Association between dopamine transporter (DAT1) genotype, left-sided inattention, and an enhanced response to methylphenidate in attention deficit hyperactivity disorder (ADHD).

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Abstract

A polymorphism of the dopamine transporter gene (DAT1, 10-repeat) is associated with ADHD and has been linked to an enhanced response to methylphenidate (MPH). One aspect of the attention deficit in ADHD includes a subtle inattention to left space, resembling that seen after right cerebral hemisphere damage. Since left-sided inattention in ADHD may resolve when treated with MPH, we asked whether left-sided inattention in ADHD was related to DAT1 genotype and the therapeutic efficacy of MPH. Forty-three ADHD children and their parents were genotyped for the DAT1 3' VNTR polymorphism. The children performed the Landmark Test, a well-validated measure yielding a spatial attentional asymmetry index (leftward to rightward attentional bias). Parents rated their child's response to MPH retrospectively using a three-point scale (No, Mediocre or Very Good Response). Additionally, parents used a symptom checklist to rate behaviour while on and off medication. A within family control design determined whether asymmetry indices predicted biased transmission of 10-repeat parental DAT1 alleles and/or response to methylphenidate. It was found that left-sided inattention predicted transmission of the 10-repeat allele from parents to probands and was associated with the severity of ADHD symptomatology. Children rated as achieving a very good response to MPH displayed left-sided inattention, while those rated as achieving a poorer response did not. Our results suggest a sub-group of children with ADHD for whom the 10-repeat DAT1 allele is associated with left-sided inattention. MPH may be most efficacious in this group because it ameliorates a DAT1-mediated hypodopaminergic state.

Keywords: DAT1, dopamine, ADHD, methylphenidate, attention, genetics

Introduction

Attention deficit hyperactivity disorder (ADHD), a common childhood disruptive disorder affecting 3-6% of school-aged children worldwide, is characterised by age inappropriate levels of inattention, hyperactivity and impulsivity. Family, twin and adoption studies suggest that the disorder is heritable (see Kirley et al. 2002 for a review). Pharmacogenetic studies in ADHD suggest that individual differences in stimulant-response may be related to underlying genetic influences (Kirley et al. 2003; Hamarman et al. 2004). The 10-repeat allele of a variable number of tandem repeats (VNTR) situated in the 3' untranslated region of the DAT1 gene (mapping to 5p15.3) has been associated with the clinical ADHD phenotype in a number of studies (Cook et al. 1995; Gill et al. 1997; Daly et al. 1999). This variant may confer an enhanced therapeutic response to methylphenidate (MPH) (Kirley et al. 2003) (but see Winsberg and Comings 1999; Roman et al. 2002). Here we ask whether an attentional endophenotype is related to a) genetic variation in the DAT1 VNTR and b) the therapeutic efficacy of MPH in ADHD.

Several lines of converging evidence underscore the relevance of the dopamine transporter gene to ADHD. First, methylphenidate (MPH) is known to inhibit the dopamine transporter (Volkow et al. 1998). The dopamine transporter is highly expressed in the human striatum where it serves as the primary means of dopamine reuptake (Garris and Wightman 1994). Second, studies of both structural and functional imaging in ADHD have consistently implicated dopamine-rich frontostriatal circuits, particularly on the right, in the pathophysiology of ADHD (Casey et al. 1997; Vaidya et al. 1998; Teicher et al. 2000). These abnormalities are ameliorated by treatment with MPH (Vaidya et al. 1998; Teicher et al. 2000). Third, *in-vivo* measurement of DAT with single photon emission computed tomography

(SPECT) has demonstrated elevated striatal transporter densities in adults (Dougherty et al. 1999; Dresel et al. 2000), and children (Cheon et al. 2003) with ADHD, compared to controls. In adults, treatment with MPH reduces transporter densities to near normal levels (Dresel et al. 2000; Krause et al. 2000). Additionally, there is also evidence that children and adults who are homozygous for the 10-repeat DAT1 may have higher availability of DAT protein in the striatum, relative to those with the 9-repeat/10-repeat genotype (Heinz et al. 2000; Cheon et al. 2005).

These lines of evidence have lead to a biological hypothesis of ADHD under which the 10-repeat DAT1 allele is thought to be associated with a greater abundance of DAT protein, resulting in a relative hypodopaminergia, perhaps particularly within the striatum (Kirley et al. 2002). According to this hypothesis, treatment with MPH may be most efficacious in 10-repeat homozygotes because it normalises DAT density (Heinz et al. 2000; Kirley et al. 2003). There have, however, been a number of studies that have reported a poorer response to MPH in 10-repeat homozygotes, albeit often in relatively small samples (Rohde et al. 2003; Cheon et al. 2005).

