

Spatial Attentional Bias as a Marker of Genetic Risk, Symptom Severity, and Stimulant Response in ADHD

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Attention-deficit hyperactivity disorder (ADHD) is a heritable childhood onset disorder that is marked by variability at multiple levels including clinical presentation, cognitive profile, and response to stimulant medications. It has been suggested that this variability may reflect etiological differences, particularly, at the level of underlying genetics. This study examined whether an attentional phenotype-spatial attentional bias could serve as a marker of symptom severity, genetic risk, and stimulant response in ADHD. A total of 96 children and adolescents with ADHD were assessed on the Landmark Task, which is a sensitive measure of spatial attentional bias. All children were genotyped for polymorphisms (3' untranslated (UTR) and intron 8 variable number of tandem repeats (VNTRs)) of the dopamine transporter gene (DAT1). Spatial attentional bias correlated with ADHD symptom levels and varied according to DAT1 genotype. Children who were homozygous for the 10-repeat allele of the DAT1 3'-UTR VNTR displayed a rightward attentional bias and had higher symptom levels compared to those with the low-risk genotype. A total of 26 of these children who were medication naive performed the Landmark Task at baseline and then again after 6 weeks of stimulant medication. Left-sided inattention (rightward bias) at baseline was associated with an enhanced response to stimulants at 6 weeks. Moreover, changes in spatial bias with stimulant medications, varied as a function of DAT1 genotype. This study suggests an attentional phenotype that relates to symptom severity and genetic risk for ADHD, and may have utility in predicting stimulant response in ADHD.

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INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a heritable childhood onset disorder with negative adult outcomes. Like many complex disorders, ADHD is marked by significant variability across a number of levels, including clinical presentation, cognitive profile, and response to stimulant medications; this variability may partly reflect differences in underlying genetics. Allelic variation in a number of candidate genes linked to catecholamine signaling is thought to confer risk for the disorder. The 10-repeat allele of a variable number of tandem repeat (VNTR) polymorphism within the dopamine transporter gene (DAT1) has attracted much interest as a

susceptibility allele for ADHD. The *a priori* hypothesis arises principally from the pharmacology of stimulant medications, such as methylphenidate (MPH), which inhibit the action of the transporter. A number of studies suggest that DAT1 is a gene of minor effect for ADHD with an average odds ratio of around 1.2 (Brookes *et al*, 2006; Cook *et al*, 1995; Daly *et al*, 1999; Gill *et al*, 1997). More recently, a number of studies have attempted to link allelic variation in DAT1 to intermediate constructs (Bellgrove *et al*, 2005a,b; Loo *et al*, 2003), or endophenotypes, and to both clinical (Kirley *et al*, 2003) and physiological measures of stimulant response (Gilbert *et al*, 2006; Loo *et al*, 2003). These studies could provide important collateral evidence regarding the functional effects of risk variants and highlight the potential clinical utility of molecular genetics for identifying sub-populations of children with ADHD that might respond better or more poorly to stimulant medication. Here, we report an association between a neurocognitive phenotype-spatial attentional bias and DAT1 genotype in 96 children and adolescents with ADHD. We also show that spatial bias relates to symptom severity and is modified, as a function of

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DAT1 genotype, by stimulant medication. Finally, we show that independent of genotypic influences, spatial bias is a significant predictor of the clinical response to stimulant medications, such as MPH, in medication naive children with ADHD.

The DAT1 3' untranslated (UTR) VNTR is potentially functional with a number of studies reporting an influence of 10-repeat variants either on *in vitro* measures of gene expression (Fuke *et al*, 2001; VanNess *et al*, 2005) or *in vivo* transporter densities (Cheon *et al*, 2005; Heinz *et al*, 2000). The dopamine transporter is the main site of action of stimulant medications, such as MPH, which inhibit the reuptake of extra cellular dopamine by the transporter (Volkow *et al*, 1998). Both children and adults with ADHD have been reported to have increased DAT densities, in for example, the striatum and basal ganglia (Cheon *et al*, 2003; Dougherty *et al*, 1999; Dresel *et al*, 2000), but the evidence is not conclusive (Jucaite *et al*, 2005; Volkow *et al*, 2007). A recent and well-controlled PET study found increased DAT binding specifically in the right caudate of treatment naive adults with ADHD compared with matched control participants (Spencer *et al*, 2007). Stimulants have also been shown to reduce elevated dopamine transporter densities in adults with ADHD (Dresel *et al*, 2000; Krause *et al*, 2000; Vles *et al*, 2003).

Not surprisingly, a number of groups have investigated whether the 10-repeat DAT1 allele might mediate the clinical response achieved with stimulants. The results of these studies have proved inconclusive thus far with the 10-repeat allele being associated with an *enhanced* (Kirley *et al*, 2003; Stein *et al*, 2005) or *diminished* (Cheon *et al*, 2005; Rohde *et al*, 2003; Roman *et al*, 2002; Winsberg and Comings, 1999) response to stimulants. Other studies, however, have failed to find an influence of alleles at the VNTR on stimulant response (Langley *et al*, 2005; Mick *et al*, 2006; van der Meulen *et al*, 2005). A number of studies have also reported interactions between DAT1 genotype and stimulants when using a physiological measure of brain function, such as an EEG frequency band, as an outcome variable (Gilbert *et al*, 2006; Loo *et al*, 2003). Important innovations within this field include the use of prospective pharmacogenetic designs with participants who are stimulant-medication naive at intake and the use of multiple predictors—both clinical and neuropsychological—of stimulant response.

