Title: ***Subthalamic nucleus activity dynamics preceding clinical manifestations in a progressive Parkinson's disease model.***

Bertrand, Mathilde PhD[1], Chabardes, Stephan PhD, MD[1-2-3], De Leiris, Nicolas[4], Reboulet, Ghislaine[4], Baudin, Bruno PhD, MD[5], Bastin, Julien PhD[1], Piallat, Brigitte PhD[1]

Author affiliations:

1. Univ. Grenoble Alpes, Inserm, U1216, Grenoble Institute of Neurosciences, 38000 Grenoble, France
2. Univ. Grenoble Alpes, Department of Neurosurgery, Inserm, U1216, CHU Grenoble Alpes, Grenoble Institute Neurosciences, 38000 Grenoble, France
3. Clinatec-CEA Leti, 38000 Grenoble, France
4. UMR Inserm, 1039, Department of Nuclear Medecine, University Hospital of Grenoble Alpes, 38000 Grenoble, France
5. Univ. Paris-Saclay, Inserm, U1193, 91400 Orsay, France and Biochemistry Laboratory, Armand Trousseau Hospital, 75571 Paris, France

Bertrand, Mathilde[1], mbertr9@uwo.ca
Chabardes, Stephan PhD, MD[1-2-3], SChabardes@chu-grenoble.fr
De Leiris, Nicolas[4], ndeleiris@chu-grenoble.fr
Baudin Bruno, bruno.baudin@aphp.fr
Reboulet, Ghislaine[4], greboulet@chu-grenoble.fr
Bastin, Julien PhD[1], julien.bastin@univ-grenoble-alpes.frn
Piallat, Brigitte PhD[1], brigitte.piallat@univ-grenoble-alpes.fr

Corresponding author:
Brigitte Piallat
Brigitte.piallat@univ-grenoble-alpes.fr

Conflict of interest:
The authors declare no competing financial interests related to this work.

Acknowledgements:
This work was supported by the French Agence Nationale de la Recherche (ANR), under grant ANR-18-BS01-0005.

ABSTRACT

Background: Parkinson's disease (PD) diagnosis relies on motor symptoms such as akinesia, rigidity, and tremor, which manifest late in the disease course, contributing to delayed diagnosis. However, cognitive, and limbic manifestations may precede motor symptoms, offering an earlier diagnostic opportunity, but their early kinetics require further characterization. Although high frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) significantly improves motor symptoms, it does not specifically address non-motor symptoms. Here, we aimed to correlate STN activity with the onset of motor, cognitive, and limbic symptoms of PD and propose specific STN-DBS paradigm to address both motor and non-motor symptoms.

Methods: Local field potentials of the STN were recorded in two non-human primates (*Macaca fascicularis*) performing a behavioral task assessing motor, cognitive, and limbic reward-related behaviors. A progressive model of PD, consisting of small injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, 0.2-0.5mg/kg), was used to characterize behavior for several months until the onset of motor symptoms. Finally, when a stable parkinsonian syndrome was established, the behavioral effects of high- (HFS, 130Hz) and low- (LFS, 4Hz) frequency stimulations were investigated.

Results: After the first MPTP injections, we observed a progressive parkinsonian syndrome from stage 1, asymptomatic, to stage 3 with limbic, cognitive, and motor symptoms. Each stage was associated with specific changes in STN electrophysiological activity. Stage 1 was characterized by a decrease in the power of reward-related gamma/theta oscillations. Stage 2 featured an early decline in motivation and decreased theta-band activity during decision-making. Later, an increase in error on Switch trials was observed, illustrating the stage 2', along with a decrease in beta-gamma power following movement. Finally, stage 3 was defined by an increase in motor response time while maintaining all the STN neuronal changes. In stage 3, HFS applied in dorsal STN improved motor reaction time, while LFS applied in ventral STN improved motivation.

Conclusion: Our results highlight a progressive timeline in the onset of behavioral parkinsonian manifestations, with limbic symptoms followed by cognitive and then motor symptoms. We identified specific electrophysiological biomarkers in the STN correlating with and preceding the onset of each symptom, providing insights into their pathophysiology. Finally, our results suggest that combined stimulation of HFS in the dorsal STN and LFS in the ventral STN may optimize STN-DBS outcomes, reducing both motor and non-motor symptoms.

Keywords: Subthalamic nucleus; Deep brain stimulation; Parkinson's disease; Electrophysiological biomarkers; Non-human primate

INTRODUCTION

The subthalamic nucleus (STN), part of the basal ganglia, plays a crucial role in processing cortical information to elaborate and adapt goal-directed behaviors. Its significance is highlighted by the efficacy of deep brain stimulation (DBS) on motor symptoms in Parkinson's disease (PD) (Benabid et al., 1995; Benazzouz et al., 1993; Limousin et al., 1995). Abnormal STN activity in the beta range (13-30 Hz) has been associated with motor symptoms (Bergman et al., 1994; Beudel & Brown, 2016; Neumann et al., 2016) and is suppressed by high frequency stimulation (HFS) of the dorsal STN, significantly improving motor symptoms in patients (Eusebio et al., 2011; Müller & Robinson, 2018). However, PD patients also experience non-motor symptoms, including sleep disorders, cognitive impairment, and mood disturbances, which significantly impact their quality of life (Chaudhuri et al., 2010; pour review Li et al., 2024; Poewe, 2008; Pont-Sunyer et al., 2015; Postuma et al., 2015; Weintraub et al., 2022). The onset of these non-motor symptoms is not well-defined, and they generally worsen with PD progression (Aarsland et al., 2009; Hely et al., 2008; Kalia & Lang, 2015). Interestingly, some of these non-motor symptoms have been associated with changes STN activity. Disruption of theta band activity in the STN during conflict behaviors, impairing its modulating "break" role to decision-making, has been reported in PD patients (Cavanagh et al., 2011; Zavala et al., 2013). Increased STN gamma band activity has been associated with emotional valanced stimuli in PD patients, indicated its involvement in non-motor symptoms (Huebl et al., 2014). Another study also highlighted the role of the STN in reward and loss expectation, showing an increase in delta-theta activity in PD patients (Manssuer et al., 2023).

In a previous paper, we fully characterized the correlation between STN oscillations and specific behaviors in a physiological context in non-human primate (NHP), providing a valuable model for studying STN functional processes (Bertrand et al., 2024). Understanding how these neural activities change with PD progression and correlate with symptoms onset is yet to be determined. The NHP model treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is currently the gold standard for studying these manifestations, as it induces both motor and non-motor symptoms, similar to those observed in PD patients (Bezard et al., 1997; Burns et al., 1983; Jenner et al., 1984; Masilamoni & Smith, 2018; Schneider & Kovelowski, 1990). Repeated intramuscular injections of low doses of MPTP induce a progressive model, allowing the description of sleep disorders and cognitive

impairments, such as deficits in attention or cognitive flexibility, which appear before motor symptoms (Barth et al., 2020; Davin et al., 2022; Masilamoni et al., 2022; Schneider & Kovelowski, 1990; Vezoli et al., 2011).

While HFS is effective for motor symptoms, it can induce or aggravate non-motor symptoms (Houeto et al., 2002; Kurtis et al., 2017; Temel et al., 2007). The MPTP-treated NHP model allows testing of alternative STN-DBS parameters to optimize symptoms management and reduce associated side effects. It has been well described that HFS (above 100 Hz) is key to treat motor symptoms (Benabid et al., 2009; Benazzouz et al., 1993), but improving non-motor symptoms might require different parameters. In that respect, low-frequency stimulation (LFS) was first tested in MPTP-treated NHP and then in PD patients (Dorval et al., 2008; Kelley et al., 2018). Kelley and colleagues showed improved cognitive performances with 4Hz LFS, coherent with oscillations in the hyperdirect pathway connecting the prefrontal cortex to the STN (Kelley et al., 2018). PD-related cognitive dysfunctions, such as working memory or attention, have been correlated with attenuated 4Hz oscillations in the medial frontal cortical area, suggesting the use of 4Hz LFS to treat cognitive symptoms in PD (Singh et al., 2020). However, reconciliating the use of HFS for motor symptoms with the potential LFS for non-motor symptoms remains challenging, despite recent technology development allowing different stimulation frequencies in different contacts and the novel use of adaptive DBS (for review Frey et al., 2022; Little et al., 2016; Schmidt et al., 2024).

In this study, we investigated the correlation between STN local field potentials and the development of motor, cognitive, and limbic symptoms in a progressive PD model in NHP. In addition, once a stable parkinsonian syndrome was established, we examined the effects of HFS and LFS on these symptoms, when applied in the dorsal and ventral STN.

MATERIAL AND METHODS

Animals

This study was conducted with two 8 years old monkeys (*Macaca fascicularis*, CRP, Port Louis, Mauritius), one male (M1, 9kg) and one female (M2, 4kg). They were pair-housed in a temperature (22 ± 1°C) and humidity (50 ± 5%) controlled facility with a 12h light-dark cycle. They had free access to primate chow and water, and supplemental fruits were given once a day. All procedures followed the European Communities Council Directive of 2010 (2010/63/UE) for care of laboratory animals with the recommendations of the French National Committee (2013/113) and were approved by the local Ethical Committee (#04; authorization n°2019013116115695).

Behavioral task

Monkeys performed on a counter demanding task to assess motor, cognitive and limbic behaviors, as previously described (Bertrand et al., 2024). They were habituated to a primate chair (Crist Instrument Co., MD, USA) to interact with a touch screen (Elo Touch Solutions, Inc.). In each trial, monkeys can choose to work on rewarded switching task (Work, triangle at the upper center) or to check their progress with an increasing gauge informing about the proximity of a bonus reward (Check, cross at the bottom center). When selecting Work, a blue square (Non-Switch) or an orange star (Switch) appeared in the periphery (randomly left or right) and monkeys had to touch the blue square while they had to touch on the opposite side of the orange star. Targets were randomly determined, with a higher probability for Non-Switch than Switch (80% - 20%). Either way, monkeys had to respond within 2 000 ms and correct responses were rewarded (sweet liquid, 1 ml) by a computer-controlled system (Crist Instrument Co.). A red circle appeared for 1 000 ms indicating the End of the trial and the beginning of a new one with the Work or Check option. Instead of selecting Work, monkeys could choose to Check and a gauge was displayed for 5 000 ms indicating the proximity of a bonus reward. Represented by a large green circle, the gauge was filled proportionally to the number of correct responses performed on the Work option (an inner green disk filled the large green circle). Incorrect responses did not affect the gauge. The number of correct responses required to fill the gauge was randomly selected from 8, 16, 24, or 32. To receive the bonus reward (sweet liquid, 5 ml) which remained available until obtained, monkeys had to choose to Check when the gauge was full, and once delivered the gauge size was reset.

Behavioral analyses

Only sessions with more than four earned bonus rewards were included. Response times (RT), i.e., time between appearance of the stimulus and the touching response, were measured from correct trials only: motor RT (mRT, motor behavior) for Non-Switch trials and cognitive RT (cRT) for Switch trials. Differences between cRT and mRT represented the Switch-Cost (cognitive behavior), i.e., the time needed to adapt behavior to a change of rules. Error on Switch trials (Error Switch, cognitive behavior) and the probabilities to Check when the gauge was full, and the bonus reward was available (Reward Check, limbic behavior) were calculated.

