Title: Subthalamic nucleus activity modifications prior to clinical impairment in a progressive model of Parkinson's disease.

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ABSTRACT

Background: Parkinson's disease (PD) is clinically diagnosed based on motor impairments related to akinesia, rigidity, and tremor. These symptoms are delayed in the course of the disease and that contributes strongly to its late diagnosis. Cognitive and limbic symptoms may precede motor symptoms, thus opening an earlier diagnostic window, but their early kinetics need to be better characterized. Furthermore, despite adapted medications, these non-motor symptoms evolve and worsen over time. Surgical treatment with high frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN), whereas significantly improves motor symptoms, does not address specifically the non-motor symptoms. A better temporal characterization of the onset of non-motor symptoms combined with adapted parameters of stimulation of DBS could potentially optimize the surgical treatment.

Objective: We aimed to correlate STN activity with the early phase of motor, cognitive, and limbic symptoms of PD and to propose specific STN-DBS paradigm of stimulation to take over all symptoms.

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

Results

After the first MPTP injections, we observed a gradual progression of the parkinsonian syndrome from stage 1 without any symptoms, to stage 3 with limbic, cognitive, and motor symptoms. In addition, each stage was associated with specific changes in STN electrophysiological activities. Stage 1, with no significant symptoms although MPTP intoxication has begun, was marked by a decrease in the power of reward-related gamma/theta oscillations. Stage 2 was characterized by an early decline in motivation and the appearance of decreased theta-band activity during decision-making. Later, an increase in error on Switch trials was reported, illustrating the stage 2', and a decrease in beta-gamma power after motor movement occurred. Finally, stage 3 was characterized by an increase in motor response time, while retaining all the STN neuronal changes.

Conclusion: Our results suggest a progressive timeline in the onset of behavioral impairments with first limbic symptoms, followed by cognitive and then motor symptoms. Furthermore, specific electrophysiological biomarkers of each symptom are found early in the STN and can predict their onset and help to better understand their pathophysiology. Finally, we propose a combined stimulation with HFS in dorsal STN and LFS in ventral STN to optimize STN-DBS and reduce 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) is a deep brain structure that plays a key role in processing cortical information to elaborate and adapt behavior. This important role is highlighted by the beneficial effects of its modulation by deep brain stimulation (DBS) on motor symptoms in Parkinson's disease (PD) (Benazzouz et al., 1993; Benabid et al., 1994; Limousin et al., 1995). Abnormal STN activity in the 13-30 Hz beta range has been shown to correlate with motor symptoms (Bergman et al., 1994; Neumann et al., 2016; Beudel & Brown, 2016) and is suppressed by dorsal STN-DBS using high-frequency stimulation (HFS) (Müller & Robinson, 2018; Eusobio et al., 2011) thereby significantly improving motor symptoms in patients. However, PD patients also suffer from non-motor symptoms, such as sleep disorders, cognitive impairment, or anxiety and depression, which contribute to the deterioration of quality of life (Chaudhuri et al., 2010; Postuma et al., 2015; Pont-Sunyer et al., 2015). The onset of these non-motor symptoms is not precisely described, and their features generally increase with PD duration (Hely et al., 2008; Aarsland et al., 2009). To study these clinical manifestations, non-human primate (NHP) treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is recognized as the gold standard model of PD, as motor and non-motor induced symptoms are similar to those observed in PD patients (Burns et al., 1983; Jenner et al., 1984; Schneider & Kovelowski, 1990; Bezard et al., 1997; Masilomani & Smith, 2018). Furthermore, it is possible to establish a progressive model with repeated intra muscular injections of low doses of MPTP allowing to describe sleep disorders and cognitive impairments, such as deficits in attention or cognitive flexibility, appearing before motor symptoms (Davin et al., 2022; Schnieder & Kevolowski, 1990; Vezoli et al., 2011; Barth et al., 2020; Masilamoni et al., 2022). In parallel, it has been shown that these specific behavioral impairments were associated with changes in neural oscillations. Disruption of theta band activity in the STN during conflict behavior, impairing its modulating "break" role to make the best decision, has been reported in PD patients (Cavanagh et al., 2011; Zavala et al., 2013). An increase in gamma band activity has been found in the STN of PD patients upon the presentation of emotionally valanced stimuli, enhancing its involvement in non-motor symptoms (Huebl et al., 2014). Another study with PD patients also highlighted the role of the STN in reward and loss expectation, showing an increase in delta-theta activity (Manssuer et al., 2023). However, it is essential to know how these neural activities change with the progression of PD symptoms and how they correlate with their onset.

Indeed, this knowledge could contribute to better understand why STN-DBS can, in some cases, induce or aggravate non-motor components of behavior (Kurtis et al., 2017; Houeto et al., 2002; Temel et al., 2007). Additionally, the MPTP-treated NHP model allows the testing of alternative STN-DBS parameters of stimulation in order to optimize the management of all symptoms and to reduce associated side effects. It has been well described that the use of HFS (above 100 Hz) is a key element to treat motor symptoms (Benazzouz et al., 1993; Benabid et al., 2009). However, improving non-motor symptoms might require different parameters of stimulation. 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 performance in PD patients with 4Hz LFS, coherent with oscillations in the hyperdirect pathway connecting the prefrontal cortex to the STN (Kelley et al., 2018). A recent study highlighted PD-related cognitive dysfunction, such as working memory or attention, related to attenuated 4Hz oscillations in the medial frontal cortical area, providing some evidence for the use of 4Hz LFS to treat cognitive symptoms in PD (Singh et al., 2020). However, to date, it is unknown how to reconciliate the use of HFS required to improve motor symptoms and the need to use LFS to improve cognitive and other non-motor symptoms. Recent technology development allows now to use different types of stimulation frequencies in different contacts.

Here, we first investigated the correlation between local field potentials changes recorded in STN, and the development of behavioral symptoms in a progressive model of PD in NHP using a complex behavioral task. In addition, when a parkinsonian syndrome was fully developed and stable, we compared the effect of HFS and LFS on the motor, cognitive and limbic symptoms, when applied in the dorsal and ventral STN.

RESULTS

Behavior

We designed a complex behavioral task to assess motor, cognitive and limbic components of behavior (**Fig. 1a**). The task was presented on a touch screen and on each trial, monkeys could choose either to select a triangle stimulus to Work and perform a switching task, or to select a cross to Check and see if a bonus reward was available (Fig. 1a and Methods). On the switching task, a recurring blue square appeared in 80% of cases and had to be touched, symbolizing Non-Switch trials. An orange star appeared only in 20% of cases, inducing a behavioral adaptation in which monkeys had to touch on the opposite side of the screen representing Switch trials (n). When monkeys decided to select the cross stimulus at the beginning, a visual gauge, which fills up proportionally to the correct responses in the switching task, gave them access on information on how soon a bonus reward will be delivered. The bonus was delivered only if the monkeys chose to check when the gauge is full, and it remained full until the monkey decided to check. The number of correct trials required to obtain the bonus varied pseudo-randomly in successive blocks (from 8, 16, 24 or 32 trials). Thus, monkeys had to perform well in the switching task and check from time to time to gather information about the bonus availability.

