory was defined as a sequence of observations, such that at any depth along the trajectory the electrode exists in one of the inference states (figure 1(E)).

1. Str (striatum)
2. GPe
3. GPi
4. Exit (i.e. white matter)

For each trajectory, an expert electrophysiologist lowered the electrode and labelled the states. Since the recordings started at the level of the striatum, the subsequent labels were: the detection of the GPe, the demarcation between the GPe and GPi, and the detection of the GPi ventral border (GPi-exit). For the training dataset, a single neurophysiologist labelled the trajectory state for all trajectories. Detection of the striatum-GPe and GPi-exit transitions were based on intraoperative neuronal analysis by the electrophysiologist as well as the NRMS plots. The GPe-GPi transition was distinguished by visual inspection of the NRMS and PSD, by identification of an NRMS gap (white matter) and a change in oscillatory activity. Occasionally, typical border cell activity was detected at the transition and supported the decision. However, not all trajectories had clearly defined Str-GPe and GPe-GPi transitions; therefore, only trajectories that started 15 mm above the calculated target and

traversed > 7 mm of GPe and GPi were included in this study. The known state transitions for different classes of disease are depicted in the NRMS plots by red lines and in the PSD plots by black lines (figure 6). These transitions defined a known state sequence for estimating and testing the HMM.

In our own practice we do not advance the micro-electrode beyond the ventral border of the GPi. We are very cautious because damage to the optic tract may cause hemianopsia and stimulation that spreads to the optic tract may cause patients to experience visual perceptions commonly referred to as ‘flashes’ [42]. In trajectories with >5 mm of GPe and >5 mm within GPi we pull back the microelectrode immediately after we reach 0 mm or as soon as we notice a clear decline in the NRMS value. Therefore, in some trajectories the ventral border of GPi (i.e. GPi-exit) has not been reached across all classes of disease; specifically for Parkinson’s disease, non-genetic and genetic dystonia patients (number of detected GPi-exit borders: $n = 23, 30$ and 31 out of $33, 47$ and 36 trajectories, respectively).

The maximum likelihood estimate of the HMM transition and emission probability matrices were estimated based on the known (human expert defined) state sequences. Since the training data were fully labelled (there were known state sequences for the whole dataset), there was no need to implement the expectation-maximization (EM) algorithm or iterative procedures (which would require initial guessing of the probability matrices), and the matrices could be directly estimated. In our HMM, transitions between states take place according to (1) a fixed probability (i.e. transition matrix and emission matrix) depending solely on the inference state of the electrode at the depth immediately preceding the current inference state and (2) a probability value calculated from the current MER.

In the operating room the MERs are considered temporal data in the spatial domain rather than time domain. We used a left-right HMM procedure for the characterization of temporal data recorded during the electrophysiological mapping of sequential brain structures (figure 2); i.e. as a sequence progresses, it is possible to remain in the same state, but it is not possible to return to a previous state (e.g. from the GPi to the GPe).

Validation

The performance of the HMM was assessed by two measures on three classification cases: striatum-GPe, GPe-GPi, and GPi-exit transitions. First, we validated the machine learning algorithm using leave-one-trajectory-out cross-validation. This ensured independence between the trajectories used for developing the HMM parameters (i.e. transition and emission matrices) and the trajectories used for validation. Three HMMs were estimated for three classes of disease using the known state sequences of all trajectories, excluding one (e.g. Parkinson’s disease,

non-genetic and genetic dystonia $N - 1 = 32, 46$ and 35), and then tested on the excluded trajectory (with no assumption of its sequence) by comparing the inferred HMM state transitions to the trajectory's known state transitions. The HMM inference state sequence was calculated as the most probable sequence beginning with the HMM in the striatum (state 1) before the first observation (using the Viterbi algorithm) [40]. This method was repeated N (33, 47 and 36) times, thus testing each trajectory individually across all three diseases. The resulting mean (of 33, 47 and 36 trajectories) HMM transition and emission matrices are presented in the supplementary information table S3.

Second, we validated the machine learning algorithm against three electrophysiologists' manual

detection of ten patients in the operating room. We incorporated the pallidal navigation algorithm into three electrophysiological systems (at three medical centers) for intraoperative use. The test dataset was composed of 27 trajectories (six Parkinson's disease patients, two genetic and two non-genetic dystonia patient). This dataset included some MER segments collected when active and passive limb movement were tested; however, the HMM was not updated with limb movement data during the real-time validation. Thus, the algorithm did not use the changes in MER related to active or passive movement as additional input (i.e. these movements were treated as were the other spontaneous movements during the recording), nor did it use the experts' interpretation of approaching the target.

Statistical analysis

All statistics and analysis were performed in MATLAB (version 7.5 and R2013a) using both the machine learning and statistics toolbox and custom software. An unpaired, one-tailed Student's t-test was used to test the hypothesis that the mean microelectrode trajectory times were shorter in surgeries using our machine learning algorithm than in surgeries without the algorithm. The null hypothesis was that the machine learning algorithm does not reduce the mean microelectrode trajectory time. The alternative hypothesis was that the algorithm would reduce the microelectrode trajectory time. The accuracy of the algorithm was estimated via the reliability versus distance measure (between expert electrophysiologists' border estimations and the HMM output) by varying the criterion distance values of the detection at 0.1 mm increments. The statistics presented in this report, if not specified otherwise, are the mean $\pm$ standard error of the mean (SEM).

Results

Oscillatory characteristics of dystonia classes

The mean power spectra and NRMS of the MER segments were calculated in the striatum, GPe, and GPi of the four dystonia classes (figure 3(A)), awake and lightly anesthetized non-genetic and genetic dystonia, $n = 2380, 2202, 1752$ and 2556 MER segments, respectively; a summary of the dataset is presented in supplementary table S2). The mean power spectra of the striatum in both the non-genetic and genetic dystonia classes under light anesthesia (figure 3(A), light green) manifested a unique signature: an alpha (8–12 Hz) oscillation, most likely due to light nitrous oxide and isoflurane or sevoflurane anesthesia [43]. In contrast, the GPe in both genetic and non-genetic dystonia (figure 3(A), light and dark blue) displayed relatively less alpha and beta-oscillatory activity. The power spectra of the GPi in the non-genetic awake dystonia class (figure 3(A) left, dark red) exhibited a peak in the high beta range (20–30 Hz). In contrast, the power spectra of the GPi in the genetic dystonia class in both the lightly anesthetized and awake patients displayed decreased beta-oscillatory activity.

Awake versus anesthetized dystonia classes

To evaluate the number of classes required for the classification system, we calculated the L_1 -distance (see Methods) of the mean relative power spectra (calculated on samples in the 3–70 Hz range) and NRMS. The distances were calculated between each region (for example, the striatum) to all other regions (for example, striatum, GPe and GPi) for the non-genetic and genetic dystonia classes. The three possible permutations of light general anesthesia (GA) and awake (Aw) groups can be seen in figures 3(B) and (C) (i.e. GA versus Aw, Aw versus Aw, GA versus GA). Across all four panels, the GA versus Aw group corresponded

to the minimal distance values (shortest bars) in comparison to both Aw versus Aw and GA versus GA. This indicated there were minimal differences between the light GA versus Aw dystonia classes for both the PSD (in the 3–70 Hz range; figure 3(B)) and NRMS (figure 3(C)). Similar results were obtained for the power spectral density in the 3–300 Hz range. We therefore merged the Aw and light GA cases for the two (non-genetic and genetic) dystonia classes and reduced the number of dystonia disease classes to two different dystonia classes instead of four.

Characteristics and spatial distribution of neural activity in the three classes of disease

The NRMS and power spectra were calculated across the striatum, GPe and GPi in PD, non-genetic and genetic dystonia as a function of the distance from the ventral border (figure 4; $n = 2884, 4582$, and 4308 MER segments, respectively, averaged across electrode trajectories). Plotting the striatum spectrogram-by-depth demonstrated a similar spatial oscillatory distribution across all three classes of disease (figure 4, first column). The transition into the GPe was characterized by high tonic firing rates and increased background activity, which is indicated by the increased NRMS (figure 4, second column). The spatial distribution with low-frequency activity for both the GPe and GPi was nearly identical across genetic and non-genetic dystonia patients (figures 4(B) and (C), second and third columns). In contrast, the GPe and GPi in PD exhibited tremor (4–5 Hz) frequency oscillation (figure 4(A), second row, second and third columns). The beta-oscillatory activity (12–30 Hz, with a maximal peak at 15 Hz) in GPi PD was found primarily in the ventral portion of the trajectory (figure 4(A), second row, third column). Similar oscillatory activity can be seen in the mean plots (figure 4, right column, averaged across all patients and electrode trajectories). These results are consistent with local field potential studies [15, 17, 44], which have described the ventro-lateral spatial location of beta and theta (4–8 Hz) oscillatory activity.

The mean relative PSDs of the spiking activity in GPi PD exhibited increased activity in the tremor (4–5 Hz) frequency, beta-oscillatory activity and 150 to 250 Hz range, in comparison to the genetic and non-genetic dystonia (figure 5, third column, orange trace). The GPe PD exhibited low (9–20 Hz) and high beta (20–35 Hz) oscillatory activity (figure 5, second column, orange trace). In contrast to PD, the GPe and GPi in both genetic and non-genetic dystonia (figure 5, second and third columns) demonstrated relatively lower beta-oscillatory activity. This is in line with previous studies that have described different pallidal characteristics in PD and dystonia patients [15–17, 44–48]. The recordings in the striatum exhibited nearly identical activity across all three classes of disease (figure 5, first column).

domain enables the best discrimination between regions, we calculated the absolute difference in the mean power spectra. We then examined eight different frequency bands (approximately logarithmically equally distributed) bands along the frequency axis (the discrimination matrix is presented in supplementary table S4). Frequency bands at 3–30 Hz, 8–35 Hz, 30–95 Hz and 180–245 Hz provided the greatest discrimination for the striatum-GPe and GPe-GPi transitions (supplementary material figure S2). These frequency bands were used to calculate the input features of the HMM.

Classification of pallidal borders for each of the three classes of disease

The mostly flat NRMS (figure 4) allowed us to assume a chain of stationary MER segments within each structure. Under this assumption, we utilized an HMM to model the space-varying stochastic neural activity as a probabilistic Markovian chain of *four* stationary states corresponding to each structure. The HMM uses MER features and trajectory history to enable real-time decisions about electrode placement. The use of trajectory history in addition to the MER features enable the HMM to reduce variability in the

inference of the location based on firing characteristics of the neurons encountered along the striato-pallidal trajectory. Based on our finding of minimal differences between the awake and light anesthesia dystonia classes (figure 3), we restricted the training and validation of HMM to three classes of disease: PD, non-genetic dystonia and genetic dystonia. Figure 6 presents a typical classification example of pallidal borders for each of the three classes of disease.

The reliability versus distance was tested using both leave-one-trajectory-out cross-validation and against three electrophysiologists in the operating

room using newly collected data. The PD algorithm exhibited a robust demarcation of the Str-GPe and GPi-exit borders which achieved 84% and 95% accuracy within a 0.3 mm distance, respectively, using leave-one-trajectory-out cross-validation (figure 7(A), left and right columns). The test using new data shows 95% and 83% accuracy within 0.3 mm distance, respectively (figure 7(B), left and right column). In contrast, many trajectories lacked a clearly defined GPe-GPi border (figures 7(A) and (B), middle column). The PD algorithm achieved 78% and 45% accuracy within a 0.3 mm distance on the two validation measures, respectively. These results are not surprising given that the expert electrophysiologist was uncertain as to the exact location of the GPe-GPi border in 47% (54/116) of the training trajectories, which may be due to the similarity between the GPe and GPi power spectra (figure 3, right column), white matter gaps of >1 mm between the GPe and GPi, uninterrupted GPe-GPi transitions and cases with no clear

short transient reduction and increase in the NRMS (figure 6, top row, middle and right column) [21]. For example, in PD and non-genetic dystonia (figure 6, left and middle column), the HMM transition inference concurred (error < 0.3 mm) with the expert's decision for the Str-GPe and GPi-exit transitions (solid red and black lines), but overshot the GPe-GPi transition (error > 0.3 mm dot-dash red and black lines).

The lower performance of the HMM for the dystonia patients (figure 7(A)) was most likely due to the small number of trajectories and the variability in the physiology across the dystonia patients. The HMM provided the same detection reliability results when limb movement-related MER segments (i.e. data when active and passive limb movements were tested) were excluded from the validation dataset. The detection reliability of the striato-pallidal borders is novel and therefore does not have a reference for comparison, but showed results similar to the STN entry and exit detections [49].

The machine learning algorithm reduced the time it took the expert electrophysiologist to determine the striato-pallidal borders, since the duration with the algorithm was shorter than without it. The mean microelectrode trajectory time per single 15 mm trajectory with and without the algorithm was 26 ± 1.3 and 36 ± 1.5 min (mean $\pm$ SEM), for $n = 27$ and 116 trajectories, respectively (unpaired, one-tailed t-test $P < 0.05$). Note that it is likely that the border demarcation was more accurate with the HMM; however, here we could not evaluate the difference in accuracy. It took 130 milliseconds in real-time for the machine learning algorithm to compute a single DBS track and determine the striato-GPe-GPi borders (Intel Core i5 2410M processor with 4GB RAM). The time to analyze each subsequent MER was one millisecond per MER, making the HMM algorithm a practical method for use during DBS surgery.

Discussion

The goal of this study was to generate a robust procedure for GPi localization that can inform the surgical team intraoperatively, in real-time, of the electrode position. Here, we derived a machine learning approach to analyze MER segments during surgery for implanting a DBS lead in the GPi. To determine whether the machine learning algorithm could accurately detect the GPi, we utilized a large anatomically annotated database of striato-pallidal MER segments from operated awake PD patients, as well as awake and lightly anesthetized genetic and non-genetic dystonia patients. We tested its performance against three electrophysiologists in the operating

rooms of three hospitals on data that were not used to develop the machine learning algorithm.

Awake versus anesthesia dystonia classes

Several recent studies have reported differences in pallidal firing rates between dystonia classes under volatile anesthetics [50, 51]. The results of this study extend previous work by comparing the spectral oscillatory changes in neural activity within the striatum, GPe and GPi between awake and lightly anesthetized genetic and non-genetic dystonia classes (figure 3(A)). Our MER-derived results are consistent with previous findings of oscillatory patterns of pallidal local field potentials in dystonia patients [15, 16, 44, 45, 52]. Using the L_1 -distance measure, we determined that the awake and the light anesthesia (0.3–0.6 MAC range) dystonia classes could be merged (figures 3(B) and (C)). Thus, although anesthesia may reduce pallidal neuronal oscillations across all dystonia classes [25, 26], detectable relative differences in neural oscillations between genetic dystonia and non-genetic classes were preserved.

