Dopaminergic Haplotype as a Predictor of Spatial Inattention in Children With Attention-Deficit/Hyperactivity Disorder

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Context: A distinct pattern of selective attention deficits in attention-deficit/hyperactivity disorder (ADHD) has been difficult to identify. Heterogeneity may reflect differences in underlying genetics.

Objective: To document an objective deficit of selective attention in a large sample of children with and without ADHD using spatial orienting paradigms. By stratifying samples according to the gene dosage of a risk haplotype of the dopamine transporter gene (*DAT1*), we could determine whether genetic factors predict spatial inattention in ADHD.

Design: A case-control design was used.

Setting: Children with ADHD were recruited from clinics or support groups in Ireland. Typically developing children were recruited from schools in and around Dublin, Ireland.

Participants: One hundred fifteen children were recruited (ADHD = 50, control = 65). Groups were matched for age but differed in estimated intelligence.

Intervention: Two versions of a visual spatial orienting task in which attention was directed by valid, neutral, or invalid cues to target locations. Sudden-onset peripheral cues (exogenous) and centrally presented predictive cues (endogenous) were used.

Main Outcome Measures: To isolate an attention deficit in ADHD, groups were first compared using analysis of variance on the spatial orienting tasks. Multiple regression was used to assess the main effect of *DAT1* haplotype status (heterozygous vs homozygous) and the interaction of diagnosis and genotype on those variables that discriminated children with and without ADHD.

Results: Children with ADHD displayed deficits in reorienting attention from invalidly cued spatial locations, particularly for targets in the left visual field. *DAT1* haplotype status predicted spatial reorienting deficits for left visual field targets ($P = .007$) but there was also a significant interaction of diagnosis and genotype ($P = .02$), which revealed the greatest impairment in children with ADHD homozygous for the *DAT1* haplotype.

Conclusion: Heterogeneity in selective attention in ADHD can be explained by a replicated genetic risk factor for ADHD, the 10/3 *DAT1* haplotype.

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CLINICAL DESCRIPTIONS OF children with attention-deficit/hyperactivity disorder (ADHD) as being inattentive and distracted by extraneous stimuli in the environment suggest a deficit of selective attention. Selective attention refers to those cognitive processes that facilitate the processing of task-relevant stimuli and suppress the processing of task-irrelevant stimuli. In the spatial domain, selective attention serves to enhance the processing of stimuli at attended, vs unattended, locations in space. However, confirmation of an attentional deficit using objective methods from cognitive science has proven elusive,[1] leading to selective attention being de-emphasized within contemporary accounts of ADHD.[2-4] Herein, we show that deficits of spatial selective attention are apparent in ADHD and are predicted by a frequent haplotype of the dopamine transporter gene (*DAT1*), a replicated genetic risk factor for ADHD.

Within cognitive science, spatial selective attention is often probed using variants of the covert visual orienting task, developed by Posner and colleagues.[5,6] In visual orienting tasks, cues predict the spatial location of an upcoming target stimulus either correctly (valid cue), incorrectly (invalid cue), or uninformatively (neutrally cued trials). These tasks yield several reaction time (RT) effects that are indica-

tive of spatial selection. First, when attention is cued validly to a target location, RTs are typically faster than when the target is preceded by a neutral cue. This RT benefit reflects the attentional enhancement of perceptual processing at validly cued locations. In contrast, the disadvantage or cost in RT conferred by invalid cues, relative to either neutral or valid cues, reflects the time taken to reorient attention from the invalidly cued location to detect a target in an uncued location. Additionally, 2 modes of visual orienting can be distinguished. Stimulus-driven or exogenous mechanisms can be probed using salient peripheral cues that capture attention. In contrast, strategic or endogenous mechanisms can be probed by building expectancy across trials using a centrally presented stimulus (eg, arrowhead) that cues attention on most occasions.[7]

Human lesion, neurodisruption, and functional imaging work have helped to define the neural substrates of spatial orienting and reorienting.[8,9] Broadly speaking, tasks in which attention is strategically allocated to a spatial location activate a bilateral network of brain regions that has been conceptualized as forming a dorsal frontoparietal network.[7] This network is thought to comprise the frontal eye fields and the dorsal posterior parietal cortex along the intraparietal sulcus. Activation foci in the basal ganglia and cerebellum have also been observed for endogenous orienting.[10] This bilateral dorsal frontoparietal network may be contrasted with a right-lateralized ventral frontoparietal network that includes the inferior frontal gyrus and temporoparietal junction.[7] Classically, patients with lesions to the right parietal lobe have difficulty reorienting their attention from invalidly cued locations in the right hemifield to detect targets in the left hemifield.[5] That is, these patients display an ipsilesional orienting bias and contralesional reorienting deficit.

