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...
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)

<table>
<thead>
<tr>
<th></th>
<th>Boys A (n = 67)</th>
<th>Boys G (n = 123)</th>
<th>Boys Total (n = 190)</th>
<th>Girls AA (n = 16)</th>
<th>Girls AG (n = 100)</th>
<th>Girls GG (n = 108)</th>
<th>Girls Total (n = 224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>14.5 ± 6.4</td>
<td>14.5 ± 6.4</td>
<td>14.5 ± 6.4</td>
<td>14.5 ± 6.6</td>
<td>14.5 ± 6.6</td>
<td>14.5 ± 6.6</td>
<td>14.5 ± 6.6</td>
</tr>
<tr>
<td>VIQ</td>
<td>117.4 ± 14.9</td>
<td>115.1 ± 14.6</td>
<td>115.9 ± 14.7</td>
<td>110.4 ± 11.8</td>
<td>112.6 ± 15.2</td>
<td>113.1 ± 15.2</td>
<td>112.7 ± 14.9</td>
</tr>
<tr>
<td>PIQ</td>
<td>107.2 ± 13.7</td>
<td>107.0 ± 12.5</td>
<td>107.9 ± 12.9</td>
<td>111.8 ± 12.9</td>
<td>111.4 ± 12.1</td>
<td>109.3 ± 12.8</td>
<td>110.9 ± 12.7</td>
</tr>
<tr>
<td>ADHD Symptoms</td>
<td>2.7 ± 1.9</td>
<td>3.4 ± 2.6</td>
<td>3.1 ± 2.1</td>
<td>2.7 ± 1.9</td>
<td>2.3 ± 2.1</td>
<td>2.6 ± 2.2</td>
<td>2.4 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>0–7</td>
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<td>0–10</td>
<td>0–7</td>
<td>0–8</td>
<td>0–10</td>
<td>0–10</td>
</tr>
</tbody>
</table>

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.

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ADHD Symptoms (Strength and Difficulties Questionnaire)

ADHD symptoms were assessed using parental reports of the Strength and Difficulties Questionnaire (SDQ), a brief 25-item behavioral screening tool probing for ADHD-type problems (hyperactivity, inattention, and impulsivity), emotional symptoms, conduct problems, peer problems, and prosocial behavior (38). Our sample of 414 consisted of 28 subjects (20 boys) who “possibly” suffered from ADHD according to the SDQ. The SDQ ADHD symptom scale can be subdivided into two subscales: a hyperactivity/impulsivity subscale, composed of three items, and an inattention subscale, composed of two items (39).

Genotyping

DNA purification and genotyping was performed by the Centre National de Génotypage in Paris. DNA was extracted from whole blood samples preserved in ethylene-eiamine-tetra-acetic acid (EDTA) vacutainer tubes (BD, Becton, Dickinson and Company, Oxford, United Kingdom) using Gentra Puregene Blood Kit (QIAGEN, Valencia, California) according to the manufacturer’s instructions. Genotype information was collected at 582,982 markers using the Illumina HumanHap610 Genotyping BeadChip (Illumina, San Diego, California) as part of a previous genome-wide association study (37) (Supplement 1).

Effect of rs12843268 on MAOA Expression

Total RNA was extracted from whole blood cells using the PAXgene Blood RNA Kit (QIAGEN). Labeled complementary RNA (cRNA) from 369 individuals was generated. MAOA expression was independently validated in 40 boys using quantitative polymerase chain reaction (Supplement 1). The relative fold change in expression was measured via the comparative method using the formula $2^{-\Delta\Delta C_t}$ (40).

Monetary Incentive Delay Task

The participants performed a modified version of the MID task to study neural responses to reward anticipation and reward outcome. The paradigm has been previously described (41) (Supplement 1).

Stop Signal Task

Participants also performed an event-related SST designed to study neural responses to successful and unsuccessful inhibitory control (5,42). The task has been previously described (5,42) (Supplement 1). The dependent variable of the task is the stop signal reaction time (SSRT), which was calculated by subtracting the mean stop signal delay (the average time between go and stop signal, at which the subject managed to inhibit to 50% of trials) from the mean reaction time to go trials (43). Because of problems in the tracking algorithm, SSRT data was only available for 73 subjects.