Response times on Non-Switch trials (motor response times (mRT)) were similar for both monkeys (447.9 ± 2.1ms for M1; 445.6 ± 3.1ms for M2) (**Fig. 1b**). Switching from automatic to controlled behavior led to significant longer cognitive response times (cRT) than mRT with a similar switch-cost for all monkeys (cRT-mRT = 51.4 ± 5.0ms for M1 $p<0.0001$; 45.1 ± 7.4ms for M2 $p<0.0001$; Kruskal-Wallis) **(Supplementary Table 1, Fig. 1b).** Probabilities to check the gauge when the reward bonus was available, representing motivation to get the reward, were similar for M1 and M2 (19.8 ± 0.1% for M1; 22.0 ± 0.2% for M2) **(Fig. 1c).**

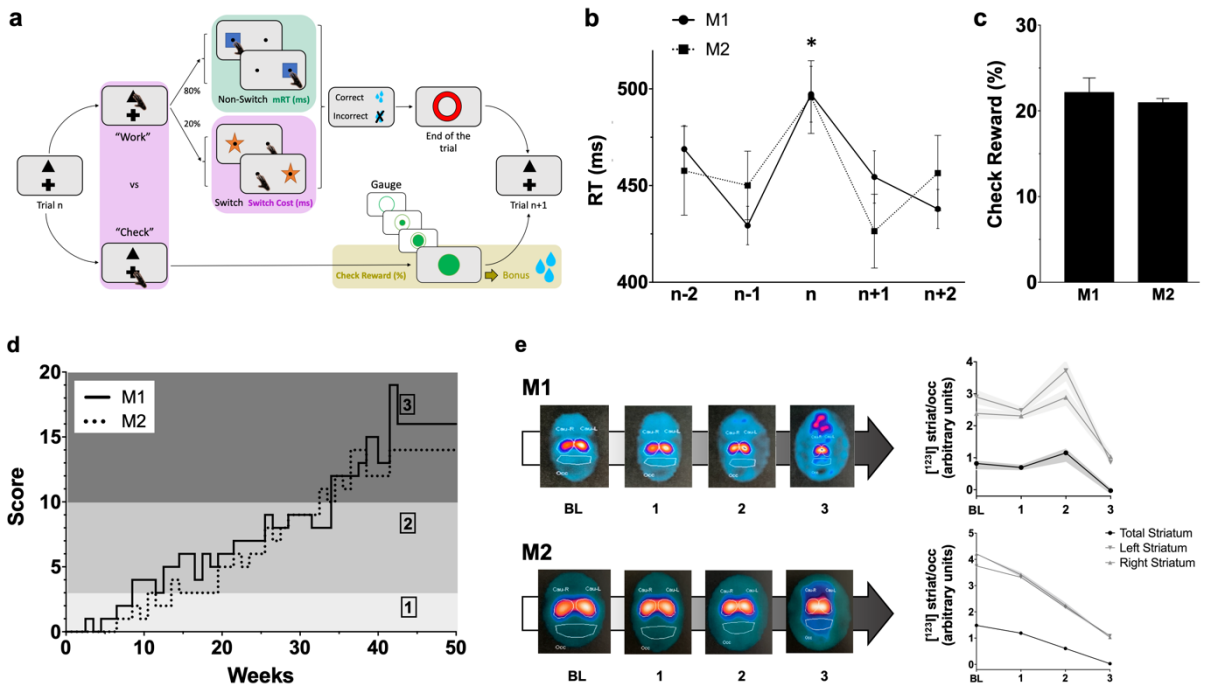


Figure 1: Behavior and dopamine depletion. (**a**) Rewarded task enabling the study of behavioral motor (green), cognitive (pink) and limbic (gold) components. On each trial, monkeys decided to "Work" on the main switching task, or "Check" the size of a gauge informing about the proximity of a bonus reward (see Methods). **(b)** Average response times (RT) in ms plotted against trial positions (n represents Switch trials) *p<0.05, and **(c)** probabilities to check when the reward is available (Check Reward) expressed in percentage (%); expressed in mean ± SEM. (**d**) Weekly motor evaluation of a parkinsonian syndrome induced by chronic low-dose MPTP injections. Based on the clinical score 3 stages were discriminated: 1 for presymptomatic (very light gray, score 0-3); 2 for mild parkinsonism (light gray, score 4-10); 3 for moderate parkinsonism (dark gray, score >10). (**e**) DaT SPECT nuclear imaging using the tracer Ioflupane (I^{123}) for each stage: baseline before MPTP treatment (BL) and stages 1, 2 and 3 of parkinsonian syndrome. Quantification ratios were performed between the left and right striatum (CauL and CauR) relative to cerebral background noise (Occ).

Progressive dopamine depletion

Chronic low doses MPTP treatment induced a progressive onset of motor signs that worsened over time (**Fig 1d**). Based on the severity of these motor symptoms, i.e., both monkeys showed bradykinesia, akinesia of the arms and legs, and some action tremors; 3 different stages of parkinsonian syndrome were identified. Stage 1 (score 0-3) was identified as a presymptomatic state with the absence of significant clinical motor signs. Stage 2 (score 4-10) was characterized by the appearance of light and unstable motor signs, identified as a mild parkinsonian state. Finally, in stage 3 (score >10), both monkeys exhibited clear and stable motor symptoms

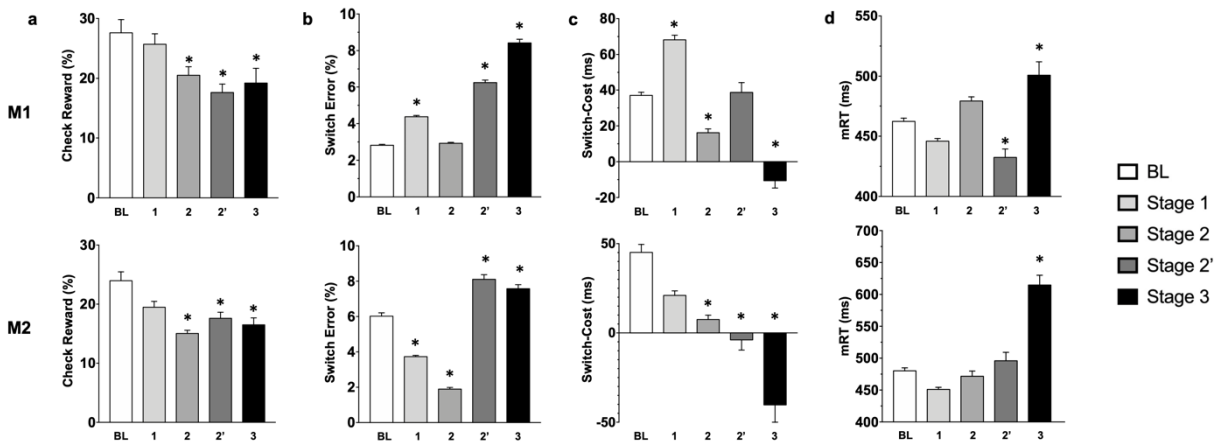
identified as a moderate parkinsonian state. Longitudinal DaT SPECT nuclear imaging revealed a progressive decrease in Ioflupane tracer activity in the striatum relative to the cerebral background noise (occipital region) (**Fig. 1e**). This decrease started after a single injection (stage 1) and both monkeys developed similar kinetics, except for stage 2. Indeed, stage 2 DaT SPECT for M1 showed a transitory increase in striatal fixation.