Recent studies of susceptibility genes for psychiatric disorders have emphasized the utility of quantitative indices for assessing disease risk, termed *endophenotypes*. Endophenotypes are traits that more accurately predict dysfunction in discrete neural systems than conventional clinical phenotypes (Castellanos and Tannock 2002). A small number of studies have examined whether genetic variants that are thought to confer susceptibility to ADHD are also associated with cognitive impairment (Swanson et al. 2000; Manor et al. 2002; Loo et al. 2003; Langley et al. 2004; Bellgrove et al. 2005). The approach of linking a genetic risk factor with a cognitive phenotype has considerable heuristic value. Rather than seeking associations between a gene and a rudimentary diagnostic category, this approach

measures the association between a gene and a strictly-operationalised and objectively-measured cognitive process.

In this context we sought to determine whether the phenomenon of left-sided inattention in ADHD, might be related to underlying DAT1 genotype and the therapeutic response to MPH. Left-sided inattention presents as spatial bias of attention away from the left side. Left-sided inattention arises from dysfunction in any one of a number of right hemisphere cortical (prefrontal, parietal) and subcortical (striatal, thalamic) components of a distributed neural network for spatial attention (Mesulam 1981). Dysfunction of the right hemisphere network results in more severe and long-lasting spatial inattention than equivalent left hemisphere dysfunction because of the dominance of the right hemisphere for the control of spatial attention: while right hemisphere networks allocate attention to both left and right hemi-spaces, left hemisphere networks do so only for the right hemi-space (Mesulam 1981). Consistent with animal studies that have reported neglect consequent upon lesions of the ascending dopaminergic pathways (Iversen 1984), treatment with dopamine agonists reduces the extent of neglect in human subjects (Fleet et al. 1987).

A number of studies have reported the presence of attentional asymmetries in ADHD using both clinical and experimental measures of attention (Voeller and Heilman 1988; Carter et al. 1995; Nigg et al. 1997; McDonald et al. 1999; Sheppard et al. 1999). Failure to replicate these effects in some studies (Wood et al. 1999; Klimkeit et al. 2003), nevertheless suggests neuropsychological heterogeneity. Left-sided inattention has also been reported in the biological mothers of children with ADHD (Nigg et al. 1997), reinforcing its candidacy as an endophenotype. Critically, there is evidence for normalization of left-sided inattention in ADHD with MPH (Nigg et al. 1997; Sheppard et al. 1999).

This study addressed two distinct but related questions. First, using a family-based genetic association design, we asked whether a continuous measure of spatial attentional asymmetry was associated with DAT1 genotype. Specifically, we first hypothesised that left-sided inattention would be associated with the 10-repeat DAT1 allele in ADHD. Second, we asked whether the same continuous measure of attentional asymmetry was associated with retrospective ratings of the therapeutic response achieved by MPH. We hypothesised that if left-sided inattention may serve as a behavioural assay for a hypodopaminergic state in ADHD, then its existence may relate to the therapeutic response conferred by methylphenidate.

Materials and Methods

Participants

43 right-handed ADHD participants were recruited as part of our ongoing genetic association studies and in accordance with the ethical guidelines of Trinity College Dublin and St James' Hospital, Dublin. DSM-IV diagnoses were confirmed using established diagnostic protocols. From our previously described cohort, ADHD probands (aged 6-16 years) were offered participation in the current study. The current sample is therefore not independent of our previously described cohort (Kirley et al. 2002; Kirley et al. 2003). Exclusion criteria included known neurological conditions including pervasive developmental disorders and epilepsy. Since Reading Disorder has been associated with attentional asymmetries (Facoetti et al. 2001), participants scoring more than 1 ½ standard deviations below the mean of the reading subtest of the Wide Range Achievement Test (WRAT-3) were also excluded (Table 1). Stimulant medication was withdrawn at least 24 hours prior to the neuropsychological testing

Predicting Methylphenidate (MPH) Response

36 of these children were currently receiving or had in the past received treatment with MPH. Ratings of MPH response were obtained from parents in two ways: First, parents were asked to rate the therapeutic response achieved with MPH on a three-point scale from "no response" to "mediocre" to "very good". Second, parents completed the Conners' Parent Rating Scale-Revised: Long Version (CPRS-R:L)(Conners 1998) twice, retrospectively rating their child's symptoms while 'on' and 'off' MPH. We have previously reported an association between the 10-repeat allele of the DAT1 VNTR and the therapeutic response to MPH using this rating system (Kirley et al. 2003).

