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## Striatal oscillations in parkinsonian non-human primates

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### Abstract

Dopamine loss in Parkinson's disease (PD) is associated with abnormal oscillatory activity in the cortico-basal ganglia network. However, the oscillatory pattern of striatal neurons in PD remains poorly defined. Here, we analyzed the local field potentials in one untreated and five MPTP-treated non-human primates (NHP) with chronic, advanced parkinsonism. Oscillatory activities in the alpha (8–13 Hz) and low-beta (13–20 Hz) frequency bands were found in the striatum similarly to the motor cortex and globus pallidus of the NHP model of PD. Both alpha and low-beta frequency band oscillations of the striatum were highly coherent with the cortical and pallidal oscillations, confirming the presence of abnormal 8–20 Hz oscillatory activity in the cortico-basal ganglia network in parkinsonian NHPs. The reversal of parkinsonism induced by acute levodopa administration was associated with reduced 8–20 Hz oscillations in the striatum. These findings indicate that pathological oscillations at alpha and low-beta bands are also present in the striatum concordant with basal ganglia network changes in the primate model of PD.

### Keywords

local field potentials; striatal projection neurons; Parkinson's disease; dopamine; nonhuman primates

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Author contributions

Design and conceptualization: A.S. and S.M.P. Investigation: A.S. Data Analysis: A.S. and S.M.P. Writing, Review and Editing: A.S. and S.M.P.

Competing interests

The authors declare no competing interests.

Data Availability

The data that support the findings of this study are available on request from the corresponding author (A.S.).

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## Introduction

Abnormal oscillatory activities in the basal ganglia network are correlated with motor impairment in Parkinson's disease (PD) (Brown, 2003; Singh *et al.*, 2013; Singh, 2018). The degeneration of nigral dopaminergic neurons that project to the striatum is the pathological hallmark of PD (Damier *et al.*, 1999), but the striatal participation in oscillatory activities of the network has remained unclear. Our previous studies have shown aberrant striatal neuronal spiking activity in parkinsonian non-human primates (NHPs) and patients with PD (Liang *et al.*, 2008; Singh *et al.*, 2015; Singh *et al.*, 2016; Beck *et al.*, 2019). Indeed, chronic dopamine loss leads to major changes in the firing of striatal projection neurons (SPNs), i.e. hyperactivity up to more than 10-fold increase in mean firing rate compared to the normal state, and unstable neuronal responses to dopaminergic stimulation, i.e. firing rate changes in response to L-Dopa that cannot be sustained during the peak-dose effect of the drug (Singh *et al.*, 2015; Singh *et al.*, 2018; Beck *et al.*, 2019). These significant changes in the SPN spiking are likely to be accompanied by altered local inputs and oscillatory activity congruent with the network. In extrastriatal basal ganglia structures, increased oscillations in the 8–30 Hz frequency band are consistently present in animal models and patients with PD (Devergnas *et al.*, 2014; de Hemptinne *et al.*, 2015; Singh *et al.*, 2020). Furthermore, improvement of parkinsonian motor disability by high frequency deep brain stimulation or L-Dopa is accompanied by suppression of the synchronized 8–35 Hz oscillations in the basal ganglia (Kuhn *et al.*, 2006). These data have led to establish the increased oscillatory activity in the cortico-basal ganglia network as a key feature of PD pathophysiology (Stein and Bar-Gad, 2013).

In contrast to the more typical 13–30 Hz (beta-band) basal ganglia oscillation found in human studies, synchronized oscillations in the 8–13 Hz frequency band are detected in parkinsonian NHPs (Stein and Bar-Gad, 2013; Devergnas *et al.*, 2014), and the improvement of parkinsonism in NHP models is also correlated with a decrease in these oscillations (Brown, 2007). These studies suggest that 8–13 Hz rhythms may be a subclass of, or similar to, the beta-band observed in patients with PD; however, the current understanding of this oscillatory activity is limited. The function of these lower frequency band (8–13 Hz) oscillations in the mechanisms of parkinsonian motor deficits remains unknown. Recent data have suggested that certain parameters of the beta-band oscillations, such as duration, are associated specifically with PD since oscillations in this frequency can also be found in normal animals (Deffains *et al.*, 2018). Additionally, the source(s) that generates the basal ganglia network oscillations has been elusive throughout diverse animal and human studies. Clearly, the oscillatory pattern of the striatum, which is the basal ganglia recipient structure, is essential to understand the mechanisms underlying the pathological oscillations in the whole cortico-basal ganglia network developed following dopamine loss in PD.

Here, we examined the striatum and other basal ganglia nuclei for oscillatory activities in normal and parkinsonian NHPs. In addition, we analyzed the striatal oscillations before and after acute L-Dopa administration in correlation with improvement of motor deficits. This study shows that abnormal oscillations in the alpha (8–13 Hz) and low-beta (13–20 Hz) bands are present in the striatum of parkinsonian primates, and that these striatal oscillations are modulated by dopamine replacement.

