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Modeling the Motor Striatum under Deep Brain Stimulation in Normal and MPTP Conditions

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Abstract

Striatum (STR) is the major input stage of the basal ganglia (BG). It combines information from cortex, subthalamic nucleus (STN) and external globus pallidus (GPe), and projects to the output stages of the BG, where selection between concurrent motor programs is performed. Parkinson's disease (PD) reduces the concentration of dopamine (DA, a neurotransmitter) in STR and changes in the level of DA correlate with the onset of PD motor disorders. Though STR plays a pivotal role in BG, its behavior under PD and Deep Brain Stimulation (DBS) is still unclear. We develop point-process models of the STR neurons as a function of the activity in GPe, cortex, and DBS. We use single unit recordings from a monkey under STN DBS at different frequencies before and after treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to develop PD motor symptoms. The models suggest that STR neurons have prominent bursting activity in normal conditions, positive correlation with cortex (3–10 ms delay), and mild negative correlation with GPe (1–5 ms lag). DA depletion evokes 30–60 Hz oscillations, and increases the propensity of each neuron to be inhibited by surrounding neurons. DBS elicits antidromical activation, masks existent dynamics, reinforces dependencies between nuclei, and entrains at the stimulation frequency in both conditions.

I. Introduction

THE processing of motor information may involve highly segregated re-entrant loops, which stem from the motor, pre-motor and somatosensory cortex, project to the sensorimotor areas of the basal ganglia (BG) and thalamus, and returns back to cortex [1][2] (Fig.1). BG filter the input from cortex through several parallel pathways (e.g., direct and indirect pathway) and are hypothesized to contribute to the selection of appropriate motor

programs [1]. BG include striatum (STR), subthalamic nucleus (STN), external and internal globus pallidus (GPe and GPi), substantia nigra pars compacta (SNpc) and reticulata (SNr). Several models have been proposed to describe the role of the BG in motor control [2–4], with focus on the polarity of the connections [2], the features of the discharge patterns in the various nuclei [4], or synaptic architecture [3]. All the models, however, agree in assigning a pivotal role to the STR. STR is the main recipient of projections from the motor and somatosensory cortex [5] and is hypothesized to integrate information from different cortical sites before projecting to GPe, GPi and SNr [5–7]. This integration is performed through a complex reticular structure, different types of cells (i.e., spiny neurons, interneurons) [5][6], and combines reentrant inputs from STN, GPe, and thalamus. It involves dopamine (DA), a neurotransmitter released by the SNpc, and is mediated by dopaminergic receptors D1 (excitatory) and D2 (inhibitory) [1][2] (Fig.1). It is hypothesized that STR modulates the BG activity and implements motor-related learning and memory functions [5][7]. DA depletion in Parkinson's disease (PD) affects the STR by altering the synaptic connectivity [8], decreasing the spiking activity [9], and unbalancing D1- and D2-mediated pathways [1][2]. These effects are hypothesized to derange the activity of the BG and elicit motor disorders [1].

The mechanisms of synaptic plasticity in normal and PD primate STR have been studied in vitro [8]. A few studies have analyzed the modulation induced by movements and high frequency (HF) stimulation on the striatal spiking activity in rats [9][10], while no evaluation has been provided for the impact of therapeutic deep brain stimulation (DBS) on the striatal activity in primates.

We investigate the spiking activity of STR neurons at rest (without DBS) and during STN DBS at multiple frequencies, in normal and MPTP conditions, by exploiting single unit recordings from a non human primate. We develop point process models (PPMs) [11] to characterize the spiking propensity of neurons as a function of their spiking histories, the DBS signal, and projections from sensory cortex (sCTX) and GPe. PPMs were recently used to characterize STN neurons from PD patients [12][13] and provided a useful description of several neuronal phenomena [14][15]. As in [12], we use generalized linear methods (GLM) [16] to represent the point process conditional intensity function (CIF) in terms of short and long-term history dependence, thus capturing oscillations, bursting, and the impact of the DBS frequency. Our models suggest that, bursting is the most recurrent phenomenon in normal conditions, while refractoriness and 30–60 Hz oscillations characterize the MPTP state. Positive correlation between STR and sCTX (which suggests possible synchronization) is more frequent than negative correlation (i.e., inhibition in with 1–5 ms lag) between STR and GPe, while, for each neuron, there is higher propensity to be inhibited by surrounding neurons (in the same ensemble) in the first few ms in MPTP than in normal conditions. Each DBS pulse induces antidromic activation and reinforcement phenomena due to the BG-thalamus-cortical connections.