Several lines of evidence suggest dopaminergic modulation of spatial attention. First, dopamine agonists modulate behavioral indexes of visual spatial orienting in healthy subjects[11] and reduce the extent of neglect in right-hemisphere patients.[12] Second, experimental lesions of ascending dopaminergic pathways in rodents induce a spatial neglect for the contralesional side.[13] Deficits in spatial orienting[14] and attentional biases have also been observed in patients with Parkinson disease, particularly those with greater dopamine loss in the right striatum.[15]

A number of studies have now applied spatial orienting tasks to the study of selective attention in ADHD.[16] Although the results from these studies have proven inconclusive, a number of studies have noted asymmetrical performance of the participants with ADHD, such that they performed more poorly than controls in one visual field. Epstein et al[17] noted increased cuing costs for left visual field targets in ADHD. Nigg et al[18] and McDonald et al[19] noted slowed responses in the left visual field for uncued targets. Increased cuing costs for left targets may be indicative of a right-hemisphere reorienting deficit whereas slowed responses to uncued left targets could reflect a right-hemisphere arousal deficit.[20] Studies using other selective attention paradigms have also described left-sided impairments.[21] Nevertheless, a number of studies using visual orienting tasks have either failed to document group differences, observed reduced rather than increased costs for left targets,[22] or observed increased costs for right targets.[23]

Inconsistencies between studies likely reflect differences in methods but also the well-documented neuropsychological heterogeneity of ADHD.[24] Herein, we sought to determine whether inconsistencies could be clarified by stratifying children according the presence of a frequent haplotype of the dopamine transporter gene (*DAT1*). Allelic variation in *DAT1* is a replicated genetic risk factor for ADHD, and a common haplotype comprising the 10-repeat and 3-repeat alleles of 2 variable number of tandem repeat polymorphisms (VNTRs) within this gene is thought to increase risk for the disorder.[25,26] No studies have yet established the functional significance of this haplotype for cognition in ADHD. In a previous report, we demonstrated an influence of DNA variants of *DAT1* on exogenous spatial attention in healthy control children.[27] If neuropsychological heterogeneity in ADHD reflects differences in underlying genetics, then spatial attention deficits, including the reorienting of attention between the visual fields, should be most pronounced in those children with ADHD with a higher gene dosage of the *DAT1* haplotype.

METHODS

PARTICIPANTS

One hundred fifteen children participated in this study (ADHD=50, control=65). Clinical and demographic data can be found in **Table 1**. Data from 51 healthy control children on the exogenous orienting task have been presented previously.[27] Children with ADHD were referred by psychiatrists or recruited via support groups in Ireland. A subset of the ADHD group had previously participated in studies linking variation in *DAT1* to clinical measures of spatial bias (eg, line bisection).[28,29] All participants with ADHD met *DSM-IV* diagnoses for ADHD, as determined through semistructured interviews by psychiatrists using the parent form of the Child and Adolescent Psychiatric Assessment[30] or the Parental Account of Childhood Symptoms.[31] Forty-four (88%) of the children met criteria for ADHD predominantly combined type and 6 (14%), for ADHD predominantly inattentive type. The frequency of oppositional defiant disorder was 32% and conduct disorder, 8%. Exclusion criteria included known neurological conditions or pervasive developmental disorders, serious head injuries, and lower than average intelligence (<70 on a short form of the Wechsler Intelligence Scale for Children III that included Block Design, Information, Picture Completion, and Vocabulary). Control children were also excluded if they had first-degree relatives with ADHD. Handedness was measured using the Edinburgh Handedness Inventory.[32]

The parents of all children also completed the Conners' ADHD Rating Scale–Revised: Long or Short versions at the time of cognitive testing. Control children had Conners' Global Index *t* scores of 60 or less. To facilitate the inclusion of as many participants with ADHD as possible, we did not apply an inclusion cutoff for Conners' ratings (eg, *t*>65). Nevertheless, the majority of the participants had Conners' Global Index *t* scores of 65 or more (n=43) and 7 had Global Index *t* scores less than 65 (range across ADHD cohort, 52-90). Given robust evidence for an association between reading disorder and spatial attention impairment,[33] participants scoring in the clinical range (>1.5 SDs lower than the mean of the reading sub-

Table 1. Clinical and Demographic Data for the ADHD and Control Participants

	Mean (SD)			
	ADHD (n=50)	Controls (n=65)	Significance Test	*P* Value
Male, No.	42	61	$\chi^2 = 0.3$	.57
Right-handed, No.	44	57	$\chi^2 = 1.9$	.37
Age, y	13.3 (1.7)	13.7 (2)	$t_{113} = 1.1$	>.05
IQ	99 (13)	111 (13)	$t_{113} = 4.9$	<.05
WRAT reading score	96 (12)	108 (13)	$t_{113} = 5.3$	<.05
WRAT spelling score	93 (13)	108 (14)	$t_{113} = 5.9$	<.05
Conners' ADHD Index score	74 (8)	45 (7)	$t_{113} = 20.8$	<.05
Conners' Global Index score	77 (10)	46 (5)	$t_{113} = 21.5$	<.05
Conners' *DSM-IV* Inattentive score	73 (9)	45 (7)	$t_{113} = 18.9$	<.05
Conners' *DSM-IV* Hyperactive/Impulsive score	79 (12)	47 (5)	$t_{113} = 20.1$	<.05
Conners' *DSM-IV* Total score	78 (9)	46 (6)	$t_{113} = 22.8$	<.05

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; WRAT, Wide Range Achievement Test.