## Material and Methods

### Animals and MPTP Treatment

Six adult macaques (four female rhesus monkeys, *Macaca Mulatta*: Gl, Va, Na, Sa; and two male cynomolgus monkeys, *Macaca Fascicularis*: Br and Ch; all 5–8 kg) were used in this study. All experimental protocols were performed in accordance with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals* (1996). We have used two species of macaques because they share behavioral similarities particularly regarding motor features of parkinsonism. Five animals received weekly intravenous injections of MPTP (0.2–0.6 mg/kg, see details in previous reports (Singh *et al.*, 2015; Singh *et al.*, 2016; Beck *et al.*, 2019) until motor disability stabilized to a non-recoverable parkinsonism of moderate-severe degree, as measured by the standardized “Motor disability scale for MPTP-treated primates” (Potts *et al.*, 2014; Singh *et al.*, 2015). All five animals had sustained a chronic parkinsonism at the time of recordings 6 months or longer after last MPTP injection. One animal (Sa) was not treated with MPTP and used as a normal control. Three parkinsonian NHPs (Gl, Va, Na) were previously treated with daily L-Dopa regimen (Sinemet®, 100–200 mg/day) to improve their health, but these animals did not develop L-Dopa-induced dyskinesias. The L-Dopa treatment was withdrawn 24 hours prior to the recording time. The other two parkinsonian NHPs (Br and Ch) had never been exposed to daily L-Dopa administration before the recordings. All the demographics and clinical characteristics are shown in Table 1. L-Dopa doses used for acute subcutaneous injections during the recordings (L-Dopa methyl ester plus benserazide) in animals Br and Ch were selected based on our previous recordings of parkinsonian primates (Singh *et al.*, 2015; Singh *et al.*, 2018; Beck *et al.*, 2019) where we used the dose sufficient to induce a measurable motor response compatible with the restraint of the animal in the primate chair (see doses in next section). MDS in the “off” state (basal parkinsonian motor disability) and the “on” state (reversal of parkinsonism by dopaminergic drug treatment) induced by L-Dopa administration during the recordings are shown in Table 1. The level of parkinsonism developed in all 5 animals was similar, as shown by motor disability scores (MDS) in “OFF” with minimal variation (MDS between 19 and 22, scale range 0–39).

### Surgical Procedures and LFP Recordings

Stainless steel recording chambers (19 mm diameter) were stereotaxically implanted in the coronal plane with a 15–20° angle in all NHPs to allow a trajectory of recording electrodes from the motor cortex to the striatum (putamen) and the internal pallidum (GPi). A head post was also implanted in surgery for head restraint in the primate chair during the recordings. Implant surgeries were conducted under general anesthesia in all animals. Following a period of recovery from surgery, the recordings began under head restraint in the primate chair. Recordings were performed lowering the recording electrode inside the recording chamber and to the brain using an electronic microdrive (NAN Instruments LTD, Israel). Data were collected using Blackrock Microsystems (sampling rate 40 kHz; spike data: high-pass filter at 750 Hz; LFP data: low-pass filter at 250 Hz). The electrophysiological mapping of the motor cortex, striatum (putamen), and GPi was performed by extracellular recordings of spiking activity using tungsten microelectrodes (FHC, Bowdoinham, ME; impedance = 0.1–0.3 MΩ at 1 kHz) (Liang *et al.*, 2008). We

determined the target locations on the basis of their signature neuronal firing pattern (see Fig. S1). We did not apply imaging techniques to determine the target location, as our mapping techniques have successfully identified target regions in basal ganglia in our previous studies (Singh *et al.*, 2015; Singh *et al.*, 2018; Beck *et al.*, 2019). The histological verification of our target regions at the end of the studies were provided in our previous reports (Singh *et al.*, 2018; Beck *et al.*, 2019). Striatal LFP signals were collected in the post-commisural, dorsolateral areas of the putamen after electrophysiologic mapping of the basal ganglia. As unipolar LFP reference, we used the recording chamber implanted on the skull or the connection to the amplified electrical ground. To determine striatal LFP changes following dopamine depletion, LFPs were recorded in the striatum (putamen) in three NHPs. Putamenal LFP were recorded in two parkinsonian NHPs in the ‘off’ state (Gl, n=9; Va, n=7), and compared to the putamenal LFPs in one normal NHP (Sa, n=54 recordings). LFPs were then recorded in parkinsonian NHPs in the ‘off’ state in motor cortex and GPI to determine the correlated oscillatory activities across animals in all three structures (in motor cortex: Na, n=12 and Va, n=8 recordings; in GPI: Gl, n=9 and Va, n=11 recordings). Due to low variability in these LFPs across animals, we analyzed the presence of coherent oscillatory activity within the cortico-basal ganglia network in one parkinsonian NHP with simultaneous recordings of LFP signals in (i) motor cortex and striatum (Va, n=13 recordings), and (ii) striatum and GPI (Va, n=11 recordings). To determine the relation between the observed oscillatory activity and the dopaminergic state, striatal LFPs were recorded before and after acute L-Dopa administration (“off” and “on” states, respectively) in two additional parkinsonian NHPs (Br, n=17; Ch, n=5 recordings). Doses of L-Dopa methyl ester/benserazide given s.c. for these experiments were 95/24 mg in Br and 90/22.5 mg in Ch. Typically, the “on” state was evidenced by behavioral changes approximately 20 minutes after the acute systemic (s.c.) injection of L-Dopa. LFP signals (sampling frequency: 2000 Hz, Blackrock Microsystems; sampling frequency: 20 kHz, Multichannel Acquisition Processor, Plexon Inc.) were amplified and low pass filtered with 750 Hz. LFPs were recorded continuously for at least 3 min in the awake condition (open eyes). Animals were monitored during the recordings to ensure that transition to the behavioral state after L-Dopa injection (“on” state) correlated with our LFP data collection. A potential limitation to the current dataset includes the lack of vehicle control injections. However, any changes in LFP induced by agitation of the animal due to the injection itself was not affecting our results because data were collected 20 min after the injection at the time of the “on” state induced by the subcutaneous L-Dopa dose. Any agitation of the animal caused by the injection disappeared after a few minutes, and the animal returned to its quiet “off” state before turning “on” 20 min later. Collected LFPs were stored for offline analysis.