Early non-motor PD signs

Monkeys performed the task throughout the MPTP treatment (**Supplemental Table 1; Fig. 2**). During stage 1, no significant effect was found on Check Reward, Error on Switch, Switch-Cost, and mRT. This stage 1 can therefore be considered as an asymptomatic stage.

In stage 2, several non-motor signs appeared in a specific chronology. First, a decrease in probabilities to check the gauge when the reward was available was 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. 2a**). Later, an increase in Error on Switch trials was found (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. 2b**). For M2, a negative Switch-Cost was found in stage 2' (BL: 45.1 ± 4.4ms vs. stage 2': -3.9 ± 5.7ms p<0.0001; Kruskal-Wallis) (**Fig. 2c**). Thus, stage 2 can be divided into two stages characterized by the appearance of limbic impairment early in stage 2, and cognitive impairment later in a stage defined as stage 2'.

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. 2d**).



<u>Figure 2:</u> Behavioral effect of MPTP treatment for M1 and M2 across all stages. (**a**) Probabilities to check when the reward is available (Check Reward), expressed in percentage. (**b**) Probabilities for errors on Switch trials (Switch Error), expressed in percentage. (**c**) Switch-Cost, difference in response time between Switch and Non-Switch trials, expressed in ms. (**d**) Motor response time (mRT) on Non-Switch trials, expressed in ms. Stages: baseline, before MPTP treatment (BL, white); stage 1, presymptomatic (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

During the reward delivery, a significant increase in gamma oscillations (>35Hz) followed by a significant decrease in theta oscillations (4-8Hz) was observed in the STN in baseline stage for both monkeys ($p<0.05$, two-sample t-test). As early as stage 1, these reward-related markers disappeared (**Fig. 3a**).

When monkeys chose to work rather than check, a significant increase in theta oscillations was observed in baseline stage 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, for M1 and M2 in baseline stage, a significant decrease in beta oscillations was found at the onset of the motor cue (Non-Switch stimulus), corresponding to the motor movement to touch the screen, followed by an increase in beta-gamma bands, called rebound ($p<0.05$, one-sample t-test). This specific pattern was also observed in stage 1 and early stage 2, and the rebound effect disappeared from late stage 2 (2') (**Fig. 3c**).

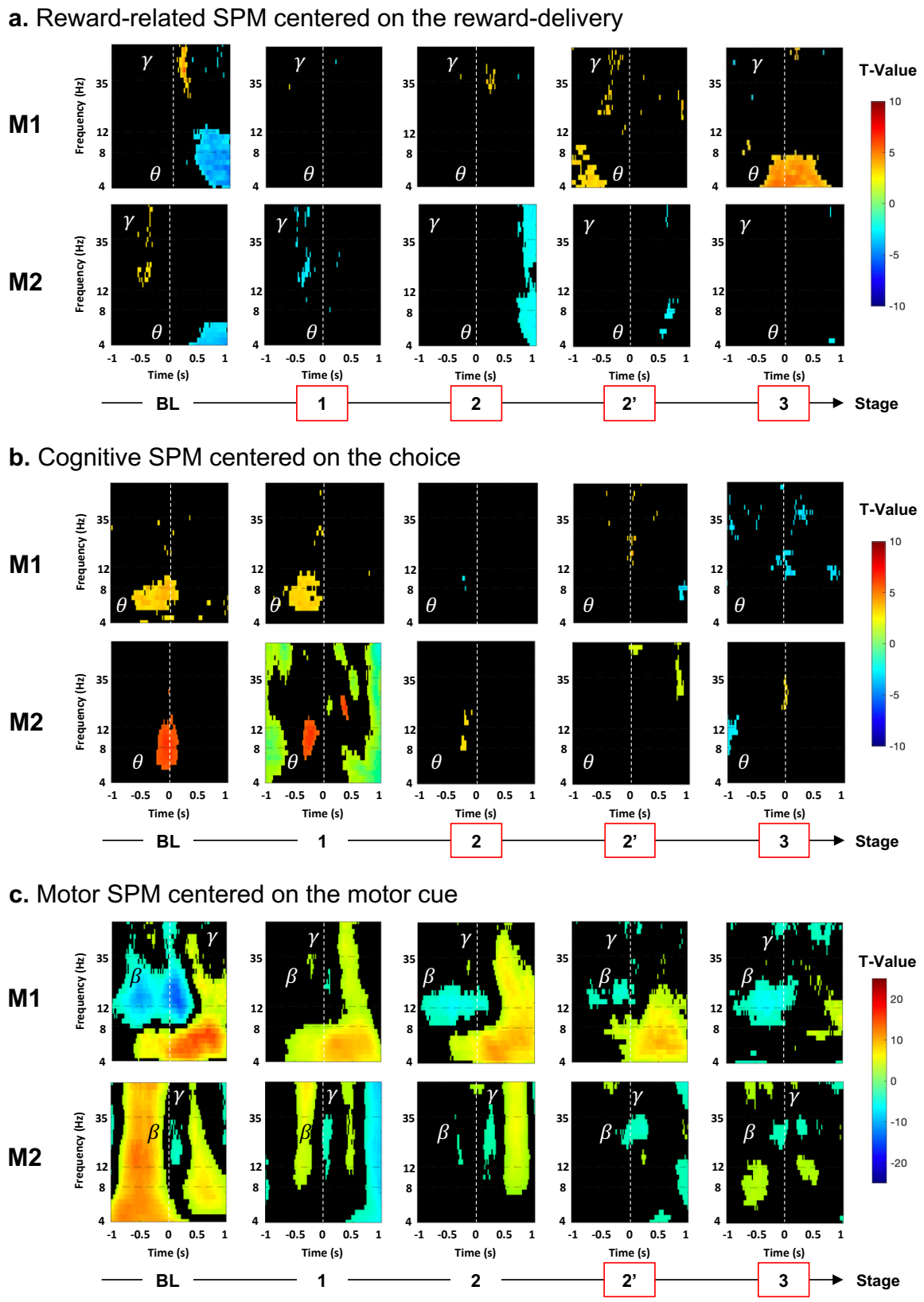


Figure 3: Effect of MPTP treatment on STN activity for M1 and M2, across all stages. (**a**) Reward-related statistical parametric maps (SPM) centered on the full gauge with reward delivery (vertical line at 0) relative to the gauge view without the reward (T-Value). (**b**) Cognitive SPM centered on 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, white); stage 1, presymptomatic (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). Only significant values are presented, $p<0.05$. Red squares show changes from baseline.