Striatal alpha oscillation under light anesthesia

A growing body of evidence suggests that anesthetics induce oscillations that alter or disrupt the normal brain's information processing [53, 54]. Because the cortex is the major afferent to the striatum [55], profound changes in neural activity in the cortex, which are reflected in major changes in the scalp electroencephalogram (EEG), might be transmitted to the striatum. Our MER-derived results that reveal alpha oscillations in the striatum under light anesthesia (figure 3(A)) are consistent with findings

showing an increase in oscillatory EEG power in the alpha frequency range under isoflurane or sevoflurane anesthesia [43]. Even though striatal neurons send inhibitory projections to the GPe and GPi [56], we found that striatal neurons did not propagate these alpha oscillations to these structures (figure 3(A)). This may be explained by studies in the non-human primates indicating that the output activity of the pallidum (or basal-ganglia downstream structures) does not reflect striatal neural activity [57]. Therefore, abnormal oscillatory activity within striatum, under light anesthesia, did not propagate to the GPe and GPi. Another possibility is that the oscillatory activity in the different domains of the striatum (e.g. ventral and dorsal striatum) is not the same. We may therefore have recorded the neural activity from those parts of the GPe and GPi that receive information from domains of the striatum that are not involved in alpha oscillations.

Differences in striato-pallidal oscillatory activity between the three classes of disease

Several studies have reported lower mean discharge rates in GPi neurons of dystonia patients compared to the non-human primates or humans with PD [45, 47]. For the purposes of this study, we chose to focus on power spectra and the RMS of the MER multi-unit (background) activity rather than the discharge rate, since well isolated single-unit studies are too time-consuming and computationally demanding to be performed in a real-time intraoperative scenario. We compared the spatial distribution of the oscillatory neural activity within the striatum, GPe and GPi between the three classes of disease (figure 4). We found differences in striato-GPe-GPi oscillatory activity between the PD, genetic dystonia and non-genetic dystonia classes (figure 5). These differences could be used in the future as electrophysiological target-specific biomarkers to optimize therapy in adaptive DBS control systems [16, 58].

Difficulty in determining the GPe-GPi transitions

The method described in this article varies in its capability to predict GPe- and GPi- entry and exit. Whereas the striatum-GPe and GPi-exit were usually clear and characterized by a distinguishable increase and fall of the NRMS, respectively, the GPe-GPi transitions were harder to detect in some trajectories (figure 7). The GPe is separated from the GPi by a thin layer of myelinated fibers called the medial medullar lamina [59]. The GPe-GPi transition can therefore be detected by a drop in previous neuronal activity and the recording of border cells in its vicinity. However, the transition from the GPe to GPi was not always clear to the expert or to our machine learning algorithm (figure 7 middle column). This may have been due in part to the sparsely distributed neurons along the pallidum and the variability in the firing characteristics between the GPe and GPi in the MER dataset [21]. Clinically, the GPe-GPi boundary reliability is

probably not very important. This is because, for accurate DBS lead placement, the critical boundary is the GPI-exit border where the PD algorithm achieved 83% accuracy (on the test data) within a 0.3 mm distance (an error considered ‘acceptable’ by our team; figure 7(B) right column). Usually, trajectories that traverse >10 mm in the pallidum or >3.5 mm of GPi enable the implanting of the DBS lead in the optimal location (with two contacts inside the GPi), even without identifying the low border of GPi.

Choosing the ‘right’ machine learning algorithm

The need for a real-time simple method (to understand, maintain and deploy in different currently available intraoperative MER software) was a crucial guideline when choosing the machine learning algorithm to work with. Because we do not advance the microelectrode beyond the ventral border of the GPi, the number of MER segments recorded in the white matter (exit) was about 10-fold smaller than that of other states (Str, GPe and GPi). For example, multiclass support vector machine (SVM) techniques typically treat all states equally; hence, it is not well suited to our imbalanced datasets, and may cause a bias in the decision boundary of the SVM classifier [60].

Previous studies have used deep neural network and hybrid SVM-HMM systems for offline state detection with large datasets (i.e. 150–750 independent trials) [61, 62]. In contrast, we used an HMM to enable accurate GPi confirmation that does not require the presence of an expert physiologist intraoperatively, in real-time. Our machine learning algorithm has four main advantages: it does not rely on spike detection and sorting procedures, state prediction is estimated with an imbalanced limited dataset (e.g. 33 independent trajectories for PD), only a short signal recording is required, and finally it is unaffected by variability in electrode properties and the noisy environment of the operating room. However, our method is constrained by the small dataset. The results may be compared to deep neural network and hybrid systems if sufficient training examples exist. There are surgical procedures, such as STN-DBS, for which the deep neural network approaches (e.g. long short-term memory networks; LSTM [63, 64]) may be effective. This is because STN-DBS datasets tend to be more balanced and consists of a much larger dataset (in most medical centers) [41, 65]. In the future, the LSTM could be used for training on the NRMS, EDT and power spectra data [62] to classify striato-pallidal regions in real-time.

Some limitations of the machine learning algorithm

Our study also has several limitations that should be addressed before the algorithm is adopted for widespread use. First, the machine learning algorithm was tested on a small number of patients intraoperatively in real-time (i.e. 27 trajectories in 10 patients), due to the relatively low rate of GPi-DBS procedures in Israel (most procedures target the STN).

Second, the entry (i.e. the white-matter-striatum transition) was not tested because our intraoperative recordings started at the level of the striatum rather than white-matter in all three medical centers. This decision reflects the desire to minimize operating time, especially in awake patients and our view that identification of the striatum-pallidum transition is more critical for optimal GPi navigation. Third, we excluded 'poor' trajectories from the training and validation dataset which for a variety of reasons (e.g. deep anesthesia) did not yield any neural activity. Although all our recordings started 15 mm above the calculated target and traversed > 7 mm of pallidum, our dataset included a variety of trajectories, such as a long GPe with a short GPi, no drop or a very long gap in neural activity between the GPe and GPi. This affected the GPe-GPi and GPi-exit border demarcation performance (figure 7).

Another potential limitation is that the current approach may not allow GP border prediction if the recordings start at the level of the pallidum. To enable HMM training on the trajectory history and comparisons across trajectories, we normalized the RMS values by the relatively MER-silent striatum activity (figure 4) in the same trajectory (see Methods). This limits our HMM's ability to 'learn new trajectories' if not all medical centers start in the striatum. However, most centers that use MER usually start their GPi exploration at 15 mm above target, as described here. It is possible that other differences between medical centers may impose difficulties on the algorithm; thus, future research is needed to determine how models trained in one center can best be implemented in other centers with different protocols. This would be especially useful for centers with limited databases and a lack of experience in pallidal electrophysiology.

What if the trajectory calculations were too lateral?

An issue that was not addressed in the present study is how to determine medial-lateral location. The GPi location differs across patients and is not easily visible pre-operatively in all cases on MR imaging. If the trajectory is too lateral, the trajectory might miss the entire GPi and only hit the GPe; if so, the method described here may not work, but the MER would still be very useful to the surgeon in deciding where to select another trajectory. The optimal trajectory in medial-lateral terms will usually have approximately equal lengths of GPe and GPi. None of the trajectories in our study missed the GPi. Nonetheless, further research and data are needed to design an algorithm to overcome this eventuality. Macrostimulation, especially in the awake patient, can also provide information concerning distance from the internal capsule.

The advantages of using MERs with a machine learning algorithm

Some experts have argued against the utility of MER. This controversy remains unresolved. In our experience, as is the case for many other experts, MER is both safe and provides high resolution target verification [28]. One rationale for the case against MER is a lack of physiological expertise. In medical centers where there is no electrophysiologist in the operating room, the machine learning algorithm can provide assistance to the neurosurgeon. Machine learning algorithms are becoming increasingly commonplace in the operating room as well as in other fields. Automating navigation and detection of brain structures intraoperatively is an important area for future investigation, and includes identifying optimal implant target locations. Machine learning can also help the neurosurgeon decide which MER track to implant and determine whether stimulating different portions of the target (i.e. ventral, dorsal, medial or lateral) will have different therapeutic benefits or side effects. We nevertheless feel that our machine learning algorithm can make a contribution to MER users, and encourage others to use it and improve their DBS outcomes.

Conclusion

Here we demonstrated the effectiveness and reliability of real-time, automatic intraoperative verification of the striatum-GPe, GPe-GPi and GPi-exit transitions during DBS surgery. An HMM trained on the trajectory history and characteristic features of striatal and pallidal activity performed on a par with all three experts in detecting striato-pallidal borders across the three classes of disease: PD, genetic dystonia and non-genetic dystonia. Further research is necessary to evaluate performance in different clinical settings, in order to validate this technique across the spatial distributions of neural activity encountered along the trajectory in the typical operating room setting. The HMM is agnostic to the type of raw data used and can

be implemented easily in existing MER devices. The ability to classify striato-pallidal regions in real-time using our classification algorithm may shorten DBS surgery considerably. The machine learning algorithm approach considers all available example trajectories equally and finds transitions between nuclei that a human researcher may miss for example, due to bias towards a given interpretation. This method allows accurate GPi confirmation without the necessity of an expert physiologist.

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Conflict of interest/financial disclosures

Dr Hagai Bergman reports receiving a travel honorarium from Alpha Omega, Medtronic and Boston Scientific and serving as a consultant for Alpha Omega. Dr Zvi Israel reports serving as a consultant for Alpha Omega.

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Appendices

Additional supplementary material is available in the online version of this article on the publisher's website.

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III. Determining the true discharge rate and pattern of the striatal projection neurons in Parkinson's disease and dystonia

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What is the true discharge rate and pattern of the striatal projection neurons in Parkinson's disease and Dystonia?

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Abstract Dopamine and striatal dysfunctions play a key role in the pathophysiology of Parkinson's disease (PD) and Dystonia, but our understanding of the changes in the discharge rate and pattern of striatal projection neurons (SPNs) remains limited. Here, we recorded and examined multi-unit signals from the striatum of PD and dystonic patients undergoing deep brain stimulation surgeries. Contrary to earlier human findings, we found no drastic changes in the spontaneous discharge of the well-isolated and stationary SPNs of the PD patients compared to the dystonic patients or to the normal levels of striatal activity reported in healthy animals. Moreover, cluster analysis using SPN discharge properties did not characterize two well-separated SPN subpopulations, indicating no SPN subpopulation-specific (D1 or D2 SPNs) discharge alterations in the pathological state. Our results imply that small to moderate changes in spontaneous SPN discharge related to PD and Dystonia are likely amplified by basal ganglia downstream structures.

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Introduction

Parkinson's disease (PD) and Dystonia are two of the most common movement disorders, and have a wide spectrum of etiologies and clinical presentations. To date, the pathophysiology of PD and Dystonia is still debated. Traditionally, PD is attributed to the degeneration of the midbrain dopaminergic neurons which also disrupts other neuromodulatory systems, including the cholinergic, serotonergic and histaminergic systems (Bolam and Ellender, 2016; Deffains and Bergman, 2015; Fox et al., 2009). Although there is no degeneration of the midbrain dopaminergic neurons in Dystonia, an imbalance between the midbrain dopaminergic and striatal cholinergic systems (Aosaki et al., 2010; Benarroch, 2012; Bonsi et al., 2011; Pisani et al., 2007), as well as cerebellum dysfunction (Fremont et al., 2017; Helmich, 2018; Helmich et al., 2012; Tewari et al., 2017; Wu and Hallett, 2013) are present in both PD and Dystonia. Nevertheless, basal ganglia (BG) dysfunction is still regarded as the source of the cardinal symptoms of both diseases (Mink, 1996; Wichmann, 2018) and deep brain stimulation (DBS) in the BG (subthalamic nucleus, STN and internal segment of the globus pallidus, GPi) is an effective invasive treatment for both diseases (Limousin et al., 1998; Moro et al., 2017; Odekerken et al., 2016; Ostrem et al., 2017).

The striatum (i.e., the main input structure of the BG network) is the main recipient of midbrain dopaminergic neurons (Menegas et al., 2015) and also receives di-synaptic cerebellar projections

(Bostan et al., 2013; Hoshi et al., 2005). Most [~95% and ~70–80% in rodents and primates, respectively (Graveland et al., 1985; Petryszyn et al., 2018; Petryszyn et al., 2014)] striatal neurons are medium spiny projection neurons (SPNs) that receive afferents from the cortex and the thalamus, and together with the STN neurons, innervate the central (i.e., external segment of the globus pallidus, GPe) and output (i.e., GPi and substantia nigra reticulata, SNr) BG structures (Albin et al., 1989; Gerfen et al., 1990). Therefore, alterations in striatal signaling disrupt normal BG activity and may lead to the manifestation of the motor and non-motor symptoms of PD and Dystonia (Albin et al., 1989; Bergman et al., 1990; Gerfen et al., 1990).

Dysregulation of BG activity may consist of changes in discharge rate (Albin et al., 1989; Gerfen et al., 1990). Unlike in all other BG structures, extracellular recordings of spiking activity in non-human primates (NHPs) reveal that SPNs have a very low discharge rate (~1–2 Hz at rest) and are phasically active (i.e. emit short bursts) around relevant behavioral events (Crutcher and DeLong, 1984; Deffains et al., 2010; Kimura et al., 1990). However, previous studies of the BG in the NHP model of PD have mainly focused on the STN, GPe and GPi which are structures with a high frequency tonic discharge (i.e. 25–70 Hz at rest) (Deffains et al., 2016; Filion and Tremblay, 1991; Wichmann and DeLong, 2003). These studies have reported excessive GPi/SNr discharge rates in PD that lead to an increase in BG inhibitory outputs to the thalamus and the frontal cortex motor areas (Wichmann and DeLong, 2003). Conversely, it is assumed that Dystonia (and other hyper-kinetic states) are characterized by reduced GPi/SNr activity (Guehl et al., 2009).

More recent studies of the BG in animal (rodent and NHP) models of PD and human patients (undergoing DBS procedures) have dealt with changes in discharge patterns and synchronization. Parkinsonism-related β oscillations have been observed in local field potentials (LFPs) recorded in all BG structures, including the striatum (Deffains et al., 2016; Kondabolu et al., 2016; Lemaire et al., 2012; Singh and Papa, 2019). Similarly, low frequency (4–12 Hz) LFP oscillations have been recorded in the BG network of dystonic patients (Piña-Fuentes et al., 2018; Silberstein et al., 2003). Finally, synchronous β oscillations are commonly observed in the spiking activity of the STN, GPe and GPi of MPTP-treated monkeys (Deffains et al., 2018; Deffains et al., 2016; Soares et al., 2004) and PD patients (Brown, 2003; Kuhn et al., 2005; Moshel et al., 2013; Zaidel et al., 2010).

Nevertheless, direct evidence of abnormal activity of the striatal SPNs is still elusive. Previous studies utilizing the NHP model of PD reported striking increases (~15 fold increase from the normal discharge rate of ~1–2 Hz) in the firing rate of the SPNs subsequent to striatal dopamine depletion and the induction of parkinsonism (Liang et al., 2008; Singh et al., 2016). The same research group also reported a high discharge rate of SPNs recorded in PD and dystonic patients (~30 Hz and 9 Hz, respectively) (Singh et al., 2016). They also found a significant change in the firing pattern of striatal neurons, with many SPNs exhibiting bursting activity in PD patients and MPTP monkeys as compared to a smaller fraction in patients with Dystonia (Singh et al., 2016). Finally, the SPNs of patients with an essential tremor (ET, regarded as a non-BG disorder) have a very low discharge rate (~2 Hz) and no tendency to burst, as reported in normal NHPs (Liang et al., 2008; Singh et al., 2016; Singh et al., 2015).