Table 2. Medication History for the Participants With ADHD

Type of Medication	No. of Children With ADHD Medicated	Medication Dose, mg, Range
Concerta	15	18-72
Ritalin	6	10-30
Ritalin SR	3	30-40
Strattera	1	NA
Dexedrine	1	7.5
Concerta and risperidone	1	72 and 1
Previously but not currently medicated	9	. . .
Never medicated	14	. . .

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ellipses, not applicable; NA, not available; SR, slow release.

Figure 1. Task schematics of the exogenous (A) and endogenous (B) covert visual orienting paradigms. In both tasks, participants fixated on a central point (500-millisecond duration) that turned from gray to yellow to signal the commencement of a trial. Each display included 4 black placeholders (2.1° diameter) that were positioned 13.3° to the left or right and 3.6° above and below fixation. Thereafter, attention was cued exogenously via a luminance increase in the peripheral placeholders (100 milliseconds; 100% contrast) or endogenously via predictive arrowheads presented above and below fixation (300 milliseconds). The target stimulus was a 100-millisecond sine-wave grating that occurred with equal probability within the upper or lower placeholder of the left or right visual field. Participants identified the vertical location of the target (upper or lower) as rapidly as possible using a joystick, irrespective of whether the target occurred on the left or right. This orthogonal cuing procedure enables mechanisms of spatial attention to be assessed independently of any potentially confounding effects of response selection or response bias.[34] Stimulus onset asynchronies were randomly either 200 or 800 milliseconds for the exogenous task and 500 or 700 milliseconds for the endogenous task.

test) of the Wide Range Achievement Test were also excluded (Table 1). Any stimulant medication was withdrawn at least 24 hours prior to the neuropsychological testing. Details regarding the medication history of the participants with ADHD can be found in **Table 2**.

Informed consent was provided according to the approved requirements of Trinity College Dublin and the Dublin Mid Leinster Health Service executive ethics committees.

SPATIAL ORIENTING TASKS

Participants performed both an exogenous and endogenous reflexive orienting task across separate sessions, each lasting approximately 1½ hours (**Figure 1**). In both tasks, participants used a joystick to indicate whether a target stimulus appeared at an upper (forward response) or lower (backward response) location, irrespective of whether it occurred on the left or right.[27] In the exogenous task, participants performed 384 trials in which the target was preceded by a peripheral cue that occurred on the same (valid, 33%) or opposite (invalid, 33%) side as the target or in the case of the neutral cue (33%), on both sides (Figure 1A). The stimulus onset asynchrony (SOA) between the cue and target events was randomly either 200 or 800 milliseconds.

In the endogenous task, arrowheads presented above and below fixation (300 milliseconds) indicated the likely spatial location of an upcoming target (Figure 1B). Sixty percent of the trials were validly cued, allowing participants to strategically speed their response to this cue. Twenty percent of trials were neutrally cued (double-headed arrowheads providing no
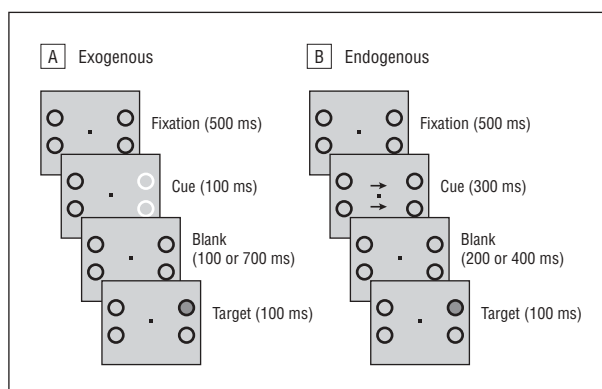
spatial cue) and 20% were invalid. To reduce the temporal predictability of each trial, the cue-target SOA was randomly either 500 or 700 milliseconds. Participants performed 320 trials. Both tasks were performed in a counterbalanced order, with eye movements monitored on a trial-by-trial basis. Trials on which a saccade occurred were excluded from analysis.

GENOTYPING

Genomic DNA was extracted from blood or saliva using Oragene DNA Self-Collection Kits (DNA Genotek Inc, Ottawa, Ontario, Canada). Polymerase chain reaction amplification of the intron 8 marker was performed as described in our previous report.[27] Polymerase chain reaction amplification and genotyping of the 3′ untranslated region (UTR) VNTR was con-

ducted as described by Cook et al.[35] Genotypes within the ADHD and control cohorts across each of the 3′ UTR and intron 8 VNTRs were in Hardy-Weinberg equilibrium (ADHD: 3′ UTR, $\chi^2=0.35$; $P>.05$; intron 8, $\chi^2=0.03$; $P>.05$; control: 3′ UTR, $\chi^2=1.77$; $P>.05$; intron 8, $\chi^2=0.05$; $P>.05$). Linkage disequilibrium between the 2 markers was calculated in the control sample as (D′) 0.77.

