Age and DRD4 Genotype Moderate Associations Between Stimulant Treatment History and Cortex Structure in Attention-Deficit/Hyperactivity Disorder

Lizanne J.S. Schweren, Catharina A. Hartman, PhD, Dirk J. Heslenfeld, PhD, Annabeth P. Groenman, PhD, Barbara Franke, PhD, Jaap Oosterlaan, PhD, Jan K. Buitelaar, MD, PhD, Pieter J. Hoekstra, MD, PhD

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Abstract

Objective
Attention-deficit/hyperactivity disorder (ADHD) has been associated with dopaminergic imbalance and subtle volume reductions in the brain. Stimulants acutely enhance dopaminergic neurotransmission. Long-term effects of chronic manipulation of the dopaminergic system on brain structure remain poorly understood; they could be beneficial or unfavorable, and may be moderated by common genetic variants and/or age.

Method
In a large observational cohort study (NADHD=316), we evaluated the effects of cumulative stimulant treatment, genotype (for DAT1 haplotype and DRD4 variants), and treatment-by-genotype interactions on striatal, frontal, and hippocampal volumes, as well as their interactions with age.

Results
We found no main effects of treatment. Associations between treatment and bilateral frontal and left hippocampal volume depended on DRD4 genotype and age. At younger age and lower treatment levels, but not at younger age and higher treatment levels, carriers of the DRD4 7R-allele showed decreased frontal cortex volumes. At older age, both carriers and non-carriers showed lower frontal volumes irrespective of treatment history. Left hippocampal volume was similar to controls at average treatment levels, and increased with treatment only in carriers of the DRD4 risk allele and at younger age. No interaction effects were found in the striatum.

Conclusion
Carriers of the DRD4 risk allele may at younger age be sensitive to cortical remodeling after stimulant treatment. The cross-sectional nature of our study warrants cautious interpretation of age effects. Our findings, although of small effect size, may ultimately contribute to optimal care for individuals with ADHD.