These spectacular changes in the discharge rate and pattern of SPNs in the NHP model of PD run counter results obtained in our research group. We recorded the activity of SPNs and other BG neurons in Vervet monkeys before and after systemic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment and the induction of severe parkinsonian symptoms. Although we found robust changes in the discharge properties (rate, pattern and synchronization) of the STN, GPe and BG output structures, we did not observe any difference in the discharge rate (~2–3 Hz) or pattern of SPNs in the MPTP-treated monkeys in comparison to the recordings in the same monkeys before MPTP treatment (Deffains et al., 2018; Deffains et al., 2016; Deffains and Bergman, 2019).

Extracellular recordings of SPN spiking activity of anesthetized (Chen et al., 2006; Mallet et al., 2006; Sharott et al., 2017) and awake (Chen et al., 2006; Kish et al., 1999) rats before and after striatal dopamine depletion by 6-hydroxydopamine (6-OHDA) treatment have revealed a significant, but very slight increase in the SPN discharge rate. Rodent studies make it possible to differentiate between SPNs expressing D1 and D2 dopamine receptors. A significant imbalance (but see Ketzev et al., 2017) in the discharge rate and calcium dynamics of D1 and D2 SPNs was observed in the dopamine-depleted striatum (Mallet et al., 2006; Parker et al., 2018; Sharott et al., 2017). In particular, D2 SPNs increased their discharge (Mallet et al., 2006; Sharott et al., 2017) and were

also prone to being entrained to parkinsonian β oscillations (Sharott et al., 2017). Nevertheless, the absolute increase in the discharge rate even of the D2 SPNs was still modest (from ~0.5 to ~2.8 Hz) (Sharott et al., 2017). Moreover, recent studies have reported no significant increase in the low discharge rate of either SPN subpopulation in striatal dopamine-depleted mice (Ketzel et al., 2017; Maltese et al., 2019).

Since only one research group has recorded drastic increases in the spontaneous spiking activity in the striatum of PD patients in comparison to either dystonic patients or the normal levels of striatal activity reported in healthy animals (Singh et al., 2016), we examined our human patient data to determine whether we could report similar changes. Our study goes beyond previous reports (Singh et al., 2016) by utilizing a machine learning algorithm to automatically detect striato-pallidal border, and applying objective methods for the identification of units and the quantification of their isolation quality and stationarity. Although extracellular recording methods cannot discriminate between the spiking activity of striatal D1 and D2 SPNs, we assumed that if only one population of striatal neurons was strongly affected by the pathological state, we should observe a significantly higher discharge rate of SPNs than that reported in normal NHPs and ET patients, and/or distinct clusters of SPN activity in our patients. Using this data-driven automated approach, we carefully examined spontaneous single-unit activity from the posterior putamen (i.e., the sensorimotor domain of the striatum) of both PD and dystonic patients undergoing GPi-DBS surgeries and compared their discharge rates and patterns.

Results

Database and spike sorting results

In this study, 93 microelectrode trajectories (48 in PD and 45 in Dystonia) were used, yielding a total of 933 and 718 microelectrode recording (MER) segments within the posterior putamen (i.e., posterior to the anterior commissure, Figure 1 and Video 1) of patients suffering from PD and Dystonia, respectively. Microelectrode trajectories from patients suffering from non-genetic ($N = 27$) and genetic ($N = 18$) Dystonia were pooled, since the results did not differ statistically. Applying automatic spike sorting on these MER segments identified 5237 units (2917 in PD and 2320 in Dystonia). The isolation score (Joshua et al., 2007) - ranging from 0 (i.e., highly noisy) to 1 (i.e., perfect isolation) - was calculated for each of these units. Moreover, since injury potentials are often observed during extracellular microelectrode recordings of striatal activity (DeLong, 1971), the stationarity of the firing rate and spike amplitude of the well-isolated units (isolation score ≥ 0.6) was assessed.

All surgeries were carried out while the patients were fully awake (no sedation or anesthesia) and the PD patients were off dopaminergic medication (overnight washout >12 hr). The DBS target was the ventro-posterior-lateral portion of the GPi for all patients, and trajectory angles were only slightly modified according to patient's anatomy. To graphically illustrate the recording locations in the striatum, we employed visualization of group-based microelectrode track trajectories in both PD and Dystonia (Figure 1, see also Video 1). All recordings were regularly sampled in space within the striatum (see Materials and methods). All patients provided their written informed consent and the study was approved by the Institutional Review Board of Hadassah Hospital in accordance with the Helsinki Declaration (reference code: 0168-10-HMO).

Figure 2A depicts examples of the striatal spiking activity recordings (left and middle). The right plots display the superimposed waveforms of the extracellular action potentials of the sorted units. The units are ordered as a function of their isolation score (Joshua et al., 2007). The median and mean discharge rates of all the recorded units with an isolation score greater than or equal to one of the 10 evenly spaced values between 0 and 0.9 were calculated (Figure 2B). A significant negative correlation between neuronal discharge rate and isolation score was found in the striatum of the PD (Pearson's $r = -0.87$ and -0.89 for median and mean discharge rate, respectively, $p < 0.01$, Figure 2B) and dystonic (Pearson's $r = -0.89$ and -0.85 for median and mean discharge rate, respectively, $p < 0.01$, Figure 2B) patients, indicating that the units with the lowest isolation score had the highest discharge rates.

Figure 1. A 3D rendering of group-based microelectrode track trajectories in the posterior putamen. (A) Posterior view of the microelectrode track trajectories from both PD and dystonic patients. An axial image from the normalized scan, at the level of the rostral midbrain, is shown as a backdrop. The image was acquired on a 7T MRI scanner with a 100 μ m T1 scan of an ex-vivo human brain. The definition of the striatum (purple), GPe (light blue) and GPi (light green) boundaries are defined by the DISTAL atlas. (B) Same as (A) but with a coronal image. A total of 36 microelectrode track trajectories, 13 in PD (green) and 23 in Dystonia (red), are visualized for four PD and six dystonic patients.

Figure 2. Striatal firing rate in parkinsonian (PD) and dystonic (DYST) patients decreases as isolation quality of the units increases. **(A)** Examples of full-length (left panels) and 1 s (middle panels) striatal spiking recordings. Above the spiking activity is the digital display of the detection (spike train) of the sorted unit from the recording. Spike waveforms are superimposed (right panels). Isolation score (Iso.Sc) indicates the isolation quality of the sorted unit. **(B)** Evolution of the firing rate as a function of the isolation score. Each bar indicates the median firing rate of the sorted units with an isolation score greater than or equal to a certain value (i.e., the bin labelled 0.8 contains all the units with an isolation score ≥ 0.8). Error bars represent MADs (i.e., median absolute deviations). Means $\pm$ SEMs (i.e., standard errors of the mean) are shown in red. N is the number of sorted units. The online version of this article includes the following source data for figure 2:

Source data 1. Firing rate and isolation score of all units in PD.

Source data 2. Firing rate and isolation score of all units in Dystonia.

Video 1. 3D rotating view of group-based microelectrode trajectories.

<https://elifesciences.org/articles/57445#video1>

No drastic increase in the firing rate of the striatal neurons of PD and dystonic patients

The median firing rate of all the sorted striatal units was relatively high (~30–40 Hz) in both diseases (**Figure 3**, first column) and consistent (at least for PD) with the values reported by *Singh et al., 2016*. Similarly, the firing rate of the dystonic patients was significantly lower than the PD firing rate (Mann-Whitney U-test, $p < 0.001$, **Figure 3—figure supplement 1**, first column). Nevertheless, this significant difference disappeared and the striatal firing rate decreased dramatically when only comparing the firing rate of the well-isolated units (isolation score ≥ 0.6) (**Fig-**

ure 3 and **Figure 3—figure supplement 1**, first column). Hence, there was no drastic change in the striatal firing rate of the well-isolated units of the PD and dystonic patients.

Inspection of the spike train of the well-isolated units (isolation score ≥ 0.6) revealed that although the units had been graded as high-isolation score units, their spike train could be non-stationary (**Figure 4**). To assess the stationarity of the spike trains, we examined the temporal (linear) evolution of their firing rates and spike amplitudes (see Materials and methods). **Figure 4A** shows three representative examples of well-isolated non-stationary units (left panels) and three representative examples of well-isolated stationary units (right panels) from the striatum of PD patients. Here, we used the slopes of the linear regression lines (reflecting the temporal evolution of the firing rate and spike amplitude of the well-isolated units) to define stationary units (**Figure 4B and C**). Interestingly, the firing rate slope values and spike amplitude slope values of the well-isolated units were uniformly distributed, thus indicating that these two spiking features were independent in both PD and Dystonia (**Figure 4D and E**). This analysis also showed that the non-stationary units (i.e., data points outside the shaded areas) did not necessarily exhibit both a non-stationary firing rate and a non-stationary spike amplitude (**Figure 4D and E**). For both PD and Dystonia, the firing rate of the stationary units was significantly lower than the firing rate of the non-stationary units (Mann-Whitney U-test, $p < 0.01$ and 0.001 for PD and dystonic patients, respectively, **Figure 4F**). Thus, inclusion of non-stationary units could have erroneously inflated the striatal firing rate in PD and dystonic patients. Removing the non-stationary units reduced the striatal firing rate of the well-isolated units in the striatum of both PD and dystonic patients (**Figure 3** and **Figure 3—figure supplement 1**, first column). Moreover, the striatal firing rate remained similar between both diseases after this maneuver.

Equally important, the mean values of the firing rate (**Figure 3—figure supplement 1**, first column) were systematically higher than the median values (**Figure 3**, first column), suggesting that whatever the quality of the isolation and the stationarity of the striatal units, the distributions of the firing rate were not normal and were skewed to the right. **Figure 5** depicts the distributions of the firing rate of all and only the well-isolated units (**Figure 5A and B**, respectively). For both PD and Dystonia, and for all levels of spike isolation, the distributions of the firing rate of the SPNs were not normally distributed, but rather were strongly skewed to the right (**Figure 5**). We therefore used the median (**Figure 3**) rather than the mean (**Figure 3—figure supplement 1**) to represent the central moment of the distributions of the discharge properties (including the discharge rate) of the SPNs. The median $\pm$ MAD (median absolute deviation) of the discharge rate was 3.85 ± 1.18 Hz and 2.55 ± 0.81 Hz for the well-isolated stationary SPNs in PD and Dystonia respectively - i.e., in the same range as reported for the controls in animal studies and with no significant difference between PD and Dystonia (Mann-Whitney U-test, $p > 0.05$, **Figure 4F**).

No evidence for bursty patterns in the striatal spiking activity of PD and dystonic patients

To characterize the pattern of the spike trains (i.e., irregular, periodic or bursty) and compare them between PD and dystonic patients, we examined the time interval histograms (TIHs) of the inter-

Figure 3. No drastic or specific change in the features (median $\pm$ MAD values) of striatal neuronal activity in parkinsonian (PD) and dystonic (DYST) patients. Comparison of the firing rate (first column), the coefficient of variation (CV) of the inter-spike interval (ISI) (second column), the β power of the multi-unit activity (MUA, spiking activity) recorded in the vicinity of a sorted unit (third column) and the β power of the spike-triggered average (STA) of the local field potential (LFP) (fourth column) when considering all (upper panels), only the well-isolated (middle panels) and only the well-isolated stationary (lower panels) units. Since each signal was Z-score normalized (using its mean and SD) prior to PSD calculations, the β power of both the MUA (third column) and STA-LFP (fourth column) are expressed in z-score²/Hz. Each bar indicates the median value and error bars represent MADs. Same y-axis scales as in **Figure 3—figure supplement 1** and **Figure 3—figure supplement 5**. Numbers in parentheses indicate the sizes of the samples. Note that the sizes of the samples differ between the columns because (i) the number of sorted units from each MUA ranged from 1 to 5 and (ii) the LFPs were not systematically recorded.

The online version of this article includes the following source data and figure supplement(s) for figure 3:

Source data 1. Spiking features of all units in PD.

Source data 2. Spiking features of the well-isolated units in PD.

Source data 3. Spiking features of the well-isolated and stationary units in PD.

Source data 4. Spiking features of all units in Dystonia.

Source data 5. Spiking features of the well-isolated units in Dystonia.

Source data 6. Spiking features of the well-isolated and stationary units in Dystonia.

Figure supplement 1. No drastic or specific change in the features (mean $\pm$ SEM values) of striatal neuronal activity in parkinsonian (PD) and dystonic (DYST) patients.

Figure supplement 2. Comparison of the spiking features between the putative well-isolated and stationary SPNs and TANs in PD patients.

Figure supplement 3. Comparison of the spiking features between the putative well-isolated and stationary SPNs and TANs in dystonic patients.

Figure supplement 4. Disease effects on the outliers of the different features of striatal neuronal activity.

Figure supplement 5. Median (upper panels) and mean (lower panels) values of the main features of striatal neuronal activity in parkinsonian (PD) and dystonic (DYST) patients.

