Interplay between stress response genes associated with attention deficit-hyperactivity disorder and brain volume.


Abstract

The glucocorticoid receptor plays a pivotal role in the brain's response to stress; a haplotype of functional polymorphisms in the NR3C1 gene encoding this receptor has been associated with attention-deficit/hyperactivity disorder (ADHD). The serotonin transporter gene polymorphism 5-HTTLPR is known to influence the relation between stress exposure and ADHD severity, which may be partly due to its reported effects on glucocorticoid levels. We therefore investigated if NR3C1 moderates the relation of stress exposure with ADHD severity and brain structure, and the potential role of 5-HTTLPR. Neuroimaging, genetic, and stress exposure questionnaire data was available for 539 adolescents and young adults participating in the multicenter ADHD cohort study NeuroIMAGE (average age 17.2 years). We estimated the effects of genetic variation in NR3C1 and 5-HTT, stress exposure, and their interactions on ADHD symptom count and gray matter volume. We found that individuals carrying the ADHD risk haplotype of NR3C1 showed a significantly more positive relation between stress exposure and ADHD severity than non-carriers. This gene-environment interaction was significantly stronger for 5-HTTLPR L-allele homozygotes than for S-allele carriers. These two- and three-way interactions were reflected in the gray matter volume of the cerebellum, parahippocampal gyrus, intracalcarine cortex, and angular gyrus. Our findings illustrate how genetic variation in the stress response pathway may influence the effects of stress exposure on ADHD severity and brain structure. The reported interplay between NR3C1 and 5-HTT may further explain some of the heterogeneity between studies regarding the role of these genes and HPA axis activity in ADHD.