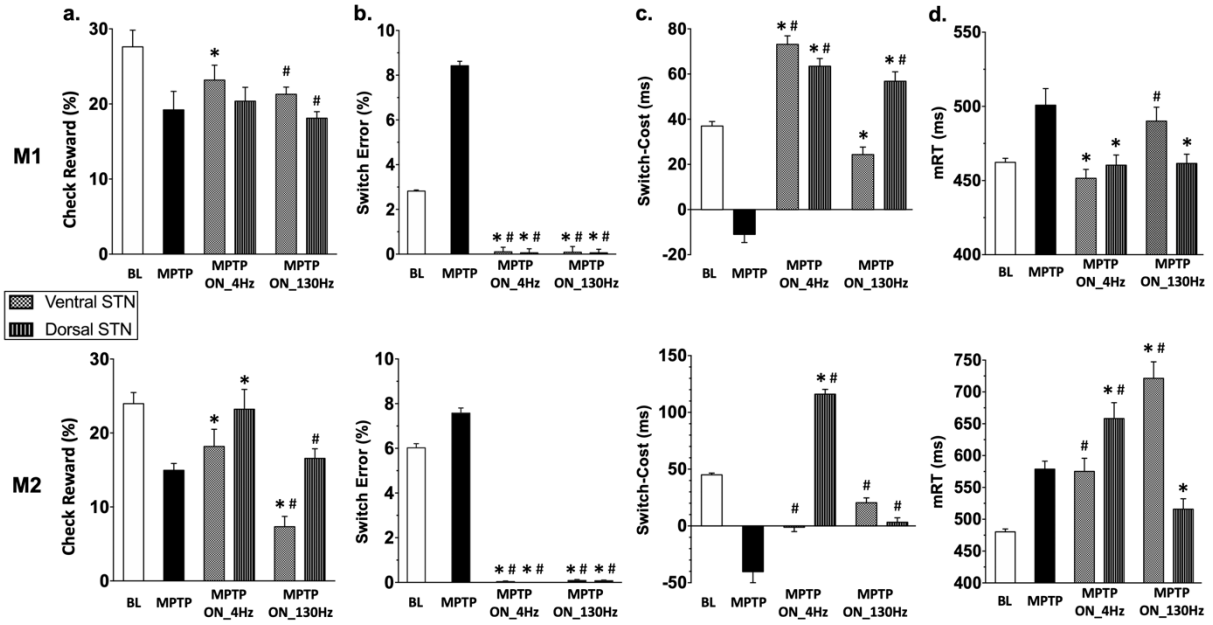
Effect of STN modulation on PD behavior

During stage 3, with stable and moderate motor and non-motor symptoms, we tested STN HFS and LFS during the behavioral task (**Supplemental Table 2; Fig. 4**).

For both MPTP-treated monkeys, LFS applied in ventral STN restored the Check Reward to a baseline state (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**). STN HFS induced a significant decrease in the check reward when applied in ventral STN for M2 (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**).

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**).

When LFS was applied in dorsal STN, a restored positive Switch-Cost was observed for both monkeys compared to MPTP state (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**). Finally, for both monkeys, only HFS in dorsal STN restored mRT to baseline values (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 LFS (130Hz) frequency stimulation on ventral (grid pattern) and dorsal (vertical lines) parts of the 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, expressed in percentage compared to MPTP condition. (**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_4Hz, LFS applied in MPTP-treated monkeys in stage 3; MPTP_ON 130Hz, HFS applied in MPTP-treated monkeys in stage 3.

DISCUSSION

Using chronic low doses of MPTP leading to a progressive model of PD, we provided evidence of the early appearance of non-motor limbic and cognitive symptoms, preceded motor symptoms, and of their correlation with changes in neural activities in the STN.

Progressive dopamine depletion

In accordance with previous studies using chronic low doses of MPTP, we replicated an experimental parkinsonian syndrome with progressive worsening motor symptoms over time (Devergnas et al., 2014; Conolly et al., 2015). Throughout MPTP treatment, we performed a dopamine transporter (DaT) SPECT imaging to assess the loss of DaT in the striatum. A progressive decrease in estimated striatal DaT levels was found and correlated with the severity of the parkinsonian syndrome, except in stage 2 for M1 where an increase in the ratio was found. This increase in DaT binding has been previously reported, suggesting complex intrinsic compensatory mechanisms accompanied by a decrease in cognitive performances likely related to the hyperdopaminergic state (Vezoli et al., 2011; Vezoli et al., 2014; Mouyanar et al., 2007; Boulet et al., 2008). These results suggest a complex stage 2 with intrinsic mechanisms, leading us to further characterize this stage in two parts, a stage 2 and a late stage 2'.

Early non-motor PD signs

Also characterized in other studies, we found a first stage, which began just after the first injection of MPTP and lasted approximately 10 weeks, characterized by significant behavioral changes, representing the presymptomatic stage 1 (Bezard et al., 1997; Vezoli et al., 2011). The next stage, early stage 2, was characterized by a decrease in the motivation to obtain the bonus reward, close to apathy found in parkinsonian rat animal model (Carnicella et al., 2014; Magnard et al., 2014) and in PD patients (Aarsland et al., 1999). The late stage 2' was characterized by an increase in error rate on Switch trials for both monkeys with still no significant motor symptoms. This deficit in switching processes may represent a mild cognitive impairment that is also found in PD patients and may precede motor symptoms (Goldman & Litvan, 2011; Aarsland et al., 2003). During this late stage 2', the increase in the error rate was

accompanied by a negative Switch-Cost for M2 that could be related to impulsivity or impairment in reactive inhibition also observed in PD patients (Greenhouse et al., 2013; Kehagia et al., 2014; Obeso et al., 2011). This negative Switch-Cost was observed later for M1, a delay that can be explained by compensatory mechanisms revealed by the increased level in DaT bindings at this stage. Finally, during stage 3, all limbic and cognitive changes persisted or even worsened with negative Switch-Cost for M1 and M2, and an increase in mRT was observed for both monkeys. These observations are consistent with PD being a progressive disease that takes several years to manifest clinically as motor symptoms and that non-motor symptoms occur before motor symptoms (Chaudhuri et al., 2006).

Behavioral and STN electrophysiology correlations

Recent studies have provided evidence for the correlation between neural activity and symptoms severity, primarily for motor parkinsonian symptoms (Lee et al., 2021; Wang et al., 2020), although one recent study has focused on non-motor symptoms (Hassin-Bear et al., 2022). Here, we demonstrated that modifications of the STN activity precede motor and non-motor symptoms in MPTP-treated monkeys according to a specific temporal hierarchy, with first limbic, then cognitive and finally motor manifestations.

From stage 1, the increase in gamma oscillations seen in relation to reward delivery disappeared in both monkeys. An early increase in gamma band activity in the STN has been observed in Dopa-treated PD patients as reward approaches and may represent local encoding of increased attention for reward (Huebl et al., 2014). Interestingly, a study provided evidence that the modulation of the cortex by reward is mediated by dopamine signaling (Kapogiannis et al., 2011), which may indicate that gamma oscillations and dopamine signaling pathway through the ganglia-thalamo-cortical network plays a role in expectancy and reward delivery. The decrease in gamma oscillations observed from stage 1 in both MPTP-treated monkeys during reward delivery could be due to the early damage of the dopaminergic system. Moreover, we also found a decrease in theta oscillations associated with reward delivery which disappeared for M1 and progressively disappeared for M2. Previous studies have associated emotional limbic processing with theta band activity in the STN of rat model of PD, as a predictor of addiction vulnerability (Degoulet et al., 2021) and in the STN of PD patients (Rappel et al., 2020; Benis et al., 2020) and PD patients with pathological gambling (Rosa et al., 2013). Thus, the disappearance of theta oscillations could reflect an alteration in reward-related limbic

processes with the progressive parkinsonian syndrome for both monkeys, with an early alteration for M1. Moreover, in a recent study, apathetic PD patients had higher baseline EEG alpha and theta power than non-apathetic patients, leading to PD patients having to overcome higher baseline neural activity to facilitate motivated movement (Zhu et al., 2019).