DAT1 10/3 haplotype status was assigned to participants using a Bayesian approach to reconstructing haplotypes implemented in the program PHASE version 2.02.[36] Haplotypes were determined for 84 participants (31 ADHD; 53 control; probability ≥0.9). Sixteen (53%) of the participants with ADHD were homozygous for the 10/3 haplotype, whereas 14 (45%) were heterozygous. One participant with ADHD did not possess the 10/3 haplotype. Sixteen (30%) of the healthy control children were homozygous and 29 (55%) were heterozygous for the 10/3 haplotype. Eight control children (16%) did not possess the 10/3 haplotype. For statistical analysis, participants were grouped as possessing two 10/3 haplotypes or fewer than two 10/3 haplotypes. A χ^2 analysis confirmed a significant association between *DAT1* 10/3 haplotype status and diagnosis ($\chi^2_1=4.69$; $P=.03$; odds ratio, 1.79 [95% confidence limit, 1.06, 3.02]). The frequency of the 10/3 *DAT1* haplotype was 76% and 65% within ADHD and control cohorts, respectively. There was no influence of 10/3 haplotype status on IQ in children with ADHD ($F_{1,29}=0.007$; $P>.05$) or typically developing children ($F_{1,51}=1.18$; $P>.05$). Nor was there an interaction between diagnosis and *DAT1* genotype for IQ ($F_{1,80}=0.37$; $P>.05$). Increasing gene dosage of the 10/3 haplotype was associated with increasing symptoms (n=84; Connors' *DSM-IV* Inattention: $r=0.27$; $P=.01$; Connors' *DSM-IV* Total: $r=0.25$; $P=.02$; Connors' ADHD Index: $r=0.28$; $P=.01$). The direction of these effects was consistent in both children with and without ADHD.

STATISTICAL ANALYSES

A 2-step approach to statistical analysis was undertaken. First, we sought to confirm a spatial attention deficit in the ADHD group, relative to controls, independent of genetic effects. Reaction time data were submitted to mixed-model analyses of variance (ANOVAs), with task factors as repeated measures and diagnosis as a between-subjects factor. The benefit of valid spatial cues for perception was assessed relative to neutrally cued trials (benefits). The cost to perception of invalid spatial cues was assessed relative to both a valid (validity effect) and neutral cue baseline (costs). Preliminary analyses showed no interactions between diagnosis and critical task factors for error rates or variability of RT. We therefore present mean RT results for correct responses only. Because cuing effects at the short and longer SOAs in the exogenous paradigm may not be directly comparable, we analyzed mean RT at each SOA separately. Although the SOA manipulation in the endogenous cuing paradigm was primarily designed to provide temporal jitter, SOA was nonetheless analyzed as a factor. Because cuing costs typically increase with SOA in endogenous cuing tasks,[37] the longer SOA might provide greater sensitivity to detect group differences than the shorter SOA. Second, we sought to determine the relationship between *DAT1* genotype and those specific cognitive indexes that discriminated children with ADHD and controls, thus reducing the potential for type I error. Multiple regression determined whether *DAT1* 10/3 haplotype status (2 copies vs <2 copies) accounted for unique variance in attentional indexes over and above that attributed to IQ and diagnosis. The interaction term (diagnosis×*DAT1* haplotype status) was included to determine whether deficits were particularly pronounced in the subset of children with ADHD who were homozygous for the 10/3 haplotype. Although geno-

types at both the 3′ UTR and intron 8 VNTRs were available, analyses focused on the 10/3 haplotype to (1) further reduce the potential for multiple comparisons and because (2) the haplotype should carry more information regarding the locus of any causative variant than either marker alone.

RESULTS

CHILDREN WITH ADHD DISPLAY SPATIAL ATTENTION DEFICITS

Exogenous Cuing Effects

RT: 200-Millisecond SOA. Reaction time data were submitted to a diagnosis × side × cue ANOVA, with IQ covaried. Significance levels for analyses without IQ covaried are also presented for comparison purposes for key effects. A significant main effect of diagnosis ($F_{1,112}=29.9$; $P=.001$) was observed, which reflected slower RTs of the children with ADHD (mean [SE], 588 [14] milliseconds) compared with controls (mean [SE], 486 [12] milliseconds). There was a significant main effect of target side ($F_{1,112}=5.023$; $P=.03$), which reflected slower responses to targets in the left visual field (mean [SE], 540 [9] milliseconds) relative to targets on the right (mean [SE], 533 [8] milliseconds). There was also a significant main effect of cue ($F_{2,224}=4.595$; $P=.01$). Responses on invalid trials (mean [SE], 544 [9] milliseconds) were slower than on neutral trials (mean [SE], 529 [8] milliseconds; $P=.001$) and tended to be slower than on valid trials (mean [SE], 538 [9] milliseconds; $P=.09$). Valid trials were slower than neutral trials ($P=.008$). The slower responses to invalid, relative to neutral, cues permitted the calculation of cuing costs. Since responses to valid trials were slower than to neutral trials, cuing "benefits" must be interpreted with caution.