## Data Analysis

Continuous LFP data were analyzed using Matlab software (MathWorks, Natick, MA), with custom codes on the basis of standardized signal analysis functions (signal analysis toolbox). Power spectral analysis of LFP signals was computed applying the “pwelch” method. All signals were resampled to 1024 Hz and band passed 1–90 Hz (Butterworth zero phase filter). A 60 Hz notch filter was also used to eliminate line-noise. Signals were segmented into 5 sec epochs, which were transformed into the power spectrum domain (pwelch method: 1024 samples window size overlapped by 50%). A frequency range of 1–90 Hz was selected to

compute relative power spectrum to reduce the inter-recording variation. Subsequently, all spectra were averaged. Visual examination was initially performed to remove time periods with obvious artifacts. We did not notice any movement artifacts in the LFPs during the “off” state. However, small movement artifacts were noticed in the LFPs during the “on” state. We eliminated epochs from the analysis whose amplitude was above 2 standard deviation from the mean of all epochs. Previous studies of the basal ganglia oscillations in MPTP-treated NHPs detected increases in the 8–20 Hz frequency range (Stein and Bar-Gad, 2013; Devergnas *et al.*, 2014). As we observed two distinct spectral peaks in the 8–13 Hz and 13–20 Hz frequency ranges, we computed the mean relative LFP-power at these two frequency bands. For graphic visualization of the relative power spectrum, we used 4–50 Hz range. Coherence analysis between cortico-striatal and striato-pallidal LFPs was computed using the “csd” matlab function with a window size of 1024, which provided a frequency resolution of ~1 Hz with 50% overlap. Differences between relative power of striatal LFPs (8–13 Hz and 13–20 Hz) recorded in normal and parkinsonian NHPs were analyzed with unpaired t-test. Differences between “off” and “on” states for 8–13 Hz and 13–20 Hz frequency bands were analyzed with paired t-tests.

The relative power of 8–13 Hz and 13–20 Hz frequency band oscillations were computed to differentiate normal from parkinsonian NHPs, and “off” from “on” states using logistic regression (LR). Since the LFP analysis revealed peaks in 8–13 Hz and 13–20 Hz frequency bands, we selected those band power values as features for further analysis. We examined the accuracy of the relation (predictor or classifier) using a two-class problem in the support vector machine (SVM) method on the average of 10-fold cross-validation tests on 8–13 Hz and 13–20 Hz frequency bands values. Data were divided into ten groups and then trained with nine groups and tested with one group. This was repeated ten times while each group was used as a test group. Subsequently, single performance estimation was calculated. We used ‘svmtrain’ and ‘svmclassify’ matlab functions for classification, and ‘classperf’ matlab function was used to estimate the performance or accuracy of the classifier. Accuracy of the classifier was displayed using a Receiver Operating Characteristic (ROC) curve, a graphical plot of the sensitivity vs. (1-specificity).

## Results

Parkinsonian NHPs exhibited aberrant striatal oscillations with relative power at 8–13 Hz and 13–20 Hz frequency bands as compared to the normal condition ( $P = 0.001$ ; Fig. 1A). In the normal NHP, there is no predominant oscillatory activity in any frequency range in the striatum. The choice of boundaries for frequency bands was based on previous data from PD models and patients, where 8–13 Hz and 13–20 Hz are the frequency bands of the oscillatory activity usually found (Stein and Bar-Gad, 2013; Devergnas *et al.*, 2014). However, comparison of the power spectra of these rhythms indicates predominance of low frequencies (8–13 Hz), which seems more characteristic of the primate (Devergnas *et al.*, 2014). Further analysis of the relation between the relative power of 8–13 Hz and 13–20 Hz frequency bands to normal and parkinsonian states in NHPs revealed a strong correlation with notable sensitivity (for both bands 8–13 Hz and 13–20 Hz: 99% LR and SVM methods), and accuracy (8–13 Hz: 97%; 13–20 Hz: 98%) for these parameters to classify

MPTP-treated NHPs versus control (Fig. 1B). These results were highly constant across algorithms (LR and SVM) and cross-validation procedure.

