

GEORGE MASON UNIVERSITY  
COLLEGE OF SCIENCE  
BIOLOGY DEPARTMENT SEMINAR  
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***“Understanding the Development of Alzheimer’s Disease from the  
Perspective of the Aging Brain”***

Aberrant changes in neuronal network activity are thought to underlie cognitive impairment in Alzheimer’s disease (AD). Functional magnetic resonance imaging (fMRI) has the potential to detect subtle aberrations in brain networks that may presage the clinical manifestations of AD. Because fMRI is quantitative and the blood oxygen level-dependent (BOLD) contrast signal is an indirect measure of neuronal activity, it is closer to the underlying biology than clinical markers. Thus, the fMRI “endophenotype” is well suited for determining the role of genetic variants in influencing the early stages of AD by following the clinical progression of normal older subjects, some of whom will go on to develop mild cognitive impairment (MCI) prior to AD. However, the majority of researchers in this field have not used functional genetic variation to guide their analyses, which is essential for designing association studies utilizing endophenotypes. Results from the Alzheimer’s Disease Neuroimaging Initiative identified quantitative phenotypes and discovered, through genome-wide association studies (GWAS), multiple common genetic variants that may influence risk of MCI and AD. Among these AD-related gene variants was one single nucleotide sequence variant (SNP) in the N-methyl-D-aspartate (NMDA) glutamate receptor 2B subunit gene (*GRIN2B* gene intronic variant rs10845840) that may contribute to increased risk of MCI and AD and was associated with minimal state scores (Stein, et al., 2010). Independently, we discovered a different *GRIN2B* SNP, in the promoter region (rs3764030) that was associated with altered brain responses to memory functioning in older adults. Our molecular evidence indicated that SNP rs3764030 alters protein-DNA binding activity *in vitro* and activation-dependent transcription in neuronal-like cells. Taken together, these findings support a role for genetic changes in an excitatory neurotransmitter pathway in the brain that may alter susceptibility to MCI.

**TUESDAY October 20, 2015**

**3:00-4:15 PM**

**Johnson Center Room Meeting Room F**