A significant interaction was observed between diagnosis, target side, and cue ($F_{2,224}=3.06$; $P<.05$). This effect was also significant without IQ covaried ($P<.05$). As shown in **Figure 2**, children with ADHD exhibited significantly higher cuing costs for left targets than did control children ($F_{1,112}=5.4$; $P<.05$); however, cuing costs did not differ for right targets ($F_{1,112}=0.39$; $P=.54$). Cuing benefits for right targets differed between the groups ($F_{1,112}=5.034$; $P=.03$), being positive for the ADHD group and negative for the control children. A negative cuing benefit for the control children indicates that, on average, the control children did not accrue a performance benefit from valid spatial cues. There were no differences in cuing benefits for left targets ($F_{1,112}=0.63$; $P=.43$). The earlier-mentioned effects for cuing benefits were driven by asymmetrical responses in the ADHD group to validly cued trials ($F_{1,112}=5.76$; $P=.02$): Children with ADHD responded more slowly to validly cued left, relative to right, targets ($P=.001$), whereas no such asymmetry existed for control children ($P=.30$). Neither the children with ADHD nor control children displayed asymmetrical responses to neutrally cued trials ($F_{1,112}=0.89$; $P>.05$).

RT: 800-Millisecond SOA. At the 800-millisecond SOA, there was no main effect of cue ($F_{2,224}=0.016$; $P=.98$). There
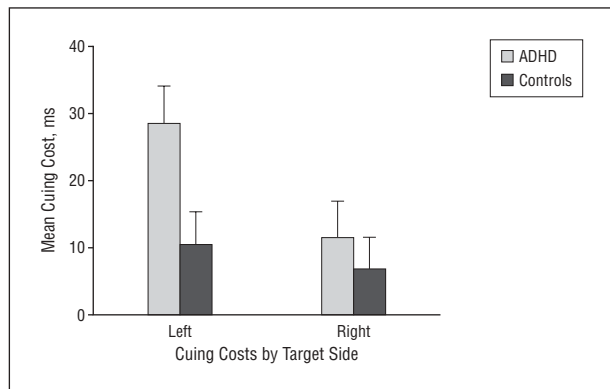
Figure 2. Mean cuing cost (invalid reaction time – neutral reaction time) as a function of target side and diagnosis at the 200-millisecond stimulus onset asynchrony for the exogenous cuing task. ADHD indicates attention-deficit/hyperactivity disorder.

Figure 3. Mean validity effect (invalid reaction time – valid reaction time) as a function of stimulus onset asynchrony (SOA) and diagnosis for the endogenous cuing task. ADHD indicates attention-deficit/hyperactivity disorder.

was, however, a main effect of diagnosis ($F_{1,112}=27.5$; $P=.001$) and a diagnosis × cue interaction ($F_{2,224}=5.26$; $P=.006$), which reflected a greater effect of cues in the children with ADHD than controls ($P=.002$ without IQ covaried). Cuing costs were higher in the ADHD group (mean [SE], 14 [3] milliseconds) than in controls (mean [SE], 3 [3] milliseconds) ($F_{1,112}=6.07$; $P<.02$), as was the validity effect (invalid RT – valid RT) (ADHD: mean [SE], 12 [4] milliseconds; controls: mean [SE], –5 [4] milliseconds) ($F_{1,112}=8.433$; $P<.005$)]. The results for the control children at the 800-millisecond SOA were as expected: at a longer cue-target delay, attention shifts away from the cued location, resulting in less cost to perception of invalid cues.[38] In contrast, even at the longer SOA, children with ADHD demonstrated increased cuing costs and higher validity effects, suggesting that attention shifted from the cued location more slowly. Cuing costs and the validity effect correlated with each other ($r=0.47$; $P=.001$), suggesting that both measures index a common spatial reorienting mechanism. There were no differences between the groups in terms of cuing benefits ($F_{1,112}=1.2$; $P>.05$).

