Norepinephrine Genes Predict Response Time Variability and Methylphenidate-Induced Changes in Neuropsychological Function in Attention Deficit Hyperactivity Disorder

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Abstract: Noradrenergic dysfunction may be associated with cognitive impairments in attention-deficit/hyperactivity disorder (ADHD), including increased response time variability, which has been proposed as a leading endophenotype for ADHD. The aim of this study was to examine the relationship between polymorphisms in the α2A-adrenergic receptor (ADRA2A) and norepinephrine transporter (SLC6A2) genes and attentional performance in ADHD children before and after pharmacological treatment.

One hundred one medication-naive ADHD children were included. All subjects were administered methylphenidate (MPH)-OROS for 12 weeks. The subjects underwent a computerized comprehensive attention test to measure the response time variability at baseline before MPH treatment and after 12 weeks. Additive regression analyses controlling for ADHD symptom severity, age, sex, IQ, and final dose of MPH examined the association between response time variability on the comprehensive attention test measures and allelic variations in single-nucleotide polymorphisms of the ADRA2A and SLC6A2 genes and MPH treatment.

Increasing possession of an A allele at the G1287A polymorphism of SLC6A2 was significantly related to heightened response time variability at baseline in the sustained (P = 2.0 × 10⁻³) and auditory selective attention (P = 1.0 × 10⁻³) tasks. Response time variability at baseline increased additively with possession of the T allele at the Dra1 polymorphism of the ADRA2A gene in the auditory selective attention task (P = 2.0 × 10⁻³). After medication, increasing possession of a G allele at the MspI polymorphism of the ADRA2A gene was associated with increased MPH-related change in response time variability in the flanker task (P = 1.0 × 10⁻³).

Our study suggested an association between norepinephrine gene variants and response time variability measured at baseline and after MPH treatment in children with ADHD. Our results add to a growing body of evidence, suggesting that response time variability is a viable endophenotype for ADHD and suggesting its utility as a surrogate end point for measuring stimulant response in pharmacogenetic studies.

Key Words: attention-deficit/hyperactivity disorder, norepinephrine, ADRA2A, SLC6A2, methylphenidate response, comprehensive attention test


Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is characterized by inattention, hyperactivity, and impulsive behavior (American Psychiatric Association, 1994). Attention-deficit/hyperactivity disorder is believed to be polygenic and has an estimated heritability of 0.8 and a prevalence in school-aged children of about 9% to 10%. Although the etiology of this disorder is not well understood, evidence from neurobiological and pharmacological research has suggested that, in addition to impaired dopaminergic function, dysregulation of the central noradrenergic systems contributes to the pathophysiology of ADHD. Norepinephrine (NE) is involved in the modulation of attention, working memory, behavioral inhibition, planning, alertness, arousal, and vigilance, and it has been suggested that it improves attention by narrowing attentional focus and by blocking the effects of distractors via its interactions with underlying levels of arousal. The presumed mechanisms of action of guanfacine and atomoxetine, which have shown clinical efficacy in treating ADHD patients, involve α2A-adrenergic receptor agonist functions and NE reuptake inhibitor functions, respectively.

Although the primary mode of action of methylphenidate (MPH) in ADHD treatment is blockade of the dopamine (DA) transporter, emerging evidence from animal studies demonstrates that MPH may also inhibit the NE transporter (NET). For example, a recent study found that in regard to blocking human and mouse catecholamines, the sensitivity of NET to MPH was...
similar to that of DA transporter. Berridge et al reported that low doses of MPH produced a maximal increase in NE concentrations of approximately 280% above baseline, substantially larger than the increase produced for DA by the same dose of MPH. Whereas Andrews and Lavin demonstrated that the MPH-induced increase in cortical cell excitability is mediated by activation of α-2-adrenergic receptors and suggested that the therapeutic actions of this stimulant may involve preferential activation of noradrenergic and/or dopaminergic neurotransmission within the prefrontal cortex. Taken together, these findings suggest that the effects of MPH could be mediated in part by the noradrenergic system.

