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Research Use Statement for Application for Genomic Data from NIAGADS
Please limit to 2,200 characters max. The statement should include:
Objectives of the proposed research, Study design, and an Analysis plan including the phenotypic characteristics that will be evaluated in association with genetic variants

Research Use Statement:

Memory formation has been mapped to the brain's Default Mode Network (DMN) including the medial prefrontal cortex, hippocampus, and the inferior parietal lobule. Aberrant functional connectivity occurs during memory impairment, providing evidence that the DMN sub serves episodic memory. Neuroimaging evidence indicates strong genetic regulation of neural networks governing attention, intelligence, and cognition while neural foci regulating episodic memory have yet to be examined through an integrative lens combining neuroimaging, genomics and metabolomics big data.

Hypothesis: Genes regulating cellular metabolism, bioenergetics, signaling, structure, and redox maintenance underlie functional connectivity in the DMN and Memory**.** To investigate this hypothesis, I will: **Aim 1)** Conduct GWAS analyses to identify novel single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) associated with altered resting-state functional connectivity; **Aim 2)** Conduct GWAS analyses to identify novel SNPs and CNVs associated with altered Grey Matter in DMN areas; **Aim 3)** Perform gene set-based association analysis with a priori defined functional variants to determine effects on DMN structure and function; **Aim 4)** Establish relationships between DMN structural and functional connectivity with memory, cognition, and biomarkers of metabolism.

Methods: PLINK will assess genetic associations with GIFT ICA derived subject-specific DMNs. SNPs/CNVs constituting independent loci reaching genome wide significance ($P<5.0\times10-8$) in models corrected for age and sex will be selected. Selected variants will be validated in GIFT ICA using voxel-wise analyses, to determine if DMN associations are localized to temporal, parietal, and/or prefrontal regions. Latent growth models will examine how genomic variants affect memory, cognition, glucose, and markers of inflammation. **Subjects:** Humans (40-75 years) from the 1000Connectomes, ADNI, Schitzophrenia Connect, Religious Order Study, and NACC/ NIAGADS databases with existing rsFMRI, GWAS and memory data. Replication analyses will use an independent cohort from the UK biobank. **Design:** Large multi-center cohort collaboration where N = 20,000

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Non-Technical Summary for Application for Genomic Data from NIAGADS

Investigators will provide a non-technical summary of their proposed research. If the project is approved, this statement will be publicly available for lay audiences to read the purpose and objectives of the research. Please limit to 1,100 characters.

First, the investigators will search for genes related to parts of the brain that function together to create memories. They will test how these genes relate to the brain's structure or activity while at rest. After identifying genes associated with these brain regions, they will test if they are related to tests focused on learning and remembering words, letters, numbers, and objects. Finally, they will assess if these genes are related to chemical changes in the body.

The investigators will also test if genes involved in energy production are associated with the structure and function of the brain regions that form memories. They will select these genes to test if they are associated with people's ability to learn or remember words, letters, numbers, and objects. They will conclude by comparing how genes related to both memory and brain structure or function influence chemicals related to hormones, immune system, and nutrition.

The investigators will follow the timeline below and replicate all analyses in 2 separate groups of people.

Timeline

	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Year 1	Data Transfer & Organization				Pre-processing MRI				Genome Imputation			
Year 2	Data Analysis Aim 1				Data Analysis Aim 2				Data Analysis Aim 3			
Year 3	Prepare Publications				Replicate Analysis Aim 1				Replicate Analysis Aim 2			
Year 4	Replicate Analysis Aim 3				Aim 4 & Replicate				Prepare Publications			