Endogenous Cuing Effects: RT

Of the total sample of 115 children, data on the endogenous orienting task were available for 49 children with ADHD and 63 control children. Mean RT data were submitted to a diagnosis × target side × cue × SOA mixed-model ANOVA. In addition to a main effect of diagnosis ($F_{1,109}=45.57$; $P<.001$), there was a diagnosis × target side × cue interaction ($F_{2,218}=3.04$; $P=.05$) ($P=.09$ without IQ covaried). Costs, benefits, and the validity effect were calculated over SOA as a function of target side. There was a significant interaction between diagnosis and target side for the validity effect (invalid RT – valid RT; $F_{1,109}=5.5$; $P=.02$) ($P=.04$ without IQ covaried). This was driven by the larger validity effect for left targets (mean [SE], 44 [5] milliseconds) relative to right targets (mean [SE], 28 [6] milliseconds) in the children with ADHD ($P=.007$), but not in controls (left: mean [SE], 26 [5] milliseconds; right: mean [SE], 30 [6] milliseconds) ($P>.05$). Further, validity effects for left targets were greater in the children with ADHD compared with the control children ($P=.02$). There was no interaction between diag-
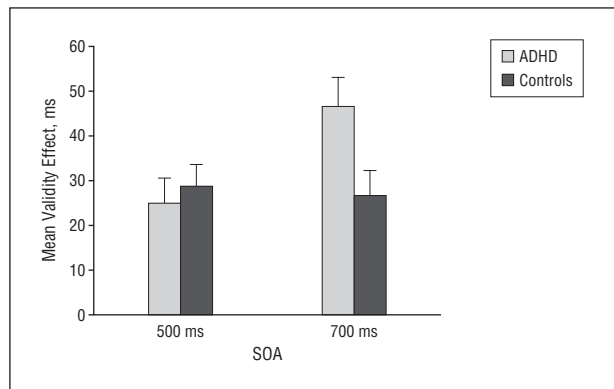
nosis and target side for cuing costs (invalid RT – neutral RT; $F_{1,109}=1.31$; $P>.05$) or cuing benefits (neutral RT – valid RT; $F_{1,109}=2.01$; $P>.05$).

There was also a significant interaction between diagnosis, cue, and SOA ($F_{2,218}=3.8$; $P<.05$). Costs, benefits, and the validity effect were compared as a function of diagnosis and SOA, collapsing across target side. Diagnosis and SOA did not interact for cuing costs ($F_{1,109}=2.01$; $P>.05$) or benefits ($F_{1,109}=2.5$; $P>.05$). There was a significant interaction between diagnosis and SOA for the validity effect ($F_{1,109}=6.03$; $P=.02$) ($P=.06$ without IQ covaried) (**Figure 3**). Children with ADHD had significantly higher validity effects at the 700-millisecond SOA (mean [SE], 47 [6] milliseconds), compared with controls (mean [SE], 27 [6] milliseconds) ($P=.03$). Further, validity effects increased as a function of SOA in the ADHD group ($P=.002$), but not in controls ($P=.73$). This effect was driven by a significant interaction between diagnosis and SOA for invalid RTs ($F_{1,109}=5.58$; $P=.02$), but not for valid RTs ($F_{1,109}=0.67$; $P>.05$). Reaction time differences between children with ADHD and control children for invalid trials increased with SOA as a result of an increase in RT for the children with ADHD, and a decrease in RT for control children, over SOA.

Taken together, compared with validly cued trials, the children with ADHD were slower to reorient attention to targets in the left, relative to right, visual field and showed increased validity effects for left targets than control children. Irrespective of lateral effects, group differences in invalid RT were maximal at the longer SOA.

DOPAMINERGIC HAPLOTYPE PREDICTS SPATIAL INATTENTION IN ADHD

Exogenous Cuing Effects

DAT1 10/3 haplotype status accounted for significant variance in cuing costs for targets in the left, but not right, visual field at the 200-millisecond SOA (**Table 3**). Diagnosis and *DAT1* interacted: cuing costs for left visual field targets were highest in children with ADHD who were 10/3 *DAT1* homozygotes (**Figure 4**).

Although there was no association between *DAT1* 10/3 haplotype status and cuing costs at the 800-millisecond

Table 3. Regression Analyses Examining the Influence of *DAT1* Haplotype Status on Key Attentional Indexes[a]

Attention Index	Effect	*F* Test	*P* Value	R^2 Change, %	B Value	SE	β	95% CL[b]
Exogenous 200-ms SOA								
Left cuing cost	*DAT1*	7.6	.007	8.5	20.7	7.5	0.3	5.8, 35.6
	Diagnosis × *DAT1*	5.4	.02	5.8	−34.5	14.8	−0.97	−64.0, −5.0
Right cuing cost	*DAT1*	0.32	>.05	0.4	4.4	7.7	0.06	−10.9, 19.7
	Diagnosis × *DAT1*	0.85	>.05	1.1	−14.4	15.6	−0.42	−45.5, 16.7
Exogenous 800-ms SOA								
Cuing cost	*DAT1*	1.7	>.05	1.9	6.5	5.1	0.14	−3.5, 16.6
	Diagnosis × *DAT1*	3.3	.07	3.6	−18.3	10.1	−0.77	−38.4, 1.8
Validity effect	*DAT1*	0.05	>.05	0.1	−1.5	6.5	−0.02	−14.5, 11.5
	Diagnosis × *DAT1*	0.52	>.05	0.6	9.5	13.3	0.32	−16.9, 36.0
Exogenous over SOA								
Cuing cost	*DAT1*	5.6	.02	6.2	9.5	4.0	0.26	1.5, 17.6
	Diagnosis × *DAT1*	7.4	.008	7.5	−21.4	7.9	−1.1	−37.1, −5.7
Endogenous 500-ms SOA								
Validity effect	*DAT1*	0.02	>.05	0.0	0.97	8.1	0.14	−15.1, 17.03
	Diagnosis × *DAT1*	0.44	>.05	0.6	−10.9	16.4	−0.31	−43.6, 21.8
Endogenous 700-ms SOA								
Validity effect	*DAT1*	2.6	>.05	3.1	13.4	8.3	0.18	−3.15, 29.9
	Diagnosis × *DAT1*	4.3	.04	4.9	67.67	27.48	0.91	12.9, 122.4
Endogenous over SOA								
Left validity effect	*DAT1*	0.009	>.05	0.0	0.69	7.3	0.11	−13.9, 15.2
	Diagnosis × *DAT1*	0.005	>.05	0.5	−8.9	14.9	−0.28	−38.5, 20.7

