Impaired temporal resolution of visual attention and DBH genotype in attention deficit hyperactivity disorder (ADHD).

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Abstract

Background: Dopamine beta hydroxylase (DβH) catalyses the conversion of dopamine to noradrenaline. ADHD has been associated with the A2 allele of a Taq I polymorphism of the DBH gene. Since catecholamines regulate visual attention, we examined whether participants with ADHD were impaired on a task requiring temporal attention, and how DBH genotype influenced temporal attention in ADHD.

Methods: Thirty-seven children and adolescents with ADHD and 52 matched, normal controls participated. Participants were presented with two visual stimuli, separated in time by either 50, 100 or 200ms, and were asked to judge the temporal order of their onset. Genotypes for the Taq 1 polymorphism were available for 33 of the ADHD participants.

Results: ADHD participants were more error prone than controls, particularly when stimuli were presented close together in time (i.e., at the 50ms asynchrony). Moreover, ADHD individuals homozygous for the A2 allele performed more poorly than those without this allele; and this difference was accentuated at the 50ms asynchrony.

Conclusions: ADHD participants have an impaired rate of perceptual processing for rapidly presented visual events. Deficits in the temporal resolution of visual attention in ADHD are associated with the A2 allele of the Taq I DBH polymorphism, or another variant with which it is in linkage disequilibrium.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a child-onset disorder with negative adult outcomes. While the etiology of the disorder remains unclear, a strong genetic component is suggested by twin (Levy et al 1997; Thapar et al 1995), family (Biederman et al 1990; Faraone et al 1994), adoption (Cadoret and Stewart 1991) and more recently, molecular genetic studies (e.g.Daly et al 1999; Faraone et al 2001). Molecular genetic studies have revealed a number of polymorphisms associated with ADHD, each of which is thought to confer a small amount of susceptibility to the disorder (see Hawi et al 2003 for review). Linking susceptibility genes to neuropsychological and neurophysiological processes has recently met with some success (Bellgrove et al 2005a; Bellgrove et al in press-a; Bellgrove et al in press-c; Durston et al 2005; Langley et al 2004; Loo et al 2003). These studies have helped to establish the functional consequences of the possession of "risk" variants for behaviour and cognition in ADHD. One such variant is the A2 allele of a Taq I polymorphism located within intron 5 of the gene (DBH) encoding dopamine beta hydroxylase (DβH). DβH catalyses the conversion of dopamine to noradrenaline, and is critical to the regulation of catecholamines in the brain. Catecholamine signalling in prefrontal and parietal cortices mediates distinct aspects of attention (Aston-Jones et al 1998; Posner and Peterson 1990; Witte and Marrocco 1997). ADHD has been associated with lowered plasma DβH activity (Rogeness et al 1989). Allelic variation in a Taq I polymorphism has been associated with ADHD in a number of studies (Daly et al 1999; Roman et al 2002; Smith et al 2003). Here we investigate the association between this polymorphism and the temporal allocation of visual attention in children and adolescents with ADHD.

It is well established that regions within the frontal and parietal cortices, particularly of the right cerebral hemisphere, are critical to both temporal and spatial aspects

of visual selective attention (Corbetta and Shulman 2002; Coull et al 2000; Coull et al 2003; Husain and Rorden 2003). Temporal attention is often probed using rapid serial visual presentation (RSVP) of stimuli presented at fixation. In a typical RSVP task the participant is required to monitor for the appearance of two targets that occur in rapid succession within a stream of distractors. In a baseline condition, subjects are required to discriminate a nominated target (e.g. S) from distractors. In a second condition, a first target precedes the presentation of the second target (the S, for example). Relative to the baseline condition, detection of the target in the second condition is impaired when it follows the first target by up to 500ms (Raymond et al 1995; Shapiro et al 1994). This impaired detection of the second of two targets is known as the attentional blink (AB), and is thought to reflect a capacity limit in the ability to selectively attend to events that are presented close together in time. Human lesion studies indicate that disruption of the right inferior parietal and frontal areas increases the duration of the AB and is thus associated with impairments in the temporal allocation of visual attention (Husain and Rorden 2003). These same parietal and frontal areas have also been implicated by human functional neuroimaging (Marois et al 2000) and reversible neural disruption studies (Cooper et al 2004). Crucially, the brain regions thought to underlie the temporal control of visual attention overlap substantially with the cortical projection sites of DβH-containing noradrenergic neurons arising in the locus coeruleus (LC) of the brainstem (Foote and Morrison 1987). Indeed, computational models of LC function have recently been extended to show that the capacity limitations of visual attention may be due to specific dynamics of the LC-noradrenaline neuromodulatory system (Nieuwenhuis et al in press). Anomalies in the temporal allocation of visual attention have been reported in both children and adults with ADHD (Hollingsworth et al 2001; Li et al 2004). These studies have shown that participants with ADHD are significantly poorer at detecting the second of two rapidly successive targets. Deficits in the temporal allocation of visual attention in ADHD are

consistent with established right-hemisphere prefrontal deficits, and with more recent reports of structural and functional anomalies in the parietal lobe (Silk et al 2005; Sowell et al 2003).