Evidence for central noradrenergic dysregulation in the pathophysiology of ADHD suggests that allelic variation in the α-2A-adrenergic receptor gene (ADRA2A), located on chromosome 10q24-26, and/or the NET gene (SLC6A2), located on chromosome 16q12.2, can confer genetic risk for ADHD. Indeed, a -1291 C-to-G single-nucleotide polymorphism (SNP), which creates an MspI site (rs1800544) in the promoter region of the ADRA2A gene, and a C-to-T polymorphism in the Dral site (rs553668) of the 3′ untranslated region (3′-UTR) are the 2 major ADRA2A polymorphisms investigated in relation to ADHD. The potential functional significance of the MspI polymorphism has been reported in a previous study, which suggested that allelic variation at this site may affect the expression and function of ADRA2A. In line with this proposal, our recent genetic imaging data reported that ADHD subjects who carried the C allele at the MspI polymorphism showed reduced perfusion in bilateral orbitofrontal regions as compared with those without the C allele. With respect to the SLC6A2 gene, a -3081 A-to-T SNP (rs28386840) in the promoter region has been associated with ADHD, and a G1287A SNP (rs5569) at exon 9 has been linked to MPH response during the treatment of ADHD. In addition to genetic evidence, 1 biochemical study has indicated that all indices of the continuous performance test including, errors of omission, errors of commission, response time, and response time variability, are significantly correlated with urinary excretion of NE metabolites, but not DA metabolites, in children with ADHD.

We have previously provided evidence for the involvement of the ADRA2A MspI and Dral polymorphisms in the etiology of ADHD in Korean subjects. In addition, we have reported a possible role for these 2 polymorphisms in increased response time variability in ADHD. Noradrenergic dysfunction with respect to either α-2A-adrenergic receptor– or NET-mediated mechanism may be associated with cognitive impairments in ADHD, including increased response time variability, which has been proposed as a leading endophenotype for ADHD. The adoption of neuropsychological tests as endophenotypes may enhance the power of genetic studies of ADHD by providing an increased sensitivity to specific dimensions of the disorder.

The aim of this study was therefore to examine the relationship between genotypes of the aforementioned ADRA2A and SLC6A2 polymorphisms and response time variability in drug-naïve ADHD subjects. Furthermore, we examined the relationship between these polymorphisms and changes in response time variability after treatment with MPH in childhood ADHD.

MATERIALS AND METHODS

Participants

The present sample comprised 101 ADHD children (aged 8.7 ± 2.1 years, 81 boys) recruited from child psychiatric clinics at 6 university hospitals in South Korea. Inclusion criteria were (1) diagnosis with ADHD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and (2) age 6 to 12 years. Exclusion criteria were (1) any other mental disorders except for transient tic disorder, oppositional defiant disorder, mild anxiety disorder, and enuresis; (2) history or presence of brain damage or convulsive disorder; (3) mental retardation (IQ < 70), autism, or language difficulties; or (4) history of exposure to psychostimulants such as MPH.

The study was approved by the institutional review board for human subjects at the Seoul National University Hospital and other hospitals. Parents/guardians provided written informed consent, and the children or adolescents provided verbal assent regarding participation in this study.

Clinical Assessments

Kiddie-Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version

Attention-deficit/hyperactivity disorder was diagnosed using the Kiddie-Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version. The Korean version of Kiddie-Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version was translated, and its validity and reliability for ADHD, tic disorder, and oppositional defiant disorder were established before use.

ADHD Rating Scale IV

Composed of a total of 18 items, the ADHD Rating Scale IV (ARS) is the ADHD symptom severity scale designed by DuPaul et al according to the DSM-IV criteria. Each item has a 4-point scale (0 to 3). The 18 items are composed of 9 items reflecting symptoms related to inattention and 9 items reflecting symptoms related to hyperactivity and impulsivity. The Korean version of ARS was standardized by So et al. The K-ARS has good reliability and validity among Korean children, and a high interrater reliability was established before commencement of the study (κ = 0.92).

Neuropsychological Measurements

We used a computerized comprehensive attention test (CAT) to measure the response time variability of children with ADHD.

Visual and Auditory Selective Attention Tasks

The visual selective attention task assessed the ability to respond to directed visual stimuli. Various geometric figures (300 in total) appeared on the screen one at a time every 2 seconds, and the subject had to respond with a button press as quickly as possible whenever a circle was shown. The auditory selective attention task was identical except that the stimuli were various sounds, and the subjects had to respond to the target sound of a bell. In each case, the target presentation frequency was 50%, and the task took approximately 10 minutes to complete.