Abbreviations: CL, confidence limit; SE, standard error; SOA, stimulus onset asynchrony.
[a] Multiple regression, controlling for diagnosis and IQ, was used to test the association of the *DAT1* 10/3 haplotype with those attentional indexes that most discriminated children with attention-deficit/hyperactivity disorder and control children. Interactive effects of diagnosis and *DAT1* genotype were also tested.
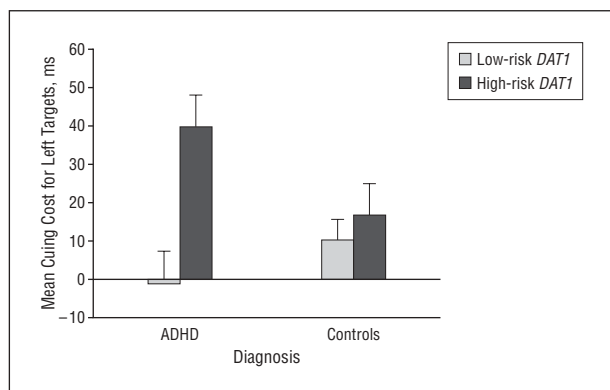[b] Of the unstandardized B values.

Figure 4. Mean cuing cost (invalid reaction time − neutral reaction time) for targets in the left and right visual field at the 200-millisecond stimulus onset asynchrony for the exogenous task as a function of diagnosis (attention-deficit/hyperactivity disorder [ADHD], controls) and *DAT1* haplotype status (low or high risk) (low risk = heterozygous for 10/3 haplotype; high risk = homozygous for 10/3 haplotype).

SOA, there was a trend for an interaction between diagnosis and *DAT1* genotype. Calculating cuing costs over SOA yielded both an effect of *DAT1* genotype and an interaction of diagnosis and *DAT1* genotype.

Endogenous Cuing Effects

At the 500-millisecond SOA, there was neither a main effect of *DAT1* haplotype status nor an interaction of *DAT1* and diagnosis. At the 700-millisecond SOA, however, there was a significant interaction between *DAT1* and diagnosis. Validity effects were highest in the children with ADHD who were homozygous for the *DAT1* 10/3 haplotype (**Figure 5**).

COMMENT

Past studies of spatial orienting in ADHD have yielded equivocal results. To our knowledge, this study has presented the largest ADHD-control comparison in children yet, using the covert visual orienting task. Across exogenous (stimulus-driven) and endogenous (strategic) forms of the task, children with ADHD were slower than control children in redirecting their attention from invalid cues presented in the visual field opposite to the target. This reorienting deficit was particularly pronounced for left visual field targets, suggesting dysfunction to right-hemisphere spatial attention systems. Yet despite these overall group differences, neuropsychological heterogeneity was evident in the ADHD cohort and predicted by variation in a frequent haplotype of *DAT1*. Children with ADHD who had a higher gene dosage of the 10/3 *DAT1* haplotype displayed pronounced deficits across measures but were particularly impaired in reorienting attention to detect targets in the left visual field at short (200-millisecond) SOAs. Our results provide the first evidence, to our knowledge, that a frequent (10/3) haplotype of *DAT1* has a functional effect on cognitive performance in ADHD.

The results of the current study show that children with ADHD experience difficulty in reorienting attention, indicative of impairment in spatial selection. In the exogenous task, this deficit was evident across SOAs and at longer SOAs for the endogenous task. In both tasks, however, interactions with cue validity were further modified by higher-order effects involving target side. For the exogenous task at the 200-millisecond SOA, cuing costs in the ADHD group,

relative to controls, were greater for left-sided targets. The ability of the current study, relative to past studies, to detect lateralized group differences may be partly attributable to increased trial numbers with an attendant reduction in error variance, exclusion of potentially confounding comorbid reading impairments,[33] and exclusion of trials on which a saccade was made.