Figure 4. Inclusion of non-stationary units can erroneously increase the striatal firing rate in parkinsonian (PD) and dystonic (DYST) patients. (A) Examples of well-isolated (non-stationary and stationary) units recorded in the striatum of PD patients. Grey trace is the band-pass filtered signal and depicts the spiking activity. Above the spiking activity is the digital display of the detection (spike train) of the sorted unit. The firing rate of the sorted unit overlays the spiking activity. The spike waveforms extracted from the spiking activity are superimposed and displayed on the right. The isolation score (Iso.Sc) indicates the isolation quality of the identified unit. Below the spiking activity panel is the assessment of the stationarity of the firing rate and spike amplitude. For each spike train, the data comprised between the first and the last spike of the spike train were segmented into 10 equal non-overlapping time bins. Then, the firing rate and the average spike amplitude in each bin were Z-score normalized using the mean and the SD of either the firing rate or the average spike amplitude calculated over the 10 bins. Solid and dotted lines represent the linear regression lines between the firing rate/spike amplitude of the sorted unit and bin number. Slope value (z-score/bin) of the linear regression line (m) was used to assess stationarity. (B–C) Distributions of the slope values of the linear regression line for the firing rate and the spike amplitude of the units. Vertical lines indicate the 70th percentile for the two diseases (PD: 0.2363 and 0.2344 z-score/bin for firing rate and spike amplitude, respectively; Dystonia: 0.2292 and 0.2294 z-score/bin for firing rate and spike amplitude, respectively). Units with slope values of the linear regression line for firing rate or spike amplitude greater than

Figure 4 continued on next page

Figure 4 continued

or equal to the 70th percentile were defined as non-stationary units. (D–E) Scatter plots showing the firing rate slope values and spike amplitude slope values of the well-isolated (non-stationary and stationary) units recorded in the striatum of PD and dystonic patients. Shaded areas represent the zones of the stationary units which are delineated by the 70th percentile of both the slope values and spike amplitude slope values. (F) Comparison of the firing rate of the non-stationary and stationary units. Each bar indicates the median firing rate of the sorted units. Error bars represent MADs. Means $\pm$ SEMs are shown in red. Numbers in parentheses indicate the numbers of non-stationary and stationary units. **, *** and NS indicate significant ($p < 0.01$ and 0.001) and non-significant differences, respectively (Mann-Whitney U-test).

spike intervals (ISIs). Although weak (Figure 3, second column), there was a significant difference in the coefficient of variation (CV) of the ISIs of all the sorted striatal units between the PD and dystonic patients (Mann-Whitney U-test, $p < 0.001$, Figure 3—figure supplement 1, second column). Nevertheless, as was the case for the striatal firing rate, this difference vanished when only considering the well-isolated or well-isolated stationary units (Figure 3 and Figure 3—figure supplement 1, second column). Again, the mean values of the CV of the ISIs (Figure 3—figure supplement 1, second column) were systematically higher than the median values (Figure 3, second column), indicating skewed distributions. Moreover, the distributions of TIHs of the ISIs of the well-isolated stationary units matched the Poisson temporal distribution of the spikes (Figure 6A). Accordingly, the mean autocorrelograms of the spike trains did not reveal any periodic or bursty firing patterns in the

Figure 5. Distributions of the striatal firing rate are skewed to the right in parkinsonian (PD) and dystonic (DYST) patients. (A) Firing rate of all sorted units regardless of their isolation quality. (B) Firing rate of the well-isolated stationary units only. Skewness = 2.34 and 3.94 for PD and dystonic patients, respectively. Insets: Firing rate of the well-isolated units (non-stationary and stationary units pooled). Skewness = 1.73 and 2.36 for PD and dystonic patients, respectively. N is the number of sorted units.

Figure 6. No evidence for burst patterns in the striatal spiking activity of parkinsonian (PD) and dystonic (DYST) patients. (A) Time interval histograms of the inter-spoke intervals (ISI) of the well-isolated (isolation score ≥ 0.6) stationary units. For better visualization, 191 and 292 ISIs > 0.5 s were removed from the PD and DYST striatal units, respectively. Abscissas are in log scale. (B) Average (mean $\pm$ SEM) autocorrelograms of the well-isolated stationary units. For each autocorrelogram, values were normalized so that the autocorrelation values ranged from 0 to 1. Abscissas are in log scale. N is the number of well-isolated stationary units averaged. (C) Distributions of the values of burst prevalence for the spike train of the well-isolated stationary units. For each unit, episode prevalence represents the probability that the discharge pattern was bursty. (D) Mean values of burst prevalence for the well-isolated stationary units recorded in the striatum of parkinsonian and dystonic patients. Error bars represent SEMs. N is the number of well-isolated stationary units averaged. NS: non-significant (Mann-Whitney U-test).

The online version of this article includes the following figure supplement(s) for figure 6:

Figure supplement 1. No evidence for burst patterns in the striatal spiking activity of parkinsonian (PD) and dystonic (DYST) patients.

striatal well-isolated stationary units (**Figure 6B**). Similarly, the prevalence of bursts [detected using the Poisson surprise method with the surprise maximization (SM) search algorithm (**Legéndy and Salcman, 1985**), see Materials and methods] was relatively low (**Figure 6C**) and did not differ significantly between PD and dystonic patients (Mann-Whitney U-test, $p > 0.05$, **Figure 6D**).

Absence of oscillatory spiking activity in the striatum of PD and dystonic patients

Theoretical studies have shown that neural oscillations can emerge at the population level in networks of neurons exhibiting an irregular (i.e., non-oscillatory) discharge pattern and a low firing rate (**Brunel and Hakim, 2008**; **Kopell and LeMasson, 1994**). To overcome the possible confounding effects of the low discharge rate and spatial under-sampling of the striatal SPNs, we investigated multi-unit oscillatory activity rather than single-unit oscillatory activity. Striatal multi-unit activity (MUA) reflects the spiking activity of an ensemble of striatal neurons around a sorted unit.

Comparison of the power spectral densities (PSDs) of the spiking activities recorded in the striatum of the PD and dystonic patients did not reveal any oscillatory phenomena between 3 and 75 Hz, including the β (13–30 Hz) band (**Figure 7A and B**). Accordingly, no significant difference in the β power of the striatal spiking activities (whatever the quality of the isolation and the stationarity of the striatal units) was observed between PD and dystonic patients (Mann-Whitney U-test, $p > 0.05$, **Figure 3**, and **Figure 3—figure supplement 1**, third column). Moreover, we found no significant increases of the β (13–30 Hz) power in the spiking activities recorded in the vicinity of the striatal well-isolated stationary units compared to the linearly interpolated baseline β power (Wilcoxon signed rank test, $p > 0.05$, **Figure 7C**), thus supporting the claim of no oscillatory spiking activity in the striatum of PD and dystonic patients.

No locking between spike and β LFP oscillations in the striatum of PD and dystonic patients

The mean PSD of the mono-polar LFPs recorded in the striatum of PD and dystonic patients (**Figure 8A**) exhibited (ignoring 50 Hz artifacts) two and three distinct peaks, respectively (at 11 and 21 Hz for PD patients and 8, 22 and 30 Hz for dystonic patients, **Figure 8A**, insets). Therefore, we calculated the spike-triggered averages of the LFPs (STAs LFPs). The β power in the LFPs recorded around the time of the spikes of all the striatal sorted units was significantly higher in PD than in dystonic patients (Mann-Whitney U-test, $p > 0.001$, **Figure 3** and **Figure 3—figure supplement 1**, fourth column). However, this difference disappeared when using the spikes of the well-isolated (non-stationary and stationary or only stationary) units (**Figure 3** and **Figure 3—figure supplement 1**, fourth column). Thus, the spiking activity of well-isolated stationary units recorded in the striatum of both PD and dystonic patients failed to lock with 13–30 Hz LFP oscillations (**Figure 8B**).

TANs are hardly distinguishable from SPNs in our human databases

In order to differentiate between the SPNs and the striatal cholinergic interneurons, the tonically active neurons (TANs, presumably the cholinergic interneurons) were retrospectively identified by three experts (DV, HB and MD) from the well-isolated and stationary striatal units included in both the PD and Dystonia databases. This identification was based on offline visual inspection of their electrophysiological features. The 3D-classifications of the putative SPNs and TANs, using their firing rate, the CV of their ISI and the score of the first principal component (PC1) of their spike waveform did not clearly discriminate them in either PD or dystonic patients (**Figure 3—figure supplement 2A** and **Figure 3—figure supplement 3A**, respectively). The same 3D-classification, but using the score of PC2 or PC3 (instead of PC1) yielded the same qualitative results. Unexpectedly, we found that the averaged spike waveform hardly varied between these two subtypes of striatal units in either PD or dystonic patients (**Figure 3—figure supplement 2B** and **Figure 3—figure supplement 3B**, respectively). Besides, we did not find significant differences in the firing rate of the putative SPNs and TANs in PD (**Figure 3—figure supplement 2C and D**, first column) or dystonic (**Figure 3—figure supplement 3C and D**, first column) patients. However, the CV of the ISI was significantly smaller for the putative

Figure 7. Absence of oscillatory spiking activity in the striatum of parkinsonian (PD) and dystonic (DYST) patients. Average (mean $\pm$ SEM) power spectrum densities (PSDs) of (A) all spiking activities and (B) only spiking activities recorded in the vicinity of well-isolated stationary units. Insets: Average PSDs of the spiking activities recorded in the vicinity of the well-isolated units (non-stationary and stationary units pooled). Since each band-pass filtered spiking signal was Z-score normalized (using its mean and SD) prior to PSD calculations, PSDs are expressed in $z\text{-score}^2/\text{Hz}$. Abscissas are in log scale. N is the number of spiking activities averaged. (C) Average β (13–30 Hz) power of the spiking activities recorded in the vicinity of well-isolated stationary units. To interpolate the β power, PSDs were linearly interpolated [based on the two closest points that flanked the 13–30 Hz band - namely, the values at 12 and 31 Hz (spectral resolution of 1 Hz)]. Interpolated β power is the mean of the linearly interpolated values between 13 and 30 Hz. Total β power is the mean of the observed values between 13 and 30 Hz. Error bars represent SEMs. NS: non-significant (Wilcoxon signed rank test and Mann-Whitney U-test).

Figure 8. No locking between spike and β LFP oscillations in the striatum of parkinsonian (PD) and dystonic (DYST) patients. **(A)** Average (mean $\pm$ SEM) PSDs of striatal LFPs. In the insets, the ordinates are truncated for better visualization of the power. Abscissas are in log scale. N is the number of LFPs averaged. **(B)** Population (mean $\pm$ SEM) spike-triggered averages (STAs) of LFP. LFP was recorded in the vicinity of well-isolated stationary units (i.e., spiking activity and LFP were recorded on the same electrode) and offline band-pass filtered from 4 to 12 Hz (upper panels) or from 13 to 30 Hz (lower panels). For comparison, STAs-LFP were also calculated after randomly shifting the timestamp of each spike of the spike train [i.e., random time (comprised between 0 and 1 s) was added to the timestamp of each spike of the spike train] in order to abolish any relationship between LFP and spiking activity (Shift predictor). Dashed grey vertical lines indicate the time of the spikes (time = 0). N is the number of STAs-LFP averaged. Since each LFP was Z-score normalized (using its mean and SD) prior to PSD and STA calculations, PSDs and magnitudes of the STA-LFPs are expressed in z-score²/Hz and z-score, respectively.

TANs than for the putative SPNs in both diseases (**Figure 3—figure supplement 2C and D** and **Figure 3—figure supplement 3C and D**, second column), thus corroborating the view that TANs fire in a more regular fashion than the SPNs which are thought to be phasically activated (**Crutcher and DeLong, 1984; Deffains et al., 2010; Kimura et al., 1990**). The lack of significant differences in the spike waveform and the firing rate between our putative human SPNs and TANs can be accounted in several ways: misclassification of certain neurons, presence of other striatal interneurons (i.e., FSI) and/or differences in extracellular recording techniques (microelectrode type, position/placement, and impedance). Overall, it was difficult to distinguish the TANs from the SPNs in our human databases. Moreover, our spectral analyses did not reveal any significant differences between these two subtypes of striatal neurons in either disease (**Figure 3—figure supplement 2C and D**, and **Figure 3—figure supplement 3C and D**, third and fourth columns). Therefore, we considered our sorted striatal spiking activity to reflect SPN spiking activity and neglected the small fraction of TANs (which was probably smaller than our estimation).

Outliers and cluster analysis of the striatal spiking features

Since we did not have a control condition or baseline levels, we could not identify the significant changes in the spiking features of the striatal neuronal activity. Nevertheless, we searched for outliers (i.e., data points that differ significantly from other observations) of each distribution. We examined the extreme values in the distributions and characterized the data points that could belong to a different population than the rest of the sample set. For each distribution, the values of the spiking feature (i.e., firing rate, CV of ISI, β power of the MUA or β power of STA-LFP) ≥ 2 or ≤ -2 SDs of its mean value were considered outliers (empirical 68-95-99.7 rule). Remarkably, almost all of the outliers corresponded to feature values ≥ 2 SDs of the mean value, thus indicating (as already observed) that the distributions of the values of the striatal spiking features were skewed to the right in both diseases. Nevertheless, we found that the proportions of outliers (regardless of the spiking feature and the isolation level) were small (**Figure 3—figure supplement 4**). Moreover, we did not find any significant disease effect on the proportions (chi-square test, $p > 0.05$) or the values (Mann-Whitney U-test, $p > 0.05$) of these outliers when only considering the well-isolated or well-isolated stationary units (**Figure 3—figure supplement 4**).

To further test whether two distinct SPN subpopulations could be observed in the current study, we performed 2D k-means cluster analysis with $k = 2$, using the discharge rate and the CV of the ISIs of each unit as input parameters (**Figure 9**). The basic idea behind this 2D k-means clustering was to define 2 clusters of data points so that the total within-cluster variation (i.e., the sum of the Squared Euclidean distances from data points to the cluster centroid) would be minimized within each of the two clusters. Using $k = 2$ as the predefined number of clusters systematically enforced the separation into two distinct SPN subpopulations. To assess how well-separated the two resulting clusters were, we calculated the silhouette values to measure how close each data point in one cluster was to data points in the other clusters. Silhouette values range from +1 (data points are very distant from other clusters), through 0 (data points are not distinctly in one cluster or another), to -1 (data points are probably assigned to the wrong cluster). The results showed that the two predefined clusters were not well-separated, regardless of the quality of the isolation or the stationarity of the striatal units (**Figure 9**, insets). In fact, in most of the scenarios, the second cluster contained a few data points with negative silhouette values, and if not, there were not enough data points to consider it a real cluster that represented a distinct and balanced SPN subpopulation. Equally important, in contrast with the view that discharge rate elevation and bursting activity coexist in the striatum of PD patients (**Singh et al., 2016**), the tendency to burst (CV of the ISIs > 1 ; **Kaneoke and Vittek, 1996**) decreased for units with a high discharge rate (**Figure 9**). Similar 2D or higher-order (3 or 4D) k-means cluster analyses (using the discharge rate, CV of the ISIs, MUA β power or STA-LFP β power as input parameters) also failed to reveal two well-separated clusters.

Figure 9. Cluster analysis using discharge properties does not reveal well-separated subpopulations of striatal units in parkinsonian (PD) and dystonic (DYST) patients. 2D k-means cluster analysis with $k = 2$, using the firing rate and the CV of the ISIs of each unit as input parameters. Analysis was performed when considering all (upper panels), only the well-isolated (middle panels) and only the well-isolated stationary (lower panels) units. Markers (x) represent cluster centroids. Inset: silhouette values were calculated for each clustering to assess how well-separated the two resulting clusters were. Silhouette values ranges from +1 (data points are very distant from other clusters), through 0 (data points are not distinctly in one cluster or another), to -1 (data points are assigned to the wrong cluster).

The online version of this article includes the following source data for figure 9:

Source data 1. 2D k-means cluster analysis for all units in PD.

Source data 2. 2D k-means cluster analysis for the well-isolated units in PD.

Source data 3. 2D k-means cluster analysis for the well-isolated and stationary units in PD.

Source data 4. 2D k-means cluster analysis for all units in Dystonia.

Source data 5. 2D k-means cluster analysis for the well-isolated units in Dystonia.

Source data 6. 2D k-means cluster analysis for the well-isolated and stationary units in Dystonia.