Flanker Interference Task

This task assessed the ability to respond to a directed stimulus while ignoring other simultaneously presented interfering stimuli. A set of visual stimuli was shown, and the subject’s ability to respond to the characteristics of 1 specific stimulus was evaluated. Five squares each with one of their sides open (left or right) were shown simultaneously in a row, and the subject had to press 1 of 2 buttons as quickly as possible according to the laterality of the open side of the middle square. Each of the 150 trials of this task included a target, and completion time was approximately 5 minutes.
Sustained Attention Task

This task assessed the ability to retain attention and suppress impulsivity, by evaluating response inhibition toward a specific stimulus when it was presented in a temporal sequence among other stimulus types. Various geometric symbols (300 in total) were shown serially on the screen, and the subject has to press the button as quickly as possible for all symbols other than "X." The target presentation frequency was 75%, and the task took approximately 10 minutes to complete.

The variable recorded for each of the 4 tasks was the SD of the response times for correct responses to the target (response time variability), which is interpreted as a measure of variability or consistency of attention. The ADHD subjects underwent the CAT at baseline before MPH treatment and after 12 weeks of MPH treatment.

MPH Administration

Medication-naïve participants took part in a prospective 12-week, open-label study to achieve symptomatic remission by OROS-MPH. All of the ADHD subjects were administered MPH-OROS for 12 weeks. The MPH administration guidelines were as follows. Initial dosage of OROS-MPH was determined by body weight of the child: if 30 kg or greater, 27 mg was administered; if less than 30 kg, 18 mg was administered. Dose of MPH was adjusted at the second, fourth, and eighth weeks.

The neuropsychological data (at baseline and post-treatment) were assessed in regard to its suitability for dimension reduction. Dimension reduction was conducted by certified child and adolescent psychiatrists who had completed the interrater reliability establishment courses at baseline before medication.

Genotyping

Genomic DNA was extracted from whole-blood lymphocytes using a G-DEX II Genomic DNA Extraction Kit (Intron, Seongnam, Korea). The detection of an SNP was based on analysis of primer extension products generated from previously amplified genomic DNA, using a chip-based matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry platform (Sequenom, San Diego, CA). The detection of an SNP was based on analyses that corrected for baseline ARS score, age, sex, and IQ association between marker genotype and neuropsychological measures was assessed for association with the MALDI-TOF MassARRAY system (Bruker-Sequenom). Allele “C” of the MspI polymorphism characterizes the absence of the MspI restriction site, whereas the C→G transversion at position -1291 creates it. Allele “T” of the Dral polymorphism contains the Dral restriction site, whereas allele “C” does not.

The SLC6A4 polymorphisms were genotyped as previously described, with slight modifications. In brief, oligonucleotide primers (5′-ACG TTG GAT GAG ACC AT for MspI; 5′-ACG TTG GAT GCT AT for Dral) were used to generate PCR products. The PCR was performed in a volume of 5 μL containing 1× PCR buffer (TAKARA), 2.5 mM MgCl₂, 0.2 mM of each dNTP, 0.1 U HotStar Taq Polymerase (Qiagen), 8 μM of each primer, and 4.0 ng of genomic DNA. The reaction consisted of denaturation at 95°C for 15 minutes, followed by 45 cycles at 95°C for 20 seconds, 56°C for 30 seconds, and 72°C for 1 minute, with a final extension at 72°C for 3 minutes. Following the PCR, unincorporated dNTP was removed by the addition of 0.3 U of shrimp alkaline phosphatase and incubation for 20 minutes at 37°C, followed by 5 minutes at 85°C for enzyme inactivation. The total volume of each reaction was 9 μL including hME enzyme (Thermo Sequenase; GE Healthcare), ACT termination mix, and 5 μM of extension primer. The primer extension protocol was started at 94°C for 2 minutes, followed by 55 cycles of 94°C for 5 seconds, 52°C for 5 seconds, and 72°C for 5 seconds. After desalting of the reaction products with SpectroCLEAN (Sequenom), samples were analyzed in the fully automated mode with the MALDI-TOF MassARRAY system (Bruker-Sequenom). The degree of correlation structure between our neuropsychological measures was examined using principal components analysis. Dimension reduction was not appropriate for the baseline data as only a single factor was extracted, and the solution could not be rotated. Likewise, dimension reduction was not appropriate for the posttreatment data as the Kaiser-Meyer-Olkin measure of sampling adequacy was lower than the recommended level of 0.6. Consequently, each of the neuropsychological measures was assessed for association with each genetic marker in a separate regression. At baseline, the association between genotype at the markers and neuropsychological measures was investigated with additive regression analyses that corrected for baseline ARS score, age, sex, and IQ using SNPstats. After 12 weeks of MPH treatment, the association between marker genotype and neuropsychological measures (baseline score − end point) was investigated with additive regression analyses that corrected for final MPH dose in addition to the aforementioned covariates. Although dimension reduction was not found to be appropriate, it is likely that there was some degree of correlation structure between our neuropsychological...
variables. Nevertheless, for each of baseline and posttreatment data, we took the conservative approach of treating each neuropsychological test as an independent comparison (see below).