Magnetic Resonance Imaging Data Acquisition and Analysis

Structural and functional magnetic resonance imaging (fMRI) data were acquired at eight IMAGEN assessment sites with 3T MRI scanners of different manufacturers (Siemens, Munich, Germany; Philips, Best, The Netherlands; General Electric, Chalfont St Giles, UK; Bruker, Ettlingen, Germany). The scanning variables were specifically chosen to be compatible with all scanners. The same scanning protocol was used at all sites. In brief, high-resolution T1-weighted three-dimensional structural images were acquired for anatomical localization and coregistration with the functional time series. Functional MRI BOLD images were acquired with a gradient-echo, echo-planar imaging sequence. For the MID task, 300 volumes were acquired for each subject. For the SST, 444 volumes were acquired for each subject. For both tasks, each volume consisted of 40 slices aligned to the anterior commissure/posterior commissure line (2.4-mm slice thickness, 1-mm gap). The echo time was optimized (echo time = 30 msec, repetition time = 2200 msec) to provide reliable imaging of subcortical areas (Supplement 1).

Functional MRI data were analyzed with SPM8 (Statistical Parametric Mapping; http://www.filion.ucl.ac.uk/spm). We extracted regions of interest using the Marsbar toolbox (http://marsbar.sourceforge.net). The IFG opercularis was extracted based on the Montreal Neurological Institute Automated Anatomical Labeling. Because the VS is not available in Automated Anatomical Labeling, it was created using Marsbar based on the peak of the “anticipation high win versus no win” contrast (xyz = ±9, 11, −2, 9-mm radius; Figure S2 and Table S2 in Supplement 1). Averaged beta values based on all voxels in the regions of interest were used for all analyses.

Association Analyses

The general linear model was used to determine associations among the SDQ measure, BOLD responses, and MAOA genotype. Correlations between fMRI BOLD-responses and SSRT were derived through Pearson correlations. All analyses were two-sided. Permutations with 100,000 iterations were used to control for hemisphere specific tests of VS BOLD response. Where $P_{\text{corrected}}$ is indicated, $p$ values were corrected for statistical tests performed in the left and right hemisphere.

Results

Identification and Characterization of MAOA SNP

We extracted eight SNPs covering the MAOA locus and identified two haplotypes with a frequency greater than 5%, which accounted for 92.3% of the variance of the gene (Table 2; Figure S4 in Supplement 1). Among the SNPs segregating the two haplotypes was rs12843268, which has previously been associated with ADHD symptoms (27,32). We therefore selected rs12843268 for further analyses. G allele carriers of rs12843268 represent the major haplotype with a frequency of 63.4%, whereas A allele carriers represent the minor haplotype with a frequency of 28.9%. Gene expression data of MAOA from peripheral blood were available from 171 boys and 198 girls of the IMAGEN sample. In boys, we found significant differences between genotype groups of rs12843268 ($F_{1,162} = 7.82, p = .006$), with higher MAOA messenger RNA (mRNA) expression in the G hemizygotes compared with A hemizygotes. The expression analysis was not significant in girls ($F_{1,189} = .58, p = .45$). The association was independently validated through quantitative polymerase chain reaction in RNA from 40 boys, which showed a relative fold change in expression between the two genotypes of 6.34 (SE: .296) (Figure S5 in Supplement 1).

Effects of MAOA Genotype on ADHD Symptoms

Because of the X-linked nature of MAOA, we tested the association between the SNP rs12843268 and ADHD symptoms in boys and girls separately. We found a significant association of SNP rs12843268 and ADHD symptoms in boys ($F_{1,181} = 4.12, p = .044$, partial $\eta^2 = .022$) with G hemizygotes ($n = 123$) showing significantly more ADHD symptoms compared with A hemizygotes ($n = 67$) (Table 1). Rs12843268 genotype accounted for 2.2% of the variance in ADHD symptoms in boys. We did not find...
a significant association between MAOA SNP rs12843268 and ADHD symptoms in girls ($F_{1,215} = 1.47$, $p = .23$), suggesting that the effects of MAOA are gender specific. On the basis of these findings, we performed imaging genetic analyses in boys only.

