CRCNS: Propagation of beta oscillations in cortico-basal ganglia-thalamic loop

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CRCNS: Propagation of beta oscillations in cortico-basal ganglia-thalamic loop

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Parkinson's disease & PD-related disorders

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Research Abstract
DESCRIPTION (provided by applicant): Parkinson’s disease is a chronic, disabling neurologic

disorder causing resting tremor, muscular rigidity, bradykinesia and impairment of gait. It is estimated that 5 million people worldwide have Parkinson's disease, and this number is projected to reach 8.7 million by 2030. A pathologic hallmark of Parkinson's disease is degeneration of the dopaminergic neurons in the substantia nigra pars compacta projecting to the striatum. Treatment often consists of dopamine replacement therapy with L-dopa. However, its efficacy is limited by the ""wearing off"" phenomenon and its potential to engender potentially disabling dyskinesias . The search for alternative therapies has begun to focus on the interactions of networks within the cortico-basal ganglia-thalamic loop. The efficacy of new treatments such as deep brain stimulation (DBS) to the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPi) highlights the fact that Parkinson's disease is a network disorder, involving alteration of the dynamics within and between the nuclei of the basal ganglia, the thalamus and the cortex. Intellectual Merit: This proposed research is designed to characterize the network dynamics that allow the propagation of beta oscillations through the cortico-basal ganglia-thalamic loop in both the normal and parkinsonian states. Modulation of beta oscillations occurs with normal movement, and exaggeration of beta oscillations in the basal ganglia and cortex are characteristic of Parkinson's disease. Furthermore, there exists correlation between the exaggerated beta oscillations and the bradykinesia and rigidity characteristic of the parkinsonian state. Thus, we seek to understand the networks supporting transmission of beta oscillations in the normal cortico-basal ganglia-thalamic loop and then determine how the network interactions are altered to allow the exaggeration and abnormal propagation of beta oscillations in the parkinsonian state. This will help us understand not only points of interception of the pathologic beta rhythm in Parkinson's disease, which may help alleviate symptoms of motor disability, but also identify how to minimize side effects of potential therapeutic interventions such as DBS that are thought to interfere with the transmission of beta oscillations in Parkinson's disease. Drs. Han and McCarthy have successfully worked together integrating mathematical modeling and experimentation to put forth a new hypothesis for the origin of the pathologic beta rhythm in Parkinson's disease. Their previous analyses revealed that the striatum is capable of generating robust beta oscillations in response to high cholinergic tone, a state highly relevant to the parkinsonian striatum. The research proposed here will make use of their model of striatal beta rhythm generation to understand the propagation of beta oscillations throughout the cortico-basal ganglia-thalamic loop in both the normal and low dopamine states. They propose to extend this model to include mathematical models of each of the nuclei of the cortico-basal ganglia-thalamic loop. The dynamics of our model neurons will be constrained by the experiments of Dr. Han, who will induce beta oscillations in the striatum in both normal and parkinsonian mice and record simultaneously from the striatum, STN and cortex. The results of the combined mathematical and experimental work will promote insight into the networks both within and between the nuclei of the cortico-basal ganglia-thalamic loop that support the propagation of beta rhythms in the normal dopamine state and the alterations that occur to these networks in the parkinsonian state. Broader Impact: Dysfunction of cortico-basal ganglia-thalamic loop has been implicated in other disorders of importance on both the individual and societal levels including Parkinson's disease, schizophrenia, Huntington's disease, depression, obsessive-compulsive disorder, addiction, Tourette's syndrome, dystonias and dyskinesias. Defining the micro-circuitry of the cortio-basal ganglia-thalamic loop is not only a critical step towards understanding alternative therapeutic interventions in Parkinson's disease, it has the potential to advance new therapeutic options for individuals with other disorders with basal ganglia involvement. Elucidating the dynamical aspects of disease, though the combination of mathematical modeling and experimentation, will expand our understanding

of the network mechanisms at work not only in the normal basal ganglia and their dysfunction in Parkinson’s disease but also the role they play in other disorders of the cortico-basal ganglia-thalamic loop.

Lay Summary
Dysfunction of cortico-basal ganglia-thalamic (CBT) loop has been implicated in disorders of importance to public health including Parkinson’s disease, Huntington’s disease, schizophrenia, obsessive-compulsive disorder, depression, Tourette’s syndrome, dystonias and dyskinesias. Defining the micro-circuitry of the CBT loop is a critical step towards understanding alternative therapeutic interventions in Parkinson’s disease and advancing new theraneutic options for individuals with other disorders involving the CBT loop.

Further information available at:

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