Spatial attention refers to the perceptual enhancement of stimuli that are presented at certain locations in space. In most circumstances, healthy observers show a subtle bias of attention in favor of stimuli or events presented to the left, relative to right, side of space (Bradshaw, 1989). This lateral bias of attention to the left is thought to reflect the dominance of right-hemisphere neural networks for spatial processes; while right hemisphere networks direct attention to both left and right hemifields, left hemisphere networks do so only for the right hemifield (Mesulam, 1981). The dominance of the right-hemisphere for spatial attention is exemplified by the syndrome of unilateral neglect. Here, dysfunction in any one of the number of right hemisphere cortical (prefrontal, parietal) and subcortical (striatal, thalamic) nodes gives rise to a pathological bias of attention away from the left side (*left-sided inattention*) (Robertson and Marshall, 1993). A number of studies of children and

adults with ADHD and the biological parents of children with ADHD have shown abnormal biases of spatial attention (Carter *et al*, 1995; Epstein *et al*, 1997; Nigg *et al*, 1997; Sheppard *et al*, 1999). Most typically, these studies show a subtle rightward bias or left-sided inattention associated with ADHD (Epstein *et al*, 1997; Sheppard *et al*, 1999), which is consistent with the predominantly right-hemisphere pathology of the disorder (Casey *et al*, 1997; Castellanos *et al*, 1994, 1996; Silk *et al*, 2005; Sowell *et al*, 2003).

We have previously reported an association between the 10-repeat DAT1 allele and spatial bias in children and adolescents with ADHD (Bellgrove *et al*, 2005a,b). Specifically, 10-repeat homozygotes displayed left-sided inattention, relative to 10-repeat heterozygotes (Bellgrove *et al*, 2005b). We also reported an association between left-sided inattention in ADHD and an enhanced response to MPH: children who were homozygous for the 10-repeat DAT1 allele and were retrospectively rated by their parents as responding favorably to MPH, were more likely to show left-sided impairment of spatial attention than those who were heterozygous for the 10-repeat allele and were rated as achieving a poorer response (Bellgrove *et al*, 2005b). These studies suggest that spatial bias may be a marker of stimulant response in ADHD, with left-sided inattention being associated with an enhanced response to stimulants. A limitation of this previous work, however, was the recruitment of medication-withdrawn, rather than naive, participants and the use of retrospective ratings of clinical response.

There are a number of good reasons to suspect that lateral biases of spatial attention—potentially mediated by weaker right-hemisphere (striato-parietal) function—might be associated with stimulant response in ADHD. First, pathological biases of attention have been shown to be ameliorated by dopaminergic agents in a number of clinical conditions, including stroke, schizophrenia, and ADHD (Fleet *et al*, 1987; Maruff *et al*, 1995; Sheppard *et al*, 1999). Conversely, spatial biases can be induced by lesioning ascending dopaminergic pathways (Iversen, 1984) or via drugs, such as clonidine, which attenuate catecholamine function (Coull *et al*, 2001). Second, stimulants are known to act on areas of the brain that are important for directed attention, including the striatum and frontal and parietal cortices (Mehta *et al*, 2000; Volkow *et al*, 1998). High densities of DAT-immunoreactive axons have also recently been reported in the parietal lobe (Lewis *et al*, 2001). Third, an important role for the parietal lobe in ADHD has recently emerged from brain imaging studies. Thus, for example, a number of structural and functional imaging studies have shown prominent abnormalities in right parietal areas (Konrad *et al*, 2006; Silk *et al*, 2005; Smith *et al*, 2006; Sowell *et al*, 2003; Tamm *et al*, 2006). Reduced cortical thickness within the right parietal lobe has been reported in children and adults with ADHD (Makris *et al*, 2007). Shaw *et al* (2006) reported normalization of cortical thickness within the right parietal lobe over time in those ADHD children with an improved clinical outcome. Moreover, a recent physiological study showed lower regional cerebral blood flow in the right superior parietal lobule of nonresponders after 8 weeks of treatment with MPH (Cho *et al*, 2006).

These converging lines of evidence lead us to propose that lateral biases of spatial attention may relate to allelic

variation in DAT1 *and* have utility as a marker of stimulant response in ADHD.

The aims of the current study were fourfold. First, we examined whether the 10-repeat allele of the DAT1 VNTR was associated with symptom severity in a cohort of 96 Irish families. We predicted that homozygosity for the 10-repeat allele would be associated with greater symptom severity. Association with a potentially functional VNTR within intron 8 of the DAT1 gene, the three-repeat allele of which was recently reported to be associated with ADHD (Brookes *et al*, 2006) was also examined. Brookes *et al* (2006) reported association of ADHD with a common haplotype comprising the 10- and 3-repeat alleles of the DAT1 VNTRs. Asherson *et al* (2007) recently confirmed this haplotype association with an average odds ratio of 1.4 in a multicenter study involving 1159 probands with DSM-IV combined-type ADHD. (It should be noted that Asherson *et al* identified additional repeat units in the intron 8 VNTR and relabeled the three-repeat allele as a six-repeat allele. The associated haplotype therefore comprised the 10- and 6-repeat alleles of the 3' UTR and intron 8 VNTRs.) We therefore also examined whether ADHD symptom severity varied as a function of possession of this 'risk haplotype'.

