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Information in pallidal neurons increases with parkinsonian severity

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ABSTRACT

Introduction: The motor symptoms of Parkinson's disease (PD) present with pathological neuronal activity in the basal ganglia. Although neuronal firing rate changes in the globus pallidus internus (GPi) and externus (GPe) are reported to underlie the development of PD motor signs, firing rates change inconsistently, vary confoundingly with some therapies, and are poor indicators of symptom severity.
Methods: We explored the relationship between parkinsonian symptom severity and the effectiveness with which pallidal neurons transmit information. We quantify neuronal entropy and information – alternatives to firing rate and correlations respectively – in and between GPe and GPi neurons using a progressive, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, non-human primate model of PD.
Results: Neuronal entropy and symptom severity were not linearly correlated: in both pallidal segments, entropy increased from naive to moderate parkinsonism, but decreased with further progression to the severely parkinsonian condition. In contrast, information transmitted from GPe to GPi increased consistently with symptom severity. Furthermore, antidromic information from GPi to GPe increased substantially with symptom severity. Together, these findings suggest that as parkinsonian severity increases, more and more information enters GPe and GPi from common sources, diminishing the relative importance of the orthodromic GPe to GPi connection.
Conclusions: With parkinsonian progression, the direct and indirect pathways lose their independence and start to convey redundant information. We hypothesize that a loss of parallel processing impairs the ability of the network to select and implement motor commands, thus promoting the hypokinetic symptoms of PD.

1. Introduction

The motor symptoms of Parkinson's disease (PD) are hypothesized to correlate with changes in neural activity that results from the progressive degeneration of dopamine-producing neurons in the basal ganglia. The nature of these electrophysiological changes however, and how they relate to motor symptom severity, is poorly understood. In the present study, we quantify these electrophysiological changes with respect to the information transmitted between neurons in two nuclei: the globus pallidus internus (GPi) and externus (GPe). Extracellular unit activity was recorded from a progressive, non-human primate (NHP) model of PD at increasing levels of parkinsonian severity through staged, serial exposure to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). We then quantified the relationship between symptom severity and information transmission between GPe and GPi.

Basal ganglia efferents project from GPi to the pallidal receiving area of motor thalamus with GABAergic, inhibitory connections (Fig. S1). The standard rate model hypothesized that these inhibitory efferents are hyperactive in the parkinsonian state, over-inhibiting thalamic neurons, and thus suppressing movements [1]. This model has been refined to posit that changes in firing rate are less consequential than changes in firing patterns; increases in oscillatory patterning [2,3], neuronal bursting [2,4,5], and spike-train irregularity [4,6] all correlate with parkinsonian symptom severity. Supporting this refinement, therapeutic deep brain stimulation (DBS) of the subthalamic nucleus (STN) or GPi exacerbates PD-associated firing rate changes [7,8], but reverses PD-associated increases in oscillatory [9,10], bursty [7,11], and irregular [8,12] firing patterns.

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Thus, some characteristics of neuronal firing patterns co-vary with parkinsonian symptom severity. In previous work we have summarized these characteristics with neuronal entropy [13], an optimal measure of firing pattern disorder that bounds the information transmitted in a spike train. Information processing in basal ganglia relies on changes in pallidal entropy, which is less than expected from the wide range of inter-spike intervals [14], and decreases with therapeutically effective high-frequency DBS but increases with therapeutically ineffective low-frequency DBS [15]. From a rodent model of PD, we reported that neuronal entropy in globus pallidus and substantia nigra pars reticulata increases with parkinsonian onset, and decreases with therapeutic DBS of the STN [6]. These prior efforts compared entropy between discrete cases: PD or no PD, DBS or no DBS. In the present work, we take advantage of a progressive model of PD to ascertain how firing pattern entropy varies with parkinsonian motor severity.

While firing pattern entropy may be an esoteric metric, the information transmitted between neurons is a concrete concept that might frame our understanding of how impaired neural processing drives neurological symptoms. Work in a rodent model reports that information from STN to GPe increases with parkinsonism onset [16], suggesting that excess information through the basal ganglia correlates with symptoms. Computational studies support this finding, suggesting that low-entropy pallidal activity improves information processing in thalamic neurons [17].

For the present work, we recorded neural activity simultaneously in GPe and GPi, from an NHP progressive model of PD. In a recent study on the same animals, we explored the relationship between oscillatory activities in particular bandwidths and severity of disease [18]. We observed the presence of beta activity in normal animals with no consistent relationship in the incidence of such activity to the disease severity. However, an emergence of coupling between the phase of beta and the amplitude of high frequency oscillations (256–362 Hz) in the mild state suggested a significant relationship between the phase-amplitude coupling and disease severity. We concluded that rather than the emergence of oscillatory activity in one frequency spectrum or the other, parkinsonian motor signs may relate more to the development of altered coupling across multiple frequency bands [18].