II. Methods

A. Data Collection

Recordings from a non-human primate (macaca mulatta) were used in this study. Details about surgical procedures and data collection are in [17][18]. Briefly, the primate was implanted with a recording chamber and received STN DBS via a reduced scale model of the human DBS lead. Micro-electrode recordings were alternatively obtained from sites in sCTX, STR (post-commissural part of putamen), and GPe during DBS (Fig.1). DBS frequencies were 50, 100, 130 Hz. Stimulation/recording sessions were made both before and after that the primate was treated with MPTP and developed a stable PD state with contralateral rigidity and bradykinesia. During each session, continuous recordings of neuronal activity were made 30 s before and 30 s during DBS. Extracellular signals were band-pass filtered, amplified, digitized (25 kHz), and sorted offline into individual unit activities (Q^E units per session, with Q^E ranging from 2 to 7, depending on position and session, Fig.1). For each unit, time stamps of the detected spikes were recorded [17][19]. Neurons included in our study are reported in Table I.

B. Point Process Modeling

We formulated PPMs to relate the spiking propensity of STR neurons to their own spiking history, the history of STR neurons simultaneously recorded (same ensemble), neurons in GPe and sCTX, and DBS. We used the model parameters to analyze the effects of intra- and inter-nuclei dependencies, and DBS [12]. A neural spike train is treated as a series of random binary events that occur continuously in time (point process) [11]. A PPM of a neural spike train is completely characterized on an interval $(0, T]$ by the CIF

$$\lambda(t|H_t) = \lim_{\Delta \rightarrow 0} Pr(N(t+\Delta) - N(t) = 1 | H_t) / \Delta \quad (1)$$

where $N(t)$ is the number of spikes in $(0, t]$ for t in $(0, T]$, H_t the history of spikes up to t , Pr the probability [11]. $\lambda(t|H_t)$ is a generalized history-dependent rate function completely characterizing a spike train [11][15]. For each neuron, we discretized $\lambda(t|H_t)$ ($= 1$ ms) [11] and defined the GLM model:

$$\lambda(k|H_k) = e^\alpha \lambda_O(k|H_k) \lambda_S(k|H_k) \lambda_E(k|H_k) \lambda_C(k|H_k) \lambda_G(k|H_k) \quad (2)$$

where λ_O accounts for the neuron own spiking history, λ_S for DBS (if applied) and λ_E for dependencies from STR neurons in the same ensemble. λ_C and λ_G show dependencies from neurons in sCTX and GPe respectively. k is the k -th bin (ms) and e^α accounts for history-independent activity. Specifically,

$$\log \lambda_O(k|H_k) = \sum_{r=1}^{10} \beta_r dN(k-r, k-r+1) + \sum_{r=11}^{18} \beta_r dN(k-5(r-8), k-5(r-9)) \quad (3)$$

$$\log \lambda_S(k|H_k) = \sum_{\nu=1}^8 \gamma_\nu dN_s(k-\nu, k-\nu+1) \quad (4)$$

$$\log \lambda_i(k|H_k) = \sum_{q=1}^{Q^i} \left\{ \sum_{h=1}^{10} \delta_{h,q}^i dN_q^i(k-h, k-h+1) + \sum_{r=11}^{18} \delta_{h,q}^i dN_q^i(k-5(h-8), k-5(h-9)) \right\} \quad (5)$$

with $i = E, C, G$. $dN(a, b)$ and $dN_q^i(a, b)$ is the number of spikes fired by the given neuron and the q -th neuron in region i in $[a, b]$ (in ms) respectively, and $dN_S(a, b)$ is the number of DBS pulses delivered in the same interval.

$\{\beta_r\}_{r=1}^{10}$ measure the effects of the spiking history in the previous 10 ms, thus detecting refractoriness and bursting [12][18]. For example, if $e^{\beta_1} \approx 0$, then for any given time bin k , the probability to spike in that bin is close to 0 if the neuron spiked in the previous bin (refractory period). Similarly, $\{\beta_r\}_{r=11}^{18}$ account for the history in the previous 10–50 ms and detect oscillations [12]. $\{\delta_{h,q}^i\}_{h=1}^{18}$ $q = 1, \dots, Q^i$ show dependencies from other neurons in region i . For example, for a given value of q , if $e^{\delta_{5,q}^E}$ is significantly larger than 1, then for any bin k , the probability that the neuron spikes is modulated up if the q -th neuron in its own ensemble spiked 5 ms prior to k , suggesting phase-locked activity of the two neurons.

Similarly, $\{\gamma_\nu\}_{\nu=1}^8$ measure the dependency from the DBS input in the previous 8 ms.