Surgery

Surgery for electrode implantation was performed under aseptic conditions and general anesthesia. Monkeys were initially anesthetized with ketamine (7 mg/kg) and xylazine (0.6 mg/kg), and, maintained under general anesthesia with isoflurane. Lidocaine 1% was used for local anesthesia. Saline solution (NaCl 0.9%, Sigma-Aldrich) was continuously infused intravenously during the operation for drug access and hydration. Pre-operative 7T MRI (Grenoble MRI facility IRMaGE) allowed the STN identification and per-operative X-rays were used to localize the bi-commissural ventriculographic landmarks (anterior and posterior commissures, ACPC), injecting 2ml of ventricular contrast (Iopamiron 200, iodine 200 mg/ml, Bracc) though a cannula placed in the left lateral ventricle. Micro-recordings (microelectrode of 250 µm diameter, 0.8-1.2 MOhm, FHC) were used to locate the STN borders, based on firing rate and pattern. Right STN was implanted with a DBS electrode of 0.8 mm diameter with four 0.5 mm contacts arranged in two rows (0.5 mm apart) and two columns (Heraus©, USA), allowing recordings and two-level stimulations. For both monkeys, the electrode was placed at the following stereotactic coordinates: anterior 6/12th of ACPC, 4–5 mm from the midline, with deepest contacts at the lower border of the STN. The implantation was confirmed by radiography and ventriculography. The reference was fixed at the left occipital level. A stainless-steel head holder (Crist Instruments, MD) was placed at the back of the skull to maintain the head. Post-operative analgesic/anti-inflammatory therapy (Ketoprofen 2mg/kg) were administrated during the one-week.

Recordings analyses

STN activity was recorded using a common reference located at the occipital level and a multichannel system (AlphaOmega Engineering, Israel). Signals were sampled at 1375 Hz, clipped around specific events (± 1 000 ms) and analyzed using MATLAB and ImaGIN

toolbox. Time-frequency representations of spectral power between 2 and 200 Hz were obtained using a multitaper sliding window. Orthogonal discrete prolate Slepian spheroidal (DPSS) tapers were applied in a frequency-dependent manner and according to the length of the sliding window. Single-trial power spectra were averaged for each valence condition and normalized on a pre-stimulus baseline interval (-1 000 to -250 ms) using a base-10 logarithm ratio (LdB) to calculate peristimulus power/baseline power (P/B) and multiplying it by 10 to return decibel (dB) values. Power values are denoted as LdB power ± SEM. Specific frequency bands (theta, 4-8Hz; alpha, 8-12Hz; beta, 12-35Hz; gamma, 35-200Hz) were selected with band filters and represented as average power versus baseline over time (mean ± SEM).

STN stimulation

Low frequency (LFS: 4 Hz) and high frequency (HFS: 130 Hz) were applied using continuous bipolar stimulations at two levels in the STN (dorsal and ventral). For each frequency, ranges of stimulations were conducted until side effects occurred (e.g., ipsilateral monocular deviation, head rotation, lip contraction). Intensities were applied at 80% of the threshold of onset of side effects (from 0.08 mA to 0.2 mA), with a fixed pulse width of 60 µs. The number of trials for each level of stimulation at both frequencies is presented in supplementary Table 2.

MPTP treatment

Following baseline recordings (healthy state), monkeys were chronically intoxicated with intramuscular injections of MPTP under light anesthesia (Ketamine 2-4 mg/kg), as previously described (Davin et al., 2022). This progressive protocol aimed to mimic the clinical pathology with a prodromal period and consisted in small injections of MPTP (0.2-0.5 mg/kg, in NaCl 0.9%) every two weeks until the parkinsonian syndrome was stable. After each injection, the motor score was assessed, and the next dose was either similar or adjusted based on the clinical signs. M1 received 20 injections (5.45 mg/kg total) and M2 received 18 injections (6.7 mg/kg total). Both animals exhibited a similar and stable state of parkinsonian syndrome.

Motor score

The parkinsonian syndrome was evaluated before, during and after MPTP treatment in the home cage, using a rating scale based on the most used criteria to study parkinsonian syndrome in macaques (Imbert et al., 2000). This scale evaluates eight criteria, including frequency of movement of each arm, general activity, posture, bradykinesia, tremor, feeding, freezing and

vocalizations (**Supplemental Fig. 1**). Each criterion is scored between 0 and 3, 0 representing no impairment and 3 representing maximum impairment, for a total score out of 25. According to the literature, three stages are distinguished by severity: stage 1, asymptomatic (score 0-3); stage 2, mild parkinsonism (score 4-10); and stage 3, moderate parkinsonism without care needed (score >10) (Devergnas et al., 2014).

DaT SPECT imaging

In addition to the motor evaluation, the striatal dopaminergic system was evaluated for both monkeys in the healthy state and for each stage of the parkinsonian syndrome. The use of the Ioflupane tracer (I123), which binds to presynaptic dopamine transporters (DaT), assessed the dopaminergic damage during the development of the parkinsonian syndrome. For all exams, monkeys were anesthetized to perform an intravenous injection of a 90 MBq dose followed by the acquisition of images 3 hours later. A zoom lens was applied for imaging M2 (female) due to sexual dimorphism. The analysis of the radioactivity level of the three consecutive images showing the highest radioactivity allowed a semi-quantitative analysis of the regions of interest in the striatum, compared to a reference in the occipital cortex.

CSF biomarker analysis

Throughout the study, cerebrospinal fluid (CSF) was collected. Monkeys were anesthetized, the lumbar area was shaved and cleaned with chlorhexidine and iodin solution. A 22 g Quincke spinal needle (BD™) was inserted in the intrathecal space between L4/L5 and CSF was collected in a sterile 1.5 mL polypropylene tube, immediately kept on ice and stored at -80°C. Monoaminergic metabolites, homovanillic acid (HVA), 5-hydroxyindole acetic acid (5-HIAA), 3-methoxy-4-hydroxyphenylglycol (MHPG), and 3-orthomethyl-DOPA (3-OMD), were measured by ion pair high performance liquid chromatography with electrochemical detection, as previously described (Ormazabal et al., 2005).

Statistical analyses

Statistical tests for all data comparisons were conducted using GraphPad Prism 8 (GraphPad Software Inc., USA). After testing the normal distribution with Shapiro tests, Kruskal-Wallis followed by Dunn's multiple comparisons tests were used for behavioral analysis (mRT, cRT; Switch-Cost, Check Reward) throughout the MPTP-treatment (**Supplemental Table 1**) and to compare the ON and OFF stimulation conditions (**Supplemental Table 2**). Data are presented as mean ± SEM and a difference was considered statistically significant for a p-value <0.05.

Time-frequency representations were analyzed with one-sample t-test to compare signal of one event, and two-sample t-test to discriminate significant differences between two events (T-Values). Bonferroni corrections were applied. These analyses were plotted as statistical parametric maps (SPM) showing only significant statistical differences (p-value <0.05): motor SPM at the presentation of the motor cue and the beginning of the movement compared to a resting state; cognitive SPM centered on the selection to work compared to check; and limbic SPM at the reward delivery with a full gauge compared to the gauge being filled.

RESULTS

Progressive parkinsonian syndrome

Chronic low doses MPTP treatment induced a progressive onset of motor signs, worsening over time. Three distinct stages of a parkinsonian syndrome were identified based on the severity of these symptoms (**Fig. 1A**). Stage 1, asymptomatic (score 0-3), was defined by the absence of clinical motor signs. Stage 2, mild parkinsonism (score 4-10), was characterized by the appearance of light and unstable motor signs. In stage 3, moderate parkinsonism (score >10), both monkeys exhibited significant and stable motor symptoms, including decreased general activity, bradykinesia, and flexed posture. Longitudinal DaT SPECT imaging showed a progressive decrease in Ioflupane tracer activity within the striatum, relative to the occipital cortex (**Fig. 1B**). This decrease started after the first MPTP injection and both monkeys developed similar kinetics, except during stage 2 where M1 exhibited a transient increase in striatal fixation, which led to a closer behavioral examination during this stage. For both monkeys, lumbar cerebrospinal fluid (CSF) analyses showed a progressive decrease in homovanillic acid (HVA) and only M1 exhibited a progressive decrease in 5-hydroxy indoleacetic acid (5-HIAA). For both monkeys, a significant reduction in 3-methoxy-4-hydroxyphenylglycol (MHPG) has been found starting at stage 1, and no significant changes in 3-orthométhyl-methyldopa (3-OMD) (**Fig. 1C**).

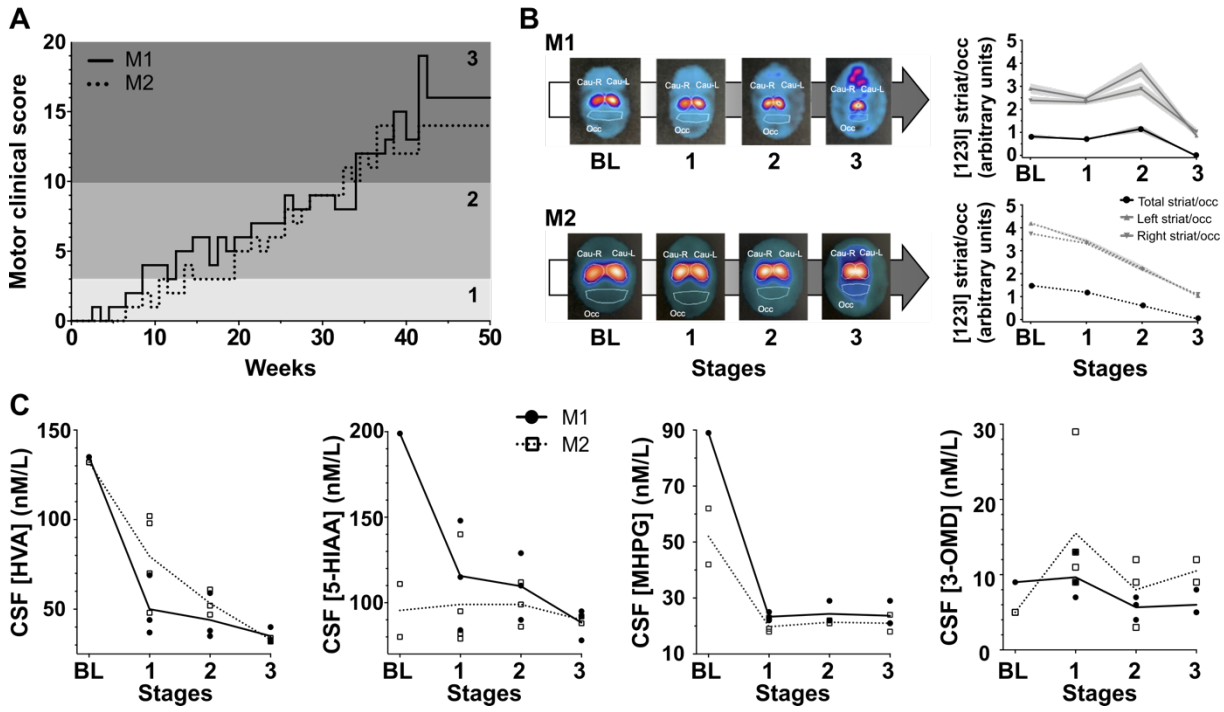


Figure 1: Progressive parkinsonian syndrome for M1 (solid line) and M2 (dotted line). (A) Weekly motor evaluation of the parkinsonian syndrome induced by chronic low-dose MPTP injections. Motor score discriminated 3 stages: 1-asymptomatic (very light gray, score 0-3); 2-mild parkinsonism (light gray, score 4-10); 3-moderate parkinsonism (dark gray, score >10). **(B)** DaT SPECT imaging using Ioflupane (I^{123}) tracer for each stage with ratios quantification between the left and right striatum (Cau-L and Cau-R) relative to cerebral background noise (Occ). **(C)** Lumbar cerebrospinal fluid (CSF) concentrations of homovanillic acid (HVA), 5-hydroxyindole acetic acid (5-HIAA), 3-methoxy-4-hydroxyphenylglycol (MHPG), and 3-orthomethyl-dopa (3-OMD). BL, baseline before MPTP treatment.