In early stage 2, before the cognitive behavioral impairment, theta band neural activity linked to decision-making disappeared for both monkeys. It has been proposed that direct anatomical connections between the prefrontal cortex and STN would facilitate a more deliberative response process to choose the most appropriate behavior during a conflict state (Miller, 2000; Cavanagh et al., 2011; Alegre et al., 2013; Haynes and Haber, 2013). These cognitive processes 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. These electrophysiological changes have been followed by an increase in cognitive errors. STN lesions have been associated with impulsive choices as opposed to the role of intact STN in inhibiting inappropriate response to incentive stimuli (Uslaner & Robinson, 2006). Moreover, 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). Thus, the decrease in theta activity in the STN during decision-making for both monkeys may be correlated with impulsive and compulsive responses. Studies conducted in the alpha-synuclein mouse model, and the MPTP-treated monkey model have shown early serotonin denervation in the limbic, prefrontal, and motor cortex (Wihan et al. 2019; Masilamoni et al., 2022). They suggested that this could contribute to the non-motor cognitive and psychiatric symptoms in PD. Similarly, in MPTP-treated monkey, studies have found a noradrenergic depletion in the locus coeruleus, as observed in PD patients (Masilamoni et al., 2011 – 2017 – 2018). Serotonin, dopamine, and noradrenergic systems have been shown to be involve in cognition, mood, and limbic-related behaviors. Thus, their denervation could contribute to non-motor limbic and cognitive symptoms observed in PD and animal model of PD (Rodriguez-Oroz et al., 2009; Brichta et al., 2013; O'Callaghan and Lewis, 2017; Guthrie et al., 2013). The involvement of STN in motivation is also reflected by the increase of motivation to check for the reward with LFS of the ventral part. In addition, 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 components of behavior occurs according to a specific spatial organization.

During late stage 2', just before motor symptoms onset, the decreased beta power during movement progressively tended to reduce, and the increased beta-gamma rebound after movement disappeared for both monkeys. Increased beta oscillations in the STN are the most prominent electrophysiological markers in resting and awake PD patients (Brown et al., 2001; Neumann et al., 2016) and correlate with symptoms severity (Kühn & Volkmann, 2017; Cagnan et al., 2017). Thus, we can suggest 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 the promotion of synaptic plasticity, especially in the motor cortex (Bartos et al., 2007; Cardin et al., 2009; Girardeau et al., 2009; Nowak et al., 2018). In line with these results, a recent study with PD patients demonstrated that impaired gamma oscillations in the basal ganglia-thalamo-cortical network were related to impaired long-term potentiation-like plasticity in the primary motor cortex (Guerra et al., 2020). For both monkeys, we showed that gamma oscillations decrease with parkinsonian syndrome, from late stage 2' and before motor clinical signs. Interestingly, this impairment was found in early stage 2 for M2, correlating with the hypothesized lack of compensatory mechanisms suggesting in DaT SPECT imaging.

Finally, after these beta/gamma oscillations changes, stage 3 is characterized by the occurrence of significant motor symptoms with an an increase in mRT. Several studies have demonstrated an increase in beta power in the cortex and the STN, in animal models and in PD patients (Avilla et al., 2010; Deffains et al., 2018; Brown et al., 2001; Neumann et al., 2016). This biomarker has been associated with motor symptoms such as bradykinetic-rigid symptoms and velocity (Tinkhauser et al., 2018; Kuhn et al., 2008; Lofredi et al., 2019) and been correlated with the severity of the symptoms (Kühn et al., 2016; Neumann et al., 2016; Cagnan et al., 2016). The progressive loss of decreased beta during movement could be caused by the general increase of beta in the STN with the progressive motor symptoms induced by MPTP injections. In this way, a recent study with PD patients observed a decrease in STN gamma burst rates during movement (Lofredi et al., 2018). The authors associated this electrophysiological marker with bradykinesia found in PD. In addition, the improved mRT by the HFS of the dorsal part of STN is consistent with a major implication of the dorsal part of the STN in motor component supported by an overexpression of beta oscillation in this part (Bergman et al., 1994; Limousin et al., 1995; Benabid et al., 2009).

Conclusion

We characterized different stages of the disease in a progressive model of PD in NHP (**Fig. 5**). We found a hierarchy in the onset of behavioral symptoms, with motivational impairments in early stage 2, followed by cognitive impairments in late stage 2' and finally motor impairments in stage 3. We described neural signatures in the STN correlated with, and even predicting, the onset of symptoms in this progressive model of progressive PD.

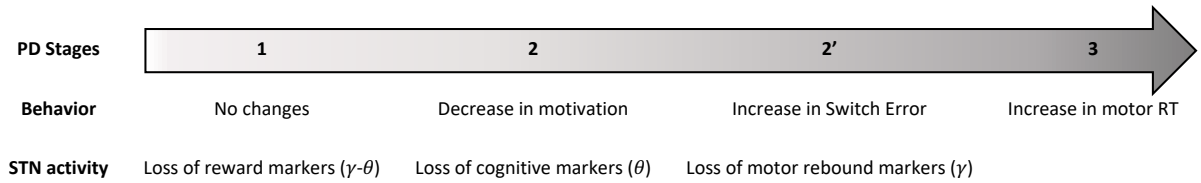


Figure 5: Study-based correlation between subthalamic nucleus (STN) changes and symptoms in a non-human primate model of progressive Parkinson's disease (PD). Weekly motor evaluation of a parkinsonian syndrome induced by chronic low-dose MPTP injections, discriminating stage 1 for presymptomatic, stage 2 for mild parkinsonism, novel stage 2', and stage 3 for moderate parkinsonism. RT, response time; γ, gamma activities; θ, theta activities.

This study shows that progressive dopamine depletion alters the functional activity of the STN. Altered STN activity precedes the appearance of symptoms, suggesting the presence of various compensatory mechanisms. Limbic and cognitive components of the behavior appear to be more sensitive than the motor one. Early detection of limbic and cognitive impairments, with very sensitive tests, could be useful for an early diagnosis of PD that would be essential for the use of neuroprotective treatments. In addition, these results support the involvement of the STN in the limbic, cognitive, and motor components of behavior and suggest that an adaptive STN-DBS, combining HFS in the dorsal STN and LFS in the ventral STN could reduce both motor and non-motor symptoms.

MATERIAL AND METHODS

Animals

This study was conducted with two monkeys of 8 years old (*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 were trained to perform a counter demanding task, specifically assessing motor, cognitive and reward-related limbic components of the behavior. They were habituated to sit in a primate chair (Crist Instrument Co., MD, USA) to interact with a touch screen (Elo Touch Solutions, Inc.). In each trial, monkeys had the choice 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 side) and monkeys were required to touch the blue square while they had to touch on the opposite side of the orange star. Targets were randomly determined trial to trial, with a higher probability for Non-Switch than Switch (80% - 20%) to induce automatic behavior. In both cases, 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.). Then, 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), monkeys had to choose to Check when the gauge was full (same size of the inner green disk and the large green circle). This bonus reward remained available until the Check option was chosen, and once delivered, the gauge size was reset and a new random number was picked (8, 16, 24, 32).