Discussion

There is no consensus as to the impact of aberrant striatal signaling on the spontaneous discharge rate and pattern of the SPNs in PD and Dystonia (Deffains et al., 2016; Ketzeff et al., 2017; Liang et al., 2008; Mallet et al., 2006; Sharott et al., 2017; Singh et al., 2016; Singh et al., 2015). Recordings of the activity of the SPNs are inherently difficult to perform given their very low firing rate and small size, leading to frequent loss and damage of these units (DeLong, 1971). Thus, a particular feature of striatal in vivo extracellular recordings is frequent 'injury activity'. These difficulties can distort the reported population averages of SPNs. For these reasons, we used an automated data-driven approach. A total of 933 and 718 MER segments from the posterior putamen [i.e., sensorimotor area of the striatum (Parent and Hazrati, 1995; Yin and Knowlton, 2006)] of PD and dystonic patients were analyzed. Here, striatal activity was not recorded in the caudate nucleus, but previous studies have shown that putaminal neurons fire at higher rate than the neurons of the caudate nucleus in PD patients (Singh et al., 2016). The striato-pallidal border was automatically detected using a machine learning algorithm (Valsky et al., 2020). MER segments were regularly spaced within the striatum and no manual search for units with low or high discharge rates was performed. Spike detection was performed offline with fully automatic quantification of the isolation quality and stationarity of the identified units. In contrast to previous reports (Singh et al., 2016), we found no drastic modulation in the SPN discharge rate and pattern (compared to values reported for normal/control animals or ET patients) in PD and dystonic patients.

Low discharge rate and similar levels of striatal activity in PD and Dystonia

We found that the firing rate of the SPNs of both the PD and dystonic patients was extremely sensitive to the quality of the isolation of the units. Specifically, we found a negative correlation between striatal firing rate and isolation score (Figure 2A and B). The negative correlation between the discharge rate of the detected units and their isolation quality revealed that - unlike in the STN (Deffains et al., 2014) - the spike detection and sorting algorithm used in this study and/or the physical properties of the striatal neurons tended to erroneously classify noise events as spikes (false positives) rather than missing real spikes (false negatives). The amplitude of the extracellular action potentials (or the signal-to-noise ratio) is mainly sensitive to the impedance of the microelectrode and the distance between the recorded neurons and the microelectrode, and is not related to firing rate of the neurons. Therefore, we can rule out the possibility that fast firing striatal neurons were less frequently well-isolated and under-represented in the high-score bins. Removing the non-stationary units also reduced the striatal firing rate of SPNs in both the PD and dystonic patients (Figure 3 and Figure 3—figure supplement 1, first column first column). This may indicate that the inclusion of non-stationary ('injured') units can also erroneously increase the striatal firing rate in PD and dystonic patients. Our automatic approach to spike detection, sorting and quality assessment revealed that the median firing rate of the striatal well-isolated stationary units was 3.85 and 2.55 Hz in PD and dystonic patients, respectively (Figure 3 and Figure 3—figure supplement 1, first column).

Thus, our results are inconsistent with a recent study by Singh et al., 2016 where the SPN discharge rate in PD (30.2 ± 1.2 Hz) and dystonic (9.3 ± 0.6 Hz) patients increased by ~15 and 5-fold compared to the low striatal discharge rate (2.1 ± 0.1 Hz) found in patients suffering from ET (i.e., a disorder without any known BG malfunction). In the current study, we did not have a control condition, nor did we record the striatal activity from ET patients. Therefore, we cannot rule out the possibility of an increase in the striatal firing rate of both PD and dystonic patients compared to human controls. Moreover, the small fraction of striatal interneurons (including the TANs, presumably the cholinergic interneurons) that was probably included in our sample may have slightly distorted our results (Figure 3 and Figure 3—figure supplement 1). Nevertheless, the putative TANs were hardly distinguishable from the putative SPNs in our human databases (Figure 3—figure supplement 2 and Figure 3—figure supplement 3) and most of the striatal neurons are SPNs (Graveland et al., 1985; Petryszyn et al., 2018; Petryszyn et al., 2014). Finally, in the normal NHP, the discharge rate of the TANs is higher than that of the SPNs, so that their possible inclusion would shift our results towards a higher striatal discharge rate. In any case, we did not find any significant difference between PD and dystonic patients that might reflect a distinct level of striatal hyperactivity in PD

(**Figure 3** and **Figure 3—figure supplement 1**, first column). The different results between our study and *Singh et al., 2016* may be due to: (i) a difference between machine learning detection vs. manual electrophysiologist detection of the striato-pallidal border, (ii) different spike sorting and detection methods, (iii) the use of algorithms for the quantification of the isolation quality and stationarity of the units vs. manual electrophysiologist decision-making, and (iv) different recording techniques (microelectrode type, step size and regular spaced recordings vs. manual search of the recording sites).

Lack of bursty and oscillatory pattern in the SPN spiking activity of PD and dystonic patients

The emergence of bursty and periodic oscillatory patterns after striatal dopamine depletion has been observed in other BG nuclei than the striatum (*Deffains et al., 2018; Deffains et al., 2016; Fillion and Tremblay, 1991; Heimer et al., 2002; Raz et al., 2000*). Previous studies by our research group reported the emergence of oscillatory spiking activity in the TANs recorded in the striatum of MPTP-treated monkeys, thus indicating that abnormal oscillatory activity following striatal dopamine depletion did not spare the striatum (*Deffains et al., 2016; Raz et al., 1996*). However, we found no significant parkinsonism-related oscillations in SPN spiking activity (*Deffains et al., 2018; Deffains et al., 2016*). Here, in line with this finding, we did not observe the emergence of bursting (**Figure 3**, **Figure 3—figure supplement 1**, second column and **Figure 6**) or oscillatory (**Figure 3**, **Figure 3—figure supplement 1**, third column and **Figure 7**) spiking activity of the striatal units sorted in the PD and dystonic patients.

In contrast to our results, Singh and collaborators reported large increases in the bursting activity of the SPNs in PD and dystonic patients (*Singh et al., 2016*) and MPTP-treated monkeys (*Singh et al., 2015*). Levodopa-induced increases or decreases of the SPN firing rate may be the result of D1 or D2 receptor activation, respectively (*Hernandez-Lopez et al., 2000; Kitai and Surmeier, 1993; West and Grace, 2002*). Using the recognized responses to dopaminergic stimulation, *Singh et al., 2015* showed that most bursty SPNs in the parkinsonian NHP exhibited a D1 receptor response to levodopa, thus suggesting that the emergence of an abnormal firing pattern predominantly affected the D1 SPNs (i.e., the SPNs of the direct pathway). However, when using a single-cell juxtacellular recording-labeling technique in the 6OHDA rodent, *Sharott et al., 2017* showed that in addition to their excessive firing rate, D2 SPNs (that primarily compose the indirect pathway) displayed aberrant phase-locked burst firing to cortical β oscillations. In that study, it might be assumed that D2 SPNs, rather than D1 SPNs, would exhibit an abnormal firing rate and pattern in the dopamine-depleted striatum. Therefore, technical advances and further studies in PD patients and animal models should be carried out to reach a consensus.

As reported previously (*Deffains et al., 2018; Deffains et al., 2016; Kondabolu et al., 2016; Lemaire et al., 2012; Piña-Fuentes et al., 2018; Silberstein et al., 2003; Singh and Papa, 2019*), abnormal oscillations of the LFP have been recorded in the striatum of both PD and dystonic patients (**Figure 8A**). The LFP most likely represents the sub-threshold (e.g., synaptic input) activity, whereas the MUA reflects the efferent (output) activity of the local neuronal population (*Buzsáki et al., 2012; Logothetis, 2003*). In both diseases, striatal SPNs were therefore bombarded with pathological oscillations by their major afferent neurons, thus suggesting that the emergence of striatal β LFP oscillations is network-driven. Interestingly, other studies have shown that changes in the intrinsic properties of striatal neurons (i.e., increasing SPN excitability through amplification of striatal cholinergic tone) is sufficient to induce robust β LFP oscillations in the striatum (*McCarthy et al., 2011*). Due to the limitations of human extracellular recordings, we were not able to investigate the intrinsic properties of the striatal neurons and therefore cannot rule out the possibility that the intrinsic properties of the striatal neurons played a role in the emergence of β LFP oscillations in the striatum. In fact, it is likely that network-based and cell-autonomous mechanisms are not mutually exclusive. In any case, we found no significant phase-locking between striatal spiking activity and monopolar recorded LFP β oscillations (**Figure 3**, **Figure 3—figure supplement 1**, fourth column and **Figure 8B**), thus suggesting that the striatal oscillating synaptic inputs were probably not strong enough to entrain the spiking activity of the striatal SPNs. Indeed, the striatal SPNs failed to express pathological β oscillatory activity in either PD or Dystonia. Moreover, recent studies have demonstrated that monopolar and bipolar BG LFPs may be contaminated by the volume conductance of cortical electroencephalogram (EEG) activity (*Lalla et al., 2017; Marmor et al., 2017*).

Therefore, it is likely that BG LFPs, including the LFPs recorded in the striatum, do not accurately reflect local cellular activity and should be at best interpreted with caution. Exaggerated striatal LFP oscillations in PD and Dystonia cannot therefore be regarded as direct evidence for the presence of SPN spiking oscillatory activity.

Is the imbalance in the activity of SPN subpopulations evident in PD and Dystonia?

Obviously, striatal activity must be affected in PD and dystonic patients. A popular theory is that the hypoactivity of the direct pathway (originating from D1 SPNs) and the hyperactivity of the indirect pathway (originating from D2 SPNs) lead to excessive GPi/SNr inhibitory inputs to the thalamus in PD (Wichmann and DeLong, 2003) and vice-versa in Dystonia (Guehl et al., 2009). These aberrant GPi/SNr inhibitory inputs to the thalamus lead to the release of abnormal output commands and result in the emergence of the clinical symptoms. Unlike in rodent studies [see e.g., (Sharott et al., 2017)], extracellular recordings of spontaneous activity cannot discriminate between the spiking activity of the striatal D1 and D2 SPNs. However, if striatal dopamine depletion drastically enhances the differences (in discharge rate and pattern) between the two distinct SPN subpopulations (but see Ketzev et al., 2017), one would expect to see a bimodal distribution of SPN discharge properties after dopamine depletion and/or distinct clusters of SPN activity in our patients. Instead, visual inspection of the distributions of the discharge rate (Figure 5) and the CVs of ISIs (Figure 6A) revealed long-tailed unimodal distributions in both diseases. Moreover, the cluster analysis using SPN discharge properties failed to identify two well-separated SPN subpopulations (Figure 9).

In conclusion, our results in patients extend our previous study in the MPTP NHP model of PD (Deffains et al., 2016) and studies in the 6-OHDA rodent model (e.g., Ketzev et al., 2017; Maltese et al., 2019) and demonstrate that abnormal activity along both the direct and indirect pathways of the BG network is not caused by drastic changes in spontaneous SPN spiking activity. Recently, Maltese et al., 2019 reported abnormal recruitment (e.g., during behavior) of D1 and D2 SPNs (which are mostly silent at rest in the healthy condition) in parkinsonism that resulted in an aberrant net balance of striatal outputs, although there were no changes in the firing rate of the individual neurons. Our experimental approach (i.e., extracellular recordings in awake patients in the operating room) does not allow us to estimate the sample size of activated neurons. Moreover, we did not have a control condition and recordings were not performed during behavior to minimize surgical procedure time. Therefore, further experiments in primates (at least in monkeys, if not in patients) are needed to validate or refute this possibility. It is likely that these small to moderate changes in spontaneous SPN discharge are amplified by BG downstream structures (Crompe et al., 2020), thus leading to the clinical symptoms of PD and possibly of Dystonia.

Materials and methods

Patients and surgery

Patients with PD and Dystonia were recruited from the movement disorders clinics at the Hadassah Medical Center in Jerusalem. All patients were scheduled to undergo implantation of DBS electrodes into the GPi and underwent MR imaging, and evaluation for motor and non-motor impairments within 30 days prior to surgery. Data were collected from 16 PD and 13 dystonic (non-genetic and genetic Dystonia) patients. Patient demographic information appears in Table 1. Note that our DBS recordings in ET patients started 10 mm above the thalamic target and therefore did not include striatal recordings. All patients met the criteria for DBS and signed a written informed consent for surgery that involved microelectrode recordings. This study was authorized and approved by the Institutional Review Board of Hadassah Hospital in accordance with the Helsinki Declaration (reference code: 0168–10-HMO).

Surgery was performed using a CRW stereotactic frame (Radionics, Burlington, MA, USA). BG target coordinates were chosen as a composite of the indirect anterior commissure-posterior commissure (AC-PC) atlas-based location and direct (1.5 or 3Tesla) T2 magnetic resonance imaging, using Framelink 4 or 5 software (Medtronic, Minneapolis, USA). All recordings used in this study were made while the patients were fully awake (no sedation or anesthesia) and the PD patients were off dopaminergic medication (overnight washout >12 hr).

Table 1. Patient demographic information.

Patient no.	Disease	Surgery side	Trajectories	Gender	Age at onset	Age at surgery	Disease duration (y)
1	PD	bilateral	R(2) ; L(1)	M	40	62	22
2	PD	unilateral	R(1)	F	45	62	17
3	PD	bilateral	R(2) ; L(2)	F	50	62	12
4	PD	unilateral	L(1)	F	45	62	17
5	PD	unilateral	R(2)	F	49	60	11
6	PD	bilateral	R(2) ; L(2)	F	66	72	6
7	PD	bilateral	R(2) ; L(1)	F	43	59	16
8	PD	bilateral	R(2) ; L(2)	F	54	68	14
9	PD	bilateral	R(2) ; L(2)	F	55	62	7
10	PD	bilateral	R(2) ; L(2)	F	46	58	12
11	PD	bilateral	R(2) ; L(2)	F	41	57	16
12	PD	bilateral	R(2) ; L(2)	M	53	66	13
13	PD	unilateral	L(2)	F	53	63	10
14	PD	bilateral	R(2) ; L(2)	M	35	44	9
15	PD	bilateral	R(1) ; L(1)	M	41	57	16
16	PD	unilateral	R(2)	M	50	57	7
17	Dystonia (NG)	bilateral	R(1) ; L(2)	F	36	56	20
18	Dystonia (NG)	bilateral	R(2) ; L(2)	M	44	49	5
19	Dystonia (NG)	bilateral	R(1) ; L(2)	F	45	65	20
20	Dystonia (NG)	bilateral	R(2) ; L(1)	F	58	60	2
21	Dystonia (NG)	bilateral	R(2) ; L(2)	F	13	19	6
22	Dystonia (NG)	bilateral	R(1) ; L(1)	F	60	63	2
23	Dystonia (NG)	bilateral	R(2) ; L(2)	M	60	62	2
24	Dystonia(NG)	bilateral	R(2) ; L(2)	F	69	71	2
25	Dystonia (G)	bilateral	R(2) ; L(2)	M	16	25	9
26	Dystonia (G)	bilateral	R(2) ; L(2)	M	12	18	6
27	Dystonia (G)	bilateral	R(1) ; L(2)	M	24	39	15
28	Dystonia (G)	bilateral	R(2) ; L(2)	M	39	54	15
29	Dystonia (G)	bilateral	R(1) ; L(2)	M	53	56	3

PD patients (5 males and 11 females) were 60.7 ± 6.1 years old and with a disease duration of 12.8 ± 4.4 years (mean $\pm$ standard deviation, SD). Dystonic patients (7 males and six females) were 49.0 ± 18.0 years old and with a disease duration of 8.2 ± 6.9 years (mean $\pm$ standard deviation, SD). NG: non-genetic; G: genetic; R: right; L: left; Numbers in parentheses indicate the number of microelectrode trajectories; M: male; F: female.