Testing Attentional Asymmetry: The Landmark Task

In this well validated and brief (5 minutes) test, participants judge which end of a pre-bisected line looks shorter to them (Figure 1). 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 judgements to be determined. On the remaining 10 trials the horizontal line was bisected in the middle.

INSERT FIGURE 1 ABOUT HERE

DAT1 Genotyping

DNA was extracted from blood samples or buccal cells using the standard phenol chloroform procedure from both parents and the ADHD proband in each family. Primer sequence and amplification conditions can be found elsewhere (Kirley et al. 2002). Two investigators, who were blind to the identity of the sample, independently scored all genotypes.

Statistical analyses

Testing the association between DAT1 genotype and attentional asymmetry

In vitro studies indicate that the 10-repeat allele of the DAT1 VNTR may increase DAT expression (see Asherson 2004 for review). For example, Fuke et al (2001) showed that the 10-repeat allele, relative to the 7- or 9-repeat alleles, increased gene expression using a reporter system. Mill et al (2002) also reported that mRNA levels in human brain and lymphocyte tissue, varied with DAT1 VNTR, being higher in individuals with the 10- versus 9-repeat allele. Based upon this evidence of differential gene expression as a function of VNTR alleles and the low frequency of individuals homozygous for the non 10-repeat alleles (less than 5% in the current sample), we compared the Landmark Asymmetry Indices of those ADHD probands without the 10-repeat DAT1 allele and those in possession of one copy of this allele (designated as Low-Risk DAT1) (n=21), to those in possession of two copies of this allele (designated as High-Risk DAT1) (n=22). Preliminary analyses revealed that performance measures were normally distributed and therefore parametric tests were used in statistical comparisons.

Using a family based design and a logistic regression adaptation of the transmission disequilibrium test (LR-TDT) (Waldman et al. 1999), we also used parental genotype information to examine whether the Landmark Asymmetry Index predicted biased transmission of high-risk (10-repeat), versus low-risk (other alleles), parental DAT1 alleles to ADHD probands. This method is robust against any population stratification effects.

Testing the association between attentional asymmetry and response to MPH

Landmark Asymmetry Indices were firstly compared, as a function of Medication Response Group (None or Mediocre vs. Very Good) using a Univariate

ANOVA. Secondly, Landmark Asymmetry Indices were compared, as a function of the combination of Medication Response Group and DAT1 Genotype (Low-Risk DAT1 vs. High-Risk DAT1).

Results

Testing the association between DAT1 genotype and attentional asymmetry

When symptomatology was measured dimensionally, significant differences emerged between the Low- and High-Risk DAT1 ADHD groups in both DSM-IV Inattentive and Total age-related normative scores (t-scores), as measured by the CPRS-R:L (Table 1). Further, Landmark Asymmetry Indices correlated positively with continuous measures of DSM-IV Inattentiveness ($r(41)=.35, p=0.02$) and DSM-IV Total symptom scores ($r(41)=.40, p=0.01$) but not DSM-IV Hyperactivity/Impulsiveness ($r(41)=.29, p=0.065$). The direction of these correlations suggests that greater symptom severity, particularly with respect to inattentive symptoms, is associated with left-sided inattention.

There was a significant effect of DAT1 genotype group on the Asymmetry Index [$F(1,41)=10.9, p=0.002$; $r^2=.19$] that was driven by the right spatial bias/left-sided inattention of the High-Risk DAT1 ADHD group (M= +0.09, SD=.29), in comparison to the left spatial bias/right-sided inattention of the Low-Risk DAT1 ADHD (M= -0.17,SD=.23) (Figure 2). Despite the small number of participants not in possession of a 10-repeat DAT1 allele (n=2), regression revealed a parametric effect of increasing number of 10-repeat DAT1 alleles (0,1, or 2) on Landmark Asymmetry Indices [($F(1,41)=12.23$, $p=0.001$; $r^2=.21$] (see Table 2). This result suggests an additive effect of possession of the 10-repeat allele.