Early non-motor manifestations

Monkeys performed the behavioral task throughout the MPTP treatment (**Fig. 2A**). During stage 1, no similar significant changes were found for both monkeys on Check Reward, Switch Error, Switch-Cost, and mRT. This stage can therefore be considered asymptomatic. In stage 2, several non-motor signs appeared in a specific chronology, distinguishing two substages: early stage 2 with limbic impairment and late stage 2' with cognitive impairment. Indeed, a decrease in Check Reward probabilities was first observed (BL: 27.6 ± 2.2% vs. stage 2: 20.5 ± 1.4% for **M1** p=0.0117; BL: 24.0 ± 1.5% vs. stage 2: 15.0 ± 0.5% for **M2** p=0.0009; Kruskal-Wallis) (**Fig. 2B**). Later, an increase in Switch Error was found, characterizing stage 2' (BL: 2.8 ± 0.1% vs. stage 2': 6.3 ± 0.1% for **M1** p<0.0001; BL: 6.0 ± 0.2% vs. stage 2': 8.1 ± 0.3ms for **M2** p<0.0001; Kruskal-Wallis) (**Fig. 2C**). For M2, a negative Switch-Cost was found during stage 2' (BL: 45.1 ± 4.4ms vs. stage 2': -3.9 ± 5.7ms p<0.0001; Kruskal-Wallis) (**Fig. 2D**). Finally, for both monkeys in stage 3, mRT increased (BL: 462.3 ± 2.7ms vs. stage 3: 500.8 ± 11.2ms for **M1** p<0.0001; BL: 480.2 ± 4.5ms vs. stage 3: 614.6 ± 15.5ms for **M2** p<0.0001; Kruskal-Wallis) (**Fig. 2E**).

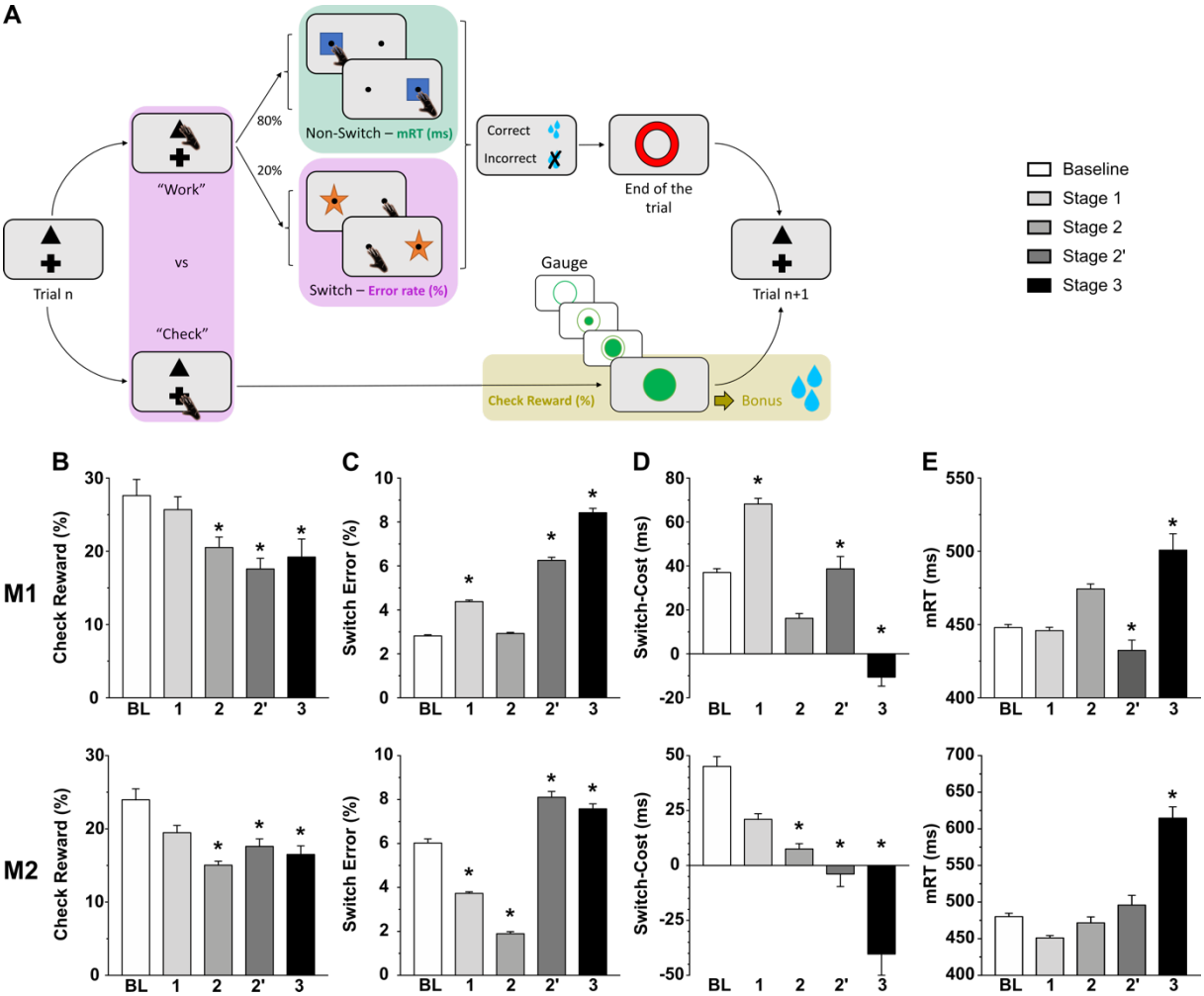


Figure 2: Behavioral effect of MPTP treatment across all stages. **(A)** Rewarded task assessing motor (green), cognitive (pink) and limbic (gold) behaviors. On each trial, monkeys decided to "Work" on the main switching task, or "Check" the size of a gauge informing about the proximity of a bonus reward (see Methods). **(B)** Probabilities to check when the reward is available (Check Reward), expressed in percentage. **(C)** Probabilities for errors on Switch trials (Switch Error), expressed in percentage. **(D)** Switch-Cost, difference in response time between Switch and Non-Switch trials, expressed in ms. **(E)** Motor response time (mRT) on Non-Switch trials, expressed in ms. Stages: baseline, before MPTP treatment (BL, white); stage 1, asymptomatic (1, very light gray); early stage 2, mild parkinsonism (2, light gray); late stage 2, mild parkinsonism (2', light gray), stage 3, moderate parkinsonism (3, dark gray). Values are expressed in mean ± SEM and *p<0.05, Kruskall-Wallis followed by Dunn's multiple comparisons test.

Evolution of STN neural activity

STN neural activity was recorded while monkeys performed the behavioral task, throughout the MPTP treatment. During reward delivery, a significant increase in gamma oscillations (>35Hz) followed by a significant decrease in theta oscillations (4-8Hz) was observed in the STN during baseline for both monkeys ($p<0.05$, two-sample t-test). These reward-related

markers disappeared from stage 1 (**Fig. 3A**). When monkeys chose to work rather than check, a significant increase in theta oscillations was observed during baseline for both monkeys ($p<0.05$, two-sample t-test). This theta activity was preserved in stage 1 and disappeared in early stage 2 (**Fig. 3B**). Finally, a significant decrease in beta oscillations was found during baseline, at the onset of the motor cue (Non-Switch stimulus) and the beginning of the movement, followed by an increase in beta-gamma bands, known as rebound ($p<0.05$, one-sample t-test). This specific pattern was also observed in stage 1 and early stage 2, but the rebound effect disappeared in the stage 2' (**Fig. 3C**).

