Neural Mechanisms of Attention-Deficit/Hyperactivity Disorder Symptoms Are Stratified by *MAOA* Genotype

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Background: Attention-deficit/hyperactivity disorder (ADHD) is characterized by deficits in reward sensitivity and response inhibition. The relative contribution of these frontostriatal mechanisms to ADHD symptoms and their genetic determinants is largely unexplored.

Methods: Using functional magnetic resonance imaging and genetic analysis of the monoamine oxidase A (*MAOA*) gene, we investigated how striatal and inferior frontal activation patterns contribute to ADHD symptoms depending on *MAOA* genotype in a sample of adolescent boys ($n = 190$).

Results: We demonstrate an association of ADHD symptoms with distinct blood oxygen level–dependent (BOLD) responses depending on *MAOA* genotype. In A hemizygotes of the expression single nucleotide polymorphism rs12843268, which express lower levels of *MAOA*, ADHD symptoms are associated with lower ventral striatal BOLD response during the monetary incentive delay task and lower inferior frontal gyrus BOLD response during the stop signal task. In G hemizygotes, ADHD symptoms are associated with increased inferior frontal gyrus BOLD response during the stop signal task in the presence of increased ventral striatal BOLD response during the monetary incentive delay task.

Conclusions: Depending on *MAOA* genotype, ADHD symptoms in adolescent boys are associated with either reward deficiency or insufficient response inhibition. Apart from its mechanistic interest, our finding may aid in developing pharmacogenetic markers for ADHD.

Key Words: Attention-deficit/hyperactivity disorder, genetics, inferior frontal gyrus, monoamine oxidase A, neuroimaging, ventral striatum

Attention-deficit/hyperactivity disorder (ADHD) symptoms include impulsivity, hyperactivity, and inattention. The disorder is thought to be dimensional, with the most extreme manifestations clinically diagnosed as ADHD according to DSM-IV (1,2). Evidence from neuroimaging studies suggests that impulsivity and hyperactivity are associated with striatal and frontal activation patterns during reward anticipation and response inhibition, respectively (3–7). Despite the clinical relevance of these neural mechanisms, we know little about how reward anticipation and response inhibition jointly affect ADHD symptoms.

Studies of ADHD patients frequently report reduced blood oxygenation level–dependent (BOLD) response of the ventral striatum (VS) during reward anticipation (6,8–11). This hyporesponsiveness of the VS has been observed during both immediate and delayed rewards (11) in ADHD patients as well as in healthy female subjects (12). However, there is conflicting evidence

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showing that there may also be a positive correlation of impulsivity and VS activation during reward anticipation (13,14) and during immediate compared with delayed rewards in the normal population (15).

ADHD has been associated with poor response inhibition resulting either from insufficient activation of the inferior frontal gyrus (IFG) (5,16,17) or from a requirement for larger frontal recruitment for optimal task performance (4,7,18,19). Rubia and colleagues reported that the IFG of ADHD patients is hypoactivated during inhibition trials of the stop signal task (SST) relative to the IFG of healthy control subjects (20), but others have observed a hyperactivation of the IFG during successful inhibition in ADHD patients (4,7). Previous studies suggest that the right IFG in particular is a crucial structure underlying response inhibition (21).

Thus it appears that BOLD responses of the subcortical reward system and inferior frontal inhibitory mechanisms, particularly the right IFG, are crucially related to ADHD symptoms (8,21). However, there is inconsistency regarding whether they are associated with enhanced or decreased BOLD responses in these two systems. Furthermore, because reward processing and response inhibition have never been tested together in adolescents, it is unclear whether ADHD symptoms in the same individuals are associated with abnormalities in either or both systems. We therefore interrogated both systems and investigated potential determinants of brain activity in the regions involved.

Because the mean heritability of ADHD is estimated at 76% (22), we hypothesized that these determinants might include genetic factors (23). ADHD symptoms are more commonly observed in males than females with gender ratios varying from 3:1 to 9:1 (24,25). It has therefore been suggested that genes on the X chromosome may be involved in the development of the disorder. The monoamine oxidase A gene *(MAOA)* is localized on the human X chromosome (26–28). *MAOA* encodes a mitochondrial enzyme, which degrades monoamines, including norepinephrine, dopamine, and serotonin (29), which are thought to underlie neural functions associated with ADHD. Several studies have identified associations between specific *MAOA* polymorphisms and ADHD (26,27,30,31). Most recently, a screen of 23 candidate genes (including *COMT DRD1-DRD4, DAT1, SNAP25, MAOA,* and *MAOB*) reported that *MAOA* was the most promising candidate gene underlying ADHD out of the genes investigated (27). Of 12 *MAOA* polymorphisms that were tested for association with ADHD, rs12843268 showed the strongest association. A haplotype analysis that included the *MAOA* single nucleotide polymorphism (SNP) rs12843268 reported an association with adolescent ADHD and response inhibition in boys (32). Earlier studies showed that a variable number tandem repeat (VNTR) within the promoter of *MAOA*, which is linked to ADHD (33), was also associated with inhibitory control (34) as well as novelty seeking (35,36).