Convergent evidence from human lesion (Posner et al 1984), neuroimaging (Corbetta and Shulman 2002) and reversible neural disruption studies (Chambers et al 2004) confirms that fronto-parietal networks also play a critical role in the control of spatial aspects of visual attention. Spatial attentional mechanisms prioritise sensory input for further processing based upon their locations in space (Posner and Peterson 1990). Damage within this right-hemisphere-dominant spatial attention system may cause the syndrome of unilateral spatial neglect, in which the ability to detect and act upon contralesional stimuli is impaired (Robertson and Marshall 1993). Asymmetrical deficits in the control of spatial attention have also been observed after destruction of catecholamine pathways in animals (Iversen 1984), and after the administration of drugs such as clonidine, which suppress central noradrenaline transmission (Coull et al 2001). Spatial asymmetries have been reported in children and adults with ADHD (Carter et al 1995; Epstein et al 1997; Nigg et al 1997; Sheppard et al 1999; Voeller and Heilman 1988). These studies have tended to suggest a subtle left-sided inattention in participants with ADHD (but see Klimkeit et al 2003; Wood et al 1999).

Given the evidence for catecholaminergic modulation of both the temporal and spatial mechanisms of visual selective attention, we sought to test for any association between these cognitive mechanisms and allelic variation of the Taq I polymorphism of the DBH gene in a cohort of children and adolescents with ADHD. Evidence of association would suggest that DBH gene variants confer risk to ADHD, in part because of the varying effects of this gene on the neural mechanisms underlying visual attention.

In our study, participants were presented with two spatially lateralised stimuli (left and right of fixation) that were separated in time by a variable stimulus-onset asynchrony (SOA). In a non-speeded task participants were asked to judge the temporal order of onset of

these two stimuli. The SOA manipulation indexed the temporal resolution of attention: accuracy of judgements should decrease with shorter SOAs. Presenting half of the stimuli first in the left-hemifield relative to the right-hemifield, and *vice versa*, allowed us to determine whether the temporal resolution of attention differed between the two hemifields.

An initial comparison between participants with ADHD and matched control children was used to establish the efficacy of the temporal order judgement for documenting group differences in visual attention. We predicted that children with ADHD would make more errors of temporal order judgement, particularly at shorter SOAs, than controls. Further, if visual attention deficits can index susceptibility to ADHD, then we would expect an association between the A2 allele of the Taq I DBH polymorphism and performance on the temporal order judgement task. Association was tested in three ways: First, performance of the ADHD children on the visual attention task was compared using ANOVA as a function of possession of A2 alleles (0 vs. 1 vs. 2) (Waldman 2005). Second, a family-based analysis examined whether performance measures could predict biased transmission of A2 alleles, versus other alleles, from heterozygous parents to probands (Waldman et al 1999). This analysis guards against population stratification effects. Third, we split the ADHD cohort into good and poor performers and predicted a higher frequency of A2 allele homozygotes in a group of poor versus good performers.

Methods and Materials

Participants

Thirty-seven right-handed children and adolescents with ADHD (32 male) were recruited as part of ongoing work at the Trinity College Institute of Neuroscience, Dublin. The mean age of the sample was 11.7 years (SD=2.2) and the mean IQ, as assessed by the WISC-III, was 102 (SD=14.5)[1]. Exclusion criteria included known neurological conditions, including pervasive developmental disorders and epilepsy. As in our previous studies (Bellgrove et al 2005a; Bellgrove et al 2005b; Bellgrove et al 2005c; Kirley et al 2002) DSM-IV diagnoses were made using parental reports gathered during administration of the Child and Adolescent Psychiatric Assessment (CAPA)(Angold et al 1995). Additional information regarding symptom pervasiveness was gathered using the Child Attention-Deficit Hyperactivity Disorder Teacher Telephone Interview (CHATTI)(Holmes et al 2004). Parents also completed the Conners' Parent Rating Scale-Revised: Long Version (CPRS-R:L)(Conners 1998). In instances where the child was taking medication, the parents were asked to rate their child's behaviour when the child was not taking his or her medication. Seventy-three percent of participants met diagnostic criteria for ADHD-Combined Type (ADHD-CT), 19% for ADHD-Predominantly Inattentive Type (ADHD-In) and 8% for ADHD-Predominantly Hyperactive-Impulsive Type (ADHD-H/I). Seventy-three percent of the ADHD probands met diagnostic criteria for other disorders, such as Oppositional Defiant Disorder and Conduct Disorder. Stimulant medication was withdrawn at least 24 hours prior to the neuropsychological testing. Sixty percent of the ADHD probands were routinely maintained on stimulants, whereas 40% were either no longer taking stimulants or were medication-naïve.

