Genome-wide pathway analysis of memory impairment in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort

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Abstract

Memory deficits are prominent features of mild cognitive impairment (MCI) and Alzheimer's disease (AD). The genetic architecture underlying these memory deficits likely involves the combined effects of multiple genetic variants operative within numerous biological pathways. In order to identify functional pathways associated with memory impairment, we performed a pathway enrichment analysis on genome-wide association data from 742 Alzheimer's Disease Neuroimaging Initiative (ADNI) participants. A composite measure of memory was generated as the phenotype for this analysis by applying modern psychometric theory to item-level data from the ADNI neuropsychological test battery. Using the GSA-SNP software tool, we identified 27 canonical, expertly-curated pathways with enrichment (FDR-corrected p-value < 0.05) against this composite memory score. Processes classically understood to be involved in memory consolidation, such as neurotransmitter receptor-mediated calcium signaling and long-term potentiation, were highly represented among the enriched pathways. In addition, pathways related to cell adhesion, neuronal differentiation and guided outgrowth, and glucose- and inflammation-related signaling were also enriched. Among genes that were highly-represented in these enriched pathways, we found indications of coordinated relationships, including one large gene set that is subject to regulation by the *SP1* transcription factor, and another set that displays co-localized expression in normal brain tissue along with known AD risk genes. These results 1) highlight key pathways and their candidate genes that appear to underlie susceptibility to memory impairment in this population, 2) suggest mechanistic targets for future studies related to diagnosis and treatment of memory deficits, and 3) validate the promise of pathway analysis in elucidating key processes underlying complex traits.