In parkinsonian NHPs, the relative powers of 8–13 Hz and 13–20 Hz frequency bands in the striatum were similar to those recorded in the motor cortex and GPi (Fig. 2). In the normal NHP, fixed electrodes in the striatum prevented recordings of LFPs in the cortex and GPi. LFPs recorded simultaneously in the motor cortex and the striatum or the striatum and GPi show increased coherence in the 8–13 Hz and 13–20 Hz frequency bands in parkinsonian NHPs (Fig. 3). Similarly, previous human and rodent studies have demonstrated an increase in coherence at the same frequency bands between cortical and basal ganglia regions in the parkinsonian state (Sharott *et al.*, 2005; Litvak *et al.*, 2011). Overall, these results confirm that synchronized striatal oscillations in the 8–20 Hz frequency band may reflect a network pattern that occurs after dopamine loss in the primate.

Power spectral analysis of the striatal LFPs recorded in NHPs after acute L-Dopa injection inducing a motor response (“on” state) revealed markedly reduced relative power in the 8–13 Hz ( $P = 0.001$ ) and 13–20 Hz ( $P = 0.01$ ) frequency bands (Fig. 4A and B). Reductions of both 8–13 Hz and 13–20 Hz frequency band oscillations following dopamine replacement were highly sensitive (8–13 Hz: 71% and 13–20 Hz: 68% LR and SVM methods; Fig. 4C) and accurate (8–13 Hz: 70%; 13–20 Hz: 66%) to distinguish the “off” and “on” states in parkinsonian NHPs. These results are in line with previous human and animal studies that have shown reduced alpha and beta-band power in extrastriatal regions after L-Dopa administration (Kuhn *et al.*, 2006; Devergnas *et al.*, 2014).

## Discussion

The present results showed augmented 8–13 Hz and 13–20 Hz oscillations in the striatum of MPTP-treated NHPs with chronic, advanced parkinsonism. It has been previously reported that the acute reduction of dopamine in the striatum of rodents amplifies striatal beta oscillations (Costa *et al.*, 2006). However, the lack of significant striatal oscillatory activity in the normal primate indicates a pronounced change in the primate MPTP model. These data are consistent with findings in extrastriatal regions of basal ganglia showing the relationship between oscillatory activity in the 8–13 Hz and 13–20 Hz frequency bands and dopamine depletion in NHP (Stein and Bar-Gad, 2013; Devergnas *et al.*, 2014). In rodents, low-beta band oscillations (14–20 Hz) has also been associated with dopamine depletion in a recent experiment (West *et al.*, 2018), as opposed to earlier data showing abnormally amplified high-beta band oscillation (15–30 Hz) in the cortico-subthalamic nucleus (STN) network (Mallet *et al.*, 2008). Interestingly, West *et al.* study presents a comparative analysis of these frequency bands showing changes in the network oscillations following “chronic” dopamine depletion. Plastic changes may occur due to progressive dopamine depletion where the oscillatory activity in the network synchronizes at a lower-beta band frequency. In patients with PD, basal ganglia oscillations were also reported in the 13–20 Hz frequency range with LFP recordings (Brown, 2003; Singh *et al.*, 2013; Singh, 2018), and 10–25 Hz frequency range with single-unit recordings (Levy *et al.*, 2002). Altogether, data indicate that oscillatory dynamics in the cortico-basal ganglia circuitry extend mostly from 8 to 20 Hz frequencies in the parkinsonian state.



Different neuronal populations in the striatum may participate in the changes of field potentials observed after dopamine loss. In dopamine-depleted rodents, SPNs in the indirect pathway exhibit increased spiking activity and abnormal phase-locked spiking to ongoing cortical oscillations in the 15–30 Hz frequency band (Sharott *et al.*, 2017). Although these data indicate spectral differences of oscillatory activities between rodent and primate models, there is consistency with respect of unit activity changes. In Sharott *et al.* study, the synchronization of indirect striatal neurons to the 15–30 Hz oscillation revealed a cell-type selective entrainment of striatal spiking to parkinsonian beta oscillations. Nevertheless, the role of cell subtypes in basal ganglia regions in the generation, propagation, and interaction of oscillatory dynamics throughout the network is still unclear. The present study reports the network coherence of striatal oscillation in the primate model of advanced, chronic parkinsonism. The spiking synchronization to oscillatory activity in the striatum of this primate model remains to be investigated.