[1] Note that IQs were not available for 3 of the ADHD participants.

Fifty two right-handed control children (45 male) were recruited from schools in and around Dublin, Ireland. These children had a mean age of 11.4 years (SD=1.6) and a mean estimated IQ of 105 (SD=10.9). The clinical and control children did not differ in Age [$F(1,87)=0.61, p>0.05$], IQ [$F(1,84)=1.30, p>0.05$], or gender distribution [$\chi^2(1)=0.00, p>0.05$]. In contrast, groups differed significantly on the Conners' Global Index (Conners 1997) [ADHD: Mean T-score =78.7 (8.3); Controls: Mean T-score= 49.1 (8.4); $F(1,85)=264$, $p<0.001$]. All participants gave informed consent according to the ethical guidelines of Trinity College Dublin and St James' Hospital, Dublin, Ireland.

DBH genotypes were available for the 33 participants with ADHD. Eleven participants were homozygous for the A2 allele of the Taq1 DBH polymorphism, 16 were heterozygous for this allele, and 6 did not possess this allele. These three DBH groups did not differ in Age [$F(2,30)=1.51, p>0.05$] or IQ [$F(2,27)=2.84, p>0.05$]. DBH genotype groups did not differ in terms of gender distributions or the frequency of DSM-IV subtypes or comorbid disorders (see Table 1).

INSERT TABLE 1 ABOUT HERE

We also employed a family-based design to determine whether attentional performance measures could predict distorted parental transmission of high-risk (A2 allele of the Taq I polymorphism) versus low-risk (A1) alleles to ADHD probands. This analysis employed the logistic-regression based extension of the transmission disequilibrium test (LR-TDT) (Waldman et al 1999). Thirty-three informative transmissions from heterozygous parents to ADHD probands were analysed.

Apparatus

Participants performed a temporal order judgement (TOJ) task, similar to that of Rorden et al (1997) (see Figure 1). Each trial commenced with a white fixation cross (10 ×10mm) in the centre of the screen that remained visible for the duration of the trial. After 350ms a white asterisk (10 ×10mm) appeared 90mm to the left or right of the central fixation cross. After a variable stimulus-onset asynchrony (SOA) of 50ms, 100ms or 200ms, a second white asterisk appeared in the homologous location in the opposite hemifield. Participants were presented with a randomised sequence of 40 trials at each of the three SOAs (120 trials). On half of these trials, the asterisk appeared first to the left of fixation, and on the other half it appeared first to the right. Side of first presentation was randomised across trials. Participants viewed the display from 50cm. They completed three blocks of 40 trials, with rest periods after the first and second blocks.

Participants were instructed to fixate on the central cross and then to nominate verbally which of the two stimuli (left or right) appeared first. The experimenter recorded each response. All stimuli, including the fixation cross, remained on screen until a response was given. The experimenter initiated each trial once stable fixation had been maintained.

Errors were coded as a function of SOA (50,100,200) and side of first stimulus appearance. Results were analysed using ANOVA with factors of SOA and side of first stimulus appearance (Side). Interactions were decomposed using analysis of simple main effects with Bonferroni corrections for multiple comparisons.

INSERT FIGURE 1 ABOUT HERE

DBH Genotyping

DNA was extracted from buccal cells or blood samples from ADHD probands and their parents. The DBH gene was amplified with primers as follows: forward (5’ CTG TAT TTG GAA CTT GGC ATC 3’) and reverse (5’ AGG CAT TTT ACT ACC CAG AGG 3’). Thirty cycles of denaturing were performed at 94 ° C for 1 min, followed by annealing at 59 ° C for

1 min and then extension at 72 ° C for 1.5 min. A first denaturing step of 95 ° C for 3.5 min and a final extension step of 72 ° C for 5 min were added. The PCR product was digested with Taq I, and fragments separated in 2% agarose. Two alleles were identified: a two allele polymorphism with an undigested band of 464 bp (A1) and two bands of 300bp and 164bp (A2) (see Daly et al 1999).

