THE HARTWELL FOUNDATION

2022 Individual Biomedical Research Award

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Predicting Intrinsic Excitability of Brain Neuronal Circuits in Neurodevelopmental Disorders to Identify Targeted Therapies

Neurons, the building blocks of the brain, communicate with each other through electrical signals generated by the movement of certain charged ions (e.g., sodium, potassium, calcium, chloride) across their cell membranes. The electrical signals are governed by the selective opening or closing of membrane channels which, together with neuronal pathways, represent the circuitry of the brain. Mutations in ion channel genes may cause a loss or a gain of channel function (channelopathy) that during brain development contribute to disruption of normal neuronal circuitry and neurodevelopmental disorders (NDD), including autism, developmental delays, intellectual disabilities, and epilepsies. The hallmark of these disorders is an imbalance in excitatory or inhibitory electrical activity in the brain cortex. In most cases multiple factors affect the balance, such as genetic expression, environmental factors, and complex compensatory mechanisms. Unfortunately, how channelopathies lead to NDD is poorly understood, and therapies for millions of affected children are designed by trial-and-error based on clinical history, not on rational interventions that are specific to the child. To address this unmet need, I propose to demonstrate how alteration of ion channel function affects the electrical activity of brain motor cortex neurons observed empirically in healthy and disease states. I will use an algorithm of my design to mathematically simulate ion channel models that mimic experimental data. Such a computational tool provides an opportunity to examine the underlying neuronal mechanisms of NDD and how targeted therapy might be translated to the clinic to ultimately return excitability to neurotypical levels. Translating this approach for a specific mutation of a sodium channel, I have already been able to demonstrate improvement in the health of a 9-year-old patient who progressed from having five seizures per day to becoming almost seizure-free. My working hypothesis is that a simulation platform to model large cortical networks of recurrent neuronal circuits will make it possible to examine the effects of a wide range of channelopathies. In principle, I will model human primary motor cortex to simulate how altered neuronal firing patterns that arise from ion channel gene mutations in a known carrier affect the intrinsic excitability of single neurons in cortical circuits. In turn, I will iteratively modulate the biophysical properties of different ion channels to simulate the effect of known drugs, which will enable the identification of targets for new drug development. Open-source software will facilitate simulation, analysis, and optimization of biological neuronal networks. If I am successful, this approach will greatly increase understanding of NDD, enabling pediatricians to restore proper neuronal function to alleviate the symptoms of the disorder and to accelerate the discovery of effective therapies tailored to each child's condition.