In the present study, we report that directed information increased from neurons in GPe to those in GPi with parkinsonian severity, but also increased in the antidromic direction from neurons in GPi to those in GPe. This severity-dependent increased functional connectivity between neurons is consistent with the previously observed severity-dependent increased phase-amplitude coupling of the local field activity. Further, bi-directional increases in information may derive from increasingly redundant signals arriving via common inputs from STN or the striatum.

2. Methods

Analyses were performed on data collected during previously published experiments [18]. Surgical and experimental procedures were approved by the Institutional Animal Care and Use Committee of the University of Minnesota, and complied with United States Public Health Service policy on care and use of laboratory animals.

2.1. Data acquisition

Briefly, data were collected from two rhesus monkeys (female, 5.2 kg; male, 9.4 kg) acclimated to the laboratory environment and to passive manipulation of the limbs for determination of neuronal receptive fields. Motor severity was assessed twice per week with a modified UPDRS that was used to rate rigidity, bradykinesia, akinesia, and tremor of the upper and lower extremities bilaterally, as well as six global motor features of parkinsonism (i.e., gait, posture, balance, turning, defense reaction and food retrieval). Scoring for each feature (0–3) was performed during observation of spontaneous behavior, investigator interaction, and passive limb manipulation. The maximum possible score was 42; composite scores within the ranges of 3–13, 18–28, and 32–42 were used to define the mild, moderate, and severe parkinsonian conditions, respectively. Once data collection was complete for the control condition, each animal was made progressively hemiparkinsonian through staged, unilateral intracarotid injections of the neurotoxin MPTP (0.2–0.8 mg/kg, 1 mg/ml solution, 15-min infusion) using aseptic surgical procedures under isoflurane anesthesia.

Paired, extracellular recordings were made from the GPi and GPe using epoxylite-insulated tungsten microelectrodes (~1.0 MΩ at 1 kHz; FHC Inc., Bowdoin, ME USA) lowered through permanently implanted cephalic chambers on the awake, head-fixed subjects [18]. Neuronal activity was transduced acoustically, allowing on-line evaluation of isolated neurons for somatosensory responsiveness through passive limb manipulation. Each recording lasted at least 30 s, with data amplified (x10,000), filtered (0.3–6.0 kHz), and digitized (25 kHz) for offline analysis. Neural activity was segmented into single-unit spikes with a supervised valley-seek algorithm in Offline Sorter (Plexon Inc., Dallas TX). Spike times for each unit were stored for subsequent information analyses. In control, mild, moderate, and severe conditions, we analyzed data from 211, 78, 42 and 61 neurons in GPe, and 47, 40, 30 and 55 neurons in GPi, respectively. Subsequent to all recordings, electrode locations were confirmed histologically.

2.2. Data analyses

Information theoretic and statistical analyses were performed in MATLAB (Mathworks, Natick MA).

Firing pattern entropy was calculated from the distribution of inter-spike intervals (ISIs) [19,20], and binned logarithmically to help differentiate categorically distinct patterns [13,15], e.g., bursting from tonic firing [21]. In short, ISI probability distributions were generated by rounding ISIs into bins of logarithmic time divided into 5 bins per decade. Maximum likelihood estimates of the entropy, in bits per spike, were calculated for each neuron y as: $H_y = -\Sigma_i P(ISI_i) \log_2 P(ISI_i)$, where the sum is over all ISI bins. Neither increasing the dimension to ISI pairs nor decreasing the bin width affected the qualitative results. We restrict our presented results to the one dimensional, 5 bin per decade case, to ensure enough data for reliable estimates of information from all cell pairs (Fig. 1).

Information was estimated from the entropy of logarithmically binned interval distributions [22]. Direct information between neuronal pairs was calculated from the conditioned entropy ($H_{y|x}$) and single unit entropy (H_y). The conditioned entropy depends on the cross-spike interval (CSI), the time between a spike in output neuron y and the most recent spike in input neuron x. For the present work: $H_{y|x} = -\Sigma_j P(CSI_j) \Sigma_i P(ISI_i \mid CSI_j) \log_2 P(ISI_i \mid CSI_j)$, where the inner sum is over all ISI bins for neuron y, and the outer sum is over the CSIs binned with the same resolution. The direct information was found as the information about the input spike train present in the output spike train: $I_{dir} = H_y - H_{y|x}$ (Fig. 2, *left*).

Inherent bias in this measure can be estimated by shuffling the CSIs and finding the entropy that would have been calculated given that redistribution of CSIs, $H_{y|s}$. We repeated this shuffling process 1000 times for each neuronal pairing, and found the expected information bias as: $I_{bias} = H_y - \langle H_{y|s} \rangle$, where $\langle H_{y|s} \rangle$ is the mean value of $H_{y|s}$ over all shuffles. Subtracting that bias from the direct information, we found our estimate of the true information in spike train x about spike train y: $I_{x \to y} = I_{dir} - I_{bias}$. While a neuron cannot