For any given gene, cosegregation entails that alleles at different polymorphisms may be correlated within an individual. Hence, we controlled the experiment-wise significance level using SNP spectral decomposition,31 which determines the effective number of independent loci (Meff/MeffLi) for each gene. Following the suggestion of Nyholt,31 the smaller of Meff9/32 and MeffLI33 was used as the effective number of independent marker loci. This process returned values of 2.0 and 1.6 for the SLC6A2 and ADRA2A markers, respectively, giving a critical P = 0.0034 [0.050 / effective number of independent loci (3.4) × number of tests (4)]. The sample was sufficiently powered to detect small effects at P < 0.025 and medium effects at P < 5.0 × 10⁻⁴ based on Cohen F2.

RESULTS

Demographic and Clinical Characteristics

The initial mean dosage of OROS-MPH was 0.24 ± 0.31 mg/kg per day (range, 18–27 mg/kg per day), and the final mean dosage was 0.98 ± 0.52 mg/kg per day (range, 18–54 mg/kg per day). The mean overall ADHD symptom score according to investigator-measured ARS decreased from 34 ± 9.6 at baseline to 13 ± 5.2 after 12 weeks of MPH-OROS treatment. Of the DSM-IV subtypes of ADHD, the combined subtype was the most common in our subjects (68%), followed by the inattentive (26%) and hyperactive-impulsive (6.0%) subtypes. With regard to comorbidity, anxiety disorder (8.8%) was the most common, followed by oppositional defiant disorder (6.8%), transient tic disorder (6.8%), and enuresis (5.9%) (Table 1).

<table>
<thead>
<tr>
<th>ADHD (n = 101)</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>8.7</td>
<td>2.1</td>
</tr>
<tr>
<td>IQ</td>
<td>102</td>
<td>12</td>
</tr>
<tr>
<td>ARS baseline scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>9.6</td>
</tr>
<tr>
<td>Inattentive</td>
<td>19</td>
<td>5.8</td>
</tr>
<tr>
<td>Hyperactivity/impulsivity</td>
<td>15</td>
<td>6.0</td>
</tr>
<tr>
<td>Mean dosage of MPH, mg/kg per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline dose</td>
<td>0.24</td>
<td>0.31</td>
</tr>
<tr>
<td>Final 2 weeks’ dose</td>
<td>0.98</td>
<td>0.52</td>
</tr>
<tr>
<td>Male</td>
<td>82</td>
<td>80</td>
</tr>
<tr>
<td>ADHD subtypes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>Inattentive</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Hyperactive-impulsive</td>
<td>6</td>
<td>6.0</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>9</td>
<td>8.8</td>
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<tr>
<td>Oppositional defiant disorder</td>
<td>7</td>
<td>6.8</td>
</tr>
<tr>
<td>Transient tic disorder</td>
<td>7</td>
<td>6.8</td>
</tr>
<tr>
<td>Enuresis</td>
<td>6</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Association Between the ADRA2A and SLC6A2 Polymorphisms and Neuropsychological Test Performance at Baseline Before MPH Treatment

Significant genetic associations were found with response time variability. In the auditory selective attention task, mean response time variability in ADHD subjects increased additively with possession of the A allele (A/A genotype) at the G1287A polymorphism of the SLC6A2 gene (A/A > G/A > G/G) (after controlling for baseline ARS score, age, sex, and IQ), P = 1.0 × 10⁻³, Cohen F2 = 0.090 (small to medium effect size).

The A allele at this site also showed a significant additive effect on response time variability scores (A/A > G/A > G/G) in the sustained attention task (P = 2.0 × 10⁻³, Cohen F2 = 0.10), and a trend toward the same was observed in the visual selective attention task, P = 4.0 × 10⁻³ (Table 2).

Furthermore, in the auditory selective attention task, response time variability increased additively with possession of the T allele at the DraI polymorphism of the ADRA2A gene after correction for the aforementioned covariates (P = 2.0 × 10⁻³, Cohen F2 = 0.070), and an association at the uncorrected significance level was observed in the sustained attention task (P = 0.030) (Table 3).