Behavioral analyses

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

Surgery

Surgery to implant a DBS lead was performed under aseptic conditions and general anesthesia. Monkeys were first 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) was acquired to identify the STN and per-operative radiographic X-rays allowed the localization of ventriculographic bi-commissural landmarks (anterior and posterior commissures, ACPC), obtained using a cannula stereotactically placed on the left lateral ventricular through which 2ml of ventricular contrast (Iopamiron 200, iodine 200 mg/ml, Bracc) was injected. Micro-recordings (microelectrode of 250 µm diameter, 0.8-1.2 MOhm, FHC) were used to locate borders of the STN, using specific firing rate and pattern. Right STN was implanted with a DBS electrode of 0.8 mm diameter consisting in 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 the ACPC line, 4–5 mm from the midline,

with deepest contacts at the lower border of the STN. The implantation was verified by radiography and ventriculography. The reference was fixed on the skull at the left occipital level. A stainless-steel head holder (Crist Instruments, MD) was placed at the back of the skull to maintain monkey's head. Analgesic/anti-inflammatory therapies (Ketoprofen 2mg/kg) were delivered during the one-week post-operative period.

Recordings analyses

Electrophysiological activity of the STN 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 (The Mathworks, Natick MA, USA) 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) by calculating the base-10 logarithm of the ratio L_{dB} (peristimulus power/baseline power (P/B)) and multiplying it by 10 to return decibel (dB) values: $L_{dB}=10 \log_{10}(P/B)$. Power values are denoted as LdB power ± SEM. Specific frequency bands have been selected with band filters (theta, 4-8Hz; alpha, 8-12Hz; beta, 12-35Hz; gamma, 35-200Hz) and are represented as average power versus baseline over time (mean ± SEM).

STN stimulation

Low frequency (LFS: 4Hz, highlighted to improve cognitive deficits in PD patients (Kelley et al., 2018)) and high frequency (HFS: 130Hz, known to improve motor symptoms in PD (Benabid et al., 2009)) continuous bipolar stimulations were tested on two levels in the STN (dorsal and ventral). For each frequency, ranges of stimulations were performed until side effects occurred (e.g., monocular and ipsilateral 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 (60 µs). Number of trials for each level of stimulation at both frequencies are presented in supplementary Table 2.

MPTP treatment

After recordings of the baseline during the healthy state, monkeys were chronically intoxicated by intramuscular injections of MPTP under light anesthesia (Ketamine 2-4 mg/kg), based on a previous study (Davin et al., 2022). This progressive protocol, allowing a long non-motor phase to mimic the clinical pathology, 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, we assessed the motor score, and the next dose was either similar or adjusted according to the clinical signs observed. M1 received 20 injections (5.45 mg/kg total) and M2 received 18 injections (6.7 mg/kg total). Both animals had similar and stable state of parkinsonian syndrome.

Motor score

The parkinsonian syndrome was evaluated before, during and after MPTP intoxication in the home cage, using a rating scale based on the most used criteria to study the parkinsonian syndrome in macaques (Imbert et al., 2000). This scale evaluates eight criteria between 0 and 3 (0 representing no impairment and 3 representing a maximum impairment) with a total score out of 25: frequency of movement of each arm, general activity, posture, bradykinesia, tremor, feeding, freezing and vocalizations. According to the literature, three stages are distinguished by severity: stage 1, presymptomatic (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 throughout the MPTP treatment. The use of the Ioflupane tracer (I123), which binds to presynaptic dopamine transporters (DaT), has allowed the assessment of 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 3 hours later by the acquisition of images. 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 pseudo-quantitative analysis of the regions of interest, in the striatum, compared to a reference, in the occipital cortex.

Statistical analyses

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

Statistical parametric maps: Time-frequency representations were analyzed with "one-sample" t-test to compare signal of one event, and "two-sample" t-test allowed the discrimination of significant differences between two events (T-Values) and Bonferroni corrections were performed. Those analyses were plotted as statistical parametric maps (SPM) showing only with significant statistical p-value <0.05, with motor SPM, at the presentation of the motor cue and the beginning of the movement compared to a resting state; cognitive SPM, around the touch to either choose to work compared to check; and reward-related SPM, at the significant changes for the reward delivery with the full gauge compared to the gauge being filled.