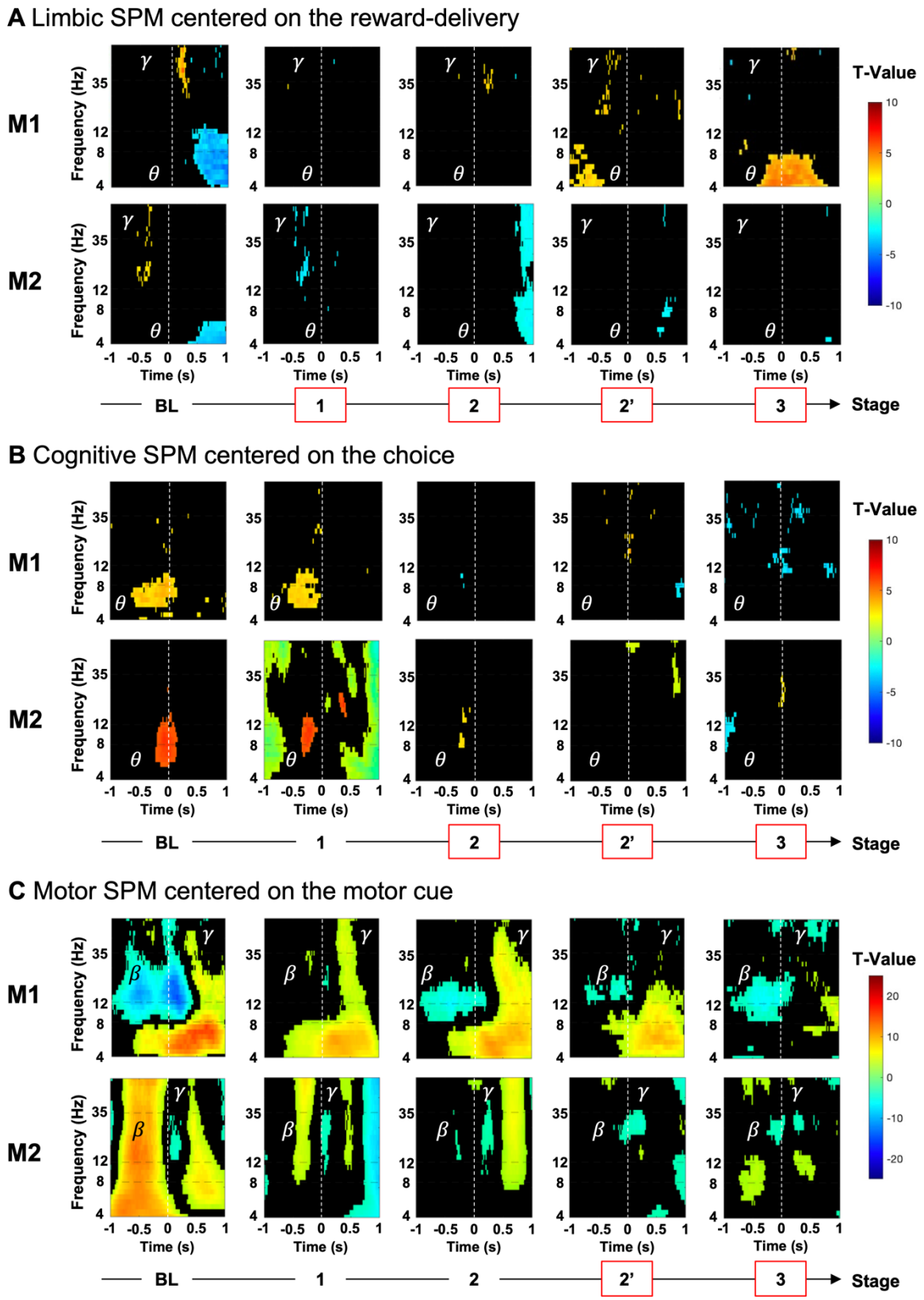


Figure 3: Effect of MPTP treatment on STN activity across all stages. (A) Limbic statistical parametric maps (SPM) centered on the full gauge with reward delivery (vertical line at 0) relative to the gauge view without the reward (T-Value). **(B)** Cognitive SPM centered on cognitive choice (vertical line at 0) to work relative to check (T-Value). **(C)** Motor SPM centered on the onset of Non-Switch stimulus (vertical line at 0) relative to a resting state (T-Value). Stages: baseline, before MPTP treatment (BL); 1,

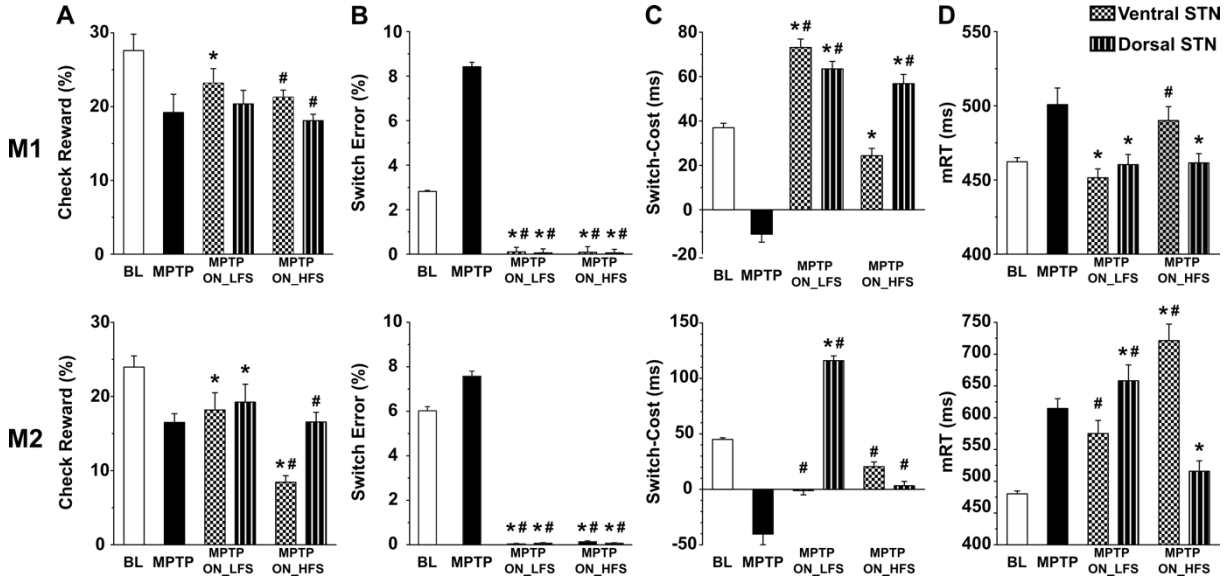
asymptomatic; 2, early mild parkinsonism; 2', late mild parkinsonism, 3, moderate parkinsonism. Only significant values are presented, $p<0.05$. Red squares show changes from baseline.

Effect of STN modulation on PD behaviors

During stage 3, with stable and moderate parkinsonian syndrome, STN HFS and LFS were tested during the behavioral task. For both MPTP-treated monkeys, LFS applied in ventral STN restored the Check Reward to baseline (MPTP: 19.2 ± 2.5% vs. MPTP Ventral LFS: 23.2 ± 2.0% p=0.4447 vs. BL: 27.60 ± 2.2% p=0.3211 for **M1**; MPTP: 16.5 ± 1.2% vs. MPTP Ventral LFS: 18.2 ± 2.3% p=0.9340 vs. BL: 24.0 ± 1.5% p=0.1796 for **M2**; Kruskal-Wallis) (**Fig. 4A**). For M2, STN HFS induced a significant decrease in the Check Reward when applied in ventral STN (MPTP: 14.96 ± 0.8% vs. MPTP Ventral HFS: 8.4 ± 0.9%; p=0.0295 vs. BL: 23.96 ± 1.5%; Kruskal-Wallis) (**Fig. 4A**).

Both LFS and HFS applied in ventral and dorsal STN reduced, almost eliminated, the error on Switch trials for both monkeys (MPTP: 8.42 ± 0.2% vs. MPTP Ventral LFS: 0.1 ± 0.2%; MPTP Dorsal LFS: 0.06 ± 0.2; MPTP Ventral HFS: 0.09 ±0.3%; MPTP Dorsal HFS: 0.06 ± 0.2; p<0.001 for **M1**; MPTP: 7.6 ± 0.2% vs. MPTP Ventral LFS: 0.04 ± 0.03%; MPTP Dorsal LFS: 0.1 ± 0.03%; MPTP Ventral HFS: 0.1 ±0.04%; MPTP Dorsal HFS: 0.1 ± 0.03; p<0.001 for **M2;** Kruskal-Wallis) (**Fig. 4B**).

LFS applied in dorsal STN lead to a positive Switch-Cost for both monkeys compared to stage 3 (MPTP Dorsal LFS: 63.5.0 ± 3.4ms and MPTP: -10.6 ± 4.1ms for M1; MPTP Dorsal LFS: 116.0 ± 4.3ms and MPTP: -40.3 ± 10.6ms for **M2)** (**Fig. 4C**). For both monkeys, only HFS in dorsal STN restored mRT to baseline (MPTP: 500.8 ± 11.2ms vs. MPTP Dorsal HFS: 461.5 ± 6.3ms; p=0.0011, BL: 462.3 ± 2.7ms for **M1**; MPTP: 614.6 ± 15.5ms vs. MPTP Dorsal HFS: 515.9 ± 16.3ms; p<0.001, BL: 480.2 ± 4.5ms for **M2**; Kruskal-Wallis) (**Fig. 4D**). HFS applied in ventral STN increased mRT for M2 (MPTP: 614.6 ± 15.5ms vs. MPTP Ventral HFS: 721.4 ± 25.9ms; p<0.0001; Kruskal-Wallis) (**Fig. 4D**).



<u>Figure 4:</u> Effects of LFS (4Hz) and HFS (130Hz) on ventral (grid pattern) and dorsal (vertical lines) STN, on MPTP-treated monkeys during the behavioral task. (A) Probability to check when the bonus reward is available (Check Reward), and **(B)** error on Switch trials (Switch Error), expressed in percentage. **(C)** Switch-Cost and **(D)** motor response time (mRT), expressed in milliseconds (ms). Values are expressed in mean ± SEM. *p<0.05 different from MPTP off stimulation and #p<0.05 different from baseline. BL, baseline (in white); MPTP, MPTP-treated monkeys in stage 3 (in black); MPTP ON_LFS, 4 Hz applied in stage 3; MPTP ON_HFS, 130 Hz applied in stage 3.

DISCUSSION

Using chronic low doses of MPTP to develop a progressive model of PD, we provided evidence of the early onset of non-motor limbic and cognitive symptoms preceding motor manifestations. These clinical signs were correlated with early changes in STN neural activity. Additionally, we demonstrated the positive effect of LFS on ventral STN in managing non-motor symptoms in a stable parkinsonian syndrome.

Progressive model of a parkinsonian syndrome

Our results replicated a progressive parkinsonian syndrome characterized by worsening motor symptoms over time, consistent with previous studies using chronic low doses of MPTP (Connolly et al., 2015; Devergnas et al., 2014). Throughout MPTP treatment, we performed DaT SPECT imaging. A progressive decrease in estimated striatal DaT levels was observed, indicating a decrease in presynaptic dopamine reuptake, and correlating with the severity of the syndrome. Interestingly, during stage 2 for M2, an increase has been observed. This transient increase, previously reported, suggests complex intrinsic compensatory mechanisms associated with cognitive impairments likely related to a hyperdopaminergic state (Boulet et al., 2008; Mounayar et al., 2007; Vezoli et al., 2011, 2014).

In parallel, we measured the concentrations of various metabolites in the lumbar CSF. We found a decrease in 5-HIAA, a serotonin metabolite, along with decreases in HVA and MHPG, dopamine metabolites, but no change in 3-OMD levels. It is worth noting that M2 5-HIAA levels remained stable throughout MPTP treatment, which could be attributed to its low baseline levels compared to M1. The observed decreases in 5-HIAA, HVA and MHGP reflect deficiencies in serotonin and dopamine metabolism pathways (Elsworth et al., 1987; Van Der Heyden et al., 2003). This is likely due to the common role of aromatic amino-acid decarboxylase (AACD) in presynaptic serotonin and dopamine production, which is not involved in 3-OMD metabolite production (Bräutigam et al., 1999; Van Der Heyden et al., 2003). Stable levels of 3-OMD may contribute to reduced dopamine levels. Indeed, a rat study showed that 3-OMD inhibits striatal DaT and dopamine uptake, contributing to neuronal damage and the toxic effects of L-DOPA treatment, leading to motor adverse effects (E.-S. Y. Lee et al., 2008). Low concentrations of 5-HIA have been associated with depression and suicidal behavior in depressive illness (G. L. Brown & Linnoila, 1990; Cooper et al., 1992). Similarly, decreased CSF concentrations of both HVA and MHPG have been reported in PD and multiple system atrophy synucleinopathies (Goldstein et al., 2012, 2024; Kwon et al.,

2022). These reductions reflect a degeneration of locus coeruleus neurons, suspected to contribute to non-motor manifestations of PD, such as cognitive dysfunction, anxiety, and depression (Del Tredici & Braak, 2013).

Early non-motor signs

The MPTP macaque model remains the gold standard for studying PD, as it mimics the pathology by inducing dopamine depletion and PD-like motor and non-motor manifestations (Durand et al., 2015; Porras et al., 2012). However, it fails to reproduce all clinical symptoms and the exact pathophysiology of PD patients, requiring caution in interpretations.

