Female-specific association of NOS1 genotype with white matter microstructure in ADHD patients and controls

Hanneke van Ewijk, Janita Bralten, Esther D.A. van Duin, Marina Hakobjan, Jan K. Buitelaar, Dirk J. Heslenfeld, Pieter J. Hoekstra, Catharina Hartman, Martine Hoogman, Jaap Oosterlaan, Barbara Franke

Journal of Child Psychology and Psychiatry, 2017
DOI: 10.1111/jcpp.12742

Abstract

Background
The nitric oxide synthase gene (NOS1) exon 1f (ex1f) VNTR is a known genetic risk factor for Attention-Deficit/Hyperactivity Disorder (ADHD), particularly in females. NOS1 plays an important role in neurite outgrowth and may thus influence brain development, specifically white matter (WM) microstructure, which is known to be altered in ADHD. The current study aimed to investigate whether NOS1 is associated with WM microstructure in (female) individuals with and without ADHD.

Methods
Diffusion Tensor Imaging (DTI) scans were collected from 187 participants with ADHD (33% female) and 103 controls (50% female), aged 8–26 years, and NOS1-ex1f VNTR genotype was determined. Whole-brain analyses were conducted for fractional anisotropy (FA) and mean diffusivity (MD) to examine associations between NOS1 and WM microstructure, including possible interactions with gender and diagnosis.

Results
Consistent with previous literature, NOS1-ex1f was associated with total ADHD and hyperactivity-impulsivity symptoms, but not inattention; this effect was independent of gender. NOS1-ex1f was also associated with MD values in several major WM tracts in females, but not males. In females, homozygosity for the short allele was linked to higher MD values than carriership of the long allele. MD values in these regions did not correlate with ADHD symptoms. Results were similar for participants with and without ADHD.

Conclusions
NOS1-ex1f VNTR is associated with WM microstructure in females in a large sample of participants with ADHD and healthy controls. Whether this association is part of a neurodevelopmental pathway from NOS1 to ADHD symptoms should be further investigated in future studies.