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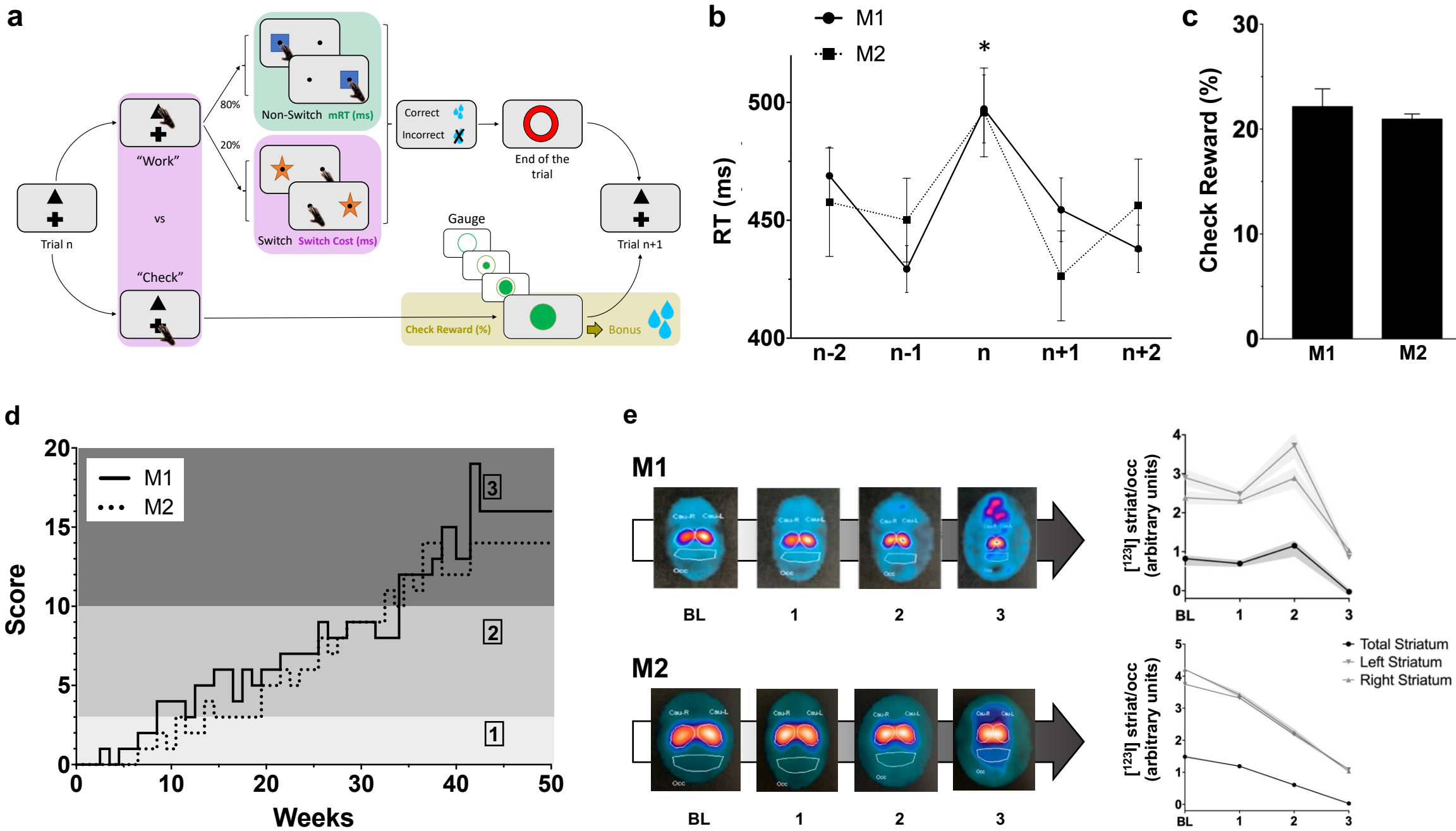
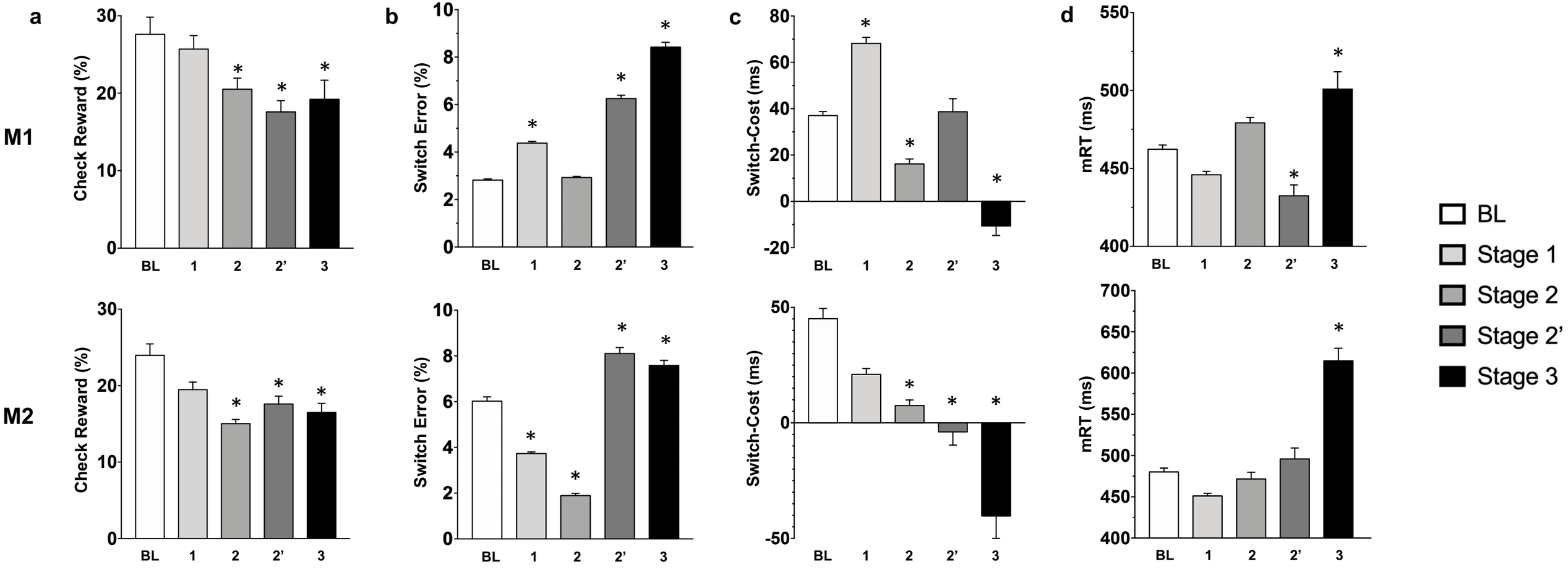
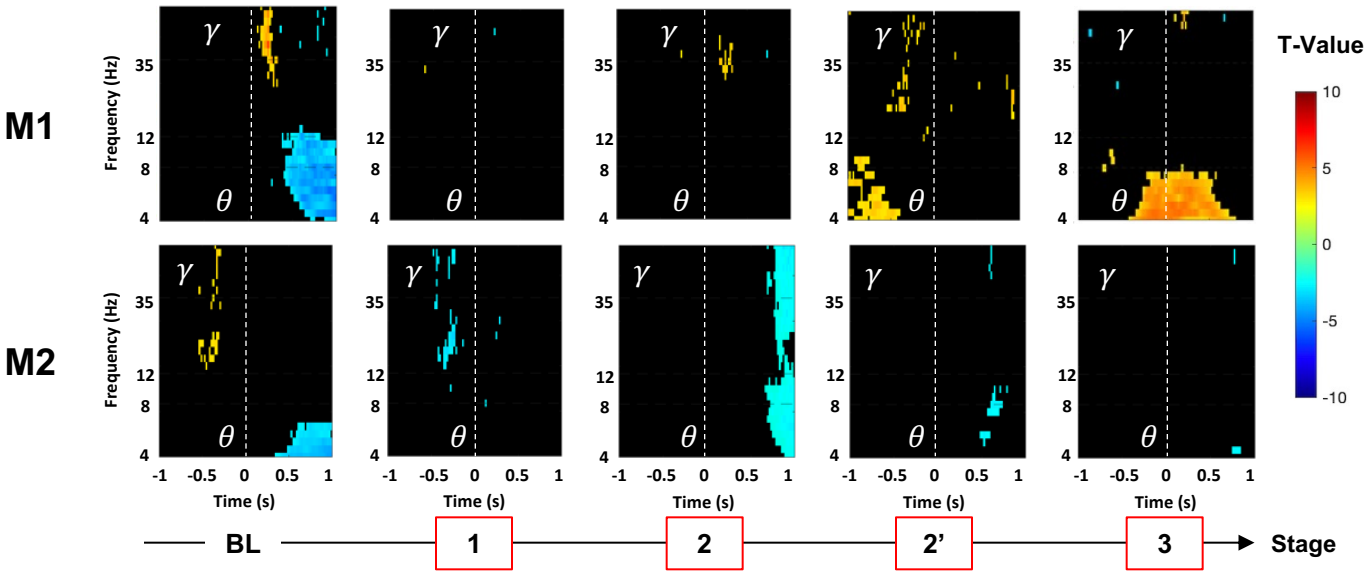
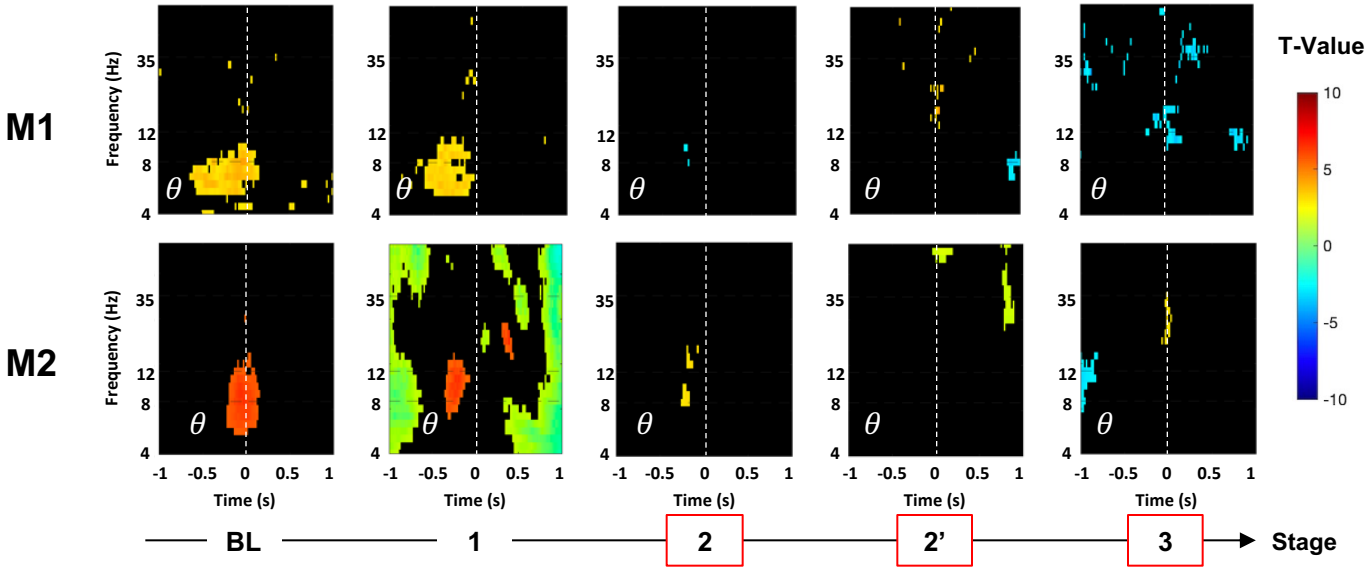