Consistent with previous studies, we found a first stage that began after the first MPTP injection and is characterized by the absence of significant behavioral signs, representing the asymptomatic stage 1 (Bezard et al., 1997; Vezoli et al., 2011). The next stage, early stage 2, was defined by a decrease in motivation for the reward, close to apathy found in parkinsonian rat models (Carnicella et al., 2014; Magnard et al., 2016) and in PD patients (Aarsland et al., 1999). Late stage 2' was characterized by an increase in error rate on Switch trials without significant motor symptoms. This deficit in switching processes may represent mild cognitive impairment, also found in PD patients, which may precede motor symptoms (Aarsland et al., 2003; Goldman & Litvan, 2012). During this stage, the increased error rate was accompanied by a negative Switch-Cost for M2 but not M1, that could be related to the compensatory mechanisms observed in DaT imaging at this stage for M1, preserving some of the cognitive functions. In stage 3, limbic and cognitive changes persisted or worsened, with both monkeys exhibited a negative Switch-Cost and increased mRT. These observations are consistent with the progressivity of PD, where motor manifestations are preceded by several years of non-motor symptoms (Chaudhuri et al., 2006).

Correlations between behavior and STN activity

Recent studies have provided evidence for the correlation between neural activity and symptoms severity, primarily for motor symptoms (L.-H. N. Lee et al., 2021; Wang et al., 2022), although one recent study has focused on non-motor symptoms (Hassin-Baer et al., 2022). Here, we demonstrated that modifications in STN activity precede both motor and non-motor symptoms in MPTP-treated monkeys, following a specific temporal hierarchy, starting with limbic symptoms followed by cognitive and finally motor manifestations.

From stage 1, the increase in gamma oscillations observed during reward delivery disappeared in both monkeys. Similarly, an early increase in STN gamma band activity has been observed in Dopa-treated PD patients as reward approaches, representing local encoding of increased attention for reward (Huebl et al., 2014). The modulation of cortical activity by reward has been shown to be mediated by dopamine signaling (Kapogiannis et al., 2011), suggesting the role of gamma oscillations and dopamine signaling pathway through the ganglia-thalamo-cortical network in expectancy and reward delivery. The decrease in gamma oscillations observed from stage 1 during reward delivery could be due to the early damage of the dopaminergic system. Moreover, we observed a decrease in theta oscillations associated with reward delivery, which disappeared for M1 and progressively disappeared for M2. Previous studies have associated emotional limbic processes with STN theta band activity in rat models of PD as a predictor of addiction vulnerability (Degoulet et al., 2021), in PD patients (Benis et al., 2020; Rappel et al., 2020), and PD patients with pathological gambling (Rosa et al., 2013). Interestingly, a recent study found that apathetic PD patients had higher baseline EEG alpha and theta power than non-apathetic patients, suggesting that PD patients need to overcome higher baseline neural activity to facilitate motivated movement (Zhu et al., 2019).

In early stage 2, before cognitive behavioral impairment, theta band neural activity associated with decision-making disappeared in both monkeys. This findings aligns with the proposed role of direct anatomical connections between the prefrontal cortex and STN in facilitating more deliberative response processes for selecting the most appropriate behavior during a conflict state (Alegre et al., 2013; Cavanagh et al., 2011; Haynes & Haber, 2013; Miller, 2000). Cognitive processes impairments have been shown to be impaired in PD (Herz et al., 2018), which correlates with the disappearance of decision-making related theta oscillations in our study, which was followed by an increase in cognitive errors. STN lesions have been associated with impulsive choices, contrasting with the role of intact STN in inhibiting inappropriate response to incentive stimuli (Uslaner & Robinson, 2006). Theta oscillations have been associated with impulse control disorder in Dopa-treated PD patients (Rodriguez-Oroz et al., 2011) and with obsessive compulsive disorder (Bastin et al., 2014). Moreover, studies conducted in alpha-synuclein mouse model and MPTP-treated monkey model have demonstrated early serotonin denervation in the limbic, prefrontal, and motor cortex (Masilamoni et al., 2022; Wihan et al., 2019), suggesting a contribution to non-motor cognitive and psychiatric symptoms in PD. Similar, in MPTP-treated monkeys, studies have found a

noradrenergic depletion in the locus coeruleus, as observed in PD patients (Masilamoni et al., 2011, 2017; Masilamoni & Smith, 2018). Serotonin, dopamine, and noradrenergic systems are known to be involved in cognition, mood, and limbic-related behaviors, and their denervation could contribute to non-motor limbic and cognitive symptoms observed in PD and animal models of PD (Brichta et al., 2013; Guthrie et al., 2013; O'Callaghan & Lewis, 2017; Rodriguez-Oroz et al., 2009). This alignment with the observed depletion of serotonin and dopamine CSF metabolites in our study explains the limbic and cognitive impairments in this stage. The involvement of the STN in motivation is also reflected by the increase in reward check with LFS of the ventral part. Both LFS and HFS reduced the rate of cognitive errors in Switch trials. However, only HFS on the ventral STN restored the Switch-Cost to baseline. These results highlight that the involvement of STN in non-motor behaviors occurs according to a specific spatial organization.

In late stage 2', just before motor symptoms onset, both monkeys showed a progressive reduction in decreased beta power during movement, and the increased beta-gamma rebound after movement disappeared. Increased STN beta oscillations are prominent electrophysiological markers in resting and awake PD patients (Brown et al., 2001; Neumann et al., 2016), correlating with symptoms severity (Cagnan et al., 2017; Kühn & Volkmann, 2017). Therefore, we hypothesize that the neural activity variations on the motor cue could be flattened due to the overall increase in beta oscillations induced by the development of the parkinsonian syndrome. Previous studies have correlated increased gamma oscillations with intra-cortical synchronization processes and synaptic plasticity, especially in the motor cortex (Bartos et al., 2007; Cardin et al., 2009; Nowak et al., 2018). Consistent with these findings, a recent study with PD patients demonstrated that impaired gamma oscillations in the basal ganglia-thalamo-cortical network were associated with impaired long-term potentiation-like plasticity in the primary motor cortex (Guerra et al., 2020). In both monkeys, we observed a decrease in gamma oscillations with the progressive parkinsonian syndrome, starting from late stage 2' and before motor signs.

Finally, stage 3 is characterized by the occurrence of significant motor symptoms with an increased mRT. Several studies have demonstrated an increase in beta power in the cortex and the STN in animal models and PD patients (Avila et al., 2010; P. Brown et al., 2001; Deffains et al., 2018; Neumann et al., 2016). This biomarker is associated with motor symptoms such as bradykinetic-rigid symptoms (Kuhn et al., 2005, p. 200; Lofredi et al., 2019; Tinkhauser et al.,

2018) and correlated with the symptoms severity (Cagnan et al., 2017; Neumann et al., 2016). The progressive loss of decreased beta during movement could be attributed to the general increase of STN beta with the progressive motor symptoms induced by MPTP injections. Indeed, a recent study with PD patients observed a decrease in STN gamma burst rates during movement, which was associated with bradykinesia (Lofredi et al., 2018). In addition, the improved mRT with HFS of the dorsal STN is consistent with the implication in motor behaviors and the overexpression of beta oscillation of this region (Benabid et al., 2009; Bergman et al., 1994; Limousin et al., 1995).

Conclusion

Our study elucidates the impact of progressive dopamine depletion on STN functional activity, leading to clinical manifestations (**Fig. 5**). Limbic and cognitive impairments preceded motor signs, indicating a greater sensitivity. Early detection of limbic and cognitive impairments using highly sensitive tests could be useful for an early diagnosis of PD, which is essential for neuroprotective treatments. Furthermore, our results suggest that adaptive STN-DBS, combining HFS in the dorsal STN and LFS in the ventral STN, may reduce both motor and non-motor symptoms.

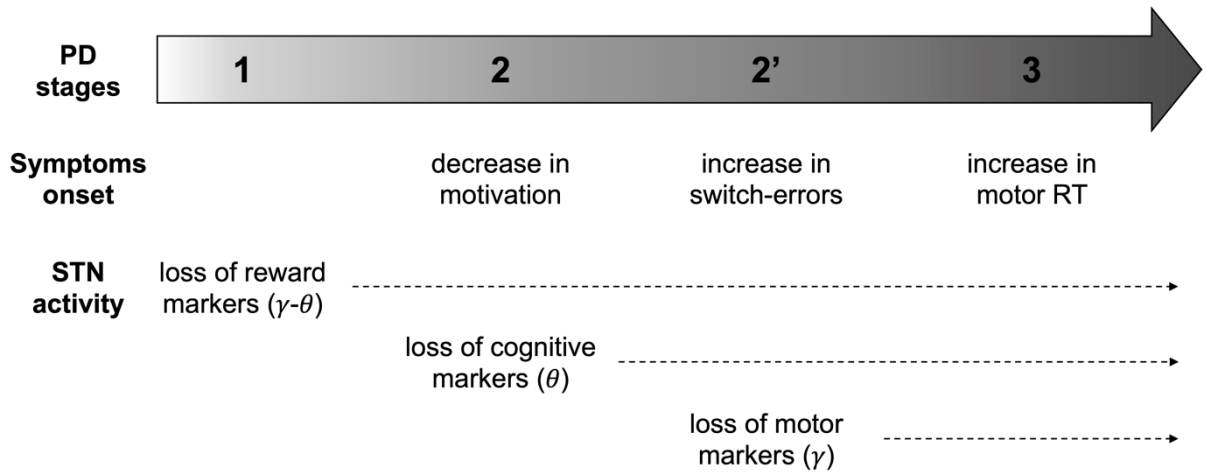


Figure 5: Study-based correlation between symptoms onset and preceding subthalamic nucleus (STN) changes in macaque model of progressive Parkinson's disease (PD). Behavioral impairments induced by chronic low-dose MPTP injections, characterizing stage 1: asymptomatic, stage 2: mild parkinsonism with motivational decrease, novel late stage 2': with cognitive impairment, and stage 3: moderate parkinsonism with significant motor signs. RT, response time; γ, gamma activities; θ, theta activities.

