The Pathophysiology of Network Synchrony in Parkinsons Disease

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Parkinson's disease & PD-related disorders

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Research Abstract

Project Summary/Abstract The pathophysiology underlying the motor symptoms of Parkinson’s disease (PD) remains incompletely understood with recent conflicting reports of changes in neuronal activity in distinct nodes within the basal ganglia-thalamocortical (BGTC) motor circuit. A unified approach that accounts for conflicting results is needed. Emphasizing the relatively underexplored dynamic relationship between nodes in the circuit, we build upon the hypothesis

that exaggerated network-level coupling is the pathophysiologic process underlying the rigidity and bradykinesia of PD by impeding effective information flow. Accordingly, we propose that modulation of network coupling is the common therapeutic mechanism across pharmacologic and surgical therapies; other physiologic sequelae are specific to the target of therapeutic intervention and account for disparate results in the literature. We will simultaneously assess cortical and subcortical physiology in relation to clinical symptoms and in response to deep brain stimulation (DBS), cortical stimulation and pharmacologic therapy in patients undergoing DBS implantation surgery. This approach enables superior investigation of spatially specific cortical phenomena compared to extraoperative studies. We propose that it is critically important to understand the functional connectivity of the extended BGTC network, including not only the motor cortex with subthalamic nucleus (STN) as most studies do, but also connectivity with globus pallidus internus (GPi, the final common output of the basal ganglia) and the supplementary motor area (SMA) and dorsal premotor cortex (PMd), which are to where pallidal-receiving thalamic regions dominantly project. Moreover, our analyses will focus on the differential physiological significance of low vs high ? oscillations with respect to normal motor function, disease, and therapeutic intervention. In Specific Aim 1, we aim to understand the clinical correlates of the untreated BGTC motor network in PD both at rest and with movement, taking specific advantage of temporal variation in disease symptomatology (as measured with objective clinical rating scales and comprehensive kinematics) with simultaneously recorded measures of network connectivity. In Specific Aim 2, we will use subcortical and cortical stimulation to specifically perturb distinct nodes in the BGTC motor network, in order to confirm that network coupling is the common mechanism underlying therapeutic brain stimulation, regardless of target, and to also identify target specific effects that can account for known clinical differences in DBS at STN vs GPi. Finally, in Specific Aim 3, we will evaluate pharmacologic modulation of the BGTC motor network, with an aim to understand the temporal relationships between symptom amelioration and network modulation. Taken together, we will significantly enhance the existing BGTC motor network wiring diagram by elucidating the role of motor network coupling in PD. Addressing this fundamental knowledge gap will facilitate therapeutic innovations, including identification of control signals that can be used for closed loop DBS as well as provide a wiring diagram of the BGTC motor circuit that could guide pharmacologic innovation.

Lay Summary

Project Narrative Despite the prevalence and disability attributable to Parkinson’s disease (PD), we still do not have an integrated understanding of how brain circuits go awry and cause symptoms in PD. The goal of this proposal is to develop a more comprehensive understanding of motor network dysfunction by recording signals from multiple areas of the brains of patients with PD undergoing deep brain stimulation (DBS) implantation surgery. The knowledge gained will provide a critical framework for the development of novel therapies, contribute to improvements in surgical targeting and techniques, and potentially be used for the design of closed-loop DBS systems, all of which can lead to improving the quality of life of PD patients, improving the efficacy of therapies, and reducing health care expenditures.

Further information available at:

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Investments > €500k

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United States of America

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