Our lateralized results imply dysfunction to the posterior orienting system that is dominant in the right hemisphere and resemble effects reported in patients with lesions to the right parietal cortex.[5] Similarly, our findings of increased cuing costs in children with ADHD at the 800-millisecond SOA, although not lateralized, suggest a sluggish posterior reorienting mechanism in ADHD.[17,22] Other studies using a variety of selective attention paradigms have also found evidence of left-sided impairment in ADHD, indicative of disruption to right-hemisphere posterior attentional systems.[21,39,40] Recent brain imaging work also suggests an important role for the right parietal cortex in both the pathology[41] and clinical outcome associated with ADHD.[42] In the current study, children with ADHD were also slower to reorient attention to endogenously cued targets in the left visual field relative to a valid trial baseline. This finding is comparable with that reported previously in adults with ADHD[17] and may suggest additional involvement of frontostriatal systems implicated in the volitional control of attention.[10] Taken together, the results of the present study suggest a broad disruption to right-hemisphere spatial attention systems in ADHD.

Neuropsychological heterogeneity in ADHD is present across multiple cognitive domains[24] and likely explains the failure of a number of studies to document selective attention deficits in ADHD. We sought to dissect this heterogeneity by asking whether a common haplotype of *DAT1* predicted spatial attention deficits in ADHD. At the short (200-millisecond) SOA for the exogenous cuing task, *DAT1* haplotype status (2 copies vs <2 copies) accounted for 8.5% variance in cuing costs for left visual field targets.[27] Importantly, however, there was also an interaction between diagnosis and *DAT1* haplotype: children with ADHD who were also homozygous for the high-risk *DAT1* haplotype had the most significant impairment in reorienting attention overall and in particular to targets in the left visual field (5.8% variance). A similar interaction, albeit of smaller effect size (4.9% variance), was observed for endogenous cuing costs at the longer SOA. These effect sizes are of similar magnitude to those reported between working memory and *COMT* genotype (4%), for example.[43] Our findings represent the first evidence, to our knowledge, that a common haplotype of *DAT1* is a predictor of neuropsychological heterogeneity in ADHD. The largely intact performance of children with ADHD who were heterozygous for the haplotype may help to explain why previous studies of selective attention in ADHD might have failed to document group differences, particularly in relatively small samples. Although there have been isolated reports that *DAT1* variants also influence other cognitive domains, such as vigilance and response time variability, in participants with ADHD,[44,45] a number of studies have failed to document an effect of *DAT1* on neurocognitive function in ADHD when using executive and motoric measures.[46] The current results are, however, consistent with our previous ob-
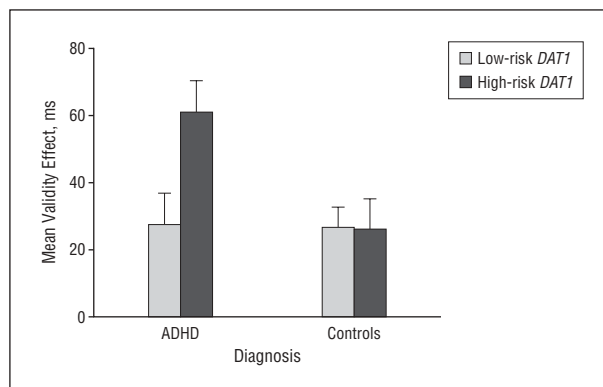

Figure 5. Mean validity effect (invalid reaction time – valid reaction time) at the long (700-millisecond) stimulus onset asynchrony in the endogenous cuing task as a function of diagnosis (attention-deficit/hyperactivity disorder [ADHD], controls) and *DAT1* haplotype status (low or high risk) (low risk = heterozygous for 10/3 haplotype; high risk = homozygous for 10/3 haplotype).

servations in the Irish population that parietal-dependent measures of attentional asymmetry are associated with *DAT1* variation and predict stimulant response in ADHD.[28,29]

The association between *DAT1* and spatial selective attention, particularly for the exogenous orienting task, implies dopaminergic modulation of posterior attentional systems, including the parietal cortex. The parietal cortex receives strong dopaminergic input[47] and dopamine transporter immunohistochemistry in the posterior parietal cortex has been reported.[48] Yet our results run counter to work suggesting cholinergic modulation of spatial selective attention. Cholinergic agonists such as nicotine reduce the costs of invalid spatial cues in human subjects and the cholinergic antagonist scopolamine increases cuing costs in nonhuman primates.[49] However, an interaction between these systems seems likely since cholinergic agonists promote dopamine signaling.[50] Furthermore, nicotine may bind to the dopamine transporter, mimicking the effect of methylphenidate and increasing dopamine reuptake.[51] Future studies should therefore investigate this potentially important pharmacological interaction and its effects on spatial selective attention.

Taken together, the results of this study demonstrate that DNA variation in a risk haplotype for ADHD predicts spatial inattention in ADHD. Heterogeneity in the extent of selective attention deficit across individuals with ADHD may reflect, in part, genetic differences.

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