Second, within this Irish cohort, we sought to verify the association between spatial bias in ADHD and genotype at these DAT1 markers. We predicted that homozygosity for the 10-repeat DAT1 allele would be associated with left-sided inattention.

Third, using a prospective pharmacogenetic design with a medication naive cohort ($n=26$), we examined whether stimulant treatment modified spatial bias, as a function of DAT1 genotype.

Finally, we also examined whether spatial bias measured when ADHD children were stimulant naive, could predict stimulant response at 6 weeks, independent of genotypic influences. We hypothesized that children displaying left-sided inattention at baseline would show an enhanced clinical response to stimulant medication.

MATERIALS AND METHODS

Participants

A total of 96 children and adolescents with ADHD (81 male) participated in this study. Data from 43 of these participants has been presented previously (Bellgrove *et al*, 2005b). A total of 46 of the children were stimulant-medication naive and were recruited as part of a larger pharmacogenetic study. Participants from the pharmacogenetic study were stimulant naive and had not been prescribed any other psychotropic medication. In all other respects, the inclusion, exclusion, and diagnostic criteria were identical for the entire sample of 96 participants (see below). All recruitment was conducted in accordance with the approved ethical guidelines of participating institutions and hospitals. The mean age of the current sample was 10.3 years ($SD=3$) with a mean IQ of 97 ($SD=14$). Children were also assessed using the reading and spelling subtests of the Wide Range Achievement Test 3 (Wilkinson, 1993). Participants scoring $1\frac{1}{2}$ SDs below normative levels on the reading subtest were classified as having reading disorder (RD). Handedness was

assessed using the Edinburgh Handedness Inventory with 82% of the sample being right-handed.

Participants were referred to this study either via support groups or collaborating consultant child and adolescent psychiatry teams. For the pharmacogenetic aspect of this study, all children had been referred to consultant child and adolescent psychiatrists in the community. Confirmation of clinical diagnoses were made by trained psychiatrists (AK, EB) using the parent version of the Child and Adolescent Psychiatric Assessment interview (Angold *et al*, 1995). Additional information regarding symptom pervasiveness was obtained using The Child Attention-Deficit Hyperactivity Disorder Teacher Telephone Interview (Holmes *et al*, 2004). All children met DSM-IV diagnosis for ADHD. In this cohort of 96 participants, 74 (77%) of the ADHD participants had a diagnosis of ADHD combined type (ADHD-CT), 12 (13%) participants had a diagnosis of ADHD predominantly inattentive type (ADHD-In) and 10 (10%) participants had a diagnosis of ADHD predominantly hyperactive/impulsive type (ADHD-Hyp/Imp). These frequencies did not differ as a function of genotype at the DAT1 markers. Parents of children also rated behavior using either the brief or long forms of the Conners' Parent Rating Scale (Conners, 1997). The mean value for the parent-rated ADHD index was 77 ($SD=7.3$; range = 50–91). (Since a greater range of values was beneficial for correlational analyses using the ADHD index, we did not exclude participants with T -scores less than 65, unless otherwise stated. Nevertheless, only 4 participants had ADHD index T -scores less than 65 and excluding these participants did not change the association between DAT1 genotype and spatial bias reported.) The frequency of oppositional defiant disorder (ODD) and conduct disorder (CD) within this sample was 51 and 19%, respectively. Detailed clinical information for the cohort of 96 participants can be found in Table 1.

Establishing Stimulant Response Using Clinical Ratings

Predictors of stimulant response were also examined in a subsample of 26 (22 male, 17 right-handed) stimulant-naive children with ADHD (see Table 2). These children met the inclusion criteria for this aspect of the study by having baseline Conners' ADHD index T -scores greater than 65 and having performed the Landmark Task at baseline and then again after 6 weeks of stimulant medication. Additionally, these children did not have a primary diagnosis of pervasive developmental disorder, were free of neurological disorder, and did not have fetal alcohol disorder or prenatal drug abuse. Diagnostic procedures were as described above and 19 (73%) of these children met criteria for ADHD-CT, 4 (15%) for ADHD-In, and 3 (12%) for ADHD-Hyp/Imp. The frequency of ODD and CD were 39 and 23%, respectively. Stimulant type and dose was at the discretion of the treating consultant psychiatrist within the community. A total of 25 (96%) of the ADHD participants were treated with MPH-based preparations (Ritalin (11); Concerta (11); Ritalin LA (3)) and one participant with dextroamphetamine. Dose was calculated as mg/kg of MPH equivalent and varied between participants from 0.21 to 1.0 mg/kg (mean = 0.59 mg/kg, $SD=0.19$). MPH equivalent dosages were calculated to facilitate comparison across all types of stimulant medication by

doubling the dextroamphetamine dose to reach an equivalent MPH-dose (see (Efron *et al*, 1997)). Dose at 6 weeks was corrected for weight (milligram per kilogram of MPH equivalent).

Table 1 Clinical Characteristics of ADHD Participants ($n = 95$)

	Mean	SD	Range
Age (years)	10.3	3	4–15.8
IQ	96	14.2	71–137
WRAT reading	93	14	55–121
WRAT spelling	91	15	52–149
ADHD index T-score	77	7.3	50–91

	Number (%)
Handedness (right-handed)	79 (82)
Gender (male)	81 (84)
Reading disorder	17 (18)
ADHD-CT	74 (77)
ADHD-In	12 (13)
ADHD-Hyp/Imp	10 (10)
Oppositional defiant disorder	49 (51)
Conduct disorder	15 (16)

Abbreviations: WRAT, wide range achievement test; ADHD-CT, ADHD combined type; ADHD-In, ADHD inattentive type; ADHD-Hyp/Imp, ADHD hyperactive/impulsive type.

