Shared Polygenic Risk for ADHD, Executive Dysfunction and Other Psychiatric Disorders

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Transl Psychiatry. 2020 Jun 9;10(1):182.
doi: 10.1038/s41398-020-00872-9

Abstract

Many psychiatric disorders are associated with impaired executive functioning (EF). The associated EF component varies by psychiatric disorders, and this variation might be due to genetic liability. We explored the genetic association between five psychiatric disorders and EF in clinically-recruited attention deficit hyperactivity disorder (ADHD) children using polygenic risk score (PRS) methodology. Genome-wide association study (GWAS) summary data for ADHD, major depressive disorder (MDD), schizophrenia (SZ), bipolar disorder (BIP) and autism were used to calculate the PRSs. EF was evaluated by the Stroop test for inhibitory control, the trail-making test for cognitive flexibility, and the digital span test for working memory in a Chinese ADHD cohort (n = 1147). Exploratory factor analysis of the three measures identified one principal component for EF (EF-PC). Linear regression models were used to analyze the association between each PRS and the EF measures. The role of EF measures in mediating the effects of the PRSs on ADHD symptoms was also analyzed. The result showed the PRSs for MDD, ADHD and BIP were all significantly associated with the EF-PC. For each EF component, the association results were different for the PRSs of the five psychiatric disorders: the PRSs for ADHD and MDD were associated with inhibitory control (adjusted P = 0.0183 and 0.0313, respectively), the PRS for BIP was associated with working memory (adjusted P = 0.0416), and the PRS for SZ was associated with cognitive flexibility (adjusted P = 0.0335). All three EF measures were significantly correlated with ADHD symptoms. In mediation analyses, the ADHD and MDD PRSs, which were associated with inhibitory control, had significant indirect effects on ADHD symptoms through the mediation of inhibitory control. These findings indicate that the polygenic risks for several psychiatric disorders influence specific executive dysfunction in children with ADHD. The results helped to clarify the relationship between risk genes of each mental disorder and the intermediate cognitive domain, which may further help elucidate the risk genes and motivate efforts to develop EF measures as a diagnostic marker and future treatment target.