INSERT FIGURE 2 ABOUT HERE

A logistic regression model was used to examine whether the Landmark Asymmetry Index predicted preferential transmission of high-risk (10-repeat), versus low-risk (other alleles), parental DAT1 alleles. The coding of transmitted alleles from heterozygous parents resulted in 40 informative transmissions. The Landmark Asymmetry Index significantly predicted biased transmission of high-risk, versus low-risk, parental DAT1 alleles [χ^2(df=1) =7.43,p=0.006, 37% variance explained]. This association was stronger than when using DSM-IV Inattentive [χ^2(df=1) =3.6,p=0.058], Hyperactive/Impulsive [χ^2 (df=1) =2.5,p=0.115] or Total Symptoms [χ^2 (df=1) =3.6,p=0.059] as continuous predictor variables. Thus while left-spatial inattention is related to dimensional measures of ADHD symptomatology, the former is more strongly associated with DAT1 genotype than the latter. This result satisfies a key assumption of the endophenotype approach.

Testing the association between attentional asymmetry and response to MPH

Retrospective ratings of MPH response using the three-point scale (No Response vs. Mediocre Response vs. Very Good Response) were available for 36 children and adolescents with ADHD. 15 of these participants were rated as achieving No Response or a Mediocre Response, while 21 were rated as achieving a Very Good Response. There was a significant difference in the Landmark Asymmetry Index as a function of Medication Response Group [F(1,34)=5.22,p=0.03, r^2=.11], that was driven by the right spatial bias/left-sided inattention of the Very Good Response group (M=+0.05,SD=0.29), in comparison to the left spatial bias/right-sided inattention of the No/Mediocre Response group (M= -0.15,SD=0.19).

Given the *a priori* prediction that those children achieving a very good response to MPH *and* possessing two "high-risk" 10-repeat DAT1 alleles would show

left-sided inattention (right bias) on the Landmark Task, we compared the performance of this group (High-Risk DAT1/Very Good Response) (n=12) to the three other Genotype/Medication Response groupings (see Figure 3).

INSERT FIGURE 3 ABOUT HERE

There was a significant effect of DAT1 Genotype/Medication Response Group on the Landmark Asymmetry Index [$F(3,32)=4.12, p=0.01, r^2=.21$] (Figure 3). Figure 3 indicates that Asymmetry Indices became increasingly right biased as a function of DAT1 Genotype/ Medication Response Group. As hypothesised, the High-Risk DAT1/Very Good Response group were the only group to display left-sided inattention (M= +.13, SD=.32), with the Low-Risk DAT1/Mediocre Response Group showing a leftward bias (M= -.25, SD=.11). Both the Low-Risk DAT1/Very Good Response (M= -.07, SD=.21) and High-Risk DAT1/Mediocre Response (M= -04,SD=.21) groupings had small leftward biases. Pair-wise comparisons with Bonferroni corrections revealed that the Asymmetry Indices of the High-Risk DAT1/Very Good Response Group and the Low-Risk DAT1/Mediocre Response Group were significantly different ($p<0.01$). No other pair-wise comparisons were significant.

Changes in symptom severity when on and off MPH, as rated retrospectively by parents using the CPRS-R:L, were available for 32 ADHD participants. The High-Risk DAT1 ADHD group achieved greater symptom reduction than the Low-Risk DAT1 ADHD group in terms of both DSM-IV Hyperactive/Impulsive [$F(1,30)=5.289, p=.03, r^2=0.12$] and DSM-IV Total symptoms [$F(1,30)=4.40, p=0.04, r^2=0.13$] but not DSM-IV Inattentive symptoms [$F(1,30)=1.99, p=0.169, r^2=0.06$].

Discussion

This study reports that left-sided inattention is related to clinical ADHD symptomatology, the 10-repeat DAT1 allele and the therapeutic response to MPH. 10-repeat DAT1 homozygotes displayed left-sided inattention whereas those possessing one or no copies of this allele did not. The greater effect in 10-repeat homozygotes compared to heterozygotes suggests additive rather than dominance effects of the 10-repeat allele. As we hypothesised, left-sided inattention was associated with an enhanced therapeutic response to MPH, irrespective of DAT1 status, but was most pronounced in 10-repeat DAT1 homozygotes who achieved a very good response to MPH. Our data support the existence of a sub-group of ADHD, that is linked to the 10-repeat allele of the DAT1 VNTR, and is defined a) in symptom terms, by higher levels of inattentive and total symptomatology (but see Waldman et al. 1998); b) in neuropsychological terms, by left sided inattention, and perhaps also poor sustained attention (Loo et al. 2003); and c) in pharmacogenetic terms, by an enhanced response to MPH (Kirley et al. 2003).