WRAT reading and spelling measures were not available for nine participants with ADHD.

Table 2 Clinical Characteristics of ADHD Participants Involved in the Medication–Response Study ($n = 26$), as a Function of DAT1 3'-UTR VNTR Genotype Group

	Total medication response ADHD Sample ($n = 26$)			Low-risk DAT1 ($n = 15$)		High-risk DAT1 ($n = 11$)		
	Mean	SD	Range	Mean	SD	Mean	SD	F(1,24) p
Age (years)	9.1	3	5–15	8.5	2.8	9.9	3.2	1.4 0.26
IQ	93.9	16.1	71–134	92.5	18.5	95.8	12.9	0.23 0.61
WRAT reading	102.3	13.4	79–137	100.8	12.3	104.4	15.2	0.44 0.52
WRAT spelling	93.5	9.5	76–114	94.3	10.5	92.5	8.4	0.22 0.64
Baseline parent-rated ADHD Index T-score	78.6	6.1	69–90	78.5	5.9	78.9	6.8	0.03 0.86
Percentage change in parent-rated ADHD Index T-score at 6 weeks	25.2	12.3	1.4–43.8	25.1	13.6	25.5	10.8	0.006 0.94
Dose (mg/kg MPH-equivalent)	0.59	0.19	0.21–1.00	0.61	0.18	0.56	0.21	0.42 0.52

	Number (%)	Number (%)	Number (%)
Handedness (right-handed)	17 (65)	9 (64)	8 (80)
Gender (male)	22 (85)	13 (87)	9 (82)
ADHD-CT	19 (73)	11 (73)	8 (73)
ADHD-In	4 (15)	2 (13)	2 (18)
ADHD-Hyp/Imp	3 (12)	2 (13)	1 (9)
Oppositional defiant disorder	10 (39)	7 (47)	3 (27)
Conduct disorder	6 (23)	4 (27)	2 (18)

WRAT, wide range achievement test; ADHD-CT, ADHD combined type; ADHD-In, ADHD inattentive type; ADHD-Hyp/Imp, ADHD hyperactive/impulsive type. Low-risk DAT1: no or one copy of the 10-repeat allele; high-risk DAT1: two copies of the 10-repeat allele.

In the current analysis, stimulant response was assessed using parental ratings of symptomatology obtained at baseline and then again after 6 weeks of stimulant treatment. Here, we focus on medication-related changes in parent-rated Conners' ADHD indices at baseline and then at 6 weeks. A categorical stimulant-response variable was also defined based upon whether ADHD indices were normalized with stimulant treatment (T -scores ≤ 60) or not ($T > 60$).

Using Spatial Bias as a Marker of Stimulant Response

Spatial bias, or asymmetry, was assessed using the Landmark Task (Bellgrove *et al*, 2005b; Binder *et al*, 1992; Fink *et al*, 2001). In this brief (5 min) test, participants judge which end of a pre-bisected line looks shorter to them. Participants performed 20 trials of the Landmark Task. On 10 of these trials, the bisecting line was offset (either to the right or left) allowing accuracy of judgments to be determined. On the remaining 10 trials, the horizontal line was bisected in the middle. Trials on which the left end of the line was nominated as the shorter were designated 'right-biased'. Trials on which the right end of the line was nominated as the shorter were designated 'left-biased'. A continuous measure of spatial bias—the Landmark Asymmetry index—was calculated as $(N_{\text{right-biased trials}} - N_{\text{left-biased trials}}) / 10$. This yielded values ranging from -1 (leftward bias) to $+1$ (rightward bias). Normally developing children tend to show a subtle leftward bias on versions of line bisection giving rise to negative values for asymmetry indices (Dobler *et al*, 2001; Failla *et al*, 2003). Human lesion and functional

neuroimaging studies have shown that this task is a particularly sensitive assay of right parietal function (Binder *et al*, 1992; Fink *et al*, 2000, 2001). A total of 96 children and adolescents performed the Landmark Task while either medication naive (48%) or withdrawn from stimulant medication for at least 24 h. A total of 26 of those children who were medication naive also performed the task again after 6 weeks of stimulant treatment. Changes in the Landmark Asymmetry index as a function of medication phase (baseline vs 6 weeks) and DAT1 genotype were of interest, as well as the relationship between baseline Landmark Asymmetry indices and stimulant-response variables.

DAT1 Genotyping

DNA was extracted from blood samples or saliva using the standard phenol chloroform procedure from both parents and the ADHD proband in each family. Primer sequence and amplification conditions for the 3'-UTR VNTR can be found elsewhere (Daly *et al*, 1999). Polymerase chain reaction (PCR) amplification of the intron 8 VNTR was performed using the following primers (10 pmol/ μ l each): (forward: 5'-GCTTGGGGAAGGAAGGG-3'; reverse 5'-TGTTGCGGTGCATGTGG-3'). The following PCR cycling protocol was adopted: 95°C for 15 min, with 30 cycles of annealing 66°C for 1 min, and extension 72°C for 1 min. A final 10-min extension at 72°C was also added. Amplification products were visualized on 2% agarose gels, denoting the two common repeats as alleles 2 and 3 at 339 and 369 bp, respectively. All genotypes were in Hardy-Weinberg Equilibrium (3'-UTR VNTR: $\chi^2 = 0.86$, $p = 0.65$; intron 8 VNTR: $\chi^2 = 0.31$, $p = 0.86$).

