

Impacts of a unicellular mechanism on network behaviors

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1 Introduction

Parkinson’s disease (PD) is a neurodegenerative disorder affecting the basal ganglia (BG), a set of small subcortical nervous system nuclei. The hallmark of the disease is a dopaminergic denervation of the striatum—the input stage of the BG—altering information patterns along movement-related ganglia-mediated pathways in the brain. Severe motor symptoms result from the pathological state: tremor at rest, bradykinesia—the slowness and impaired scaling of voluntary movement—and akinesia—the poverty of voluntary movements. It is still unclear how dopamine depletion causes those motor symptoms. Experimental studies have shown that abnormally synchronized oscillatory activities—rhythmic bursting activity at the unicellular level and beta frequency band (from 8 to 30Hz) oscillations at the network level—emerge in PD at multiple levels of the BG-cortical loops and correlate with motor symptoms. The mechanisms underlying these pathological beta oscillations remain elusive. We propose that a cellular mechanism generates bursting activities and beta band oscillations at the network level.

2 The unicellular mechanism

Neurons in the subthalamic nucleus (STN) and the external and internal parts of the globus pallidus (GPe and GPi, respectively) exhibit tonic pacemaker activity in their physiological state and bursting activity under PD conditions [1]. To model those neurons, and particularly their ability to switch from tonic to bursting activity, we use a novel hybrid model which exploits a revisited neuronal phase portrait in light of calcium channels [2]. A single parameter in this model controls the relative strength of the calcium conductance with respect to other ionic channels. For a low calcium conductance, the model captures the classical view of the reduced Hodgkin-Huxley model and the neuron is tonically firing; in contrast, for a high calcium conductance, the model reveals novel excitability properties and the neuron is in a bursting mode [2]. As a consequence, the low dimensional model captures the important electrophysiological property with the modulation of the calcium conductance (e.g. through the (de)inactivation of the low-threshold T-type calcium current, by hyper- or de-polarization of the neuron’s membrane) to enable the neuron to switch from a tonic ‘transferring’ mode to a bursting ‘endogenous’ rhythm prone to synchronization.

3 Network oscillations

We propose a novel mechanism for the generation of oscillations at the network level. In contrast to existing models, our model predicts that the decrease of the dopamine level in PD turns the GPe and the STN into their bursting mode, revealing an abnormal dynamical states of underlying normal networks. The organization and intrinsic connections within the BG are well identified and are represented, for the indirect pathway, in Fig. 1. In the physiological state, neurons are tonically firing. Under reduced dopaminergic conditions, such as in PD, the firing rate in the striatum increases and hyperpolarizes the GPe. As a result, the GPe switches from a tonic healthy firing mode to a burst mode with a strong endogenous rhythmic activity. The pallidal inhibitory input to the STN is therefore augmented and turns the STN into the same burst mode. The interconnection and interplay of those endogenous bursters generate the pathological beta band rhythmic activity at the network level.

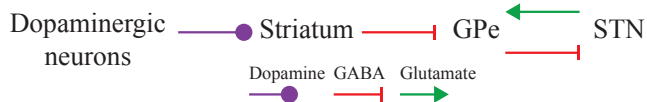


Figure 1: Schematics of the indirect pathway of the BG.

4 Conclusion

We use a mechanism to explain pathological oscillatory activities at the cellular and network levels. The cellular calcium-conductance-dependent switch to the burst mode of firing generates synchronous bursting and beta band network oscillations under PD conditions. This mechanism can be exploited to demystify the event-related desynchronization of the STN beta oscillations prior to voluntary movements and the suppression of beta oscillations during STN high-frequency deep-brain stimulation treatments.

References

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