Characterizing Intrinsic Functional Cortical Networks in Parkinson Disease Dementia

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Characterizing Intrinsic Functional Cortical Networks in Parkinson Disease Dementia

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Parkinson's Dementia, Magnetoencephalography, motor symptom, Parkinson Disease, Dementia

Research Abstract
? DESCRIPTION (provided by applicant): Parkinson’s disease (PD) affects 1% of adults over age 65. While traditionally defined by motor symptoms, up to 75% of PD patients will eventually develop PD-related dementia (PDD) making it the leading cause of nursing home placement in PD. Although there is currently no cure for PD, our ability to treat motor symptoms has advanced tremendously since the 1960’s based on advances in our understanding of motor

symptom neurophysiology. We propose that the treatment and prevention PDD may also prove possible by advancing our understanding of the neurophysiology underlying cognitive dysfunction. We will use modern network theory as a theoretical and mathematical framework for this endeavor. The long- term goal is to advance our understanding of the neurophysiology underlying cognitive dysfunction in PD to provide empirically testable models, clinically relevant biomarkers, and novel therapeutic targets. The central hypothesis of this proposal is that patterns of functional connectivity critical to normal cognition are disrupted by subcortical pathology in PDD. This hypothesis was formulated on the basis of our own preliminary data and other recent research. We will accomplish the objectives of this proposal through three Specific Aims: 1) Determine whether graph theory measures of network functional connectivity are associated with cognitive phenotypes in PD based on either a) the severity of cognitive dysfunction; or b) specific cognitive domains affected; 2) Develop a novel state-defining biomarker for PDD based on measures of intrinsic network functional activity using a machine learning approach; and 3) Explore the potential role of subcortical sources on cortical network activity and cognition using dynamic causal modeling (DCM). These Aims are achievable within a two-year timeframe as they will involve analyses of a single data set of resting MEG data from 25 control subjects, 25 PDD subjects, 25 PD subjects with normal cognition and 25 PD subjects with mild cognitive impairment. The feasibility of this proposal is aided by leveraging a currently funded NINDS K02 Independent Scientist Award (1 K02 NS080885-01A1). Data and biomarkers generated by this R21 Exploratory/Developmental Research Grant will provide a foundation for future studies to validate state- defining and predictive biomarkers; mechanistic studies on the role of acetylcholine and dopamine in cognition; and therapeutic studies of physiologic or pharmacologic interventions targeting physiological and regional abnormalities. The approach is innovative as the first study to apply graph theory measures to understanding the relationship of cortical physiology and cognitive dysfunction across cognitive domains and severity levels in PD; the first study to apply machine learning approaches to PDD biomarker development; and the first use of DCM to model cortical and subcortical contributions to PDD. The proposed research is significant because it will advance our understanding of the neurophysiology of PD-related cognitive dysfunction and will provide biomarkers, empiric models and therapeutic targets essential to developing more effective interventions.

Further information available at:

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