Linkage disequilibrium (LD) between the 3' UTR and intron 8 VNTRs was estimated at $D' = 0.67$ for the entire sample. DAT1 10/3 haplotype status was assigned to participants using a Bayesian approach to reconstructing haplotypes implemented in the program PHASE (v2.02 Stephens and Donnelly, 2003). Haplotypes could be determined for 90 participants at a probability ≥ 0.9 . A total of 46 (46%) participants were homozygous for the 'high-risk' 10/3 haplotype, 38 (42%) were heterozygous, and 12 (12%) did not possess this haplotype. The frequency of the 10/3 haplotype within this Irish cohort was 66%.

Statistical Analysis

Statistical analyses of the relationships between DAT1 genotype and both symptom severity and spatial bias were performed using analysis of variance (ANOVA). Participants who were homozygous for risk alleles (10-repeat 3'-UTR VNTR or three-repeat intron 8 VNTR) were classified as 'high-risk'. Participants possessing <two copies of the risk alleles were classified as 'low-risk'. Genotypes at both markers were entered as between-subjects factors in analyses in order to examine the main effect of one in the presence of the other. The effect of increasing possession of the 10/3 DAT1 risk haplotype was also examined using ANOVA with a between-subjects factor of DAT1 haplotype status (0 vs 1 vs 2 10/3 haplotypes). Significance was assessed at an α of 0.05 and all *post hoc* comparisons were Bonferroni corrected.

For the medication-response aspect of this study, all analyses were covaried for IQ and dose (milligram per kilogram of MPH equivalent). The interaction of DAT1 genotype and medication phase (naive vs 6 weeks of stimulant treatment) on Landmark Asymmetry indices was assessed using ANOVA, with repeated measures on the Landmark Asymmetry index assessed at baseline and then again after 6 weeks. To examine whether spatial bias predicted stimulant-related symptom reduction after 6 weeks of treatment, the Landmark Asymmetry index was used as a predictor in regression, independent of the influences of IQ and dose. Baseline Landmark Asymmetry indices were compared using ANOVA, as a function of the categorical medication-response variable (normalization vs non-normalization of ADHD indices).

RESULTS

DAT1 Variants Influence Symptom Severity in ADHD

The association between DAT1 variants and dimensional measures of ADHD symptomatology was firstly examined using the ADHD index from the Conners' scales. There was a significant main effect of 3'-UTR genotype on the ADHD index ($F(1,92) = 5.34$, $p < 0.05$, $\eta^2 = 0.06$), such that High-Risk group had higher levels of symptomatology (mean = 80, SE = 1.6) than the Low-Risk group (mean = 76, SD = 1.1). There was no main effect of intron 8 genotype ($F(1,92) = 2.25$, $p > 0.05$, $\eta^2 = 0.02$). A separate univariate ANOVA revealed a significant main effect of DAT1 haplotype status ($F(2,85) = 3.12$, $p < 0.05$, $\eta^2 = 0.07$), after controlling for the influence of age and IQ. ADHD probands who did not possess the 10/3 haplotype had significantly lower symptom levels (mean = 72.5, SE = 2.1) than those who possessed one (mean = 78, SE = 1.1; $p = 0.05$; Bonferroni corrected) or two (mean = 78, SE = 1.1; $p = 0.08$) 10/3 haplotypes. Given the absence of an effect for the intron 8 VNTR, the 10/3 haplotype effect is most likely driven by the association with the 3'-UTR VNTR.

DAT1 Variants Influence Spatial Bias in ADHD

The association between DAT1 variants (3' UTR and intron 8) and spatial bias was next examined in a sample of 96 children and adolescents with ADHD. There was a significant main effect of DAT1 3'-UTR genotype on spatial bias ($F(1,92) = 4.76$, $p < 0.05$, $\eta^2 = 0.05$), such that the high-risk group were right-biased (mean = +0.21, SE = 0.09) and the low-risk group were left-biased (mean = -0.03, SE = 0.06). The main effect of DAT1 intron 8 genotype was not significant ($F(1,92) = 2.66$, $p > 0.05$, $\eta^2 = 0.03$). A separate univariate ANOVA found no main effect of DAT1 haplotype status (0 vs 1 vs 2 10/3 haplotypes) on spatial bias ($F(2,87) = 0.60$, $p = 0.55$, $\eta^2 = 0.01$). Restricting the above analysis to children without RD ($n = 77$; $F(1,73) = 5.76$, $p < 0.05$, $\eta^2 = 0.07$) or to right-handed children ($n = 79$; $F(1,75) = 6.07$, $p = 0.02$, $\eta^2 = 0.08$) marginally increased the strength of the association between the 3'-UTR marker and spatial bias.

There was a significant, albeit weak, correlation between spatial bias and scores on the ADHD index, indicating that

greater symptom severity was associated with poorer left-sided attention ($r = 0.19$, $p < 0.05$, one-tailed).