Results

ADHD vs controls

Figure 2 depicts the percentage errors made per condition by the control and ADHD groups. A mixed-model ANOVA with within-subjects factors of SOA and Side, revealed a main effect of Side [$F(1,87)=5.9, p=0.02, \eta^2=0.06$], such that trials in which the left field stimulus led in time were more accurately detected than trials in which the right field stimulus led. There was also a significant main effect of SOA [$F(2,174)=144.6, p=0.001, \eta^2=0.62$], such that TOJs were less accurate at shorter SOAs. Across conditions, participants with ADHD made more errors than controls [$F(1,87)=9.7, p=0.002, \eta^2=0.10$] but this main effect was modified by several interactions involving group. A Group × Side interaction [$F(1,87)=7.9, p=0.006, \eta^2=0.08$] indicated that ADHD participants made more errors on right-first than left-first trials ($p=0.01$), whereas no such asymmetry was present for controls ($p=0.76$). A Group × SOA interaction [$F(2,174)=3.08, p=0.048, \eta^2=0.03$] was also found. Although ADHD children made more errors than controls at each of the three SOAs, their impairment was most pronounced at the 50ms SOA [mean difference=8%, $p=0.005$].

INSERT FIGURE 2 ABOUT HERE

Analysis of ADHD group as a function of DBH genotype

Figure 3 displays the percentage errors per condition as a function of DBH genotype for the ADHD participants. As in the case/control analysis, main effects of Side [$F(1,30)=5.47, p=0.03, \eta^2=0.15$] and SOA [$F(2,60)=52.9, p=0.001, \eta^2=0.63$] were observed. There was also a main effect of DBH group [$F(2,30)=3.6, p=0.04, \eta^2=0.19$]. Analysis of simple main effects revealed that this main effect was driven by the poor performance of ADHD children with two copies of the A2 allele versus those without this allele ($p=0.04$); the error rates of the A2 allele heterozygotes fell between these two groups but did not differ significantly from either ($p>0.05$ for both comparisons). There was also an interaction between DBH Genotype and SOA [$F(4,60)=2.85, p=0.03, \eta^2=0.16$] that was driven by the poorer performance of the A2 allele homozygotes, relative to those without this allele, at the 50ms SOA ($p=0.03$).

INSERT FIGURE 3 ABOUT HERE

The effect of DBH genotype on temporal order judgements (TOJs) at the 50ms SOA was further supported by a family-based analysis that examined whether the total number of errors committed at each of the 50ms, 100ms, and 200ms SOAs could predict biased transmission of parental A2 alleles, versus other alleles, to probands. For the 50ms SOA, the total number of errors of TOJ predicted distorted transmission of high-risk (A2 allele) versus low-risk (other) alleles from heterozygous parents [χ^2 (df=1)= 4.97, $p=0.026$; [CI: 1.01-1.3], 33 informative transmissions]. The results reported herein are thus consistent across analyses focused on possession and transmission of the A2 allele of the Taq I DBH gene polymorphism.

A final analysis examined whether A2 allele homozygotes were over-represented in children who presented with relatively poorer, versus relatively better, performance in the visual attention task. A median split on the average number of errors of temporal order

judgement, across conditions, defined a categorical variable based upon attentional capacity (good vs. poor). There was a higher frequency of ADHD children with two copies of the A2 allele in the poor-performing, relative to good-performing group. By contrast there was a higher frequency of ADHD children without this allele or with one copy of it in the good-performing, relative to poor-performing group [χ^2 (df=1)= 3.88,p=0.04].

Discussion

The present study examined the temporal and spatial aspects of visual attention in children and adolescents with ADHD, and in healthy, matched controls. ADHD children were impaired in allocating attention to visual targets that appeared in close temporal proximity (i.e., at an SOA of 50ms), relative to normal controls. This impairment at the short SOA was equivalent for events in the left and right hemifields. Three lines of evidence suggest an association between the A2 allele of the Taq I DBH polymorphism and the temporal allocation of visual attention in ADHD. First, ADHD probands who were homozygous for the A2 allele performed more poorly than those without this allele or those with one copy of it, particularly at the 50ms SOA. Second, errors at the 50ms SOA predicted distorted transmission of A2 alleles from parents to probands. This family-based result is robust against population stratification effects. Third, ADHD probands who performed poorly on the visual attention task were more likely to be homozygous for the A2 allele. Our results suggest that the A2 allele of the Taq I DBH polymorphism is associated with an impaired temporal resolution of visual attention in ADHD.

