

**NIH COMMON FUND HIGH-RISK HIGH-REWARD RESEARCH SYMPOSIUM
DECEMBER 15 – 17, 2014
POSTER ABSTRACTS – SESSION 2 (DEC. 16, 2014)**

Memory network dysfunction as an early marker of preclinical Alzheimer's disease

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Award: Early Independence Award

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Finding a disease-modifying treatment for Alzheimer's disease (AD) is one of the greatest challenges of our generation. There is a consensus in the scientific community that the key to success in treating AD is to begin therapies as early as possible before significant brain damage occurs. Thus characterizing preclinical biomarkers and early detection paradigms, which is the focus of my work, is paramount.

A distributed network of brain regions, including the hippocampus, adjacent cortical regions in the medial temporal lobe, and other brain regions subserves memory function. Paired associative memory tasks that rely on this network have been shown to be sensitive to subtle deficits in the preclinical stages of AD. I propose to build upon my previous research with autosomal dominant AD to establish conceptual frameworks and comparisons with late-onset sporadic AD with an emphasis on the analysis of memory network disruption as an early marker of preclinical AD. To this end, I will leverage my access to two extraordinarily rich preclinical AD groups, 1) the Colombian kindred with Presenilin 1 E280A (Glu280Ala) mutation, estimated to have 1,500 mutation carriers, and 2) a group of asymptomatic older individuals who are participants in the Harvard Aging Brain Study (HABS) at Mass General Hospital and are considered at high risk (by molecular pathology imaging) to develop late onset sporadic AD.

The primary goals of this proposal are to: (i) investigate abnormalities of associative memory as a sensitive cognitive marker of preclinical AD; (ii) investigate brain hyperactivity/hyperconnectivity as a marker of early AD pathophysiology; and (iii) examine the role of tau and amyloid- β aggregation in memory network dysfunction. The research proposed will use cognitive measures, fMRI and PET imaging to examine the hypothesis that memory network dysfunction occurs in early preclinical stages of Alzheimer's disease. This research will provide insight into the interaction of cognitive and brain function biomarkers in preclinical AD. In particular, this work will provide new understanding of how amyloid and tau pathology impact memory function very early in the disease process, and their role in subsequent neuronal death and cognitive decline.