In summary, lateral biases of spatial attention in ADHD appear to be most robustly influenced by variation in the DAT1 3' UTR, with less influence of the intron 8 VNTR. ADHD probands with the high-risk DAT1 genotype at the 3' marker displayed a subtle left-sided inattention/right spatial bias whereas those with the low-risk genotype at this marker did not. Spatial bias was related to the severity of symptomatology in ADHD.

DAT1 Variants Influence the Effect of Stimulant Medications on Spatial Bias in ADHD

Spatial biases at baseline and after 6 weeks of stimulant medication were examined as a function of DAT1 variants ($n = 26$). Since lower IQ is known to moderate stimulant response (Owens *et al*, 2003), all analyses reported below were covaried for IQ. Since dose was at the discretion of the treating clinician, all analyses were also covaried for dose. Participant characteristics, as a function of DAT1 3'-UTR genotype, are presented in Table 2. RD has been associated with both a poorer response to stimulants and left-sided inattention (Facoetti *et al*, 2001). We therefore excluded children with RD from the current analysis.

Due to the smaller number of participants involved in this aspect of the study, the 3' UTR and intron 8 markers were analyzed separately. Results are reported for each of these markers along with the 10/3 haplotype.

There was a significant interaction between 3'-UTR genotype and medication phase (baseline *vs* 6 weeks) on the Landmark Asymmetry index measured at baseline and again at 6 weeks ($F(1,22) = 5.03$, $p < 0.05$, $\eta^2 = 0.19$). Effects were comparable when excluding non right-handed children ($F(1,13) = 4.61$, $p = 0.05$, $\eta^2 = 0.26$). There were no main effects of 3'-UTR genotype ($F(1,22) = 0.08$, $p > 0.05$), dose ($F(1,22) = 3.69$, $p > 0.05$), or IQ ($F(1,22) = 0.29$, $p > 0.05$). Inspection of Figure 1 indicates that lateral biases changed as a function of 3'-UTR genotype and medication phase. The high-risk group were right-biased at baseline (as reported above) and became slightly left-biased with medication. In contrast, the low-risk groups were slightly left-biased at baseline and became right-biased with medication. Analysis of simple main effects with Bonferroni corrections showed the latter effect drove the interaction ($p < 0.05$).

We also separately examined the interaction of medication phase and intron 8 genotype and DAT1 haplotype status (0/1 10/3 haplotype *vs* 2 10/3 haplotypes (Due to the smaller sample size in this aspect of the study, individuals who did not possess the 10/3 haplotype were combined with 10/3 heterozygotes and compared to 10/3 homozygotes.)) on the Landmark Asymmetry index. No interaction was found between intron 8 genotype and medication phase ($F(1,22) = 0.05$, $p > 0.05$).

An interaction was however found between DAT1 haplotype status and medication phase ($F(1,22) = 5.05$, $p < 0.05$, $\eta^2 = 0.19$) that resembled that for the 3'-UTR marker. The effect of stimulant medication on lateral biases of spatial attention was most pronounced in those with none or one 10/3 haplotype ($p < 0.05$, Bonferroni corrected).

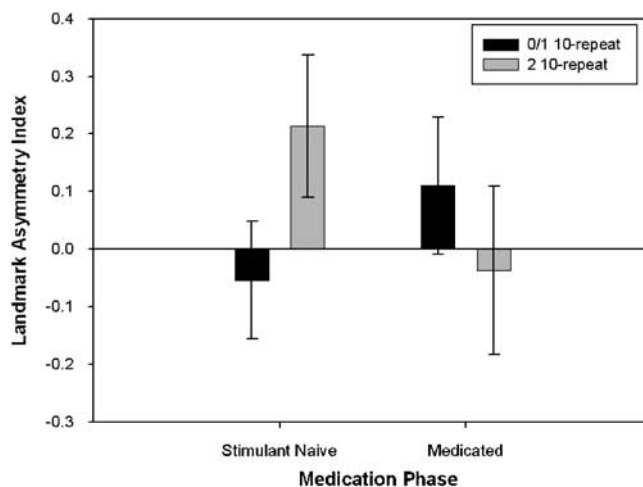


Figure 1 Interaction of DAT1 3'-UTR genotype and medication phase on the Landmark Asymmetry index (mean \pm SE).

DAT1 Variants Do Not Influence Stimulant Response in ADHD

Given reports that the 10-repeat allele of the DAT1 VNTR may mediate an enhanced response to stimulants (Kirley *et al*, 2003), we examined whether there was a relationship between DAT1 genotype and either the dose of stimulant prescribed (milligram per kilogram of MPH equivalent) or the extent of symptom reduction achieved by 6 weeks of stimulant treatment. There was no significant effect of DAT1 3'-UTR genotype on either dose ($F(1,24) = 0.42$, $p = 0.52$) or the percentage change in parent-rated ADHD index scores ($F(1,24) = 0.006$, $p = 0.94$). Effects were also nonsignificant for the DAT1 intron 8 VNTR and 10/3 haplotype. Within this cohort, the mean percentage change score in the ADHD index was 25% (SD = 12.3), with 12 participants (46%) achieving a symptom reduction of 25% or more.

Spatial Bias Predicts Stimulant Response

A linear regression was performed to examine whether the Landmark Asymmetry index measured at baseline could predict the percentage change in parent-rated ADHD index scores after 6 weeks of treatment. The Landmark Asymmetry index was a significant predictor, accounting for 19% of the variance in the parent-rated ADHD index percentage change scores ($F(1,24) = 5.45$, $p < 0.05$). Dose of stimulant drug (milligram per kilogram) and IQ were not independent predictors of symptom change.