a
Trial n
"Work"
vs
"Check"
80%
20%
Non-Switch mRT (ms)
Switch Switch Cost (ms)
Correct
Incorrect
End of the trial
Trial n+1
Gauge
Check Reward (%)
Bonus
b
M1
M2
*
RT (ms)
500
450
400
n-2
n-1
n
n+1
n+2
c
Check Reward (%)
30
20
10
0
M1
M2
d
M1
M2
Score
Weeks
0
5
10
15
20
0
10
20
30
40
50
1
2
3
e
M1
M2
BL
1
2
3
[123I] striat/occ (arbitrary units)
Total Striatum
Left Striatum
Right Striatum


a
b
c
d
M1
M2
Check Reward (%)
Switch Error (%)
Switch-Cost (ms)
mRT (ms)
BL
1
2
2'
3
BL
Stage 1
Stage 2
Stage 2'
Stage 3

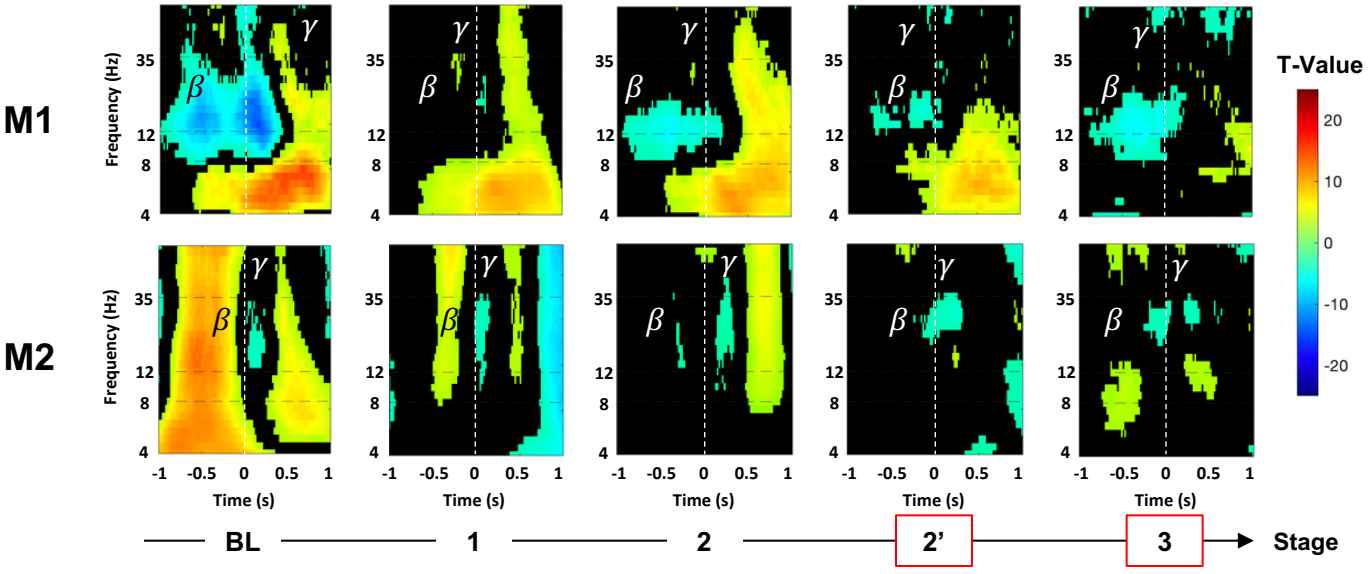
a. Reward-related SPM centered on the reward-delivery

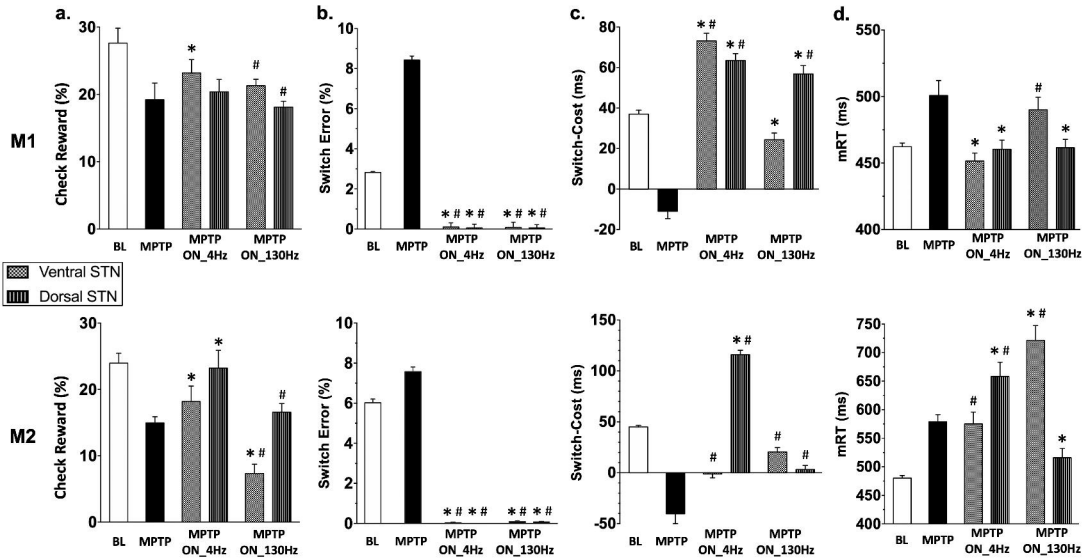


b. Cognitive SPM centered on the choice



c. Motor SPM centered on the motor cue




a.
b.
c.
d.
M1
M2
Check Reward (%)
Switch Error (%)
Switch-Cost (ms)
mRT (ms)
BL
MPTP
MPTP ON_4Hz
MPTP ON_130Hz
Ventral STN
Dorsal STN

PD Stages	**1**	**2**	**2’**	**3**
Behavior	No changes	Decrease in motivation	Increase in Switch Error	Increase in motor RT
STN activity	Loss of reward markers (γ-θ)	Loss of cognitive markers (θ)	Loss of motor rebound markers (γ)	