For each neuron with an average prestimulation rate 10 Hz we estimated the parameter

vector $\Theta = \{\alpha, \beta_r, \gamma_\nu, \{\delta_{h,q}^i\}_{q=1}^{Q^i}\}_{i=E, C, G}$ and 95% confidence bounds by maximizing the likelihood of observing the recorded spike trains [11][12]. 80% of the data was used for parameter estimation and 20% was used for validation. The sets of bins (a, b) in $dN(a, b)$ in (3–5) were chosen by minimizing the Akaike's information criterion [15]. Goodness-of-fit of each PPM was assessed on the validation data with the Kolmogorov-Smirnov (KS) plot after time rescaling of the spike trains [15], and only those models whose KS plots are within 95% confidence bounds were used in our analysis [12][15]. Finally, we note that since neurons in sCTX and GPe were not simultaneously recorded with neurons from STR ensembles, for each combination of neurons from sCTX, GPe and STR, 3 models were estimated by randomizing the sequence of sessions from each neuron used for parameter estimation.

III. Results

We compared PPMs estimated for neurons in normal and MPTP conditions, with and without DBS. Results are summarized in Fig. 2–4 and Table II–IV (the discharge frequencies are reported in tables as mean±S.E.M. [19]).

A. MPTP vs. Normal with No DBS Input

Table II and Fig.2 compare results in MPTP vs. normal conditions at rest. A few differences between MPTP and normal neurons were noted: MPTP cells show refractoriness (Fig.2b), and some propensity to oscillations in the gamma band (30–60 Hz), while very few cells show bursting or low frequency oscillations. Bursting and oscillations at 20–30 Hz are the most recurrent phenomena in normal conditions, though they involve only 10–30% of neurons. A significant decrease of the average discharge frequency is noted in MPTP vs.

normal conditions (unpaired t-test, p-value $p < 0.001$ [19]), which is accounted by differences in α (Fig.2a,e). Parameters $\delta_{h,q}^E$'s computed for each couple of neurons in the ensemble suggest that MPTP STR neurons exert a stronger inhibition on their own ensemble with a latency of 1–2 ms, and a quite uniform distribution of phase delays in the range 3–50 ms. This may be due to increased feedback inhibition of spiny neurons induced by DA depletion [5]. DA depletion also reduces synaptic plasticity, which may result in less modulation of cortical input [5][8]. This may account for the recurrent coupling between sCTX and STR suggested by $\delta_{h,q}^C$'s with 3–10 ms delay (Fig.2d).

B. Effects of DBS Frequency on Normal Neurons

Table III and Fig.3 compare the effects of DBS at various frequencies in normal conditions. PPMs suggest that DBS increases the probability of spiking 3–5 ms and 7–8 ms after the stimulus, with a recovery period in between (5–7 ms after pulse). This is confirmed by normalized peristimulus time histograms (PSTHs, bin size 0.08 ms [19]) of Fig.3e,l. The high temporal consistency of the neuronal response to the pulses suggests early antidromic activation (masked by the stimulus artifact) [19], followed by spikes at 3–5 ms and 7–8 ms after the pulse. PPMs also suggest a few differences in the neuronal behavior: 100 Hz DBS elicits a phase-locked spiking activity in the neurons (e^α strongly drops as soon as DBS is applied, $e^{\gamma_v} > 10 \forall v = 4, \dots, 8$, Fig.3i), which overrides the dependency from the previous spiking history, while 50 Hz DBS has milder impact (higher value of α , no significant difference from spike trains at rest, and lower γ_v 's, Fig.3d). The last column in Table II and III shows that DBS increases the probability of temporal dependency between STR, sCTX and GPe (e.g., 20–23% of $\delta_{h,q}^C$'s show correlation between STR and sCTX with 3–10 ms lag during DBS vs. only 17% at rest), though there is no significant difference vs. rest conditions or between 50 and 100 Hz stimulation.

C. MPTP vs. Normal Conditions under 130 Hz DBS

Table IV and Fig.4 compare results in MPTP vs. normal conditions under 130 Hz DBS. HF DBS resulted in strong antidromic activation (<2ms since DBS pulse), mild spiking 4–5 ms after the pulse and no late spike (7–8 ms), which may be overridden by the DBS pulse [17] [19]. Differently from lower frequency stimulation, HF DBS masks the effects of the other temporal dependencies both in normal and MPTP neurons, as shown by β_r 's in Fig.4: 95% confidence bounds of parameters in (3),(5) are close to or include 1, while $e^{\gamma_v} \gg 1 \forall v$, with modulation down for $v = 3, 4$ (post-stimulus refractory) and later recovery for $v = 5, 6$. The prominence of the antidromic activation is more recurrent in MPTP vs. normal conditions, suggesting a wider entrainment of neurons at the stimulation frequency. DBS decreases the average discharge frequency in both conditions, with significance ($p < 0.001$) only in the MPTP case.

