A Population-Based Imaging Genetics Study of Inattention/Hyperactivity: Basal Ganglia and Genetic Pathways

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Objective: Although attention-deficit/hyperactivity disorder (ADHD) is 1 of the most common neurodevelopmental disorders, little is known about the neurobiology. Clinical studies suggest basal ganglia morphology plays a role. Furthermore, hyperactivity/impulsivity symptoms have recently been linked to genetic pathways involved in dopamine/norepinephrine and serotonin neurotransmission and neuritic outgrowth. We aimed to assess the association between ADHD symptoms, basal ganglia volume, and the 3 proposed genetic pathways in a pediatric population-based sample. With this, we aimed to investigate the generalizability of earlier clinical findings to the general population.

Method: This study included a population-based sample of 1,871 children with data on ADHD symptoms and genetic data, and 344 children with additional neuroimaging data. Regression analyses between ADHD symptom severity and volumetric data of the basal ganglia were performed. Also, gene-set analyses investigating the association between both ADHD symptom severity and basal ganglia volume with the dopamine/norepinephrine, serotonin, and neuritic outgrowth pathways were performed.

Results: More inattention and hyperactivity/impulsivity symptoms were associated with a smaller volume of the putamen ($\beta = -0.13$, $p = .034$), which was regarded as trend-level after correction for multiple testing. Stratified analyses showed a stronger putamen–hyperactivity association in children with clinical scores, although a similar trend was visible in the nonclinical subsample. The genetic pathways were not related to either ADHD symptoms or basal ganglia volume.

Conclusion: ADHD symptoms were marginally related to putamen volume in our population-based sample. We found no evidence for a role of dopamine/norepinephrine, serotonin, or neuritic outgrowth genetic pathways in ADHD symptom severity.

Key Words: attention-deficit/hyperactivity problems, gene sets, neurotransmitter systems, neuroimaging, basal ganglia

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Attention-deficit/hyperactivity disorder (ADHD) is characterized by persistent inattention and/or hyperactivity and impulsivity problems that are thought to arise as a consequence of genetic risk factors, altered brain development, and environmental influences. The disorder has a complex and polygenic character, implying that many genes, each of very small individual effect, are involved. The clinical presentation of ADHD is highly heterogeneous, as not all children exhibit exactly the same set of problems and the same degree of severity. Although ADHD is 1 of the most common neurodevelopmental disorders, with a worldwide prevalence of about 3% to 5%,[1] little is known about its underlying neurobiology. In the current study, we aimed to assess the neurobiology of ADHD symptoms in a large population-based sample of children by applying recently developed methods and using both genetic and brain imaging data.

Recent genetic studies have shown that genetic factors play a considerable role in the development of ADHD, with heritability estimates around 70%.[2] Despite the high heritability, the identification of genes that are associated with the disorder has proved to be difficult. Genome-wide association studies (GWAS) that have been performed in recent years have not been successful,[3] likely because the small effects of single genes require very large sample sizes to reach genome-wide significance. To overcome the problems associated with this polygenic character of ADHD, new approaches have been sought, including gene-set analyses.[4,5] In gene-set analyses, single genes are combined in gene sets that are jointly tested for association with the phenotype of interest. Compared to testing multiple separate genes or single nucleotide polymorphisms (SNPs), gene-set analyses are generally more powerful, as they

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TABLE 1 Participant Characteristics