A recent primate study by Deffains *et al.* (Deffains *et al.*, 2016) reported that STN, not striatal, activity in the 8–15 Hz correlates with basal ganglia downstream activity in parkinsonian NHPs. In their study, unit recordings showed no oscillatory activity of SPNs but did show 10 Hz oscillatory activity of striatal tonically active neurons (TANs). The study also showed 8–15 Hz oscillations in striatal LFP recordings, which were exaggerated in parkinsonian monkeys compared to normal monkeys. This striatal oscillation only entrained the spiking activity of TANs, but not SPNs. In both single- and multi-unit spiking activity only TANs were phase locked to the striatal 8–15 Hz LFP oscillations. Consistently, we found similar striatal oscillatory activity in the present LFP recordings in monkeys with advanced and chronically developed parkinsonism. However, we did not determine what type of striatal neuron (SPNs or TANs) synchronizes with the global synaptic input, which is represented by the LFP oscillations. While it is possible that in our model entraining of striatal neurons by global synaptic inputs develops differently, at present we lack the data to make assumptions on the impact of the striatal LFP oscillation in the downstream activity, which is driven by the SPNs.

McCarthy *et al.* (McCarthy *et al.*, 2011) have combined computational and experimental methods to analyze the origin of striatal oscillations in the rodent model. Their results showed the participation of striatal cholinergic tone through interaction of muscarinic mediated voltage-gated  $K^+$  channels (M-currents) with GABA<sub>A</sub> currents from interconnected SPNs. Other studies have also shown the relation of the striatal cholinergic mechanism to the generation of beta oscillations and parkinsonian motor deficits (Kondabolu *et al.*, 2016). Regarding SPN interconnections, GABA<sub>A</sub> synapses between SPNs are weakened in PD models (Taverna *et al.*, 2008), and thus, the pattern of beta oscillations is likely regulated by modulators of the SPN excitability. Of note, striatal oscillations in the analyzed models were independent of GABAergic interneurons. Taken together, the available data support that the striatal network can augment or generate beta oscillations upon increased excitability of SPNs in the parkinsonian state.

Enhanced beta frequency oscillations in PD have been attributed to the cortex-STN/globus pallidus externus (GPe) patterning in the network (Magill *et al.*, 2001; Bevan *et al.*, 2002). Noteworthy, this source of oscillations and other STN/GPe activity changes depend critically

upon receiving increased striatal input via the indirect striatal output pathway (Terman *et al.*, 2002; Chu *et al.*, 2017). The striatal LFP analyzed here showed the network coherence of striatal oscillation in the primate model of advanced, chronic parkinsonism. It is important to recognize the limitations in these primate recordings avoiding the use of multiple electrodes lowered to deep brain structures due to safety reasons. The lack of multiple bipolar signals collected simultaneously limited the coherence analysis to unipolar signals, which can be affected by volume conduction. Yet, the present data are in keeping with the cumulative evidence supporting a key role of the striatum in the network changes associated with dopamine depletion in PD. However, the intrinsic striatal mechanisms and specific cell types involved in the generation of beta frequency oscillations remain unsettled. Previous studies consistently revealed SPN hyperactivity as one salient condition underlying striatal functional changes, which is congruent with the prediction of the computational model in McCarthy *et al.* (2011). The increase of SPN activity that underlies synchronized spiking in beta frequencies in the parkinsonian state also causes pathological (unstable) SPN responses to dopamine (Singh *et al.*, 2015). Notably, this abnormal activity pattern can be reversed by reducing the excitatory glutamatergic signaling (Singh *et al.*, 2018), indicating that basal SPN hyperexcitability is a major source of striatal network changes. Therefore, glutamatergic control of SPN spiking likely plays a key role in the generation of striatal beta band oscillations in PD.

The normal and pathological functions of beta rhythms are still unclear, but dopamine modulation of oscillatory activity concomitant with motor effects is significant. Consistent with previous results (Sharott *et al.*, 2005; Mallet *et al.*, 2008), the “on” state induced by levodopa administration was accompanied by reduced striatal 8–20 Hz oscillations in the present NHP experiments. Nevertheless, the present study does not address the specific relationship of striatal oscillations to parkinsonian motor impairment. These LFP recordings demonstrate that oscillatory dynamics develop in the striatum of primates with chronic, moderate parkinsonism. The study also reveals that the striatal oscillation between alpha (8–13 Hz) and low-beta (13–20 Hz) frequency bands is coherent with the rhythms found in the cortico-basal ganglia network in NHP models, thereby supporting a primary contribution of the striatum to the motor network changes in PD.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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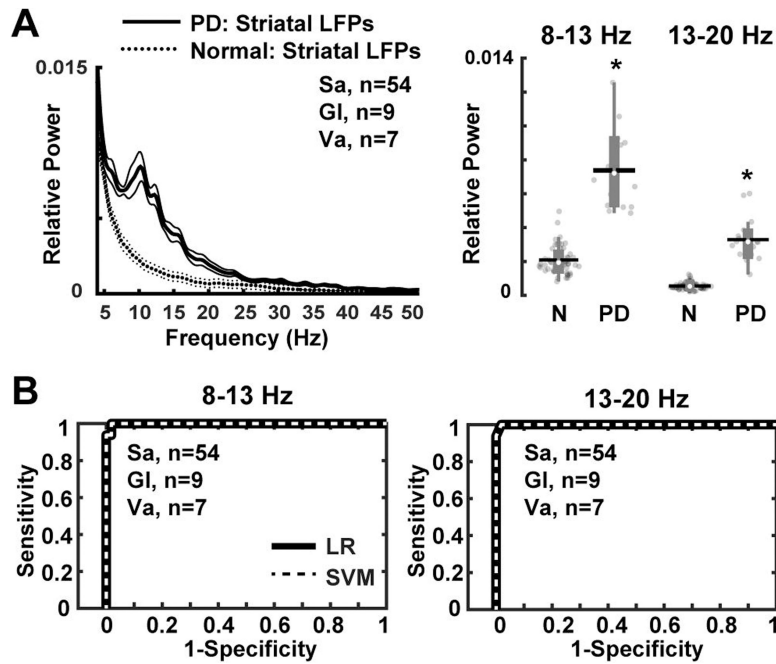