IV. Conclusion

An extremely rare experimental set up and a point process modeling framework are used to investigate the dynamical behavior of STR neurons in normal and MPTP conditions, and measure the impact of STN DBS and temporal dependencies from striato-, cortico- and

pallido-striatal projections. Our models indicate that STR neurons have no dominant spiking patterns and mild dependencies from other nuclei in normal conditions, while a higher impact of sCTX, GPe and ensemble arise in MPTP. DBS antidromically elicits spikes at the frequency of stimulation and emphasizes the impact of cortico- and pallido-striatal projections, with mild differences between MPTP and normal conditions.

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Fig. 1.
BG (white boxes), thalamus and sCTX with some connections. Black arrows are excitatory (bold) and inhibitory (dashed) projections.

Fig. 2.

PPM for a MPTP (a–d) and a normal (e–h) STR neuron: a), e) e^α ; b), f) $e^{\beta r}$, $r = 1, \dots, 18$ vs. history bins for a generic time bin k ; c), g) $e^{\delta_{h,q}^E}$, $h = 1, \dots, 18$ vs. history bins for a specific q and time bin k ; c), g) $e^{\delta_{h,q}^C}$, $h = 1, \dots, 18$ vs. history bins for a specific q and time bin k . Parameters are black lines, 95% confidence intervals are shaded green areas, $e^0 = 1$ is a red line.

Fig. 3.

PPM for normal neurons with 50 (a-e) and 100 Hz (f-l) DBS: a), f) e^α ; b), g) $e^{\delta_{h,q}^G}$, $h = 1, \dots, 18$ vs. history bins for a given q and a generic time bin k ; c), h) $e^{\delta_{h,q}^C}$, $h = 1, \dots, 18$ vs. history bins for a given q and time bin k ; d), i) e^{γ_v} , $v = 1, \dots, 8$ vs. history bins and time bin k . e), l) PSTHs (normalization to z-score based on the prestimulation activity [19]). Histograms < -1.96 or > 1.96 (red lines) mean significant inhibition or excitation respectively. Legend for a-d), f-i) as in Fig.2.

Fig. 4.

PPM for a MPTP (a–d) and a normal (e–h) STR neuron under 130 Hz DBS: a), e) e^α ; b), f) e^β , $r = 1, \dots, 18$ vs. history bins for a generic time bin k ; c), g) e^γ , $v = 1, \dots, 8$ vs. history bins for time bin k . d), h) PSTHs. Details as in Fig.3.

TABLE I

Experimental Set Up (No. of Neurons Included)

Site	Frequency	MPTP	Normal
STR	no stimulation	22	75
	50 Hz	3	19
	100 Hz	not available	24
	130 Hz	9	15
sCTX	no stimulation	4	36
	50 Hz	not available	18
	100 Hz	not available	17
	130 Hz	4	1
GPe	no stimulation	not available	20
	50 Hz	not available	6
	100 Hz	not available	6
	130 Hz	not available	8

TABLE II

MPTP vs. Normal (No DBS)

	MPTP	Normal
Discharge frequency (Hz)	24.6±0.16	26.1±0.15
Neurons with refractoriness	21/22	59/75
Neurons with bursting (3–7 ms)	3/22	25/75
Neurons with oscillations (30–60 Hz)	5/22	4/75
Neurons with oscillations (20–30 Hz)	1/22	9/75
Inhibition from ensemble (1 ms)	32/79	75/234
Dependency from ensemble (3–7 ms)	17/79	73/234
Dependency from ensemble (30–50 ms)	13/79	32/234
Dependency from sCTX (3–10 ms)	22/79	397/2298
Dependency from sCTX (10–30 ms)	7/79	159/2298
Inhibition from GPe (1–5 ms)	-	49/1009
Dependency from GPe (5–10 ms)	-	183/1009
Dependency from GPe (30–50 ms)	-	55/1009

TABLE III

50 Hz vs. 100 Hz (Normal)

	50 Hz	100 Hz
Discharge frequency (Hz)	25.5±0.49	20.8±0.27
Neurons excited 1–2 ms after pulse	2/19	9/24
Neurons excited 3–5 ms after pulse	11/19	24/24
Neurons excited 7–8 ms after pulse	4/19	24/24
Dependency from sCTX (3–10 ms)	221/1053	293/1253
Dependency from sCTX (10–30 ms)	97/1053	118/1253
Inhibition from GPe (1–5 ms)	25/353	17/437
Dependency from GPe (5–10 ms)	66/353	88/437
Dependency from GPe (30–50 ms)	22/353	47/437

TABLE IV

MPTP vs. Normal (130 Hz DBS)

	MPTP	Normal
Discharge frequency (Hz)	20.3±0.36	30.5±0.58
Neurons excited 1–2 ms after pulse	7/9	6/15
Neurons excited 3–6 ms after pulse	7/9	7/15
Neurons excited 7–8 ms after pulse	2/9	0/15