Child Characteristics	Total Sample N = 1,871	Imaging Subsample n = 344
Gender, % male	50.9	50.3
Ethnicity, %[a]		
Dutch	89.8	94.5
Other western	8.4	4.1
Nonwestern	1.8	1.4
Age at brain imaging, y[b]	—	8.08 (0.97)
Age at CPRS-R:S assessment, y	8.15 (0.22)	8.19 (0.25)
CPRS-R:S Inattention scale		
Raw score	3.10 (3.59)	3.56 (3.92)
Range	0–18	0–18
t Score	50.69 (9.44)	51.83 (9.92)
Range	41–89	41–89
t Score moderately atypical ($65 < t \leq 70$), %	2.8	2.9
T Score markedly atypical ($t > 70$), %	5.2	7.3
CPRS-R:S Hyperactivity/ Impulsivity scale		
Raw score	2.09 (2.71)	2.70 (3.33)
Range	0–18	0–18
t Score	49.07 (7.74)	50.86 (9.53)
Range	42–90	42–90
t Score moderately atypical ($65 < t \leq 70$), %	3.0	4.1
t Score markedly atypical ($t > 70$), %	2.7	6.1
Psychostimulant use, % yes[b]	—	3.2
SRS[c], score	0.19 (0.21)	0.23 (0.25)

TABLE 1 Continued

Maternal Characteristics	Total Sample N = 1,871	Imaging Subsample n = 344
Education level, %		
High	75.5	72.1
Medium	19.7	22.4
Low	4.8	5.5
Alcohol use during pregnancy, %		
Never	24.5	25.6
Until pregnancy was known	14.4	14.8
Continued occassionally during pregnancy	47.3	44.5
Continued frequently during pregnancy[d]	13.8	15.1
Smoking during pregnancy, %		
Never	80.4	80.8
Until pregnancy was known	8.1	6.4
Continued during pregnancy	11.5	12.8
Household income, %		
>2,000 euro	93.2	89.8
1,200–2,000 euro	5.2	7.3
<1,200 euro	1.6	2.9

Note: Values given as mean and standard deviation, unless otherwise indicated. CPRS-R:S = Conners' Parent Rating Scale–Revised: Short Form; SRS = Social Responsiveness Scale.

[a]*Categories include only ethnicities that are regarded as white.*

[b]*Data collected only in imaging subsample.*

[c]*SRS scores are raw scores, weighted for number of items, allowing 25% missing.*

[d]*Frequent continued use was defined as 1 drink or more per week during at least 2 trimesters of pregnancy.*

suffer less from multiple testing. In a recent study of Bralten *et al.*[6], candidate genetic pathways, as represented by gene sets, were tested in a large clinical ADHD sample (N = 930) of children and adolescents between 5 and 17 years of age. The authors selected 3 gene sets based on their suspected relation with ADHD, namely, the dopamine/norepinephrine pathway, the serotonin pathway, and a pathway consisting of genes involved in neuritic outgrowth. Aberrant dopaminergic, noradrenergic, and serotonergic neurotransmission has been frequently discussed as a potential causal pathway in ADHD,[7-9] and genes involved in neuritic outgrowth constituted the top results of ADHD GWA studies.[10] In the study by Bralten *et al.*,[6] the 3 selected gene sets were first tested against *DSM-IV* symptom count and, in a later step, against a continuous measure of ADHD symptom severity as measured using the Conners' Parent and Teacher Rating Scales. The authors found the combination of the 3 genetic pathways, as well as each of the separate pathways, to be associated with *DSM-IV* symptom count of hyperactivity/impulsivity symptoms, but not with the count of inattention symptoms. Analysis of symptom severity as rated with the Conners' Parent Rating Scale validated this result.[6] As their sample included only participants with a diagnosis of ADHD, they could draw conclusions only in the context of the association with symptom severity in a clinical sample. To test whether these results generalize to the full range of symptom severity found in the general population, validation in a population-based sample is needed.

Identification of gene sets with the severity of symptoms in ADHD suggests the involvement of specific biological pathways. However, to understand how these gene sets may influence ADHD symptom severity, we need insight into the functional consequences of genetic variation in the gene sets. One route to investigate this is the use of intermediate phenotypes. Based on the criteria that define suitable intermediate phenotypes,[11] brain morphology can be regarded as a suitable intermediate phenotype in the association between genetics and ADHD. Studies investigating subcortical brain morphology in relation to ADHD symptoms have reported the most pronounced structural abnormalities in the basal ganglia (putamen, pallidum, and caudate). A reduction in volume of these 3 structures has been consistently found in patients with ADHD.[12-14] As part of the cortico-striatal