Data acquisition

The data were acquired using two systems: MicroGuide (prior to 2015, previously described [Deffains et al., 2014]) and Neuro Omega (from 2015, previously described [Valsky et al., 2020]).

Microelectrode recordings

For every recording session, a microelectrode recording (MER) exploration using one or two micro-electrode trajectories (2 mm apart) was made starting 15 mm above the pre-operative T2 MRI image-based calculated target. Our trajectories followed a double-oblique approach (50 to 80° from the axial AC-PC plane and 0 to 10° degrees from the midsagittal plane) through the posterior putamen and the GPe and towards the ventral border of the posterior-lateral portion of the GPi target (Figure 1 and Video 1). The target coordinates were in the range of the approximate anatomic coordinates for the motor domain of the GPi: Lateral (X) = 19–22 mm from the midline or ~18 mm

from the third ventricle wall; Anterior (Y) = 1–3.5 mm from the mid-commissural point (MCP), and vertical (Z) = –1 to –4 below the AC-PC plane.

The ‘central’ electrode was directed at the ventral border of the posterior-lateral portion of the GPi and the ‘anterior’ electrode was located 2 mm anterior/ventral to the central electrode in the parasagittal plane. Some of these recordings were made by a single microelectrode trajectory (instead of two) to accommodate cortical anatomy under the burr hole and brain blood vessels (Machado et al., 2006).

MER segments were regularly sampled in space in order to avoid recording bias towards particular striatal units. For all our GPi-DBS surgeries, the step size between two MER segments ranged from 100 to 200 μm and was controlled by the neurophysiologist to achieve optimal identification of the pallidal borders. At each step, MER segments were recorded from 4 to 140 s (after a 2 s signal stabilization period).

A total of 93 microelectrode trajectories aiming at the GPi were analyzed (48 in PD and 45 in Dystonia), yielding a total of 933 and 718 MER segments within the posterior putamen of patients suffering from PD and Dystonia, respectively. Striatum-GPe borders were automatically detected using a machine learning software (Valsky et al., 2020).

Group-based microelectrode track trajectories

The trajectories of GPi DBS patients were reconstructed using the open source LeadDBS program (www.lead-dbs.org) using LeadDBS v2.2.3 (Horn et al., 2019; Horn and Kühn, 2015). Lead Group, implemented within the Lead-DBS environment (Treu et al., 2020), was used to graphically illustrate the group-based microelectrode track trajectories within the posterior putamen. Pre-operative imaging was performed on a 1.5T or 3T MRI and included a pre-operative T1 and T2 sequence. All patients received post-operative CT. The post-operative CT was co-registered to anchor modality with the pre-operative T1 MRI, using a two-stage linear registration (rigid followed by affine) as implemented in Advanced Normalization Tools (Avants et al., 2008). Linear co-registration between the MR T1 and T2 modalities was done using SPM12 (Penny et al., 2007). Pre- (and post-) operative acquisitions were spatially normalized into MNI_ICBM_2009b_NLIN_ASYM space (Fonov et al., 2011) based on pre-operative acquisitions using the Symmetric Normalization (SyN) registration approach as implemented in Advanced Normalization Tools (Avants et al., 2008). Nonlinear deformation into template space was achieved in five stages. After two linear (rigid followed by affine) steps, a nonlinear (whole brain) SyN-registration stage was followed by two nonlinear SyN-registrations that consecutively focused on the GP as defined by subcortical masks in Schöneck et al., 2009. DBS electrode localizations were corrected for brain shift in post-operative acquisitions by applying a refined affine transform calculated between the pre- and post-operative acquisitions that were restricted to the GP as implemented in the brain shift-correction module of Lead-DBS software (Horn and Kühn, 2015). DBS electrodes were automatically pre-localized in native and template space using the PaCER algorithm (Husch et al., 2018). DBS electrodes were manually localized based on post-operative acquisitions using a tool specifically designed for this task.

A total of 36 microelectrode track trajectories (13 in PD and 23 in Dystonia) of four PD and six dystonic patients were visualized (Figure 1). We failed to include some patients because of corrupted or missing pre- or post-operative images. A 100 μm T1 scan of an ex-vivo human brain, acquired on a 7T MRI scanner (Edlow et al., 2019) served as a background template in Figure 1. The definition of the striatum, GPe and GPi boundaries was informed by the Distal atlas (Ewert et al., 2018). For further visualization of microelectrode track trajectories in the posterior putamen see Video 1.

Offline spike sorting and assessment of isolation quality and stationarity of sorted units

To avoid human biases that could corrupt spike detection and sorting outcomes (Pedreira et al., 2012; Rey et al., 2015), single-unit striatal activity was assessed by sorting the spike trains from each MER segment recorded within the striatum using an automatic offline spike detection and sorting method (Offline Sorter v4.4.2.0, Plexon Inc, Dallas, Texas, RRID:SCR_000012). For each band-pass filtered spiking signal (multi-unit activity, MUA), spikes were detected using a negative voltage threshold trigger systematically set at 3SDs from the mean of its peak height histogram. Salient

features of the detected spikes were extracted with principal component analysis, using the scores of the first two principal components as features for clustering. Then, identification of different spike clusters reflecting the activity of different units was done by an automatic k-means clustering algorithm (K-Means Scan with a number of clusters between 1 and 5 and a circular seed cluster pattern for choosing the initial cluster centers). The clustering that produced the best value of the Pseudo-F statistic was then chosen as the clustering pattern for that band-pass filtered spiking signal. Finally, the isolation quality of the units identified by the spike sorter software was systematically graded by measuring their isolation scores using an independent algorithm (Joshua *et al.*, 2007). The isolation score ranges from 0 (i.e. highly noisy) to 1 (i.e. perfect isolation).

To assess the stationarity of the firing rate and spike amplitude of each well-isolated unit (isolation score ≥ 0.6), we segmented the data comprised between the first and the last spike of its spike train into 10 equal non-overlapping time bins. Then, we Z-score normalized the firing rate and the average spike amplitude in each bin using the mean and the SD of either the firing rate or the average spike amplitude calculated over the 10 bins. Finally, the slope value of the linear regression line for the firing rate and the average spike amplitude were calculated and expressed in z-score/bin. Units with slope values of the linear regression line for the firing rate or average spike amplitude that were greater than or equal to the 70th percentile were defined as non-stationary units.

Discharge pattern assessment of spike train

For each spike train of the sorted units, we calculated the inter-spike intervals (ISI) and generated their ISI histograms. In parallel, we also computed the autocorrelograms of the spike train of the well-isolated stationary units, calculated for ± 500 ms offset with 10ms-bins. For each autocorrelogram, values were normalized so that autocorrelation values ranged from 0 to 1.

For burst detection, we applied the Poisson surprise method with the surprise maximization (SM) search algorithm (Legédy and Salcman, 1985) to each spike train of the well-isolated stationary units, using the following parameters: minimal burst length = 3 spikes; threshold surprise value (S) = 10; burst ISI limit = mean (ISI)/2; add limit = 150% of burst ISI limit and inclusion criteria (IC) = 5.

For each spike train of the well-isolated stationary units, the frequency (number of bursts/s) and mean duration (s) of the burst episodes were calculated over their entire recording span. These two metrics were used to determine the burst prevalence for each unit which was defined as the burst frequency * mean burst duration. For each unit, the burst prevalence (range: 0–1) represents the probability that the discharge pattern is bursty.

Power spectral density

Prior to power spectral density (PSD) calculations, each band-pass filtered spiking signal (multi-unit activity, MUA) recorded in the vicinity of a sorted unit was Z-score normalized (using its mean and SD) to obtain an unbiased estimate (by the electrode impedance, the A/D characteristics of the recording system, or the amplitude of the recorded neuronal activity) of the oscillatory activity (Zaidel *et al.*, 2010). The Z-normalized signal was rectified by the 'absolute' operator (Deffains *et al.*, 2018; Deffains *et al.*, 2016; Deffains *et al.*, 2014; Moran *et al.*, 2008; Zaidel *et al.*, 2010). The rectified signal follows the envelope of the MUA and therefore enables the detection of periodic oscillatory activities with frequencies below the range of the online band-pass filter. Since the LFP frequency domain was filtered out, the resulting PSD only represented the oscillatory features of the spiking activity. Although up to five units could be sorted from each MUA (see above in *Offline spike sorting and assessment of isolation quality and stationarity of sorted units*), each MUA was only analyzed once.

The PSD of each rectified Z-normalized signal (expressed in $\text{z-score}^2/\text{Hz}$) was calculated using Welch's method with a 1 s Hamming window (50% overlap) and a spectral resolution of 1 Hz ($n_{\text{fft}} = 44000$ or 48000 , sampling frequency = 44 or 48 kHz depending on the acquisition system). To evaluate the β power, the baseline values in the 13–30 Hz range of each PSD were linearly interpolated [based on the two closest points that flanked the 13–30 Hz band, namely the values at 12 and 31 Hz (spectral resolution of 1 Hz, see above)] and averaged. Then, the β power (i.e., the mean of the observed values between 13 and 30 Hz) was compared to the interpolated β power (baseline).

Similarly, we also calculated the PSD of the striatal monopolar (0.1–300 Hz) LFP. To do so, the PSD of each Z-normalized LFP was calculated using Welch's method recorded in the vicinity of the cells (see above for the parameters; but $nfft = 1375$, sampling frequency = 1.375 kHz) and without prior rectification by the absolute operator.

Spike-triggered average of the LFP

To investigate the spike-LFP relationship in the temporal domain, we also calculated the spike-triggered average (STA) of the LFPs (Deffains *et al.*, 2016; Goldberg *et al.*, 2004). To do so, the LFP was recorded in the vicinity of the sorted units (i.e., spiking activity and LFP were recorded on the same electrode). Each Z-normalized LFP was offline band-pass filtered from 4 to 12 Hz or from 13 to 30 Hz (4-pole Butterworth filter, `filtfilt` Matlab function). For comparison, STAs-LFP were also calculated after randomly shifting the timestamp of each spike of the spike train [i.e., random time (comprised between 0 and 1 s) was added to the timestamp of each spike of the spike train] in order to abolish any relationship between LFP and spiking activity (Shift predictor). The PSD of the STA-LFP was calculated as for the LFP.

Software and statistics

Anatomical analysis was done with the open source LeadDBS program (www.lead-dbs.org). All the physiological data and statistical analyses were carried out using MATLAB R2016a routines (Mathworks, Natick, MA, USA, RRID:SCR_001622). Mann-Whitney U-tests and Wilcoxon signed rank tests were used for statistical comparisons of two unpaired and paired sample means, respectively. Statistical comparisons of two sample proportions were performed using Chi-square tests. Analysis of the subset of ≥ 10 s-MER segments with striatal well-isolated stationary units yielded similar results (Figure 3—figure supplement 5 and Figure 6—figure supplement 1) to those reported here, thus indicating that our results were not confounded by the shortest MER segments. The criterion for statistical significance was set at $p < 0.05$ for all statistical tests.

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Author contributions

Dan Valsky, Conceptualization, Software, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review and editing; Shai Heiman Grosberg, Software, Formal analysis, Writing - review and editing; Zvi Israel, Conceptualization, Resources, Supervision, Project administration, Writing - review and editing; Thomas Boraud, Conceptualization, Writing - review and editing; Hagai Bergman, Conceptualization, Resources, Supervision, Funding acquisition, Investigation, Methodology, Writing - original draft, Project administration, Writing - review and editing; Marc Deffains, Conceptualization, Software, Formal analysis, Supervision, Investigation, Methodology, Writing - original draft, Project administration, Writing - review and editing

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Ethics

Human subjects: All patients met the criteria for DBS and signed a written informed consent for surgery that involved microelectrode recording. This study was authorized and approved by the Institutional Review Board of Hadassah Hospital in accordance with the Helsinki Declaration (reference code: 0168-10-HMO).

Decision letter and Author response

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Additional files

Supplementary files

- Transparent reporting form

Data availability

All data generated or analysed during this study are included in the manuscript and supporting files. Source data files have been provided for Figures 2, 3 and 9.

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DISCUSSION

In this dissertation I designed machine learning methods that allow for accurate STN-ventral and striato-pallidal borders confirmation without needing an expert physiologist. Correlatively, the results help resolve a long-standing controversy on the nature of striatal dysfunction in PD. Below I discuss these findings as they emerged from my consecutive publications (Results I-III and Appendix I-II). Then, in the remainder of this discussion, I address each subject in more detail.

In the first study (Results I) we identified the neural signatures of the SNr and STN. To automatically discriminate between the STN and SNr during the DBS surgery, we designed a real-time HMM procedure. To understand the changes in the discharge rate and pattern of striatal projection neurons (SPNs) in PD and dystonia (Results III), we devised a method to delimit striato-pallidal borders (Results II). Contrary to long-standing assumptions, the third study (Results III) showed no evidence for spiny neuron dysfunction across a large data set collected from human PD and dystonic patients. Rather, the results suggest that spike sorting errors were the likely cause of the changes observed in neuronal firing rates reported in previous studies. These findings contribute to resolving the debate over the nature of striatal dysfunction in PD and suggest that changes in basal ganglia pathophysiology may arise through structures outside the striatum.

A novel method to demarcate STN and SNr borders

To date, automatic methods that use RMS and PSD values (Danish et al., 2008; J. H. Falkenberg et al., 2006; Moran et al., 2006; Novak et al., 2007; Zaidel et al., 2009) are successful in identifying STN-white matter (STN-WM) transitions, but are not as good for the direct STN-SNr transition. By adding a new feature to the machine-learning procedure; namely, the ratio of high frequency (100-150 Hz) power to low frequency (5-25 Hz) power, we developed an innovative method (Results I) that can detect the transition between STN and SNr. We used a SVM procedure to verify that the 100-150 Hz / 5-25 Hz power ratio reliably discriminated between STN and SNr populations. Then, we utilized an HMM procedure using the MER features, together with the trajectory history to detect the STN exit either to the white matter (WM) or SNr. This HMM procedure can also deal with heterogeneous variation in trajectories, since some transitions go from the VMNR STN to the SNr and others from the white matter above the STN to the SNr.

Because this real-time detection algorithm is used in the operating room it needs to function on novel data without being continually adjusted. We demonstrated that the HMM procedure can successfully process completely unknown data. We used 73 new trajectories (from 51 patients, all trajectories included both STN and SNr) to evaluate the HMM procedure. The STN OUT location error for both the STN-SNr and the STN-WM exhibited better means and standard deviations than the previous HMM procedure (Zaidel et al., 2009) or the Bayesian method (Moran et al., 2006). It only took 99 ms in real time (Intel Core I5 2410M processor with 4GB RAM) to process a new trajectory and decide whether it was the STN or not, making this a practical method for use during DBS surgery.

