Working Memory and Vigilance as Multivariate Endophenotypes Related to Common Genetic Risk for Attention-Deficit/Hyperactivity Disorder

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Abstract

Objective
Understanding the role of endophenotypes is essential for process models of psychopathology. This study examined which candidate cognitive endophenotypes statistically mediate common variant genetic risk for attention-deficit/hyperactivity disorder (ADHD).

Method
A case-control design using community-recruited volunteer children 7-11 years old (n=656, n=435 ADHD) of whom 514 were homogenous European ancestry for the primary models (n=337 ADHD, 177 non-ADHD). Children were assessed with a multi-informant, best-estimate diagnostic procedure and laboratory measures of working memory, response inhibition, executive functioning, arousal/attention, temporal information processing, and processing speed. Latent variables were created for the candidate cognitive measures and for parent- and teacher-rated ADHD dimensions. Polygenic risk scores (PGS) were computed, using a discovery sample of 20,183 individuals with ADHD and 35,191 controls from the Psychiatric Genetics Consortium. Cognitive measures that survived multiple testing correction for association with the PGS were evaluated for mediation with ADHD using structural equation models.

Results
Results were essentially identical in the homogeneous European ancestry subgroup (n=514) and in the full sample (n=656). For the European population, the PGS was associated with ADHD diagnosis (Nagelkerke R2= .045; beta=.233, SE=.053, p=.000011) and multi-indicator dimensional ADHD latent variables by parent report (beta=.185, SE=.043) and teacher report (beta=.165, SE=.042). The PGS effect was statistically mediated by working memory (indirect effect, beta=.101, SE=.029, 95% CI=.05, .16, p=.00049, 43% of genetic effect accounted for) and arousal/alertness (indirect effect beta=.115, 95% CI=.04, .20, SE=.041, p=.005, 49% of genetic effect accounted for).

Conclusion
This is the first clear demonstration from molecular genetic data that working memory and arousal regulation are promising cognitive endophenotypes for ADHD with regard to mediating genetic risk from common genetic variants.