REFERENCE

Aarsland, D., Andersen, K., Larsen, J. P., & Lolk, A. (2003). Prevalence and Characteristics of Dementia in Parkinson Disease: An 8-Year Prospective Study. *Archives of Neurology*, *60*(3), 387–392. https://doi.org/10.1001/archneur.60.3.387

Aarsland, D., Brønnick, K., Larsen, J. P., Tysnes, O. B., & Alves, G. (2009). Cognitive impairment in incident, untreated Parkinson disease: The Norwegian ParkWest Study. *Neurology*, *72*(13), 1121–1126. https://doi.org/10.1212/01.wnl.0000338632.00552.cb

Aarsland, D., Larsen, J. P., Lim, N. G., Janvin, C., Karlsen, K., Tandberg, E., & Cummings, J. L. (1999). Range of neuropsychiatric disturbances in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *67*(4), 492–496. https://doi.org/10.1136/jnnp.67.4.492

Alegre, M., Lopez-Azcarate, J., Obeso, I., Wilkinson, L., Rodriguez-Oroz, M. C., Valencia, M., Garcia-Garcia, D., Guridi, J., Artieda, J., Jahanshahi, M., & Obeso, J. A. (2013). The subthalamic nucleus is involved in successful inhibition in the stop-signal task: A local field potential study in Parkinson's disease. *Experimental Neurology*, *239*, 1–12. https://doi.org/10.1016/j.expneurol.2012.08.027

Avila, I., Parr-Brownlie, L. C., Brazhnik, E., Castañeda, E., Bergstrom, D. A., & Walters, J. R. (2010). Beta frequency synchronization in basal ganglia output during rest and walk in a hemiparkinsonian rat. *Experimental Neurology*, *221*(2), 307–319. https://doi.org/10.1016/j.expneurol.2009.11.016

Barth, A. L., Schneider, J. S., Johnston, T. H., Hill, M. P., Brotchie, J. M., Moskal, J. R., & Cearley, C. N. (2020). NYX-458 Improves Cognitive Performance in a Primate Parkinson's Disease Model. *Movement Disorders*, *35*(4), 640–649. https://doi.org/10.1002/mds.27962

Bartos, M., Vida, I., & Jonas, P. (2007). Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nature Reviews Neuroscience*, *8*(1), 45–56. https://doi.org/10.1038/nrn2044

Bastin, J., Polosan, M., Piallat, B., Krack, P., Bougerol, T., Chabardès, S., & David, O. (2014). Changes of oscillatory activity in the subthalamic nucleus during obsessive-compulsive disorder symptoms: Two case reports. *Cortex*, *60*, 145–150. https://doi.org/10.1016/j.cortex.2013.12.007

Benabid, A. L., Chabardes, S., Mitrofanis, J., & Pollak, P. (2009). *Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease*. *8*.

Benabid, A. L., Pollak, P., Gross, C., Hoffmann, D., Benazzouz, A., Gao, D. M., Laurent, A., Gentil, M., & Perret, J. (1995). Acute and Long-Term Effects of Subthalamic Nucleus Stimulation in Parkinson's Disease. *Stereotactic and Functional Neurosurgery*, *62*(1–4), 76–84. https://doi.org/10.1159/000098600

Benazzouz, A., Gross, C., Féger, J., Boraud, T., & Bioulac, B. (1993). Reversal of Rigidity and Improvement in Motor Performance by Subthalamic High-frequency Stimulation in MPTP-treated Monkeys. *European Journal of Neuroscience*, *5*(4), 382–389. https://doi.org/10.1111/j.1460-9568.1993.tb00505.x

Benis, D., Haegelen, C., Voruz, P., Pierce, J., Milesi, V., Houvenaghel, J.-F., Vérin, M., Sauleau, P., Grandjean, D., & Péron, J. (2020). Subthalamic nucleus oscillations during vocal emotion processing are dependent of the motor asymmetry of Parkinson's disease. *NeuroImage*, *222*, 117215. https://doi.org/10.1016/j.neuroimage.2020.117215

Bergman, H., Wichmann, T., Karmon, B., & DeLong, M. R. (1994). The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. *Journal of Neurophysiology*, *72*(2), 507–520. https://doi.org/10.1152/jn.1994.72.2.507

Bertrand, M., Chabardes, S., Fontanier, V., Procyk, E., Bastin, J., & Piallat, B. (2024). Contribution of the subthalamic nucleus to motor, cognitive and limbic processes: An electrophysiological and stimulation study in monkeys. *Frontiers in Neuroscience*, *18*, 1257579. https://doi.org/10.3389/fnins.2024.1257579

Beudel, M., & Brown, P. (2016). Adaptive deep brain stimulation in Parkinson's disease. *Parkinsonism & Related Disorders*, *22*, S123–S126. https://doi.org/10.1016/j.parkreldis.2015.09.028

Bezard, E., Imbert, C., Deloire, X., Bioulac, B., & Gross, C. E. (1997). A chronic MPTP model reproducing the slow evolution of Parkinson's disease: Evolution of motor symptoms in the monkey. *Brain Research*, *766*(1–2), 107–112. https://doi.org/10.1016/S0006-8993(97)00531-3

Boulet, S., Mounayar, S., Poupard, A., Bertrand, A., Jan, C., Pessiglione, M., Hirsch, E. C., Feuerstein, C., François, C., Féger, J., Savasta, M., & Tremblay, L. (2008). Behavioral Recovery in MPTP-Treated Monkeys: Neurochemical Mechanisms Studied by Intrastriatal Microdialysis. *The Journal of Neuroscience*, *28*(38), 9575–9584. https://doi.org/10.1523/JNEUROSCI.3465-08.2008

Bräutigam, C., Steenbergen-Spanjers, G. C., Hoffmann, G. F., Dionisi-Vici, C., Van Den Heuvel, L. P., Smeitink, J. A., & Wevers, R. A. (1999). Biochemical and Molecular Genetic Characteristics of the Severe Form of Tyrosine Hydroxylase Deficiency. *Clinical Chemistry*, *45*(12), 2073–2078. https://doi.org/10.1093/clinchem/45.12.2073

Brichta, L., Greengard, P., & Flajolet, M. (2013). Advances in the pharmacological treatment of Parkinson's disease: Targeting neurotransmitter systems. *Trends in Neurosciences*, *36*(9), 543–554. https://doi.org/10.1016/j.tins.2013.06.003

Brown, G. L., & Linnoila, M. I. (1990). CSF serotonin metabolite (5-HIAA) studies in depression, impulsivity, and violence. *The Journal of Clinical Psychiatry*, *51*(Suppl), 31–41.

Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P., & Di Lazzaro, V. (2001). Dopamine Dependency of Oscillations between Subthalamic Nucleus and Pallidum in Parkinson's Disease. *The Journal of Neuroscience*, *21*(3), 1033–1038. https://doi.org/10.1523/JNEUROSCI.21-03-01033.2001

Burns, R. S., Chiueh, C. C., Markey, S. P., Ebert, M. H., Jacobowitz, D. M., & Kopin, I. J. (1983). A primate model of parkinsonism: Selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Proceedings of the National Academy of Sciences*, *80*(14), 4546–4550. https://doi.org/10.1073/pnas.80.14.4546

Cagnan, H., Pedrosa, D., Little, S., Pogosyan, A., Cheeran, B., Aziz, T., Green, A., Fitzgerald, J., Foltynie, T., Limousin, P., Zrinzo, L., Hariz, M., Friston, K. J., Denison, T., & Brown, P. (2017). Stimulating at the right time: Phase-specific deep brain stimulation. *Brain*, *140*(1), 132–145. https://doi.org/10.1093/brain/aww286

Cardin, J. A., Carlén, M., Meletis, K., Knoblich, U., Zhang, F., Deisseroth, K., Tsai, L.-H., & Moore, C. I. (2009). Driving fast-spiking cells induces gamma rhythm and controls sensory responses. *Nature*, *459*(7247), 663–667. https://doi.org/10.1038/nature08002

Carnicella, S., Drui, G., Boulet, S., Carcenac, C., Favier, M., Duran, T., & Savasta, M. (2014). Implication of dopamine D3 receptor activation in the reversion of Parkinson's disease-related motivational deficits. *Translational Psychiatry*, *4*(6), e401–e401. https://doi.org/10.1038/tp.2014.43

Cavanagh, J. F., Wiecki, T. V., Cohen, M. X., Figueroa, C. M., Samanta, J., Sherman, S. J., & Frank, M. J. (2011). Subthalamic nucleus stimulation reverses mediofrontal influence

over decision threshold. *Nature Neuroscience*, *14*(11), 1462–1467. https://doi.org/10.1038/nn.2925

Chaudhuri, K. R., Healy, D. G., & Schapira, A. H. (2006). Non-motor symptoms of Parkinson's disease: Diagnosis and management. *The Lancet Neurology*, *5*(3), 235–245. https://doi.org/10.1016/S1474-4422(06)70373-8

Chaudhuri, K. R., Prieto-Jurcynska, C., Naidu, Y., Mitra, T., Frades-Payo, B., Tluk, S., Ruessmann, A., Odin, P., Macphee, G., Stocchi, F., Ondo, W., Sethi, K., Schapira, A. H. V., Castrillo, J. C. M., & Martinez-Martin, P. (2010). The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: An international study using the nonmotor symptoms questionnaire. *Movement Disorders*, *25*(6), 704–709. https://doi.org/10.1002/mds.22868

Connolly, A. T., Jensen, A. L., Bello, E. M., Netoff, T. I., Baker, K. B., Johnson, M. D., & Vitek, J. L. (2015). Modulations in Oscillatory Frequency and Coupling in Globus Pallidus with Increasing Parkinsonian Severity. *The Journal of Neuroscience*, *35*(15), 6231–6240. https://doi.org/10.1523/JNEUROSCI.4137-14.2015

Cooper, S. J., King, D. J., & Kelly, C. B. (1992). 5-hydroxyindoleacetic acid in cerebrospinal fluid and prediction of suicidal behaviour in schizophrenia. *The Lancet*, *340*(8825), 940–941. https://doi.org/10.1016/0140-6736(92)92819-2

Davin, A., Chabardès, S., Belaid, H., Fagret, D., Djaileb, L., Dauvilliers, Y., David, O., Torres-Martinez, N., & Piallat, B. (2022). Early onset of sleep/wake disturbances in a progressive macaque model of Parkinson's disease. *Scientific Reports*, *12*(1), 17499. https://doi.org/10.1038/s41598-022-22381-z

Deffains, M., Iskhakova, L., Katabi, S., Israel, Z., & Bergman, H. (2018). Longer β oscillatory episodes reliably identify pathological subthalamic activity in Parkinsonism. *Movement Disorders*, *33*(10), 1609–1618. https://doi.org/10.1002/mds.27418

Degoulet, M., Tiran-Cappello, A., Combrisson, E., Baunez, C., & Pelloux, Y. (2021). Subthalamic low-frequency oscillations predict vulnerability to cocaine addiction. *Proceedings of the National Academy of Sciences*, *118*(14), e2024121118. https://doi.org/10.1073/pnas.2024121118

Del Tredici, K., & Braak, H. (2013). Dysfunction of the locus coeruleus–norepinephrine system and related circuitry in Parkinson's disease-related dementia. *Journal of Neurology, Neurosurgery & Psychiatry*, *84*(7), 774. https://doi.org/10.1136/jnnp-2011-301817

Devergnas, A., Pittard, D., Bliwise, D., & Wichmann, T. (2014). Relationship between oscillatory activity in the cortico-basal ganglia network and parkinsonism in MPTP-treated monkeys. *Neurobiology of Disease*, *68*, 156–166. https://doi.org/10.1016/j.nbd.2014.04.004

Dorval, A. D., Russo, G. S., Hashimoto, T., Xu, W., Grill, W. M., & Vitek, J. L. (2008). Deep Brain Stimulation Reduces Neuronal Entropy in the MPTP-Primate Model of Parkinson's Disease. *Journal of Neurophysiology*, *100*(5), 2807–2818. https://doi.org/10.1152/jn.90763.2008

Durand, E., Petit, O., Tremblay, L., Zimmer, C., Sgambato-Faure, V., Chassain, C., Laurent, M., Pereira, B., Silberberg, C., & Durif, F. (2015). Social behavioral changes in MPTP-treated monkey model of Parkinson's disease. *Frontiers in Behavioral Neuroscience*, *9*. https://doi.org/10.3389/fnbeh.2015.00042

Elsworth, J. D., Leahy, D. J., Roth, R. H., & Redmond, D. E. (1987). Homovanillic acid concentrations in brain, CSF and plasma as indicators of central dopamine function in primates. *Journal of Neural Transmission*, *68*(1), 51–62. https://doi.org/10.1007/BF01244639

Eusebio, A., Thevathasan, W., Doyle Gaynor, L., Pogosyan, A., Bye, E., Foltynie, T., Zrinzo, L., Ashkan, K., Aziz, T., & Brown, P. (2011). Deep brain stimulation can suppress pathological synchronisation in parkinsonian patients. *Journal of Neurology, Neurosurgery & Psychiatry*, *82*(5), 569–573. https://doi.org/10.1136/jnnp.2010.217489

Frey, J., Cagle, J., Johnson, K. A., Wong, J. K., Hilliard, J. D., Butson, C. R., Okun, M. S., & De Hemptinne, C. (2022). Past, Present, and Future of Deep Brain Stimulation: Hardware, Software, Imaging, Physiology and Novel Approaches. *Frontiers in Neurology*, *13*, 825178. https://doi.org/10.3389/fneur.2022.825178

Goldman, J., & Litvan, I. (2012). *Mild Cognitive Impairment in Parkinson's Disease*.