There were no significant differences in neuropsychological test performance at baseline according to the genotypes of the SLC6A2 -3081 (A/T) polymorphism or the ADRA2A MspI polymorphism (data not shown, but available upon request).

Association Between the ADRA2A and SLC6A2 Polymorphisms and Changes in Neuropsychological Test Performance After MPH Treatment

After MPH treatment, no significant associations were found between the change in ARS score and genotype of the 4 SNPs in this study. However, the change in mean response time variability for the flanker interference task increased additively with increasing possession of the G allele (G/G > G/C/C/C) at the MspI polymorphism of the ADRA2A gene (after controlling for baseline ARS score, age, sex, IQ, and final dose [in mg/kg of MPH], P = 1.0 × 10⁻³, Cohen F2 = 0.090 (small to medium effect size). Furthermore, in the sustained attention task, an additive association at the uncorrected significance level was observed between response time variability and possession of the G allele at the MspI polymorphism of the ADRA2A gene after controlling for the above covariates, P = 0.024 (Table 4). Similarly, in the auditory selective attention task, an additive association at the uncorrected level was found at the G1287A polymorphism of the SLC6A2 gene, P = 0.023 (data not shown, but available upon request).

DISCUSSION

Our data suggest an association between NE gene variants and response time variability measured at baseline before MPH treatment in children with ADHD. Specifically, DNA variation in a polymorphism of the SLC6A2 gene (G1287A) was associated with response time variability, with increasing possession of the A allele related to heightened response time variability in both the sustained attention and auditory selective attention tasks. Likewise, the T allele in the DraI polymorphism of the ADRA2A gene was significantly associated with response time variability in the auditory selective attention task. Furthermore, response time variability showed strong utility as a surrogate end point for assessing stimulant response because medication-related changes in variability in the flanker task were associated with a polymorphism (MspI) of the ADRA2A gene.
TABLE 2. Association Between the SLC6A2 G1287A Polymorphism and Neuropsychological Test Performance at Baseline (Before MPH Treatment)

<table>
<thead>
<tr>
<th>Neuropsychological Test</th>
<th>G/G Genotype (n = 57)</th>
<th>G/A Genotype (n = 33)</th>
<th>A/A Genotype (n = 11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RTSD</td>
<td>RTSD</td>
<td>RTSD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
<td>SE</td>
</tr>
<tr>
<td>Visual selective attention task</td>
<td>64</td>
<td>4.4</td>
<td>76</td>
<td>6.2</td>
</tr>
<tr>
<td>Auditory selective attention task</td>
<td>77</td>
<td>3.0</td>
<td>90</td>
<td>5.3</td>
</tr>
<tr>
<td>Sustained attention task</td>
<td>84</td>
<td>2.4</td>
<td>92</td>
<td>2.7</td>
</tr>
<tr>
<td>Flanker interference task</td>
<td>66</td>
<td>4.2</td>
<td>78</td>
<td>4.6</td>
</tr>
</tbody>
</table>

*Significant at an uncorrected level after controlling for the above covariates.
†Significant (critical P = 0.0034) after controlling for the covariates of age, sex, baseline ARS score, and IQ. RTSD indicates the SD of the response times for correct responses to the target (response time variability).

the results for each of the tasks are not likely to be entirely independent of one another, these data provide further support for response time variability as a viable endophenotype for ADHD and suggest that variation in this endophenotype is related to genetic variation in NE system genes.

Recent studies have demonstrated that increased variability in response time performance may reflect altered function of the prefrontal cortex and associated brain networks, and it seems that NE levels play an important role in this process. A high tonic–low phasic NE state in ADHD appears to lead to noisier frontal cortical representations and be associated with increased response time variability. Furthermore, response time variability has been significantly correlated with urinary NE metabolites in ADHD. The current findings of a relationship between SLC6A2 polymorphisms and response time variability are consistent with the above and with those of Kollins et al. Kollins et al examined the relationship between neurocognitive measures derived from a continuous performance test and SNP variation across 10 candidate genes in 364 individuals from 152 families with at least 1 child with a diagnosis of ADHD. Association analyses identified a strong association between a SLC6A2 SNP (rs3785155) and response time variability.