Several studies of ADHD have examined mechanisms of spatial attention, but relatively few have investigated the allocation of attention in time (Hollingsworth et al 2001; Li et al 2004). The present results demonstrate that children and adolescents with ADHD have a deficit in the temporal allocation of attention for rapid events and that this impairment is spatially non-selective. Spatially non-selective deficits have also been observed in patients with right-hemisphere lesions involving the frontal or parietal lobe (Husain and Rorden 2003). The association between allelic variation in the Taq I DBH polymorphism and impairment in the allocation of temporal attention is consistent with known noradrenergic projections to the frontal and parietal cortices (Foote and Morrison 1987). Structural and functional anomalies in these regions have been reported in ADHD (Silk et al 2005; Sowell et

al 2003). We have also separately reported that the A2 allele is associated with impaired sustained attention in ADHD participants (Bellgrove et al in press-b). Sustained attention performance was also found to correlate with performance on the TOJ task in the present study (r^2=0.2) suggesting that partially overlapping mechanisms might underlie the different aspects of attention. Given that variation in the DBH gene has also been linked to working memory performance (Parasuraman et al 2005), future studies will need to employ a range of cognitive measures to determine the specificity of the association between DBH polymorphisms and cognitive function in both healthy and clinical populations.

Although we did not observe any lateralised attentional deficits as a function of DBH genotype, the ADHD participants performed more poorly overall than matched controls when targets first appeared in the right-hemifield. This result might indicate that ADHD participants have an attentional bias toward the left-hemifield that enhances the rate of perceptual processing for stimuli on that side. Although this finding is inconsistent with reports of left-sided inattention in ADHD (Carter et al 1995; Epstein et al 1997; Nigg et al 1997; Sheppard et al 1999; Voeller and Heilman 1988) , we note that others have reported right-sided impairments on visual orienting paradigms (Swanson et al 1991) . Using perceptual measures of attentional bias, such as the Landmark Task, that are used to assess clinical neglect, we have previously noted that left-sided inattention in ADHD is strongly related to the 10-repeat allele of the DAT1 VNTR (Bellgrove et al 2005b). In contrast to visual orienting paradigms (Posner and Cohen 1984), these tasks involve non-speeded, free-viewing perceptual judgements. Analysing the current data with respect to the 10-repeat DAT1 allele yielded no significant interactions involving the factors of Side or SOA. The presence of any attentional asymmetry in ADHD may therefore reflect the operation of a number of factors, including differential task demands.

Several studies have provided evidence for an association of variable strength between the A2 allele of the Taq I DBH polymorphism and ADHD (Daly et al 1999; Roman et al 2002; Smith et al 2003). Non-replications have also been reported, however (Bhaduri et al 2005; Inkster et al 2004), albeit with small samples (Bhaduri et al 2005). Associations with other potentially functional DBH gene variants have not yielded consistent results (Bhaduri et al 2005; Smith et al 2003; Wigg et al 2002). These associations with DBH gene variants are nevertheless appealing given the role of DβH in catalysing the conversion of dopamine to noradrenaline, and the central role of catecholamine dysregulation in aetiological accounts of ADHD (Castellanos and Tannock 2002; Pliszka et al 1996). DβH activity occurs in the plasma as a heritable trait, and is strongly related to variation in the DBH gene. Lower plasma DβH activity has been reported in ADHD (Rogeness et al 1989). A plausible biological hypothesis for ADHD is therefore that genetic variation in the DBH gene may alter the expression of DβH, leading to an imbalance in the conversion of dopamine to noradrenaline. Such an imbalance could feasibly give rise to attentional disturbances in ADHD of the kind reported here.

A limitation of the current study is that the Taq I variant is intronic (intron 5) and is unlikely to be functional. This variant may however be in linkage disequilibrium (LD) with potentially functional variants. Zhang et al. have recently provided evidence for an association between ADHD (combined type) and ADHD comorbid with disruptive behavioural disorder, and the T allele of a functional promoter variant (-1021 C/T SNP) (Zhang et al 2004; Zhang et al 2005). The -1021 C/T SNP is known to be the primary variant controlling plasma DβH activity, with the T allele associated with lower enzyme activity. Future studies should examine the relationship between this variant, the Taq I variant and visual attention, and conduct a haplotype analysis to confirm the role of DBH in visual attention in ADHD.

Despite the significant findings of the present study, it is important to acknowledge its limitations. Although previous family-based studies suggest that the A2 allele is over-transmitted to ADHD probands (Daly et al 1999; Roman et al 2002), the current sample was too small to test for this association. In this context, the association between the A2 allele and an attentional phenotype that is impaired in ADHD is noteworthy and supports the contention that refined phenotypes may increase the sensitivity of genetic association studies. Further, because the control group was not genotyped, we cannot determine whether the reported association between the A2 allele of the Taq I DBH variant and visual attention is specific to ADHD or is also seen in the general population. *A priori* one would expect that the A2 allele would influence visual attention in healthy children in an analogous fashion to that seen in children with ADHD. We speculate that a functional variant in LD with the A2 allele alters catecholamine signalling, particularly in fronto-parietal networks that subserve visual attention. The prior association of the A2 allele with ADHD (Daly et al 1999) suggests that this allele confers risk to ADHD. It is also possible, however, that our behavioural results for the participants with ADHD could reflect an interaction between DBH genotype and existing structural and/or functional brain changes in fronto-parietal areas (Silk et al 2005; Sowell et al 2003) in ADHD. If this were the case, then one would not expect the A2 allele to influence visual attention in the same way in healthy children. Future studies could address this issue using functional imaging in genotyped cohorts of ADHD and healthy children.