Goldstein, D. S., Holmes, C., & Sharabi, Y. (2012). Cerebrospinal fluid biomarkers of central catecholamine deficiency in Parkinson's disease and other synucleinopathies. *Brain*, *135*(6), 1900–1913. https://doi.org/10.1093/brain/aws055

Goldstein, D. S., Sullivan, P., & Holmes, C. (2024). Cerebrospinal fluid concentration gradients of catechols in synucleinopathies. *Journal of Neurochemistry*, jnc.16168. https://doi.org/10.1111/jnc.16168

Guerra, A., Asci, F., D'Onofrio, V., Sveva, V., Bologna, M., Fabbrini, G., Berardelli, A., & Suppa, A. (2020). Enhancing Gamma Oscillations Restores Primary Motor Cortex Plasticity in Parkinson's Disease. *The Journal of Neuroscience*, *40*(24), 4788–4796. https://doi.org/10.1523/JNEUROSCI.0357-20.2020

Guthrie, M., Leblois, A., Garenne, A., & Boraud, T. (2013). Interaction between cognitive and motor cortico-basal ganglia loops during decision making: A computational study. *Journal of Neurophysiology*, *109*(12), 3025–3040. https://doi.org/10.1152/jn.00026.2013

Hassin-Baer, S., Cohen, O. S., Israeli-Korn, S., Yahalom, G., Benizri, S., Sand, D., Issachar, G., Geva, A. B., Shani-Hershkovich, R., & Peremen, Z. (2022). Identification of an

early-stage Parkinson's disease neuromarker using event-related potentials, brain network analytics and machine-learning. *PLOS ONE*, *17*(1), e0261947. https://doi.org/10.1371/journal.pone.0261947

Haynes, W. I. A., & Haber, S. N. (2013). The Organization of Prefrontal-Subthalamic Inputs in Primates Provides an Anatomical Substrate for Both Functional Specificity and Integration: Implications for Basal Ganglia Models and Deep Brain Stimulation. *The Journal of Neuroscience*, *33*(11), 4804–4814. https://doi.org/10.1523/JNEUROSCI.4674-12.2013

Hely, M. A., Reid, W. G. J., Adena, M. A., Halliday, G. M., & Morris, J. G. L. (2008). The Sydney multicenter study of Parkinson's disease: The inevitability of dementia at 20 years. *Movement Disorders*, *23*(6), 837–844. https://doi.org/10.1002/mds.21956

Herz, D. M., Little, S., Pedrosa, D. J., Tinkhauser, G., Cheeran, B., Foltynie, T., Bogacz, R., & Brown, P. (2018). Mechanisms Underlying Decision-Making as Revealed by Deep-Brain Stimulation in Patients with Parkinson's Disease. *Current Biology*, *28*(8), 1169-1178.e6. https://doi.org/10.1016/j.cub.2018.02.057

Houeto, J. L., Mesnage, V., Mallet, L., Pillon, B., Gargiulo, M., du Moncel, S. T., Bonnet, A. M., Pidoux, B., Dormont, D., Cornu, P., & Agid, Y. (2002). Behavioural disorders, Parkinson's disease and subthalamic stimulation. *Journal of Neurology, Neurosurgery & Psychiatry*, *72*(6), 701. https://doi.org/10.1136/jnnp.72.6.701

Huebl, J., Spitzer, B., Brücke, C., Schönecker, T., Kupsch, A., Alesch, F., Schneider, G.-H., & Kühn, A. A. (2014). Oscillatory subthalamic nucleus activity is modulated by dopamine during emotional processing in Parkinson's disease. *Cortex*, *60*, 69–81. https://doi.org/10.1016/j.cortex.2014.02.019

Imbert, C., Bezard, E., Guitraud, S., Boraud, T., & Gross, C. E. (2000). Comparison of eight clinical rating scales used for the assessment of MPTP-induced parkinsonism in the

Macaque monkey. *Journal of Neuroscience Methods*, *96*(1), 71–76. https://doi.org/10.1016/S0165-0270(99)00184-3

Jenner, P., Rupniak, N. M. J., Rose, S., Kelly, E., Kilpatrick, G., Lees, A., & Marsden, C. D. (1984). 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism in the common marmoset. *Neuroscience Letters*, *50*(1), 85–90. https://doi.org/10.1016/0304-3940(84)90467-1

Kalia, L. V., & Lang, A. E. (2015). Parkinson's disease. *The Lancet*, *386*(9996), 896–912. https://doi.org/10.1016/S0140-6736(14)61393-3

Kapogiannis, D., Mooshagian, E., Campion, P., Grafman, J., Zimmermann, T. J., Ladt, K. C., & Wassermann, E. M. (2011). Reward processing abnormalities in Parkinson's disease. *Movement Disorders*, *26*(8), 1451–1457. https://doi.org/10.1002/mds.23701

Kelley, R., Flouty, O., Emmons, E. B., Kim, Y., Kingyon, J., Wessel, J. R., Oya, H., Greenlee, J. D., & Narayanan, N. S. (2018). A human prefrontal-subthalamic circuit for cognitive control. *Brain*, *141*(1), 205–216. https://doi.org/10.1093/brain/awx300

Kuhn, A. A., Hariz, M. I., Silberstein, P., Tisch, S., Kupsch, A., Schneider, G.-H., Limousin-Dowsey, P., Yarrow, K., & Brown, P. (2005). Activation of the subthalamic region during emotional processing in Parkinson disease. *Neurology*, *65*(5), 707–713. https://doi.org/10.1212/01.wnl.0000174438.78399.bc

Kühn, A. A., & Volkmann, J. (2017). Innovations in deep brain stimulation methodology. *Movement Disorders*, *32*(1), 11–19. https://doi.org/10.1002/mds.26703

Kurtis, M. M., Rajah, T., Delgado, L. F., & Dafsari, H. S. (2017). The effect of deep brain stimulation on the non-motor symptoms of Parkinson's disease: A critical review of the current evidence. *Npj Parkinson's Disease*, *3*(1), 16024. https://doi.org/10.1038/npjparkd.2016.24

Kwon, D. H., Hwang, J. S., Kim, S. G., Jang, Y. E., Shin, T. H., & Lee, G. (2022). Cerebrospinal Fluid Metabolome in Parkinson's Disease and Multiple System Atrophy. *International Journal of Molecular Sciences*, *23*(3), 1879. https://doi.org/10.3390/ijms23031879

Lee, E.-S. Y., Chen, H., King, J., & Charlton, C. (2008). The Role of 3-O-Methyldopa in the Side Effects of l-dopa. *Neurochemical Research*, *33*(3), 401–411. https://doi.org/10.1007/s11064-007-9442-6

Lee, L.-H. N., Huang, C.-S., Chuang, H.-H., Lai, H.-J., Yang, C.-K., Yang, Y.-C., & Kuo, C.-C. (2021). An electrophysiological perspective on Parkinson's disease: Symptomatic pathogenesis and therapeutic approaches. *Journal of Biomedical Science*, *28*(1), 85. https://doi.org/10.1186/s12929-021-00781-z

Li, X., Chen, C., Pan, T., Zhou, X., Sun, X., Zhang, Z., Wu, D., & Chen, X. (2024). Trends and hotspots in non-motor symptoms of Parkinson's disease: A 10-year bibliometric analysis. *Frontiers in Aging Neuroscience*, *16*, 1335550. https://doi.org/10.3389/fnagi.2024.1335550

Limousin, P., Pollak, P., Benazzouz, A., Hoffmann, D., Le Bas, J.-F., Perret, J. E., Benabid, A.-L., & Broussolle, E. (1995). Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *The Lancet*, *345*(8942), 91–95. https://doi.org/10.1016/S0140-6736(95)90062-4

Little, S., Beudel, M., Zrinzo, L., Foltynie, T., Limousin, P., Hariz, M., Neal, S., Cheeran, B., Cagnan, H., Gratwicke, J., Aziz, T. Z., Pogosyan, A., & Brown, P. (2016). Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *87*(7), 717–721. https://doi.org/10.1136/jnnp-2015-310972

Lofredi, R., Neumann, W.-J., Bock, A., Horn, A., Huebl, J., Siegert, S., Schneider, G.-H., Krauss, J. K., & Kühn, A. A. (2018). Dopamine-dependent scaling of subthalamic

gamma bursts with movement velocity in patients with Parkinson's disease. *eLife*, *7*, e31895. https://doi.org/10.7554/eLife.31895

Lofredi, R., Tan, H., Neumann, W.-J., Yeh, C.-H., Schneider, G.-H., Kühn, A. A., & Brown, P. (2019). Beta bursts during continuous movements accompany the velocity decrement in Parkinson's disease patients. *Neurobiology of Disease*, *127*, 462–471. https://doi.org/10.1016/j.nbd.2019.03.013

Magnard, R., Vachez, Y., Carcenac, C., Krack, P., David, O., Savasta, M., Boulet, S., & Carnicella, S. (2016). What can rodent models tell us about apathy and associated neuropsychiatric symptoms in Parkinson's disease? *Translational Psychiatry*, *6*(3), e753–e753. https://doi.org/10.1038/tp.2016.17

Manssuer, L., Wang, L., Ding, Q., Li, J., Zhang, Y., Zhang, C., Hallett, M., Li, D., Sun, B., & Voon, V. (2023). Subthalamic Oscillatory Activity of Reward and Loss Processing Using the Monetary Incentive Delay Task in Parkinson Disease. *Neuromodulation: Technology at the Neural Interface*, *26*(2), 414–423. https://doi.org/10.1016/j.neurom.2022.04.033

Masilamoni, G. J., Bogenpohl, J. W., Alagille, D., Delevich, K., Tamagnan, G., Votaw, J. R., Wichmann, T., & Smith, Y. (2011). Metabotropic glutamate receptor 5 antagonist protects dopaminergic and noradrenergic neurons from degeneration in MPTP-treated monkeys. *Brain*, *134*(7), 2057–2073. https://doi.org/10.1093/brain/awr137

Masilamoni, G. J., Groover, O., & Smith, Y. (2017). Reduced noradrenergic innervation of ventral midbrain dopaminergic cell groups and the subthalamic nucleus in MPTP-treated parkinsonian monkeys. *Neurobiology of Disease*, *100*, 9–18. https://doi.org/10.1016/j.nbd.2016.12.025

Masilamoni, G. J., & Smith, Y. (2018). Chronic MPTP administration regimen in monkeys: A model of dopaminergic and non-dopaminergic cell loss in Parkinson's disease. *Journal of Neural Transmission*, *125*(3), 337–363. https://doi.org/10.1007/s00702-017-1774-z

Masilamoni, G. J., Weinkle, A., Papa, S. M., & Smith, Y. (2022). Cortical Serotonergic and Catecholaminergic Denervation in MPTP-Treated Parkinsonian Monkeys. *Cerebral Cortex*, *32*(9), 1804–1822. https://doi.org/10.1093/cercor/bhab313

Miller, E. K. (2000). *THE PREFRONTAL CORTEX AND COGNITIVE CONTROL*.