Based on the data reported herein and the previously reviewed literature, we propose the following genetic-neurophysiological mechanism as part of the pathophysiology of ADHD. Increased transporter density (or activity) is associated with the 10-repeat DAT1 allele (or another genetic variant in linkage disequilibrium with the DAT1 VNTR) in ADHD (see Cheon et al. 2005). Overactive transporters reduce extracellular dopamine, perhaps particularly within right-hemisphere attentional networks. The resultant hypo-activation within right-hemisphere systems weakens the attentional bias of the right-hemisphere, unmasking the attentional bias of the left-hemisphere thus driving spatial attention in a rightwards direction (Kinsbourne 1993). Variation in the DAT1 gene may, therefore confer susceptibility

to ADHD, in part because of varying effects on the development of brain mechanisms modulating (spatial) attention.

Treatment with MPH may inhibit the transporter, restoring both dopaminergic balance and the reciprocal balance between spatial attentional systems. Accordingly, treatment with MPH may be most effective in those individuals with the greatest transporter densities or activities. In so far as the Landmark Asymmetry Index is able to act as a behavioural assay for this neural mechanism, then those ADHD individuals presenting with left-sided inattention may be more likely to achieve an enhanced response to MPH. Our data also suggest that knowing the DAT1 genotype of an individual may strengthen this association.

The above model, however, assumes that the DAT1 VNTR modulates transporter densities asymmetrically in ADHD, thus giving rise to the left-sided inattention reported herein. While there is, as yet, little direct evidence for this assumption, a number of studies do suggest a cerebral asymmetry in transporter densities. For example, Laakso et al (2000) reported higher striatal dopamine transporter binding in healthy subjects within the right, relative to left, striatum. Cheon et al (2003) also reported that DAT binding ratios within the basal ganglia of children with ADHD, relative to controls, were elevated by 51% on the right and 40% on the left. Further, it has recently been demonstrated that the beneficial effect of methylphenidate on attention and impulsivity in ADHD, is related to a reduction in the availability of D2/D3 receptors. This reduction in receptor availability is indicative of a pharmacologically evoked increase in extracellular dopamine by blockade of the transporter that is maximal in the right striatum (Rosa-Neto et al. 2005). It should also be noted, however, that the results reported herein could also arise from an interaction between DAT1 genotype and its associated alteration in

dopaminergic transmission, and structural and/or functional changes within right-hemisphere attentional systems (e.g., Castellanos et al. 1994; Casey et al. 1997; Bush et al. 1999; Sowell et al. 2003) that are un-related to DAT1 genotype.

There are several limitations of this study that require comment. First, the sample size is relatively small for a genetic association study. For example, only 2 probands possessed the 9/9 genotype. Nevertheless, our results are consistent across analyses focusing on possession and transmission of high-risk alleles. While the latter analysis (logistic regression TDT) sacrifices power by focusing on transmissions from heterozygous parents only, the results were highly significant and survive correction for multiple comparisons. DAT1 genotype accounted for 19% of the variance in the Landmark Asymmetry Index in the ANOVA-based analysis. This effect on spatial cognition is larger than is typically reported with functional variants, such as the COMT Val/Met polymorphism (Egan et al. 2001). Larger collaborative studies using a range of spatial attentional tasks are required to confirm and extend our results. Second, we assessed medication response using a simple non-validated three-point scale, and collected retrospective parental ratings. While these results should be viewed as preliminary until replicated within a prospective study, it should be noted that these ratings are unlikely to be biased with respect to DAT1 genotype. Third, we have proposed a biological hypothesis of the relation between left-sidede inattention, DAT1 genotype and MPH response in which dysfunction to attentional systems is centred on the right striatum. While this hypothesis is advanced based upon the known action of stimulants at transporters within the striatum, it has recently being proposed that the beneficial effect of stimulants on attention is mediated primarily via D1 receptors in the prefrontal cortex (Volkow et al. 2001). Given that left-sided inattention can also arise from right prefrontal lesions (Robertson and Marshall 1993),

we cannot discount the possibility that our behavioural results reflect prefrontal dysfunction.

In summary, our results show that left-sided inattention in ADHD is related to both underlying DAT1 genotype and the therapeutic response conferred by MPH. Our results are internally consistent in demonstrating an attentional endophenotype that relates to ADHD symptomatology, DAT1 genotype, and the therapeutic efficacy of MPH. The further study of spatial (in)attention in ADHD, in relation to DAT1 genotype, may provide a window into the neurobiology of ADHD.