In this study, we also examined the relationship between genotypes of ADRA2A and SLC6A2 polymorphisms and changes in neuropsychological test performance after treatment with MPH in ADHD. With regard to the ADRA2A polymorphisms, the ADHD subjects with more copies of the C allele of the Msp1 polymorphism showed less reduction in response time variability across the 2 time points (baseline to end point) in the flanker interference task. This result is consistent with our previous study, which also identified the C allele of the Msp1 polymorphism as a putative risk allele of the ADRA2A polymorphism. We can infer that possessing the nonrisk (G) allele of this polymorphism may contribute to a greater improvement in neuropsychological performance after MPH treatment in subjects with ADHD.

There are a few limitations to this study that should be noted. First, the total number of subjects studied (n = 101) was relatively small for a genotypic analysis, and as serum levels of MPH were not determined, we cannot entirely sure that there were no differences among the serum concentrations of MPH between the genotype groups. Nevertheless, we note that robust clinical improvements were seen across the sample and that our genotypic results, particularly for baseline measures of response variability, are consistent across a number of cognitive domains. Second, we did not stratify our results according to DSM-IV subtype and thus cannot comment upon whether our effects are driven by a particular symptom dimension. However, because of the unselected nature of our sample with respect to ADHD subtype, our results are likely generalizable to clinical settings. Finally, although we cannot exclude the possibility of population stratification biasing our findings, the Korean population is characterized by a relatively high genetic homogeneity, lowering the possibility that our results reflect a false positive due to stratification.

In summary, we have observed strong genetic association between a polymorphism of the SLC6A2 gene, ADRA2A gene, and behavioral measures of response time variability in a sample of medication-naive Korean children with ADHD. Robust

TABLE 3. Association Between the ADRA2A Dral Polymorphism and Neuropsychological Test Performance at Baseline (Before MPH Treatment)

<table>
<thead>
<tr>
<th>Neuropsychological Test</th>
<th>C/C Genotype (n = 33)</th>
<th>C/T Genotype (n = 49)</th>
<th>T/T Genotype (n = 19)</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>RTSD</td>
<td>RTSD</td>
<td>RTSD</td>
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<tr>
<td></td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
<td>SE</td>
</tr>
<tr>
<td>Auditory selective attention task</td>
<td>77</td>
<td>4.4</td>
<td>82</td>
<td>3.8</td>
</tr>
<tr>
<td>Sustained attention task</td>
<td>84</td>
<td>3.1</td>
<td>88</td>
<td>2.3</td>
</tr>
</tbody>
</table>

*Significant (critical P = 0.0034) after controlling for the covariates of age, sex, baseline ARS score, and IQ. †Significant at an uncorrected level after controlling for the above covariates. RTSD indicates the SD of the response times for correct responses to the target (response time variability).
TABLE 4. Association Between the ADRA2A MspI Polymorphism and Changes in Neuropsychological Test Performance After MPH Treatment

<table>
<thead>
<tr>
<th>Neuropsychological Test</th>
<th>G/G Genotype (n = 41) Mean</th>
<th>SE</th>
<th>G/C Genotype (n = 46) Mean</th>
<th>SE</th>
<th>C/C Genotype (n = 8) Mean</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔFlanker interference task RTSD</td>
<td>23</td>
<td>3.7</td>
<td>8.6</td>
<td>3.3</td>
<td>1.9</td>
<td>6.9</td>
<td>1.0 × 10⁻³*</td>
</tr>
<tr>
<td>ΔSustained attention task RTSD</td>
<td>15</td>
<td>2.5</td>
<td>8.1</td>
<td>2.8</td>
<td>5.6</td>
<td>4.5</td>
<td>0.020†</td>
</tr>
</tbody>
</table>

*Significant (critical P = 0.0034) after controlling for the covariates of age, sex, baseline ARS score, and IQ.
†Significant at an uncorrected level after controlling for the above covariates.

RTSD indicates the SD of the response times for correct responses to the target (response time variability); Δ, baseline — end point.

associations between the SLC6A2 G1287A SNP (rs5569), ADRA2A DraI SNP (rs553668), and response time variability were seen across a number of cognitive domains, with effects surviving multiple comparison corrections. Furthermore, response time variability proved a useful surrogate end point for testing genetic association with MPH response. Allelic variation in the ADRA2A MspI polymorphism predicted MPH-related changes in response time variability and survived corrections for multiple comparisons. These results add to a growing body of evidence implicating the noradrenergic system in the etiology and treatment of ADHD and provide further evidence for the utility of response time variability as a biomarker for ADHD.

AUTHOR DISCLOSURE INFORMATION

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