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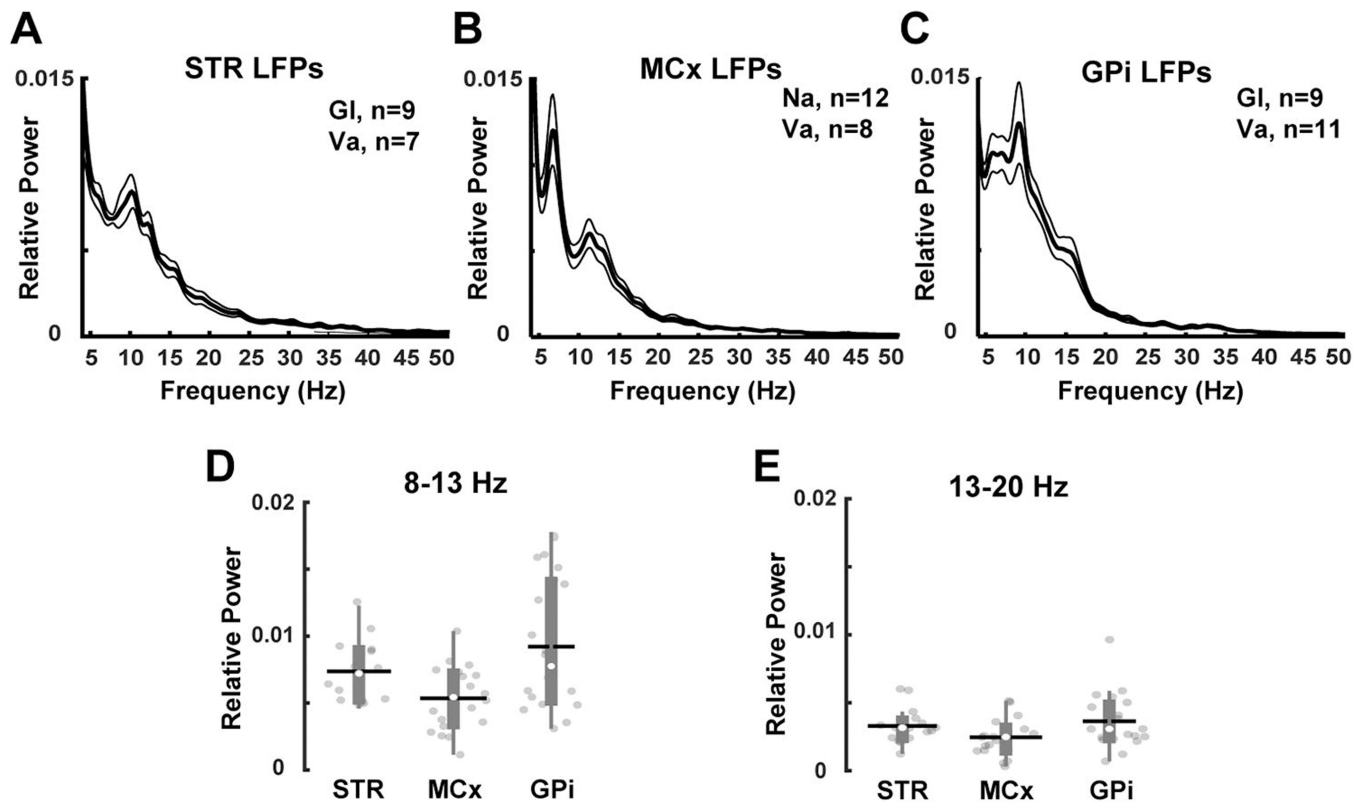
**Highlights**

- Alpha and low-beta oscillations were present in the striatum of MPTP-treated NHP.
- These oscillations were highly coherent with the cortical and pallidal oscillations.
- L-dopa reduced abnormal 8–20 Hz oscillations in the striatum of MPTP-treated NHP.
- Striatal oscillations may play a key role in the motor network changes of PD.