Oscillations in awake versus light anesthesia dystonia classes

Several recent studies have reported differences in pallidal firing rates between dystonia classes under volatile anesthetics (McClelland et al., 2016; Welter et al., 2015). In Results II, we extended previous work by comparing the spectral oscillatory changes in neural activity within the striatum, GPe and GPi between awake and lightly anesthetized genetic and non-genetic dystonia classes. Using the L_1 -distance measure, we determined that the awake and the light anesthesia (0.3-0.6 MAC range) dystonia classes could be merged. Thus, although anesthesia may reduce pallidal neuronal oscillations across all dystonia classes (Hutchison et al., 2003; Venkatraghavan et al., 2016), detectable relative differences in neural oscillations between genetic dystonia and non-genetic classes are preserved.

A growing body of evidence suggests that anesthetics induce oscillations that alter or disrupt the normal brain's information processing (Cimenser et al., 2011; Purdon et al., 2013). Because the cortex is the major afferent to the striatum (Kemp and Powell, 1970), profound changes in neural activity in the cortex, which are reflected in major changes in the scalp electroencephalogram (EEG), may be transmitted to the striatum. Our MER-derived results revealed that alpha oscillations in the striatum under light anesthesia were consistent with findings showing an increase in oscillatory EEG power in the alpha frequency range under isoflurane or sevoflurane anesthesia (Purdon et al., 2015). Even though striatal neurons send inhibitory projections to the GPe and GPi (Haber, 2003), we found that striatal neurons did not propagate these alpha oscillations to them. This may be explained by studies in non-human primates indicating that the output activity of the pallidum (or basal-ganglia downstream structures) does not reflect striatal neural activity (Deffains et al., 2016a). This suggests that abnormal oscillatory activity within striatum, under light anesthesia, did not propagate to the GPe and GPi. Another possibility is that the oscillatory activity in the different domains of the striatum (e.g., ventral and dorsal striatum) was not the same. We may therefore have recorded the neural activity from those parts of the GPe and GPi that receive information from domains of the striatum that are not involved in alpha oscillations.

Differences in striato-GPe-GPi oscillatory activity between the PD, genetic dystonia and non-genetic dystonia classes

In Results II, by comparing the spatial distribution of the oscillatory neural activity within the striatum, GPe and GPi across the three classes of the disease, we found that pathological beta-oscillations comprised a continuous stretch within the GPi PD. This is unlike the GPe PD that forms gradient beta-oscillations as a function of the distance from the ventral border. We then found that the spatial distribution of low-frequency activity for both the GPe and GPi was nearly identical across the genetic and non-genetic dystonia patients. In contrast, the GPe and GPi in PD exhibited both tremor (4-5 Hz) and beta frequency oscillations.

These differences in striato-GPe-GPi oscillatory activity between the PD, genetic dystonia and non-genetic dystonia classes could be used in the future as electrophysiological target-specific biomarkers to optimize therapy in adaptive DBS control systems (Meidahl et al., 2017; Wang et al., 2018).

Real-time machine learning for striato-pallidal localization

In Appendix II, we showed that NRMS values calculated from the MER segments were effective in detecting the striatum-GPe and GPi-exit borders because of their increase and decrease in the NRMS. In contrast, detection of the GPe-GPi borders was more difficult, since often there was no sharp increase or decrease in NRMS between these structures. However, visual inspection of the mean power spectra did reveal differences between spectra in the 3-300 Hz domain. To determine quantitatively which part of the spectral domain enables the best discrimination between regions, we calculated the absolute difference in the mean power spectra. We then examined eight different frequency bands (approximately logarithmically equally distributed) along the frequency axis (Appendix II). Frequency bands at 3-30 Hz, 8-35 Hz, 30-95 Hz and 180-245 Hz provided the greatest discrimination for the striatum-GPe and GPe-GPi transitions. We used these frequency bands to calculate the input features of the HMM.

In Results II, we designed an HMM to demarcate the striato-pallidal borders. We found that the HMM varied in its ability to predict GPe- and GPi- entry and exit. Whereas the striatum-GPe and GPi-exit were usually clear and characterized by a distinguishable rise and fall of the NRMS, respectively, the GPe-GPi transitions were harder to detect in some trajectories. The GPe is separated from the GPi by a thin layer of myelinated fibers called the medial medullar lamina (Lanciego et al., 2012). The GPe-GPi transition can therefore be detected by a drop in previous neuronal activity and the recording of border cells in its vicinity. However, the transition from the GPe to GPi was not always clear to the expert or to the HMM algorithm. This may have been due in part to the sparsely distributed neurons along the pallidum and the variability in the firing characteristics between the GPe and GPi in the MER dataset (Schiff et al., 2002). Clinically, GPe-GPi boundary reliability is probably not very important. This is because, for accurate DBS lead placement, the critical boundary is the GPi-exit border where the PD algorithm achieved 83 % accuracy (on the test data) within a 0.3 mm distance (an error considered “acceptable” by our team). Localization of the striato-pallidal borders can help the neurosurgeon decide which MER track to implant, when multiple electrodes are used for MER, and when implanting the macroelectrode at the optimal depth.

Further research is necessary to evaluate performance in different clinical settings, in order to validate this algorithm across the spatial distributions of neural activity encountered along the trajectory in the typical operating room setting. The HMM is agnostic to the type of raw data used and can be implemented easily in existing MER devices. The ability to classify striato-pallidal regions in real-time using our classification algorithm may shorten DBS surgery considerably. The machine learning algorithm approach considers all available example trajectories equally and finds transitions between nuclei that a human researcher may miss for example, due to bias towards a given interpretation. Our method allows accurate GPi confirmation without needing the input of an expert physiologist.

Discharge rate and pattern of the striatal projection neurons in Parkinson’s disease and dystonia

In Results III, we helped to resolve the long-standing controversy about the nature of striatal dysfunction in PD. The prevailing theory of basal ganglia dysfunction in PD is that it originates from alterations in the firing rates or patterns of D2-expressing spiny projection neurons in the striatum. Contrary to these assumptions we found no evidence for spiny neuron dysfunction,

and that spike sorting errors were the likely cause of the changes observed in neuronal firing rates in previous studies. The findings in Results III suggest that the changes in basal ganglia pathophysiology most probably arose in through structures outside the striatum.

The methods in Results III go beyond previous reports by utilizing a machine learning algorithm (Results II) to automatically detect the striato-pallidal border, and by applying objective methods for the identification of units and the quantification of their isolation quality and stationarity. Using these methods, we found that the firing rate of the SPNs of both the PD and dystonic patients was extremely sensitive to the quality of the isolation of the units. Specifically, we found a negative correlation between striatal firing rate and isolation score. The negative correlation between the discharge rate of the detected units and their isolation quality revealed that the spike detection and sorting algorithm used in our study and/or the physical properties of the striatal neurons tended to erroneously classify noise events as spikes (false positives) rather than missing real spikes (false negatives). The amplitude of the extracellular action potentials (or the signal-to-noise ratio) was mainly sensitive to the impedance of the microelectrode and the distance between the recorded neurons and the microelectrode, and was not related to the firing rate of the neurons. This thus ruled out the possibility that fast firing striatal neurons were less frequently well-isolated and under-represented in the high-score bins. We found that by removing the non-stationary units also reduced the striatal firing rate of SPNs in both the PD and dystonic patients. This may indicate that the inclusion of non-stationary (“injured”) units can also erroneously increase the striatal firing rate in PD and dystonic patients. The difference in results between our study and Singh et al., (2016) may be due to: (i) a difference between machine learning detection vs. manual electrophysiologist detection of the striato-pallidal border, (ii) different spike sorting and detection methods, (iii) the use of algorithms for the quantification of the isolation quality and stationarity of the units vs. manual electrophysiologist decision-making, and (iv) different recording techniques (microelectrode type, step size and regular spaced recordings vs. manual search of the recording sites).

Overall, our results on patients extend a previous study in the MPTP NHP model of PD (Deffains et al., 2016b) and studies in the 6-OHDA rodent model (Ketzef et al., 2017; Maltese et al., 2019b) and demonstrate that abnormal activity along both the direct and indirect pathways of the BG network is not caused by drastic changes in spontaneous SPN spiking activity. Recently, Maltese et al. (2019) reported abnormal recruitment (e.g., during behavior) of D1 and D2 SPNs (which are mostly silent and at rest in the healthy condition) in parkinsonism that resulted in an aberrant net balance of striatal outputs, although there were no changes in the firing rate of the individual neurons. Our experimental approach (i.e., extracellular recordings in awake patients in the operating room) does not allow us to estimate the sample size of the activated neurons. Moreover, we did not have a control condition and recordings were not performed during behavior, to minimize surgical procedure time. Therefore, further experiments in primates are needed to validate or refute this possibility. It is likely that these small to moderate changes in spontaneous SPN discharge will be amplified by BG downstream structures, thus leading to the clinical symptoms of PD and possibly of dystonia.

APPENDICES

Supplementary material for article in Results I

Discrimination matrix of the STN-SNr

Table S1: The frequency dependence of the STN-SNr discrimination matrix.

Discrimination matrix		Width of each band [Hz]			
		10 Hz	20 Hz	50 Hz	100 Hz
Starting Index [Hz]	5 Hz	4.28	5.30	1.71	0.04
	50 Hz	NA	2.62	2.02	2.41
	100 Hz	NA	NA	15.55	4.13
	200 Hz	NA	NA	NA	1.99

Values depict the discrimination between STN and SNr of 10 approximately logarithmically spaced bands throughout the 5-300 Hz range of the power spectra. The band starts at the starting index and has a specified width (e.g., top left box is the 5-15 Hz band). The starting index of the band width was simultaneously increased (e.g., for a starting index = 200 Hz, we only tested a width of 100 Hz, 200-300 Hz band). For each band the mean power (V^2/Hz) for each MER was calculated. Then, for each band, the absolute value of the difference in the mean power between the STN and the SNr was obtained. Finally, the results were normalized by the square root of the sum of the variances of the STN and the SNr to yield the discrimination index (V^2/Hz). Maximal STN-SNr discrimination was obtained in two different frequency bands: high frequency (100-150 Hz) with a value of 15.55, and low frequency (5-25 Hz) with a value of 5.3.

Support vector machine discrimination performance

Table S2: SVM discrimination performance

		Human Expert's Classification		Total
		STN	SNr	
SVM Output	STN	TP = 1528 88.83%	FP = 4 0.23%	1532
	SNr	FN = 37 2.15%	TN = 151 8.77%	188
Total		1565	155	n=1720

The discrimination performance of the SVM classifier for the training dataset. The NRMS and the 100-150 Hz / 5-25 Hz Power Ratio were evaluated by the 10-fold cross validation method and are presented as an error matrix. TP, true positive; TN, true negative; FN, false negative; FP, false positive.

The Hidden Markov Model

For the HMM procedure, a trajectory is a sequence of states, and at any depth along the trajectory the electrode exists in one of a finite set of states (functionally discrete state model, presented in Figure 1C).

1. White matter before STN
2. Dorso lateral oscillatory region (DLOR) STN
3. Ventral medial non oscillatory region (VMNR) STN
4. STN exit
 - a. White matter between STN and SNr
 - b. or SNr

A typical trajectory state sequence proceeds through the first three states consecutively and then to the white matter between the STN and SNr (solid line in Figure 1C). However, not all trajectories have clearly defined STN-WM transitions; hence, a trajectory can enter the SNr immediately after the STN (dotted line). In addition, a trajectory can start in the white matter and enter the VMNR or go directly into the SNr (dashed lines) without passing through the STN.

In the HMM, transitions between states take place according to (1) a fixed probability (i.e., transition matrix and emission matrix) depending solely on the state of the electrode at the depth immediately preceding the current state and (2) a probability value calculated from the current MER. Note that we used a feed-forward HMM procedure; i.e., as a sequence progresses, it is possible to remain in the same state, but it is not possible to return to a previous state (e.g., from the SNr to the STN state).

Table S3: The HMM transition and emission matrices.

A

Transition matrix		To			
		State-1	State-2	State-3	State-4
From	State-1	0.9510	0.0280	0.0103	0.0107
	State-2	0	0.9601	0.0397	0.0002
	State-3	0	0	0.9617	0.0383
	State-4	0	0	0	1.0000

B

Emission matrix		Observations						
		Low-NRMS	Intermediate-NRMS	high-NRMS				
				High mean beta		Low mean beta		High to Low Power Ratio
				High max beta	Low max beta	High max beta	Low max beta	
State	State-1	0.8685	0.0261	0.0348	0.0044	0.0039	0.0254	0.0365
	State-2	0.3056	0.0263	0.3786	0.0434	0.0336	0.1755	0.0367
	State-3	0.3167	0.0534	0.0769	0.0239	0.0780	0.3694	0.0814
	State-4	0.5382	0.1881	0.0130	0.0012	0.0207	0.1054	0.1330

(A) The HMM transition matrix. Values depict the probability of a transition between states (or remaining in the current state) for each step in the sequence. The states are defined as follows: 1 – WM before the STN; 2 – in the dorsolateral oscillatory region (DLOR) of the STN; 3 – in the ventro medial non-oscillatory (VMNR) of the STN; 4 – STN exit (STN-SNr or STN-WM). (B) The HMM emission matrix. Values depict the probability of each observation given the state. The states are defined as in A. The seven columns correspond to the seven observations detailed in the table header as follows:

- All MERs with NRMS<1.25 (threshold 1); i.e., below a 25% increase from the NRMS baseline (which is equal to 1 due to the normalization) were clustered together (Low-NRMS observation).

- The mean deviation from threshold 1 (i.e. $\text{NRMS} - 1.25$) of the remaining MERs was calculated. Threshold 2 was defined as threshold 1 plus 25% of the calculated mean deviation. MERs with a NRMS between threshold 1 and threshold 2 were clustered together (Intermediate-NRMS observation), and MERs with $\text{NRMS} > \text{threshold 2}$ were further divided according to their (maximum and mean) beta (13–30 Hz) oscillatory activity (above or below the median), resulting in four more (high-NRMS) observations.
- A high to low power ratio observation was calculated for all the MERs and was independent of the NRMS observations.

