THE HARTWELL FOUNDATION

2013 Individual Biomedical Research Award

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Cortical Network Dynamics and Epileptiform Activity in Autism: From Animal Models to Children

Autism spectrum disorder (ASD) is believed to affect 1 in 88 children and represents the fastest growing developmental disability of children in the United States. Remarkably, in about 30% of all ASD epileptic seizures accompany symptoms of autism. In contrast, only about 1% of the general population will experience epilepsy by 20 years of age. Treatment of ASD can be very complicated, especially when loss of social interaction, social communication, and the presence of repetitive behaviors and restricted interests of autism are overlaid with sudden recurring attacks of sensory disturbance, convulsions and often a loss of consciousness. Worse, for children affected with autism, epilepsy is often the most common cause of death. While it is known that different brainwaves correlate with different states of awareness, attention and behavior, the neurodevelopmental relationships that give rise to autism complicated by epilepsy are unknown. The emerging picture is that the overlap might be attributed to alterations in neural circuit development, where unexpected and abrupt shifts in the excitatory-inhibitory balance in the brain toward excitation can cause a sudden surge of abnormal electrical activity and an epileptic seizure. At the circuit level, however, the interplay between nerve cells and any alteration in functional connections are still largely unknown. To enable effective therapeutic interventions it is essential to understand the link between autism and epilepsy; to know whether autism and epilepsy are somehow causal in nature or just related conditions existing simultaneously. To address this unmet need, Roberto proposes to examine the interactions between brain neurons in cortical microcircuits and how they shape the propagation of abnormal neural activity in a mouse model of autism. To determine if the mouse model of autism is more susceptible to epileptic seizures than wild-type mice, he will measure and analyze electrical activity in brain tissue slices using high-density multielectrode arrays, and seek candidate drugs to restore normal activity patterns. Applying a methodology that he developed in 2013, he will pursue the differences in brain electrical activity and functional brain connectivity between children with autism and epilepsy relative to children without autism; differences that could then be used as a biomarker for measuring the efficacy of behavioral therapies. If Roberto is successful in conducting this brain network analysis, it will provide for the first time a means to evaluate the efficacy of current behavioral and epileptic therapies at a neurological level, and at the same time open new possibilities for pharmacological interventions restoring the excitatory-inhibitory balance in the brain of children affected with ASD.