An additional point worth noting is that 60% of the children with ADHD were routinely receiving treatment with stimulant medication and at the time of test had been withdrawn for at least 24 hours. Animal studies indicate that stimulant withdrawal after chronic treatment may lead to decreased dopamine neuronal firing (Brandon et al 2003). Suspension of treatment in the current study could therefore represent a confounding factor in

our analyses. Although we found no behavioural differences between children routinely taking stimulants and those who were not, it would be useful in future studies to include a group of stimulant-naïve individuals. Finally, compared with typical genetic association studies, the results reported in the present study are based upon a small sample. Although the use of a refined attentional phenotype has yielded results that are internally consistent and in the hypothesised direction, our findings should be considered preliminary until replicated in extended samples.

In sum, while associations with polymorphisms of the DBH gene and ADHD have previously been reported, the functional consequences of allelic variation within the DBH gene remain uncertain. The application of paradigms with established brain-behaviour bases may help to constrain interpretations of the causal pathways that lead from gene to disorder. The results reported in the present paper suggest that the A2 allele of Taq I variant of the DBH gene (or another gene with which it is in LD) is associated with an impaired temporal resolution of visual attention in ADHD.

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Figure Captions

Figure 1. Task schematic. Participants performed a temporal order judgement task in which they were required to judge the order of presentation of two peripherally presented

stimuli (asterisks) while maintaining gaze on the central fixation cross. Stimuli were separated in time by 50, 100, or 200ms. Participants made their response verbally. In the example illustrated, the participant should have nominated the left stimulus as the first to appear.

Figure 2. Percentage error rates for the ADHD and control participants on the temporal order judgement task. Negative values indicate a trial on which the first stimulus appeared in the left hemifield. Positive values indicate a trial on which the first stimulus appeared in the right hemifield.

Figure 3. Percentage error rates for the ADHD participants, as a function of DBH genotype, on the temporal order judgement task. Negative values indicate a trial on which the first stimulus appeared in the left hemifield. Positive values indicate a trial on which the first stimulus appeared in the right hemifield.

Table 1: Clinical and demographic data for children and adolescents with ADHD as a function of A2 alleles of the Taq I DBH polymorphism. Conners' CGI-T: Conner's Global Index T-score; Conners' DSM-In-T: Conners' DSM-Inattentive T-score; Conners' DSM- Hyp/Imp-T: Conners' DSM Hyperactive/Impulsive T-score. [1] T-scores were not available for 2 participants. ODD: Oppositional Defiant Disorder. CD: Conduct Disorder

	0 A2 alleles (n=6)	1 A2 allele (n=16)	2 A2 alleles (n=11)	Statistic
	M (SD)	**M (SD)**	**M (SD)**	
Age	11.7 (2)	11.9 (2)	10.5 (2)	F(2,30)=1.5,p=0.24
IQ	104 (11)	106 (15)	94 (9)	F (2,27)=2.8,p=0.08
Conners' CGI-T [1]	77 (8)	78 (9)	79 (9)	F(2,28)=0.1,p=.90
Conners' DSM- In-T	75 (7)	74 (9)	76 (8)	F(2,28)=0.18,p=.84
Conners' DSM-Hyp/Imp-T	77 (7)	80 (13)	79 (11)	F(2,28)=0.10,p=.91
Conners' DSM-Total-T	78 (7)	79 (9)	79 (8)	F(2,28)=0.02,p=.98
	Number (%)	**Number (%)**	**Number (%)**	
No. male (%)	6 (100)	14 (88)	8 (73)	χ^2=2.4,p=0.30
ADHD-Combined Type	4 (67)	14 (88)	5 (46)	χ^2=5.5,p=0.06
ADHD- Inattentive Type	2 (33)	1 (6)	4 (36)	χ^2=4.2,p=0.12
ADHD- Hyperactive/Impulsive Type	0 (0)	1 (6)	2 (18)	χ^2=1.9,p=0.39
Presence of ODD	3 (50)	9 (56)	7 (64)	χ^2=0.32,p=0.85
Presence of CD	0 (0)	2 (13)	1 (9)	χ^2=1.7,p=0.79