A categorical medication-response variable was formed by examining whether or not parent-rated ADHD indices normalized with 6 weeks of stimulant treatment. A total of 13 participants normalized (ADHD index T -scores ≤ 60), whereas 13 did not (ADHD index T -scores > 60). There were no baseline differences on the parent-rated ADHD index between these two groups ($F(1,24) = 0.29$, $p > 0.05$). After controlling for the effects of IQ and dose (milligram per kilogram of MPH equivalent), there was a significant difference between those who did and did not normalize in terms of their baseline Landmark Asymmetry indices ($F(1,22) = 4.82$, $p < 0.05$, $\eta^2 = 0.18$). Those who normalized

were significantly right-biased at baseline (mean = +0.17, SD = 0.28; $t(12) = 2.17$, $p < 0.05$, one-tailed), whereas those who did not tended to be left-biased at baseline (mean = -0.14, SD = 0.46; $t(12) = 1.07$, $p = 0.15$, one-tailed) (see Figure 2).

DISCUSSION

This study examined the relationship between a neurocognitive phenotype-spatial attentional bias and symptom severity and DAT1 genotype in children and adolescents with ADHD. Using a prospective pharmacogenetic design, we also investigated the utility of spatial bias for predicting the clinical response to stimulants after 6 weeks of treatment. There were several noteworthy findings.

First, variation at the 3'-UTR VNTR associated with ADHD symptom severity, such that 10-repeat homozygotes had higher levels of parent-rated symptomatology than those children possessing none or one copy of this allele. Moreover, an effect of the 10/3 haplotype on symptom severity was apparent, with lower symptom severity in probands who did not possess this haplotype. That we found no influence of the intron 8 VNTR on symptom severity suggests that variation in the 3' UTR is the primary driver of these relationships within our Irish sample.

Second, the results of the present study support our previous reports of an association between the 10-repeat allele of the DAT1 3'-UTR VNTR and spatial bias in ADHD (Bellgrove *et al*, 2005a, b). There was an association between the 10-repeat allele at the 3' marker and spatial bias, with left-sided inattention being most pronounced in ADHD probands who were homozygous for the 10-repeat allele. Moreover, left-sided inattention was associated with higher symptom severity.

Third, spatial bias was modulated, as a function of DAT1 genotype, by stimulant treatment. Stimulant treatment influenced spatial biases most dramatically in the low-risk 3'-UTR genotype group where stimulant use induced left-sided inattention. Comparable effects were seen as a function of 10/3 DAT1 haplotype status.

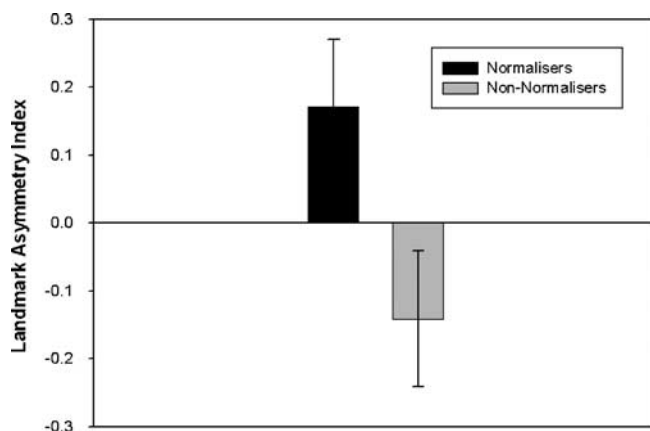


Figure 2 Landmark Asymmetry index predicts stimulant response (mean \pm 1 SE). ADHD probands who achieved normalization of the parent-rated ADHD index after 6 weeks of stimulant treatment were right-biased (left-sided inattention) at baseline whereas those who did not achieve normalization tended to be left-biased at baseline.

Fourth, irrespective of DAT1 genotype, spatial bias measured at baseline was predictive of the clinical response achieved by 6 weeks of stimulant treatment. Children who achieved a better clinical response to stimulants displayed left-sided inattention when medication naive, whereas those who achieved a poorer response showed the opposite bias. This result suggests that left-sided inattention measured at baseline is a predictor of an enhanced response to stimulant medication in ADHD.

Bellgrove *et al* (2005b) reported an association between left-sided inattention and the 10-repeat allele of the DAT1 3'-UTR VNTR in a sample of 43 ADHD probands who were free of RD. Here, we extend these findings in a partially overlapping sample to show a general effect of DAT1 genotype on spatial bias in an unselected sample of 96 participants with ADHD. In contrast to the left-sided inattention displayed by the high-risk group, the spatial bias of the low-risk group was consistent with that displayed by healthy participants. Healthy participants performing line bisection, on average, tend to bisect lines slightly to the left of the objective center (Bowers and Heilman, 1980). This subtle leftward bias is thought to arise from the dominance of the right-hemisphere for spatial judgments. The bias displayed by the high-risk group is, however, opposite in direction and is comparable—in a subclinical form—to that seen after right hemisphere lesions to frontal, parietal, or subcortical regions (Robertson and Marshall, 1993). Left-sided inattention on the Landmark Task has been particularly associated with damage to the right parietal lobe (Binder *et al*, 1992). Support for the association between DAT1 genotype and spatial bias in ADHD comes from work showing evidence of high densities of DAT-immunoreactive axons in the parietal lobe (Lewis *et al*, 2001). Given accumulating evidence suggesting functionality of the 3'-UTR VNTR, we have hypothesized that the 10-repeat DAT1 allele, or another variant with which it is in LD, might be associated with lowered dopamine in right-hemisphere spatial attention networks (eg striatum and parietal lobe), thus giving rise to left-sided inattention (Bellgrove *et al*, 2005b).