**Reward Anticipation**

In boys, we investigated the effect of rs12843268 genotype on fMRI BOLD response in the VS during reward anticipation using the MID task. G hemizyogotes showed significantly higher BOLD response than A hemizygotes in the left VS ($F_{1,180} = 10.87$, $\rho_{\text{corrected}} = .002$, partial $\eta^2: .061$; Figure 1A) and in the right VS ($F_{1,180} = 6.80$, $\rho_{\text{corrected}} = .015$, partial $\eta^2: .045$; Figure 1B).

We next examined whether individual variability in VS BOLD responses were correlated with ADHD symptoms in the full sample of 190 boys. We found a trend toward a negative correlation between the right VS BOLD response and ADHD symptoms in the full sample of boys ($r = -.16$, $\rho_{\text{corrected}} = .053$). This correlation was particularly driven by the impulsivity/hyperactivity subscale of the SDQ (right VS: $r = -.18$, $\rho_{\text{uncorrected}} = .014$). No significant correlation was identified between VS activation and the inattention subscale (right VS: $r = -.08$, $\rho_{\text{uncorrected}} = .30$; left VS: $r = -.09$, $\rho_{\text{uncorrected}} = .24$).

We carried out an interaction analysis of right VS activation*SNP rs12843268 genotype on ADHD symptoms, which was not significant ($p = .570$) due to multicollinearity for VS*SNP rs12843268, with a corresponding $r = .865$. Orthogonalization was not performed because it would either decompose or integrate variables, thus changing their meaning for this study. We then stratified our analyses by rs12843268 genotype and found that the negative correlation observed between right VS BOLD response and ADHD symptoms was driven by A hemizygotes (right VS: $r = -.29$, $\rho_{\text{corrected}} = .041$; left VS: $r = -.22$, $\rho_{\text{corrected}} = .14$). We observed no significant correlation between VS BOLD responses and ADHD symptoms in G hemizygotes (right VS: $r = -.15$, $\rho_{\text{corrected}} = .17$; left VS: $r = -.14$, $\rho_{\text{corrected}} = .21$) (Figure 2).

### Table 2. Haplotype Analysis of MAOA gene

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>rs1465108</th>
<th>rs909525</th>
<th>rs180046</th>
<th>rs12843268</th>
<th>rs6610845</th>
<th>rs2235186</th>
<th>rs2072743</th>
<th>rs1137070</th>
<th>p Value</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haplotype 1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>.016</td>
<td>.634</td>
</tr>
<tr>
<td>Haplotype 2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>.063</td>
<td>.289</td>
</tr>
<tr>
<td>Total Frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.923</td>
</tr>
</tbody>
</table>

Tagging single nucleotide polymorphism rs12843268 segregates haplotypes with a frequency of >5% and accounts for 92.3% of the variance of the gene.

**Successful Response Inhibition**

We measured BOLD response of the right IFG using the SST in 143 of the 190 boys (Supplement 1). Whereas we did not observe a significant association between right IFG and MAOA rs12843268 ($F_{1,133} = .92, p = .34$), we found a significant interaction between MAOA genotype and right IFG activation on ADHD symptoms ($F_{1,133} = 6.24, p = .014$). Upon stratification by MAOA rs12843268 genotype, we found a positive correlation between right IFG...

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**Figure 1.** (A) Associations between MAOA genotype and left activation: MAOA rs12843268 is associated with left ventral striatum (VS) activation ($F_{1,180} = 10.87$, $p = .001$, partial $\eta^2: .061$). (B) Associations between MAOA genotype and right VS activation: MAOA rs12843268 is associated with right VS activation ($F_{1,180} = 6.80$, $p = .007$, partial $\eta^2: .045$) during reward anticipation. (C) Coronal section showing genotype differences in VS activation during reward anticipation, suggesting that G hemizygotes of MAOA rs12843268 show higher activation of bilateral VS compared with A hemizygotes ($xyz: \pm 9, 11, -2, p < .01$, uncorrected).

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BOLD response and ADHD symptoms \( (r = .26, p = .017) \) among G hemizygotes, whereas in A hemizygotes, we found a negative correlation between right IFG BOLD response and ADHD symptoms \( (r = -.30, p = .049; \text{Figure 3}) \). The difference between the correlation coefficients was significant \( (z = 3.23, p = .001) \). Without MAOA rs12843268 stratification, the neural responses in the right IFG accounted for 1.9% of the variance in ADHD symptoms, whereas after stratification, the variance in ADHD symptoms accounted for in G hemizygotes increased to 6.8% and the variance in ADHD symptoms accounted for in A hemizygotes increased to 9%.