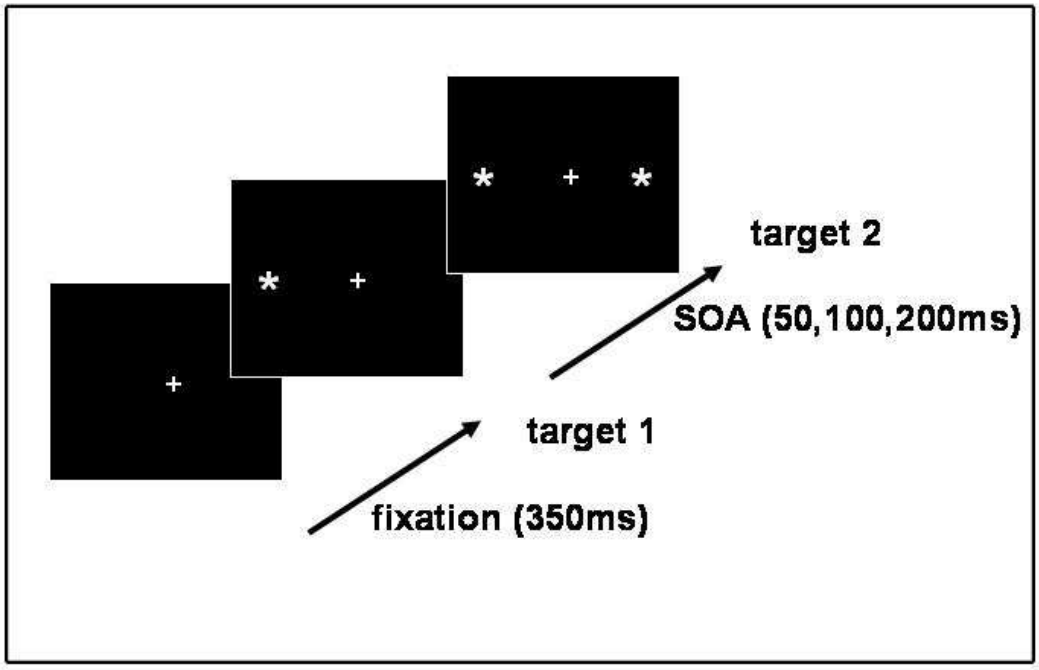

target 2
SOA (50,100,200ms)
target 1
fixation (350ms)

