THE HARTWELL FOUNDATION

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Neuroimaging Biomarkers of Circuit Pathology in Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a neurodevelopmental syndrome defined by a constellation of deficits in social interaction, communication and restricted repetitive patterns of behavior. Symptoms emerge in the first few years of life and affect an estimated 1 in 68 children in the United States. The causes of the disorder and the underlying functional changes in physiology that precede or accompany ASD remain unclear. Animal models and genetic biomarkers have revealed important new insights, but they focus on rare DNA changes that occur in just a small subset of children. Atypical patterns of functional connectivity in brain networks appear to play an important role in how ASD develops or progresses and are promising candidates for validation as biomarkers. Unfortunately, atypical connectivity patterns in ASD are variable, show significant overlap and inconsistently differentiate affected from otherwise healthy children. Connor offers that this variability reflects the prevailing way we define ASD, explainable in part because ASD deficits can arise from very different structural, biochemical or electrical abnormalities in the brain, corresponding to distinct disease subtypes with unique treatment requirements. As a result, there is an unmet need for neurobiological biomarkers that will enable targeted interventions in affected children most likely to benefit from them. Based upon his working hypothesis that abnormalities in neural circuit connectivity are the basis for ASD, Connor proposes to use functional magnetic resonance imaging (fMRI) of the brain to identify ASD “subtypes” characterized by distinct pathological features. He will seek to identify neuroimaging biomarkers of ASD subtypes in over 1100 children using an existing retrospective fMRI dataset and then, validate the sensitivity and specificity of putative biomarkers in a prospective fMRI dataset of 75 ASD children who will undergo comprehensive clinical characterization and genetic testing. In mouse models of ASD, he will use lasers to control neurons genetically sensitized to light (optogenetics) and based on the results from fMRI of ASD children, create atypical connectivity in specific brain circuits. When combined with fMRI and a battery of validated behavioral tests, this approach will demonstrate how circuit dysfunction observed in children with ASD contributes to particular ASD-related behaviors. If Connor is successful, identifying neuroimaging biomarkers of ASD subtypes has the potential to transform clinical care by informing difficult diagnostic questions (e.g., distinguishing moderate and high functioning ASD from healthy children). Expanded use of neuroimaging for ASD using validated fMRI may also satisfy the need to correctly identify affected children most likely to benefit from specific strategies for early intervention.