COMT genotype affects brain white matter pathways in attention-deficit/hyperactivity disorder

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Abstract
Increased dopamine availability may be associated with impaired structural maturation of brain white matter connectivity. This study aimed to derive a comprehensive, whole-brain characterization of large-scale axonal connectivity differences in attention-deficit/hyperactivity disorder (ADHD) associated with catechol-O-methyltransferase gene (COMT) Val158Met polymorphism. Using diffusion tensor imaging, whole-brain tractography, and an imaging connectomics approach, we characterized altered white matter connectivity in youth with ADHD who were COMT Val-homozygous (N = 29) compared with those who were Met-carriers (N = 29). Additionally, we examined whether dopamine transporter gene (DAT1) and dopamine D4 receptor gene (DRD4) polymorphisms were associated with white matter differences. Level of attention was assessed using the continuous performance test before and after an 8-week open-label trial of methylphenidate (MPH). A network of white matter connections linking 18 different brain regions was significantly weakened in youth with ADHD who were COMT Met-carriers compared to those who were Val-homozygous (P < 0.05, family-wise error-corrected). A measure of white matter integrity, fractional anisotropy, was correlated with impaired pretreatment performance in continuous performance test omission errors and response time variability, as well as with improvement in continuous performance test response time variability after MPH treatment. Altered white matter connectivity was exclusively based on COMT genotypes, and was not evident in DAT1 or DRD4. We demonstrated that white matter connectivity in youth with ADHD is associated with COMT Val158Met genotypes. The present findings suggest that different layers of dopamine-related genes and interindividual variability in the genetic polymorphisms should be taken into account when investigating the human connectome.