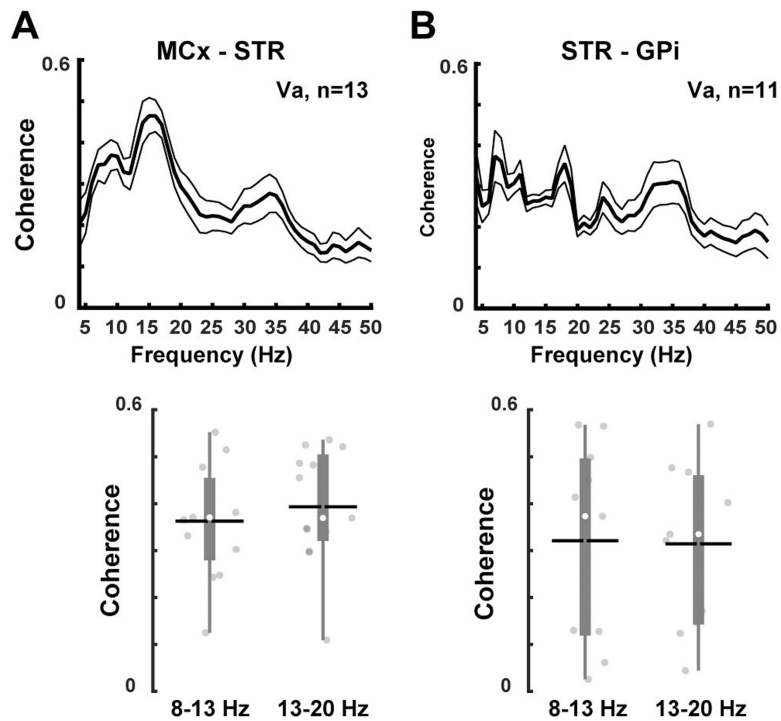
**Figure 1. Striatal LFPs in parkinsonian non-human primates (NHPs).**

(A) Relative power in the 8–13 Hz and 13–20 Hz frequency bands showing significant increases in the dopamine depleted striatum of NHPs (Gl, n=9; Va, n=7 recordings) as compared with the intact striatum in the normal NHP (Sa, n=54 recordings). (B) Classification of control (Sa, n=54 recordings) versus parkinsonian NHPs (9 Gl and 7 Va, total n=16 recordings) based on power values of 8–13 Hz and 13–20 Hz frequency bands. Receiver operating characteristic plots show the true (sensitivity) vs. false positive rates (1-specificity) of MPTP-treated vs. normal NHPs discrimination for each frequency band separately using logistic regression (LR) and support vector machines (SVM) methods. Thick and thin lines represent mean and standard error of mean, respectively. Significant difference is denoted by  $*P < 0.01$ . N = Normal NHP; PD = MPTP-treated NHP. The black horizontal lines and white circles in the box plots represent the mean and median values, respectively.



**Figure 2. LFPs recorded from motor cortex and basal ganglia nuclei.**

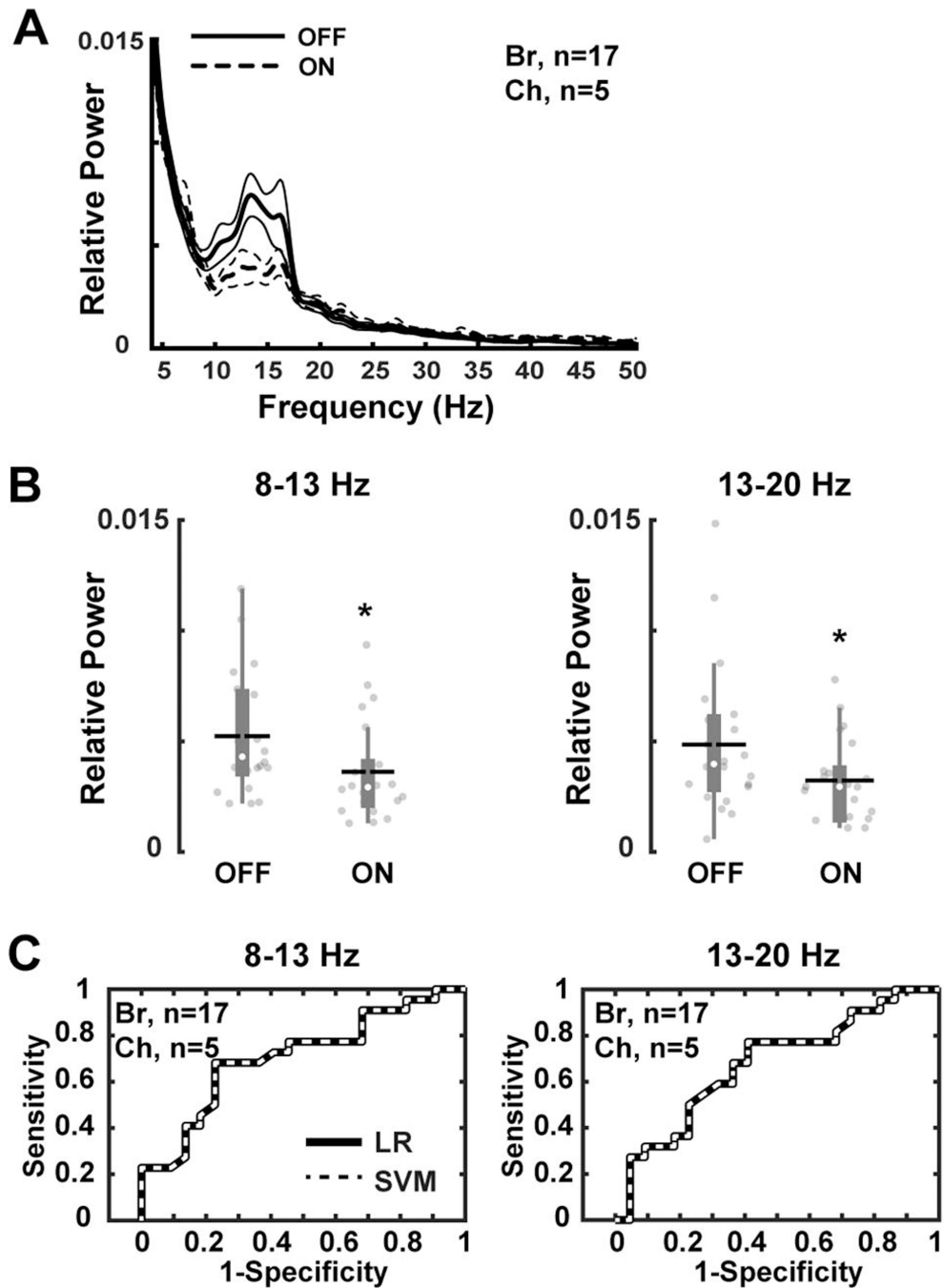
(A) Striatal (GI, n=9; Va, n=7 recordings), (B) motor cortical (Na, n=12; Va, n=8 recordings), and (C) internal pallidal (GI, n=9; Va, n=8 recordings) oscillations recorded in parkinsonian NHPs. (D-E) Comparison of the relative power of 8–13 Hz and 13–20 Hz frequency bands in each of the studied regions. The relative powers of LFPs at 8–13 Hz and 13–20 Hz were similar across the motor cortex, the striatum and the GPi. Thick and thin lines represent mean and standard error of mean, respectively. STR= striatum; MCx= motor cortex; GPi= globus pallidus internus. The black horizontal lines and white circles in the box plots represent the mean and median values, respectively.