Figure 2

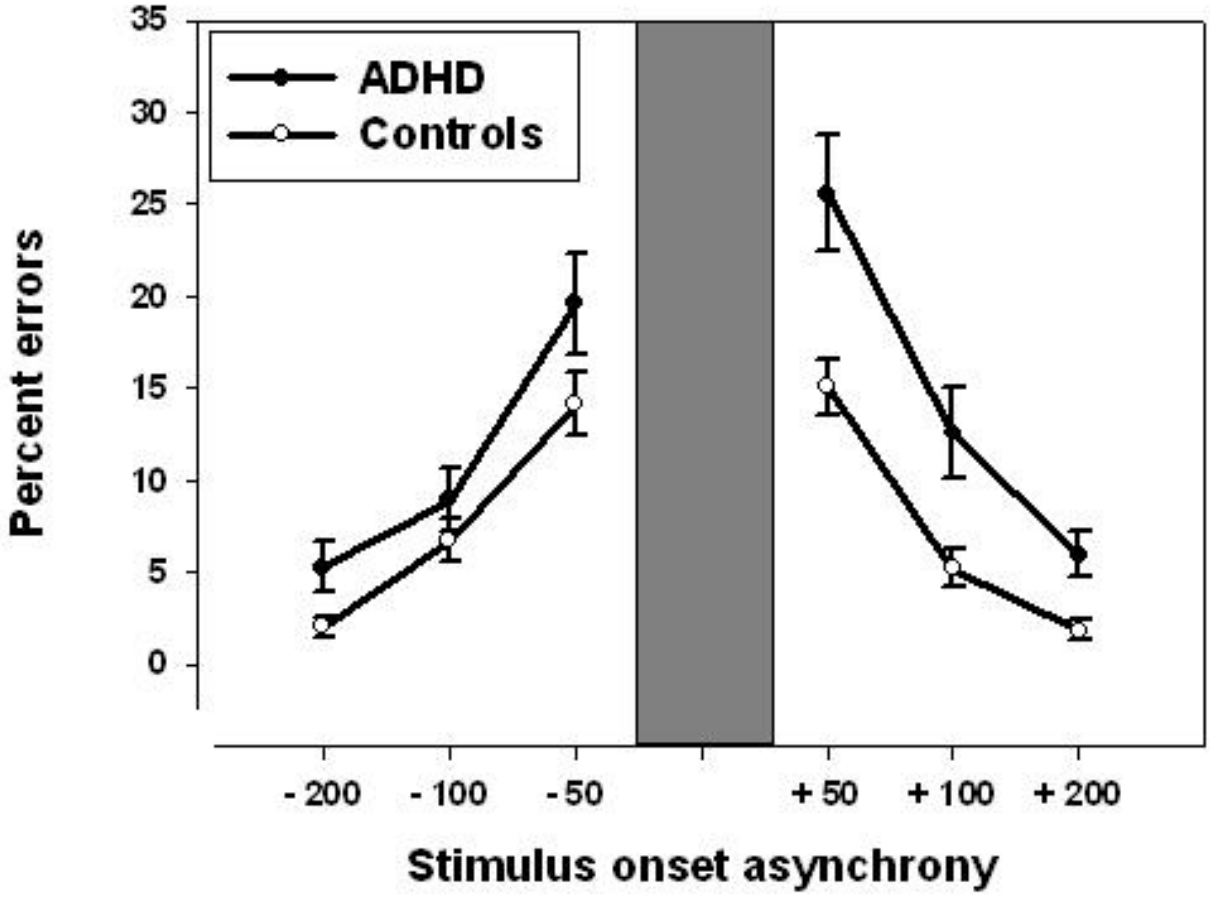
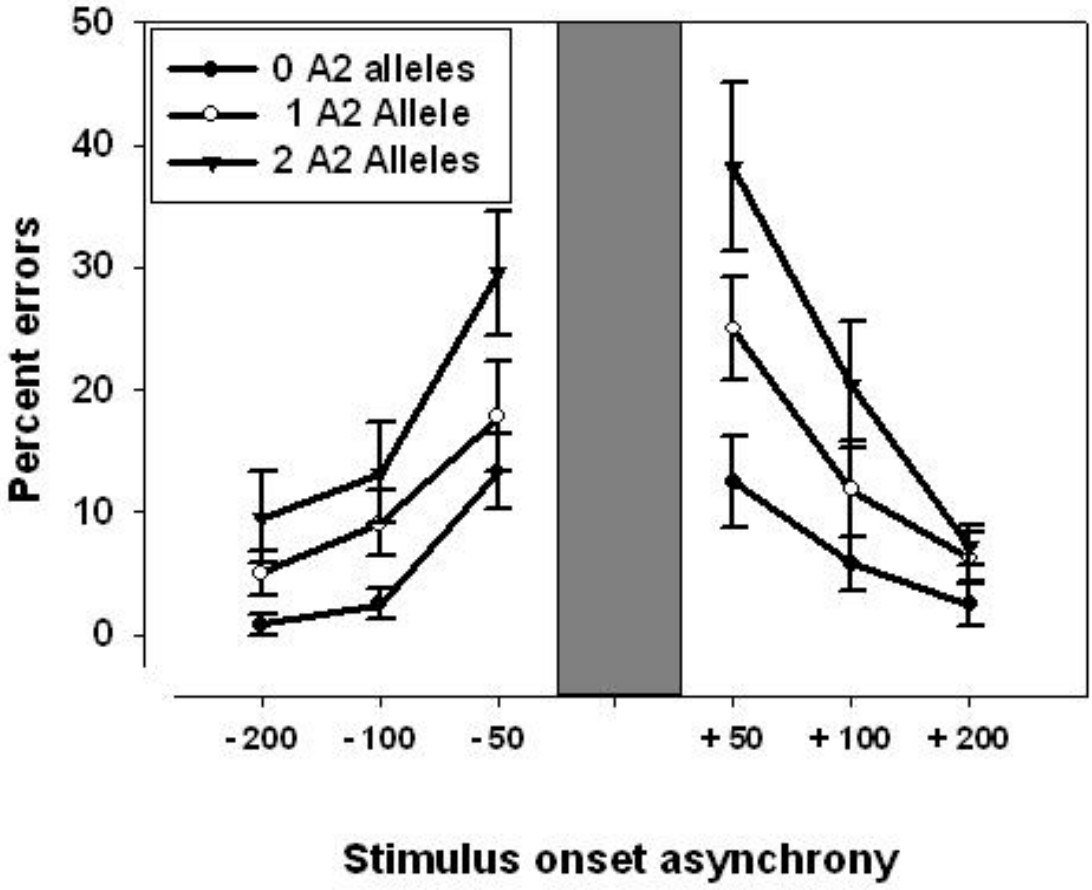

ADHD
Controls
Percent errors
35
30
25
20
15
10
5
0
- 200
- 100
- 50
+ 50
+ 100
+ 200
Stimulus onset asynchrony

Figure 3


0 A2 alleles
1 A2 Allele
2 A2 Alleles
Percent errors
50
40
30
20
10
0
-200
-100
-50
+50
+100
+200
Stimulus onset asynchrony