THE HARTWELL FOUNDATION

2014 Individual Biomedical Research Award

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Algorithm to Quantitatively Determine the Ideal Drug Dose to Treat Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most frequently diagnosed neurodevelopmental disorders of childhood. Affected children have difficulty paying attention and controlling impulsive behavior to the extent that it interferes with learning, social interaction, and communication. Currently, about 11% of children age 4-17 years of age in the USA (7 % of girls and 15% of boys) endure ADHD and worse, the rate of diagnosis has been increasing about 5% per year. Misdiagnosis is common. Therapeutic interventions consist primarily of oral administration of central nervous system stimulants, such as the generic methylphenidate. Surprisingly, drug therapy for the disorder is highly dependent on a subjective determination of severity by school teachers of the affected child. Currently, treatment requires selection of the minimal dose that will improve behavior without adverse cognitive change; but available drugs affect various cognitive/behavioral functions in children differently. Beneficial effects are typically limited to a very narrow quantitative range. At high dosage levels ADHD-like symptoms may worsen, with elevation of blood pressure and other serious side effects. It is fundamentally troubling that the effectiveness of a given dose of prescription drug to improve attention or impulsive behavior in this disorder remains subjective and determined by trial-and-error. To address this unmet need, Luis will initiate clinical trials on the effects of methylphenidate dosage on cognitive/behavioral performance in school-aged children. He seeks to evaluate the magnitude of reward-related cognitive and behavioral functions during computer generated games, using a fundamental mathematical model to interpret the data. To account for latent characteristics of ADHD, he will take into account the drift in time required for evidence accumulation (decision process) and a specific decision in the presence or absence of distraction. Eye movement recordings will validate attention. For example, the rate of change in the response time (drift) to make a decision on a particular choice (A or B) will be dependent on difficulty and memory (learning) and the degree of focus (attention) on a task, where preference for a smaller, sooner reward is a sign of greater impulsivity and poor self-control. If successful, Luis will create an algorithm using the mathematical drift-decision model to simultaneously confirm an ADHD diagnosis and quantitatively determine the ideal drug dose for treatment in an effective and personalized manner. By this rigorous methodology, children who require therapeutic intervention for ADHD will receive the most effective dose of an appropriate drug and thereby experience significant reduction of hyperactivity or impulsivity, while improving learning. His quantitative approach also has potential to be useful in diagnosis and treatment of other cognitive disorders, as well.