**Figure 3. Coherence of oscillatory activity in the cortico-striato-pallidal network in parkinsonian non-human primates**

(NHPs). (A) Increased coherence of LFPs (upper graph) between the motor cortex and the striatum (Va, n=13 recordings) similarly shown at both 8–13 Hz and 13–20 Hz frequency bands (bottom graph). (B) Increased coherence of LFPs also between the striatum and the GPi (Va, n=11 recordings) at both frequency bands. These results demonstrate the presence of augmented oscillatory activity at 8–20 Hz in the basal ganglia circuits after dopamine loss. Thick and thin lines represent mean and standard error of mean, respectively. MCx=motor cortex; STR=striatum; GPi=globus pallidus internus. The black horizontal lines and white circles in the box plots represent the mean and median values, respectively.





**Figure 4. Striatal LFPs before and after acute L-Dopa administration in parkinsonian nonhuman primates (NHPs).** (A and B) Relative power of the striatal oscillations (Br, n=17; Ch, n=5 recordings) at 8–13 Hz and 13–20 Hz frequency range showing significant decreases after L-Dopa injection. (C) Classification of “off” versus “on” states in parkinsonian NHPs based on power values of 8–13 Hz and 13–20 Hz frequency band oscillations (Br, n=17; Ch, n=5 recordings). Receiver operating characteristic plots show the true (sensitivity) vs. false positive rates (1-specificity) of “off” vs. “on” state discrimination for each frequency band separately using logistic regression (LR) and support vector machines (SVM) methods. Thick and thin lines represent

mean and standard error of mean, respectively. Significant difference is denoted by  $*P<0.01$ . The black horizontal lines and white circles in the box plots represent the mean and median values, respectively.

**Table 1.**

Subject demographics and characteristics of the primate MPTP model of PD.

Subject	Species (Macaca)	Sex	Age (years)	Weight (kg)	MPTP TCD (mg)	MDS OFF	MDS ON	Recording regions	Recording states
Sa	Mulatta	F	6	5.5	-	-	-	Putamen	Normal
Gl	Mulatta	F	8	5.1	13.7	21	-	Putamen, GPi	PD, OFF
Va	Mulatta	F	7	7.6	10.8	20	-	Motor Cortex, Putamen, GPi	PD, OFF
Na	Mulatta	F	12	8.1	20.1	19	-	Motor Cortex	PD, OFF
Br	Fascicularis	M	6	5.8	7.6	22	9.5*	Putamen	PD, Off/ON
Ch	Fascicularis	M	7	6	3	20	6.5*	Putamen	PD, Off/ON

\* : L-Dopa treatment was not administered daily but only acutely for recording sessions. The L-Dopa methyl ester/benserazide doses given s.c during the recordings were 95/24 mg for Br and 90/22.5 mg for Ch. TCD = total cumulative dose of MPTP. MDS = motor disability score in the "OFF" or "ON" state (scale range 0–39). F = female; M = male; GPi = globus pallidus internus.