Mounayar, S., Boulet, S., Tande, D., Jan, C., Pessiglione, M., Hirsch, E. C., Feger, J., Savasta, M., Francois, C., & Tremblay, L. (2007). A new model to study compensatory mechanisms in MPTP-treated monkeys exhibiting recovery. *Brain*, *130*(11), 2898–2914. https://doi.org/10.1093/brain/awm208

Müller, E. J., & Robinson, P. A. (2018). Suppression of Parkinsonian Beta Oscillations by Deep Brain Stimulation: Determination of Effective Protocols. *Frontiers in Computational Neuroscience*, *12*, 98. https://doi.org/10.3389/fncom.2018.00098

Neumann, W., Degen, K., Schneider, G., Brücke, C., Huebl, J., Brown, P., & Kühn, A. A. (2016). Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease. *Movement Disorders*, *31*(11), 1748–1751. https://doi.org/10.1002/mds.26759

Nowak, M., Zich, C., & Stagg, C. J. (2018). Motor Cortical Gamma Oscillations: What Have We Learnt and Where Are We Headed? *Current Behavioral Neuroscience Reports*, *5*(2), 136–142. https://doi.org/10.1007/s40473-018-0151-z

O'Callaghan, C., & Lewis, S. J. G. (2017). Chapter Eighteen—Cognition in Parkinson's Disease. In K. R. Chaudhuri & N. Titova (Eds.), *International Review of Neurobiology* (Vol. 133, pp. 557–583). Academic Press. https://doi.org/10.1016/bs.irn.2017.05.002

Ormazabal, A., García-Cazorla, A., Fernández, Y., Fernández-Álvarez, E., Campistol, J., & Artuch, R. (2005). HPLC with electrochemical and fluorescence detection procedures for the diagnosis of inborn errors of biogenic amines and pterins. *Journal of Neuroscience Methods*, *142*(1), 153–158. https://doi.org/10.1016/j.jneumeth.2004.08.007

Poewe, W. (2008). Non-motor symptoms in Parkinson's disease. *European Journal of Neurology*, *15*(s1), 14–20. https://doi.org/10.1111/j.1468-1331.2008.02056.x

Pont-Sunyer, C., Hotter, A., Gaig, C., Seppi, K., Compta, Y., Katzenschlager, R., Mas, N., Hofeneder, D., Brücke, T., Bayés, A., Wenzel, K., Infante, J., Zach, H., Pirker, W., Posada, I. J., Álvarez, R., Ispierto, L., De Fàbregues, O., Callén, A., … Tolosa, E. (2015). The O nset of N onmotor S ymptoms in P arkinson's disease (T he ONSET PD S tudy). *Movement Disorders*, *30*(2), 229–237. https://doi.org/10.1002/mds.26077

Porras, G., Li, Q., & Bezard, E. (2012). Modeling Parkinson's Disease in Primates: The MPTP Model. *Cold Spring Harbor Perspectives in Medicine*, *2*(3), a009308–a009308. https://doi.org/10.1101/cshperspect.a009308

Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A. E., Halliday, G., Goetz, C. G., Gasser, T., Dubois, B., Chan, P., Bloem, B. R., Adler, C. H., & Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease: MDS-PD Clinical Diagnostic Criteria. *Movement Disorders*, *30*(12), 1591–1601. https://doi.org/10.1002/mds.26424

Rappel, P., Grosberg, S., Arkadir, D., Linetsky, E., Abu Snineh, M., Bick, A. S., Tamir, I., Valsky, D., Marmor, O., Abo Foul, Y., Peled, O., Gilad, M., Daudi, C., Ben-Naim, S., Bergman, H., Israel, Z., & Eitan, R. (2020). Theta-alpha Oscillations Characterize Emotional Subregion in the Human Ventral Subthalamic Nucleus. *Movement Disorders*, *35*(2), 337–343. https://doi.org/10.1002/mds.27910

Rodriguez-Oroz, M. C., Jahanshahi, M., Krack, P., Litvan, I., Macias, R., Bezard, E., & Obeso, J. A. (2009). Initial clinical manifestations of Parkinson's disease: Features and pathophysiological mechanisms. *The Lancet Neurology*, *8*(12), 1128–1139. https://doi.org/10.1016/S1474-4422(09)70293-5

Rodriguez-Oroz, M. C., López-Azcárate, J., Garcia-Garcia, D., Alegre, M., Toledo, J., Valencia, M., Guridi, J., Artieda, J., & Obeso, J. A. (2011). Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinson's disease. *Brain*, *134*(1), 36–49. https://doi.org/10.1093/brain/awq301

Rosa, M., Fumagalli, M., Giannicola, G., Marceglia, S., Lucchiari, C., Servello, D., Franzini, A., Pacchetti, C., Romito, L., Albanese, A., Porta, M., Pravettoni, G., & Priori, A. (2013). Pathological gambling in Parkinson's disease: Subthalamic oscillations during economics decisions. *Movement Disorders*, *28*(12), 1644–1652. https://doi.org/10.1002/mds.25427

Schmidt, S. L., Chowdhury, A. H., Mitchell, K. T., Peters, J. J., Gao, Q., Lee, H.-J., Genty, K., Chow, S.-C., Grill, W. M., Pajic, M., & Turner, D. A. (2024). At home adaptive dual target deep brain stimulation in Parkinson's disease with proportional control. *Brain*, *147*(3), 911–922. https://doi.org/10.1093/brain/awad429

Schneider, J. S., & Kovelowski, C. J. (1990). Chronic exposure to low doses of MPTP. I. Cognitive deficits in motor asymptomatic monkeys. *Brain Research*, *519*(1–2), 122–128. https://doi.org/10.1016/0006-8993(90)90069-N

Singh, A., Cole, R. C., Espinoza, A. I., Brown, D., Cavanagh, J. F., & Narayanan, N. S. (2020). Frontal theta and beta oscillations during lower-limb movement in Parkinson's disease. *Clinical Neurophysiology*, *131*(3), 694–702. https://doi.org/10.1016/j.clinph.2019.12.399

Temel, Y., Boothman, L. J., Blokland, A., Magill, P. J., Steinbusch, H. W. M., Visser-Vandewalle, V., & Sharp, T. (2007). Inhibition of 5-HT neuron activity and induction of depressive-like behavior by high-frequency stimulation of the subthalamic nucleus. *Proceedings of the National Academy of Sciences*, *104*(43), 17087–17092. https://doi.org/10.1073/pnas.0704144104

Tinkhauser, G., Pogosyan, A., Debove, I., Nowacki, A., Shah, S. A., Seidel, K., Tan, H., Brittain, J., Petermann, K., Di Biase, L., Oertel, M., Pollo, C., Brown, P., & Schuepbach, M. (2018). Directional local field potentials: A tool to optimize deep brain stimulation. *Movement Disorders*, *33*(1), 159–164. https://doi.org/10.1002/mds.27215

Uslaner, J. M., & Robinson, T. E. (2006). Subthalamic nucleus lesions increase impulsive action and decrease impulsive choice − mediation by enhanced incentive motivation? *European Journal of Neuroscience*, *24*(8), 2345–2354. https://doi.org/10.1111/j.1460-9568.2006.05117.x

Van Der Heyden, J., Rotteveel, J., & Wevers, R. (2003). Decreased homovanillic acid concentrations in cerebrospinal fluid in children without a known defect in dopamine metabolism. *European Journal of Paediatric Neurology*, *7*(1), 31–37. https://doi.org/10.1016/S1090-3798(02)00137-X

Vezoli, J., Dzahini, K., Costes, N., Wilson, C. R. E., Fifel, K., Cooper, H. M., Kennedy, H., & Procyk, E. (2014). Increased DAT binding in the early stage of the dopaminergic lesion: A longitudinal [11C]PE2I binding study in the MPTP-monkey. *NeuroImage*, *102*, 249–261. https://doi.org/10.1016/j.neuroimage.2014.07.059

Vezoli, J., Fifel, K., Leviel, V., Dehay, C., Kennedy, H., Cooper, H. M., Gronfier, C., & Procyk, E. (2011). Early Presymptomatic and Long-Term Changes of Rest Activity Cycles and Cognitive Behavior in a MPTP-Monkey Model of Parkinson's Disease. *PLOS ONE*, *6*(8), e23952. https://doi.org/10.1371/journal.pone.0023952

Wang, L., Wu, P., Brown, P., Zhang, W., Liu, F., Han, Y., Zuo, C.-T., Cheng, W., & Feng, J. (2022). Association of Structural Measurements of Brain Reserve With Motor Progression in Patients With Parkinson Disease. *Neurology*, *99*(10). https://doi.org/10.1212/WNL.0000000000200814

Weintraub, D., Aarsland, D., Chaudhuri, K. R., Dobkin, R. D., Leentjens, A. F., Rodriguez-Violante, M., & Schrag, A. (2022). The neuropsychiatry of Parkinson's disease: Advances and challenges. *The Lancet Neurology*, *21*(1), 89–102. https://doi.org/10.1016/S1474-4422(21)00330-6

Wihan, J., Grosch, J., Kalinichenko, L. S., Müller, C. P., Winkler, J., & Kohl, Z. (2019). Layer-specific axonal degeneration of serotonergic fibers in the prefrontal cortex of aged A53T α-synuclein–expressing mice. *Neurobiology of Aging*, *80*, 29–37. https://doi.org/10.1016/j.neurobiolaging.2019.03.014

Zavala, B., Brittain, J.-S., Jenkinson, N., Ashkan, K., Foltynie, T., Limousin, P., Zrinzo, L., Green, A. L., Aziz, T., Zaghloul, K., & Brown, P. (2013). Subthalamic Nucleus Local Field Potential Activity during the Eriksen Flanker Task Reveals a Novel Role for Theta Phase during Conflict Monitoring. *The Journal of Neuroscience*, *33*(37), 14758–14766. https://doi.org/10.1523/JNEUROSCI.1036-13.2013

Zhu, M., HajiHosseini, A., Baumeister, T. R., Garg, S., Appel-Cresswell, S., & McKeown, M. J. (2019). Altered EEG alpha and theta oscillations characterize apathy in Parkinson's disease during incentivized movement. *NeuroImage: Clinical*, *23*, 101922. https://doi.org/10.1016/j.nicl.2019.101922