There was no significant difference between A hemizygotes and G hemizygotes in SSRT \( (n = 73) \) or Mean reaction time to go trials, and no genotype-differences in the number of successfully completed stop trials or go trials (Tables S6 and S7 in Supplement 1). However, we found a negative correlation between SSRTs and right IFG BOLD response \( (r = -.28, p = .02) \), indicating that higher BOLD response of the right IFG during successful inhibition trials was associated with lower SSRT. This association was significant in G hemizygotes \( (r = -.36, p = .02) \) but not in A hemizygotes \( (r = -.15, p = .44; \text{Table S6 in Supplement 1}) \).

To determine combined variance accounted for by right VS and right IFG activation on ADHD symptoms, we performed additional analyses in the sample of 143 boys, for whom both MID and SST information was available. We found that right VS activation alone accounts for 3.7% of the variance in ADHD symptoms \( (r^2 = .037, p = .021) \). When the right IFG was added to the model, an additional 1.9% of variance in ADHD symptoms was accounted for \( (\text{combined } r^2 = .056) \). This change in \( r^2 \) was not significant \( (p = .095) \), indicating that the contribution of the IFG to ADHD symptoms is indeed dependent on MAOA genotype as previously suggested by the significant interaction term (Figure 3).

**Discussion**

In a population-based sample of 414 adolescent boys and girls, we demonstrate that MAOA is associated with ADHD symptoms in boys only. On the basis of these findings, we investigated whether neural mechanisms thought to underlie ADHD are affected by MAOA in boys. We found that ADHD symptoms were correlated with distinct frontostriatal activation patterns, depending on rs12843268 genotype.

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**Figure 2. (A)** Correlation of ventral striatum (VS) activation and attention-deficit/hyperactivity disorder (ADHD) symptoms: the correlation between right VS activation and ADHD symptoms were driven by A hemizygotes \( (r = -.29, p = .025) \). No significant association was found in the left VS or among G hemizygotes in either left or right VS. However, the difference between correlation coefficients were not significant \( (\text{right VS}: z = .95, p = .34; \text{left VS}: z = .53, p = .60) \). (B) Coronal section showing the correlation between right VS activation and ADHD symptoms during reward anticipation in A hemizygotes \( \text{xyz: 9, 11, } -2, p < .05, \text{uncorrected}) \).

**Figure 3. (A)** Correlation between right inferior frontal gyrus (IFG) activation and attention-deficit/hyperactivity disorder (ADHD) symptoms: right IFG activation was positively correlated with ADHD symptoms in G hemizygotes \( (r = .26, p = .017) \). In A hemizygotes, a negative correlation was found between right IFG activation and ADHD symptoms \( (r = -.30, p = .049) \). The difference between the correlation coefficients was significant \( (z = 3.23, p = .001) \). (B) Coronal section showing the positive correlation between right IFG opercularis and ADHD symptoms during successful stop trials in G hemizygotes \( \text{xyz: 55, 15, 10, } p < .05, \text{uncorrected}) \). (C) Coronal section showing the negative correlation between right IFG opercularis and ADHD symptoms during successful stop trials in A hemizygotes \( \text{xyz: 57, 16, 17, } p < .05, \text{uncorrected}) \).
In A hemizygotes of rs12843268, which express lower levels of MAOA, ADHD symptoms are associated with lower VS BOLD response, indicating lower reward-related activity in this region, as well as reduced inhibition as measured by right IFG BOLD response. This may suggest that ADHD symptoms in this group arise from a blunted reward response coupled with lower prefrontal inhibitory control, as postulated by the reward deficiency syndrome hypothesis (44).

Conversely, in G hemizygotes, who express higher levels of MAOA, ADHD symptoms were associated with increased right IFG BOLD response in the presence of increased VS BOLD response. The observed negative correlation of SSRT and right IFG BOLD response in G hemizygotes indicates that higher VS BOLD responses alone may not be a risk factor for ADHD symptoms in this group but must be considered together with the requirement for larger frontal recruitment for optimal task performance (7).