Table S4: Patient characteristics

Patient No.	Sex	Age (years)	Disease duration (years)	Pre-operative		
				UPDRS 3 (OFF)	UPDRS 3 (On)	LED
1	m	69	8	55	13	1500
2	f	61	6	64	32	N/A
3	m	66	5	51	22	750
4	f	67	5	53	29	1000
5	m	67	26	55	24	550
6	m	59	8	48	13	570
7	m	52	7	38	12	540
8	m	64	8	41	6	825
9	m	60	5	39	15	1580
10	m	42	25	77	18	500
11	m	60	7	85	30	870
12	m	75	4	39	28	562.5
13	m	69	7	45	17	750
14	f	74	13	33	10	830
15	m	63	6	59	18	810
16	m	65	8	48	12	750
17	f	67	15	35	11	1147.5
18	m	59	8	36	10	900
19	f	57	8	48	19	680
20	m	53	3	49	6	200
21	m	64	4	56	34	850
22	m	74	16	57	31	750
23	f	71	22	51	35	2000
24	f	66	4	46	16	750
25	m	50	10	47	35	93.7
26	m	64	9	69	48	900
27	m	62	30	56	22	1120
28	m	66	10	63	11	600
29	m	61	7	32	7	750
30	f	59	13	75	19	1000
31	m	54	9	75	41	500
32	m	64	12	35	2	875
33	m	50	20	53	39	N/A
34	f	73	5	73	42	1250
35	m	57	7	78	37	1370
36	m	69	8	50	10	1140
37	m	66	9	34	14	1000
38	m	58	10	47	13	N/A
39	m	58	12	47	11	1120
40	f	62	14	37	9	1000
41	m	76	7	32	19	1120
42	f	62	13	32	6	925
43	m	70	10	N/A	N/A	950
44	f	59	10	50	14	455
45	f	61	10	N/A	N/A	1000
46	m	66	10	68	27	1250
47	m	73	20	60	16	1496
48	m	60	8	46	21	500
49	f	64	9	21	4	917.5
50	m	54	5	86	42	500
51	m	59	4	64	26	1000
52	f	60	8	44	12	975
53	m	78	10	N/A	N/A	2075
54	m	62	17	72	22	1550
55	f	70	13	41	13	400
56	f	69	9	33	6	1875
57	m	53	9	41	10	375
58	m	72	12	N/A	N/A	1125
59	f	50	8	N/A	N/A	550
60	f	45	9	82	55	700
61	m	59	9	42	14	150
62	m	62	12	55	19	1005
63	m	62	4	63	17	1080
64	m	52	8	27	3	510
65	f	52	10	35	9	770
66	f	66	15	48	13	1540
67	m	49	13	63	18	660
68	f	48	18	47	20	300
69	m	60	11	56	14	850
70	f	39	10	47	16	512.5
71	m	61	11	44	10	500
72	f	50	25	50	17	400
73	f	72	7	60	24	100
74	f	51	4	20	7	N/A
75	m	73	8	55	27	562.5
76	m	66	6	75	38	450
77	f	73	10	45	18	1750
78	f	62	20	56	9	517.5
79	m	74	6	61	31	750
80	f	67	8	48	3	250
81	m	72	6	42	33	640
sum/ mean $\pm$ SD	52 m 29 f	62.1 $\pm$ 8.3	10.3 $\pm$ 5.5	51.1 $\pm$ 14.8	19.4 $\pm$ 11.51	849.6 $\pm$ 425

N/A : Not Available

UPDRS 3 (OFF/ON medication) : clinician-scored motor evaluation (range 0–108)

LED : Levopoda Equivalent Dose

T2 weighted Axial MR image 6mm below the ACPC plane with coronal and sagittal reconstructions. The STN is shown approximately outlined in yellow, the SNr is shown approximately outlined in green. The dotted red lines represent possible examples of MER tracks that traverse the STN and may enter the SNR. Although the target is the dorsolateral part of the STN, we aimed to have as long a trajectory as possible traversing the STN through the target point.

Supplementary material for article in Results II

Neural Datasets

Supplementary Table S1a: Patient demographics and MER dataset for the five classes

A	Number of Patients	Number of Trajectories	Number of MER's
Parkinson's Disease	10	33	2884
Dystonia Non-Genetic awake	8	29	2380
Dystonia Non-Genetic GA	9	18	2202
Dystonia Genetic awake	5	14	1752
Dystonia Genetic GA	10	22	2556
Total	42	116	11774

B	Str	GPe	GPI
Parkinson's Disease	571	1306	1007
Dystonia Non-Genetic awake	499	974	907
Dystonia Non-Genetic GA	539	823	840
Dystonia Genetic awake	377	659	716
Dystonia Genetic GA	571	939	1046
Total	2557	4701	4516

A) The dataset included trajectories from 42 patients consisting of 11,774 MERs in five classes of the disease: awake Parkinson's disease patients, awake and lightly anesthetized genetic and non-genetic dystonia patients. B) MER dataset for the five classes of the disease in the three regions: Striatum (Str), GPe and GPI.

Supplementary Table S1b: Patient demographics and MER dataset for three classes

A	Number of Patients	Number of Trajectories	Number of MER's
Parkinson's Disease	10	33	2884
Dystonia Non-Genetic	17	47	4582
Dystonia Genetic	15	36	4308
Total	42	116	11774

B	Str	GPe	GPI
Parkinson's Disease	571	1306	1007
Dystonia Non-Genetic	1038	1797	1747
Dystonia Genetic	948	1598	1762
Total	2557	4701	4516

A) Same as in S1a, but after merging of the awake and light anesthesia dystonia classes. We used these three classes of the disease (i.e., PD, non-genetic and genetic dystonia) for our working system. B) MER dataset of Striatum (Str), GPe and GPi

Power spectral density (PSD)

The PSD was calculated from the mean-subtracted absolute value of the analog signal (Moran et al., 2008; Moran and Bar-Gad, 2010). This absolute procedure was needed to expose the frequency band of interest (below 300 Hz) since the original analog data were band-pass filtered at 300-9000 Hz (the 300 Hz cut-off was used because of operating room constraints). The average power spectral density was calculated for each trace using Welch's method, with a 3 second Hamming window (50% overlap) and a spectral resolution of 1/3 Hz (sampling frequency 44 kHz, number of discrete Fourier transform points = 132,000). Values within 2 Hz of the 50 Hz power supply artifacts and their 100 and 150 Hz harmonics were removed and interpolated from the surrounding values. To normalize the PSD we divided the PSD by the total power of the signal from 0 to 22 KHz (excluding PSD values within 2 Hz of the 50 Hz power supply artifacts and their 100 and 150Hz harmonics) creating a relative PSD. This normalization revealed the relative power across frequencies.

Discrimination matrices of the Str-GPe and GPe-GPi

Table S2: The frequency dependence of the Str-GPe and GPe-GPi discrimination matrices.

	A				B			
	Str-GPe				GPe-GPi			
Parkinson's Disease	Discrimination matrix		Width of each band [Hz]		Discrimination matrix		Width of each band [Hz]	
			27 Hz	65 Hz			27 Hz	65 Hz
	Starting Index [Hz]	3 Hz	0.24	1.02	Starting Index [Hz]	3 Hz	0.01	0.76
		8 Hz	0.29	1.4		8 Hz	0.38	0.85
		30 Hz	N/A	2.15		30 Hz	N/A	1.21
		180 Hz	N/A	1.55		180 Hz	N/A	1.46
Dystonia Non-Genetic	Discrimination matrix		Width of each band [Hz]		Discrimination matrix		Width of each band [Hz]	
			27 Hz	65 Hz			27 Hz	65 Hz
	Starting Index [Hz]	3 Hz	2.84	2.52	Starting Index [Hz]	3 Hz	2.46	1.39
		8 Hz	3.00	2.52		8 Hz	1.88	1.01
		30 Hz	N/A	1.69		30 Hz	N/A	0.05
		180 Hz	N/A	1.35		180 Hz	N/A	0.11
Dystonia Genetic	Discrimination matrix		Width of each band [Hz]		Discrimination matrix		Width of each band [Hz]	
			27 Hz	65 Hz			27 Hz	65 Hz
	Starting Index [Hz]	3 Hz	3.57	2.63	Starting Index [Hz]	3 Hz	0.90	0.82
		8 Hz	3.49	2.40		8 Hz	0.85	0.70
		30 Hz	N/A	0.93		30 Hz	N/A	0.30
		180 Hz	N/A	1.02		180 Hz	N/A	0.14

A) Values depict the discrimination between Str-GPe of 6 approximately logarithmically spaced bands along the 3-300 Hz range of the power spectra. The band starts at the starting index and has the specified width (e.g., top left box is the 3-30 Hz band). The starting index of the band width was simultaneously increased (e.g., for a starting index = 180 Hz, we only tested a width of 65 Hz, 180-245 Hz band). For each band the mean power (V^2/Hz) for each MER was calculated. Then, for each band the absolute value of the difference in the mean power between the Str and GPe was obtained. Finally, the results were normalized by the square root of the sum of the variances of the Str and GPe to yield the discrimination index (V^2/Hz). The red represents the frequency bands with the largest absolute differences between the Str and

GPe for each class (i.e., Parkinson's disease, non-genetic and genetic dystonia). For example, in Parkinson's disease (top left box), maximal Str and GPe discrimination was obtained in two different frequency bands: low frequency (30-95 Hz) and high frequency (180-245 Hz) with a value of 2.15 and 1.55 (red color), respectively. B) Similar analysis for the GPe-GPi discrimination matrices.

The Hidden Markov Model

An HMM procedure was used to estimate the inference states of the electrode at each depth along the trajectory (Fig. 1). We trained three HMMs using 33, 47, and 36 trajectories (i.e., for three classes of disease; can be seen in Fig. 1A) with striatum, GPe, GPi labels as inputs. The input data to the HMM procedure was made up of a sequence of single values based on the features of the MER (Fig. 1C). For example, the features that we used were NRMS, 3-30 Hz, 8-35 Hz, 30-95 Hz and 180-245 Hz from the PSD. For the HMM procedure, a trajectory is a sequence of observations, where at any depth along the trajectory the electrode exists in one of the inference states (Fig. 1E).

5. Striatum
6. GPe
7. GPi
8. Exit (i.e., white matter)

The HMM inference state sequence was calculated as the most probable sequence beginning with the HMM in striatum (state 1) before the first observation (using the Viterbi algorithm)(Rabiner, 1989). Hence, a typical trajectory inference state starts in the striatum and proceeds through the GPe and GPi consecutively and then to the white matter (exit). However, not all trajectories have clearly defined Str-GPe, GPe-GPi transitions or traversed GPe and GPi; therefore, only trajectories that started 15 mm above the calculated target and traversed > 7 mm of GPe and GPi were used for this study.

In the HMM, transitions between states take place according to (1) a fixed probability (i.e., transition matrix and emission matrix) depending solely on the inference state of the electrode at the depth immediately preceding the current inference state and (2) a probability value calculated from the current MER. Note that we used a feed-forward HMM procedure; i.e., as a sequence progresses, it is possible to remain in the same state, but it is not possible to return to a previous state (e.g., from the GPi to the GPe inference state).

To assess accuracy, the HMM predictions were compared to the electrophysiologist's determination of the location of striatum-GPe, GPe-GPi, and GPi-exit transitions.

Table S3a: The GP PD HMM transition and emission matrices

A

Transition matrix		State-1	State-2	State-3	State-4
From	Str: State -1	0.947	0.053	0	0
	GPe: State-2	0	0.966	0.034	0
	GPi: State-3	0	0	0.978	0.022
	Exit: State-4	0	0	0	1.000

B

Emission matrix		Observations for PD class			
		Low-NRMS	High-NRMS	High NRMS	
		High mean Gamma		Intermediate mean Gamma	Low mean Gamma
				Interm. mean 180-245 Hz	High mean 180-245 Hz
		tag-1	tag-2	tag-3	tag-4
State	Str: State -1	0.989	0	0.011	0
	GPe: State-2	0.434	0.209	0.295	0.061
	GPi: State-3	0.083	0.203	0.147	0.566
	Exit: State-4	0.742	0.007	0.221	0.029

(A) The HMM transition matrix. Values depict the probability of a transition between states (or remaining in the current state) for each step of the sequence. (B) The HMM emission matrix. Values depict the probability of each observation given the state. Numerical tags correspond to the four clusters of NRMS, mean 30-95 Hz and 180-245 Hz power spectra observations detailed in the table header. States: 1 – Str; 2 – GPe; 3 – GPi; 4 – WM after the GPi;

Table S1b: The GP dystonia non-genetic HMM transition and emission matrices

A

Transition matrix		Class-1	Class-2	Class-3	Class-4
From	Str: Class -1	0.958	0.041	0	0
	GPe: Class-2	0	0.959	0.041	0
	GPi: Class-3	0	0	0.971	0.028
	Exit: Class-4	0	0	0	1.000

B

Emission matrix		Observations for dystonia non-genetic class			
		Low-NRMS	High-NRMS	High NRMS	
		Interm. Or High mean 8-35 Hz band		Low mean 8-35 Hz band	Interm. Or High mean 8-35 Hz band
					High mean 3-30 Hz
					tag-1
Class	Str: State -1	0.991	0.004	0.002	0.002
	GPe: State-2	0.353	0.081	0.524	0.041
	GPi: State-3	0.200	0.248	0.203	0.348
	Exit: State-4	0.731	0.127	0.123	0.017

Similar to Table S1a, but the numerical tags correspond to the four clusters of NRMS, mean 8-35 Hz and 3-30 Hz power spectra observations detailed in the table header.

Table S1c: The GP dystonia genetic HMM transition and emission matrices

A

Transition matrix		State-1	State-2	State-3	State-4
From	Str: State -1	0.959	0.040	0	0
	GPe: State-2	0	0.965	0.034	0
	GPi: State-3	0	0	0.972	0.027
	Exit: State-4	0	0	0	1.000

B

Emission matrix		Observations for dystonia genetic class			
		Low-NRMS	High-NRMS	High NRMS	
		High mean 3-30 Hz		Intermediate mean 3-30 Hz	Low mean 3-30 Hz
		tag-1	tag-2	tag-3	tag-4
State	Str: State -1	0.976	0.006	0.001	0.015
	GPe: State-2	0.607	0.029	0.287	0.075
	GPi: State-3	0.313	0.060	0.278	0.347
	Exit: State-4	0.408	0.103	0.008	0.479

Similar to Table S1a-b, but the numerical tags correspond to the four clusters of NRMS and the mean 3-30 Hz power spectra observations detailed in the table header.

Values in the emission matrix depict the probability of each observation given the state. The states are defined as in the transition matrix. The four columns correspond to the four observations detailed in the table header as follows:

- All MERs with NRMS<1.25 (threshold 1); i.e., below a 25% increase from the NRMS baseline (equal to 1 due to the normalization) were clustered together (Low-NRMS observation).
- The mean deviation from threshold 1 (i.e. NRMS - 1.25) of the remaining MERs was calculated. Threshold 2 was defined as the threshold 1 plus 25% of the calculated mean deviation. MERs with a NRMS> threshold 2 were further divided according to their low,

intermediate and high mean 3-30 Hz, 8-35 Hz, 30-95 Hz and 180-245 Hz oscillatory activity (above or below the median).

MR image depicting typical anatomical targeting

T2 weighted Axial MR image 8 mm below the ACPC plane with coronal and sagittal reconstructions. The GPe and GPi are shown approximately outlined by the white circle. The red lines represent possible examples of MER tracks that traverse the GPe and GPi. Although the target is the ventro-posterior-lateral GPi, we aimed to have as long a trajectory as possible traversing the GPi through the target point.

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