Genotypic effects on episodic memory: experience from BDNF, G72, and GRM3

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Cognitive genomics is an important tool for parsing cognitive processes. In this presentation I will outline the effects of three genes on the neurobiology of episodic memory: BDNF, G72, and GRM3.

For BDNF data will be presented in large groups of normal controls, schizophrenic patients, and siblings of schizophrenic patients that show that a BDNF polymorphism 1) affects intracellular trafficking of BDNF, 2) has an impact on neurophysiology in the hippocampus as measured by the BOLD response in fMRI during encoding of visual scenes and 3) affects verbal episodic memory in behavioral testing. In sum, these results represent a mechanistic account of a role for BDNF in human memory and hippocampal function, and suggest that the val/met polymorphism produces these effects by altering intracellular trafficking and secretion of BDNF.

A recently discovered gene, G72, was found to be associated with schizophrenia and with bipolar disorder, possibly because of an indirect effect on NMDA neurotransmission. In principle, if G72 increases risk for psychosis by this mechanism, it should also impact on cortically based cognitive and neurophysiological functions associated with NMDA signaling. Diagnosis by genotype interaction effects for G72 SNP 10 were significant for cognitive variables assessing working memory, attention, and episodic memory, such that in the schizophrenia group an exaggerated allele load effect in the predicted directions was observed (i.e., epistasis was present). In the fMRI paradigms, a strong effect of G72 SNP 10 genotype was observed on fMRI BOLD activation in the hippocampus during the memory paradigm with ambiguous effects on prefrontal cortex during the working memory task. In sum, we have provided evidence that select SNP variations in the G72 gene region increase risk of cognitive impairment in schizophrenia. The nature of this impairment is broadly consistent with findings from a variety of studies of NMDA-based signaling cascades in excitatory neurotransmission.

GRM3, a metabotropic glutamate receptor modulating synaptic glutamate, is a promising schizophrenia candidate gene, the A allele of SNP 4 was over transmitted to probands. This allele was associated with poorer performance on cognitive intermediate phenotypes involving verbal fluency and free recall in a list learning task. This pattern of results suggest retrieval failure that might be based on “prefrontal” processes. This allele also predicted lower prefrontal NAA, an in vivo MRI measure of tissue glutamate. In human prefrontal cortical tissue, the SNP4 A allele was associated with lower *GRM3* mRNA expression and lower mRNA levels of the glial glutamate transporter EAAT2, a critical synaptic regulatory protein. These convergent data suggest *GRM3* variants have an impact on some aspects of episodic memory function.

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