In a sample of 414 adolescents from the IMAGEN study who did not achieve diagnostic criteria for ADHD, we investigated whether *MAOA* genotype might be used for stratification by testing the association between *MAOA* and ADHD symptoms. We then carried out stratified analyses of brain activation in the key reward area of VS and the principal inhibitory frontal area, the right IFG. On the basis of etiologic models just described, we hypothesized that there is 1) a significant association between *MAOA* genotype and ADHD symptoms, 2) a significant association between ADHD symptoms and VS and right IFG BOLD responses, and 3) that the association between ADHD symptoms and brain activation patterns during reward processing and inhibitory control is stratified by *MAOA* genotype.

Methods and Materials

Participants

We used data from the first wave of IMAGEN (n = 648). Individuals who had passed quality controls for genotyping, neuroimaging, and behavioral tests were included in the data set. Four hundred and fourteen adolescents passed the inclusion criteria for further analysis (190 boys, 224 girls). The mean age of the participants was 14.4 years (SD: .4; range: 13.3–15.6 years; Table 1).

Participants were tested at eight IMAGEN assessment centres (London, Nottingham, Dublin, Mannheim, Berlin, Hamburg, Paris, and Dresden). Local ethics research committees at each site approved the study. On the day of assessment, written consent was obtained from the parent or guardian, and verbal assent was obtained from the adolescent. A detailed description of recruitment and assessment procedures and inclusion/exclusion criteria have been published elsewhere (37). Three hundred and sixty-seven participants were right-handed, and 47 participants were left-handed or ambidextrous. Individuals with verbal (VIQ) or nonverbal (PIQ) IQ <75 or missing IQ information were excluded (n = 10). Handedness and study site were controlled for in all analyses.

Out of the 190 boys who had completed the monetary incentive delay (MID) task, 143 had also completed the SST (Supplement 1).

Table 1. Demographics Split by Gender and rs12843268 Genotype Groups, Mean ± SD (Range)

	Boys			Girls			
	A (n = 67)	G (n = 123)	Total (n = 190)	AA (n = 16)	AG (n = 100)	GG (n = 108)	Total (n = 224)
Age (years)	14.5 ± .4 (13.6–15.5)	14.5 ± .4 (13.6–15.6)	14.5 ± .4 (13.6–15.6)	14.5 ± .4 (13.9–15.6)	14.4 ± .4 (13.3–15.4)	14.4 ± .5 (13.3–15.5)	14.4 ± .04 (13.3–15.6)
VIQ	117.4 ± 14.9 (83–150)	115.1 ± 14.6 (87–155)	115.9 ± 14.7 (83–155)	110.4 ± 11.8 (88–130)	112.6 ± 15.1 (77–150)	113.1 ± 15.2 (77–152)	112.7 ± 14.9 (77–152)
PIQ	107.2 ± 13.7 (81–149)	107.0 ± 12.5 (79–135)	107.0 ± 12.9 (79–149)	111.8 ± 12.9 (92–141)	111.4 ± 12.1 (86–146)	109.3 ± 12.8 (76–135)	110.9 ± 12.7 (76–147)
ADHD Symptoms	2.7 ± 1.9 (0–7)	3.4 ± 2.6 (0–10)	3.1 ± 2.1 (0–10)	2.7 ± 1.9 (0–7)	2.3 ± 2.1 (0–8)	2.6 ± 2.2 (0–10)	2.4 ± 2.1 (0–10)

We found no significant genotype differences in age, VIQ, PIQ ($p > .05$) in boys or girls after controlling for study site. Boys carry one A allele or one G allele, girls are either AA homozygous, AG heterozygous, or GG homozygous for rs12843268.

ADHD, attention-deficit/hyperactivity disorder; VIQ, verbal IQ; PIQ, nonverbal IQ.