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List of Figures

Figure 1. The Landmark Task

Panel [A]: In the Landmark Task, participants are presented with a pre-bisected line and asked which end of the line is the shorter. Healthy participants tend to show a slight bias of attention to the *left* owing to the dominance of the right hemisphere for spatial judgements. This scenario leads to a relative inattention to the rightwards extent of the line.

Panel [B]: In patients with right hemisphere lesions and left spatial inattention, there is a bias of attention to the *right* that arises when the dominant attentional orienting bias of the right hemisphere has been weakened. This scenario leads to a relative inattention to the leftward extent of the line (shaded area) and the subjective experience of the left end of the line as the shorter.

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 spatial Asymmetry Index- was calculated as ($N_{right\text{-}biased}$ trials- $N_{left\text{-}biased}$ trials)/ 20. This yielded values ranging from –1 (leftward spatial bias/right spatial inattention) to +1 (rightward spatial bias/left spatial inattention).

Figure 2. Mean Landmark Asymmetry Indices as a function of ADHD DAT1 Genotype Group.

The performance accuracy of the groups on the Landmark task was firstly compared using those trials on which the midpoint of the line was offset. Accuracy was high across both groups (Mean Accuracies>73%) and not significantly different

between the ADHD DAT1 genotype groups [F(1,41)=0.57,p=0.45].

Figure 3. Mean Landmark Asymmetry Indices as a function of ADHD DAT1 Genotype Group and Medication Response Group.

Significant differences existed between the High-Risk DAT1/Very Good Response and Low-Risk DAT1/Mediocre Response groups.

Table 1. Clinical Characteristics of the ADHD sample.

[A] IQ was estimated using a four subtest short-form of the WISC-III, comprising Picture Completion, Information, Block Design and Vocabulary. IQs were not available for 2 participants. [B] Reading and Spelling was assessed using the Wide Range Achievement Test (WRAT). Reported scores as the standard scores for each of these subtests. [C] Clinical symptomatology was assessed dimensionally using the Conners' Parent Rating Scale-Revised: Long Version. Reported values are age-related normative scores (t-scores) for DSM-IV Inattention, Hyperactive/Impulsive and Total symptomatology. Scores on other dimensions are available from the authors. [D] Symptom severity when medicated and un-medicated was retrospectively rated by parents using the CPRS-R:L. Reported values are the change in age-related normative scores (t-scores) for DSM-IV Inattention, Hyperactive/Impulsive and Total symptomatology.

	ADHD DAT1 Genotype Group		**Associated significance test**
	Low-Risk DAT1 ADHD (n=21)	**High-Risk DAT1 ADHD (n=22)**	
Gender No. Male (%)	19 (90%)	18 (82%)	χ^2 (df_1)=0.67, p=0.41
ADHD-Combined Type	17 (81%)	16 (73%)	$\chi^2(df_1)=0.41,p=0.52$
ADHD- Inattentive Type	3 (14%)	4 (18%)	$\chi^2(df_1)=0.12,p=0.73$
ADHD-Hyperactive/Impulsive Type	1 (5%)	2 (9%)	$\chi^2(df_1)=0.31,p=0.58$
	Mean (SD)	**Mean (SD)**	

Age	12.2 (2.7)	12.2 (2.1)	F(1,41)=0.01, p=0.92
IQ [A]	101.7 (13)	99 (12)	F(1,39)=0.48, p=0.49
WRAT Reading Standard Score [B]	96 (13)	96 (10)	F(1,41)=0.00,p=.95
WRAT Spelling Standard Score	96 (18)	92 (10)	F(1,41)=.76,p=.39
DSM-IV Inattention [C]	72.1 (9.4)	77 (6.4)	**F(1,39)=4.66, p=0.04***
DSM-IV Hyperactive/Impulsive	76.3 (12.9)	82.3 (9.8)	F(1,39)=2.86, p=0.09
DSM-IV Total	75.9 (10.9)	82.2 (5.8)	**F(1,39)=5.65, p=0.02***

Table 2. Mean (SD) Landmark Asymmetry Index as a function of DAT1 alleles.

[A] One subject possessed an 11-repeat (520bp) allele and one subject possessed a rare 400bp allele

	9/9 **(n=2)**	**10 /other allele** [A] **(n=19)**	**10/10** **(n=22)**
	Mean (SD)	Mean (SD)	Mean (SD)
Landmark Asymmetry Index	-0.35 (0.07)	-0.15 (0.23)	+0.09 (0.29)