Theories based on neuroimaging studies suggest two alternative mechanisms underlying ADHD symptoms: the impulsivity hypothesis suggests that insufficient inhibitory control underlies the disorder, whereas the reward deficiency syndrome hypothesis proposes that impulsive behaviors compensate for blunted sensitivity of the reward system (3,47,48). Our results suggest that both mechanisms contribute to ADHD symptoms, depending on MAOA genotype. Thus, while supporting recent reports that provide genetic evidence for the contribution of dopaminergic mechanisms to reward anticipation and ADHD (45,46), our study is first to dissociate distinct neurobehavioral mechanisms of ADHD symptoms by applying stratification by genotype. This MAOA-dependent stratification may contribute to the resolution of seemingly contradictory findings in the ADHD literature, which report both over- or underactivation of the inhibitory control network (4,5,7,16,18).

To understand how MAOA rs12843268 affects BOLD response in our sample, we investigated the expression levels of MAOA in A hemizygotes and G hemizygotes. We find allele specific gene expression differences in peripheral blood with G hemizygotes showing a sixfold increase in MAOA expression, compared with A hemizygotes. This suggests that G hemizygotes have higher MAOA mRNA levels, which might result in increased degradation of monoamines and lower baseline levels of serotonin, dopamine, and noradrenaline. A cis-acting effect of the VNTR promoter polymorphism on a yet to be identified functional variant that is in linkage disequilibrium (LD) with rs1137070 has recently been reported (49). In our sample rs1137070 is in high linkage disequilibrium (D' = 1; r² > .9) with rs12843268. The increased MAOA mRNA levels might reflect changes in transcriptional activity due to an interaction of the promoter VNTR and rs12843268 and may therefore result in differential activation in the context of ADHD.

Reduced levels of serotonin are known to enhance premature responding and are associated with higher impulsiveness (50). Accordingly, G hemizygotes showed more ADHD symptoms than A hemizygotes. In G hemizygotes, we found an association of increased right IFG BOLD response and high ADHD symptoms as well as a negative correlation between right IFG BOLD response and shorter SSRTs. These results might suggest a requirement for higher brain activity in the key inhibitory region to achieve similar synaptic serotonin concentrations in G hemizygotes compared with A hemizygotes and to inhibit inappropriate responses in the SST to obtain similar behavioral results (4,7). Lower MAOA levels in A hemizygotes might result in increased baseline levels of monoamines in the VS relative to G hemizygotes. Because the motivational salience of a reward stimulus depends on the relative increase in dopamine (51), as opposed to the absolute level, an increased baseline might result in a smaller relative increase due to a ceiling effect in dopamine response.

Our results indicate that stratification of neuroimaging phenotypes by MAOA genotype notably increases the amount of variance explained. For example, BOLD response during reward anticipation in the right VS of A hemizygotes accounts for 8.4% of the variance in ADHD symptoms. This contrasts with 2.2% of the variance accounted for by genotype on ADHD symptoms and 2.6% of the variance accounted for by right VS BOLD response on ADHD symptoms, when both genotypes are considered jointly. In the case of right IFG BOLD response, we found that associations only became apparent upon stratification by MAOA genotype. This might explain recent results (8) that, in the absence of genetic analyses, failed to identify an association between ADHD and IFG BOLD response during inhibition trials. However, our findings also suggest a sizeable proportion of unexplained variance, which can probably be accounted for by the influence of multiple genes as well as additional brain functions underlying ADHD symptoms.

It is noteworthy that this is one of the first studies to investigate the association between neural responses and ADHD symptoms, rather than ADHD. The mean number of ADHD symptoms in our population-based sample is approximately 50% below the threshold for clinical ADHD (2.7 vs. 5). Although this does not affect the interpretation of the association of ADHD symptoms and neurobiological functions observed, it indicates the normative character of our data, and the need for validation in ADHD patients to fully assess their clinical applicability.

In conclusion, through stratification of ADHD symptoms by MAOA genotype, we identified two distinct frontostriatal mechanisms that determine the manifestation of ADHD symptoms in adolescent boys: one of blunted reward and inhibitory control and another characterized by increased reward processing coupled with enhanced efforts to recruit the top down frontal inhibitory system.

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