It is noteworthy that in the current study, we found no influence of the intron 8 VNTR or of the 10/3 DAT1 haplotype on spatial bias. This was somewhat surprising given that the 3' UTR and intron 8 VNTRs show a considerable degree of LD within our Irish sample and we have previously shown an effect of the intron 8 VNTR and 10/3 haplotype on spatial orienting in healthy children (Bellgrove *et al*, 2007). Spatial orienting paradigms examine the influence of spatial cues that are either valid, invalid, or uninformative with respect to the hemifield of an upcoming target. Over a large number of trials orienting tasks yield reaction time effects that reflect the operation of spatial selective attention. These tasks may have greater sensitivity to detect subtle genetic influences than the Landmark Task which probes directed attention over a relatively small number of trials. We cannot therefore discount an influence of the intron 8 VNTR or 10/3 haplotype on spatial attention in ADHD. Nevertheless, the current study provides additional evidence for an association between the 10-repeat allele of the DAT1 3'-UTR VNTR and spatial bias in ADHD.

Lateral biases of attention were also modified with stimulant medication differentially in each of the low- and

high-risk DAT1 3'-UTR VNTR groups, and as a function of 10/3 haplotype status. Previous work in ADHD has shown that spatial biases can be modified with stimulant treatment (Nigg *et al*, 1997; Sheppard *et al*, 1999), but to our knowledge, this is the first report to indicate that this effect is further modified by DAT1 genotype. The spatial bias of the high-risk group shifted with medication from being right-biased (left-sided inattention) at baseline to left-biased when medicated. Stimulant medication had the most profound effect, however, on lateral biases in the low-risk group with a significant rightward shift in spatial bias occurring with treatment. These results suggest that stimulant medication actually induced a pathological left-sided inattention in the low-risk group.

A primary aim of this study was to examine whether lateral biases of spatial attention measured at baseline could predict the clinical response to stimulants after 6 weeks of treatment, independent of genetic influences. A robust relationship was found between spatial bias and medication-related changes in parent-reported ADHD index *T*-scores at 6 weeks compared to baseline (19% variance explained). ADHD children who achieved greater symptom reduction displayed left-sided inattention at baseline, after controlling for the influence of IQ and stimulant dose. This relationship held when classifying clinical response according to whether ADHD symptoms were normalized with treatment or not. Our results demonstrate that lateral biases of attention have efficacy in predicting clinical response to stimulants, irrespective of genotypic influences. This result supports our previously published finding that spatial bias was related to retrospective ratings of MPH response in ADHD (Bellgrove *et al*, 2005b). Importantly, the current result cannot be attributed to prior exposure to stimulant medications, differential baseline symptom levels, or the dose required to achieve symptom reduction.

A number of studies have examined whether the 10-repeat DAT1 allele is a significant predictor of stimulant response, however, results have proved conflicting (Cheon *et al*, 2005; Kirley *et al*, 2003; Rohde *et al*, 2003; Roman *et al*, 2002; Stein *et al*, 2005; Winsberg and Comings, 1999). Kirley *et al* (2003) previously reported an association between the 10-repeat allele and an enhanced response to MPH using a three-point retrospective rating-scale within an Irish population. The present study used a prospective design to examine this issue in a relatively small sample of 26 medication naive children with ADHD but failed to find an effect of DAT1 genotype on the percentage change score for the ADHD index after 6 weeks of stimulant treatment. It should be noted, however, that the current sample of 26 children had considerably reduced power to detect this effect.

In summary, the results of the present study suggest that spatial bias may be a marker of symptom severity, genetic risk, and stimulant response in ADHD. The current study supports our previous report (Bellgrove *et al*, 2005b) of an association between spatial bias and both symptom severity and the 10-repeat allele of the DAT1 3'-UTR VNTR in our Irish ADHD sample. In the absence of definitive data linking VNTR alleles to DAT expression, these data nevertheless show a functional effect of the 10-repeat allele on directed attention in ADHD. Our results also show that stimulant medications modulate spatial bias differentially as

a function of DAT1 genotype; 6 weeks of stimulant treatment induced left-sided inattention in the low-risk DAT1 group and attenuated this phenotype in the high-risk DAT1 group. This effect implies that allelic variation in DAT1 differentially influences the sensitivity of spatial attention networks to stimulant drugs. The association between left-sided inattention at baseline and a greater symptom reduction after 6 weeks of stimulant treatment is also an important and novel finding. If confirmed within larger prospective studies, baseline assessments of spatial bias, irrespective of genotype status, may have clinical utility for predicting response to stimulants in ADHD.

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DISCLOSURE/CONFLICT OF INTEREST

Dr Bellgrove, Dr Gill, and Dr Robertson hold a patent within Ireland (Irish Patent no: 84530) on using molecular genetic and attentional markers to predict methylphenidate response in ADHD. The other authors have nothing to disclose.

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