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Association of the DAT1 genotype with inattentive behavior is mediated by reading ability in a general population sample

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) and reading disability (RD) frequently co-occur in the child population and therefore raise the possibility of shared genetic etiology. We used a quantitative trait loci (QTL) approach to assess the involvement of the dopamine transporter (DAT1) gene polymorphism in mediating reading disability and poor attention in a general population sample of primary school children aged 6–11 years in the UK. The potential confounding effects of IQ and chronological age were also investigated. We found an independent association between the homozygous DAT1 10/10 repeat genotype and RD that was not accounted for by the level of ADHD symptoms. This finding suggests that the DAT1 gene polymorphism may influence a common neural mechanism underlying both reading acquisition and ADHD symptoms.

1. Introduction

Children with attention-deficit hyperactivity disorder (ADHD) are characterized by their poor attention to detail, difficulties in maintaining attention over a sustained period of time, and moment-to-moment variability throughout task performance. ADHD frequently co-occurs with reading disability (RD), a disorder that is characterized by impairments in single word reading, reading fluency, and reading comprehension (Catts & Kamhi, 2005). The incidence of RD in samples of children selected for ADHD is estimated to be between 25% and 40% (Semrud-Clikeman et al., 1992), while 15–35% of children with RD will meet the criteria for ADHD (Willcutt & Pennington, 2000). Together, ADHD and RD represent the two most common developmental disorders of childhood, each occurring in approximately 5% of the population, with a higher frequency of boys than girls.

At the *cognitive level*, although some evidence points to commonalities across and within a range of executive function sub-domains in comorbid RD and ADHD, specifically impairments in working memory (e.g. Cohen et al., 2000; Martinussen & Tannock, 2006; Willcutt et al., 2001; Willcutt, Pennington, Olson, Chhabildas, & Hulslander, 2005), the evidence is not always consistent (de Jong et al., 2009; Marzocchi et al., 2008; Willcutt et al., 2005). In contrast, deficits in response inhibition appear to be specific to ADHD (e.g. Cornish et al., 2005; Rubia et al., 2001, but see Castellanos and Tannock (2002), for a review), One promising cognitive overlap between RD and ADHD recently reported by Willcutt et al. (2010) is a possible shared deficit in speed of processing. Willcutt et al. examined the genetic and environmental etiology of scores on composite measures derived from an extensive battery of cognitive tests administered as part of the Colorado Learning Disabilities Research Center (CLDRC) twin study. The purpose of this study was to tease apart specific neuropsychological processes that account for the phenotypic comorbidity between RD and ADHD. These authors concluded that processing speed was the only cognitive composite that could be explained by common genetic influences that increase susceptibility to both disorders.

At the *genetic level*, there is converging evidence that the substantive co-morbidity between ADHD and RD is due, in part, to shared (pleiotropic) genetic factors (Gayan & Olson, 2001; Willcutt, Pennington, & DeFries, 2000; Willcutt, Pennington, Olson, & DeFries, 2007). Luca et al. (2007) found that the dopamine receptor D1 gene (*DRD1*) showed a strong association with inattentive behavior in children selected for reading problems but showed no such relationship with reading disability, suggesting that *DRD1* uniquely contributes to inattention. To date, although no specific genes involved in the ADHD + RD phenotype have yet been identified, a number of genome-wide linkage analyses have identified potential loci pleiotropic for ADHD + RD (Bakker et al., 2003; Couto et al., 2009; Gayan et al., 2005; Loo et al., 2004; Stevenson et al., 2005; Wigg et al., 2008).

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In the present study, we focus on a possible association between RD, ADHD symptoms and the dopamine transporter (DAT1) gene polymorphism (SLC6A3) located on chromosome 5p15.3. The pharmacological effects of psycho-stimulants have made dopaminergic genes, including DAT1, logical candidates for ADHD. Several studies provide evidence in favor of an association between the 10 repeat-allele and ADHD symptoms (Brookes et al., 2008; Chen et al., 2003; Cornish, Wilding, & Hollis, 2008; Cornish et al., 2005; Doyle et al., 2009; Genro et al., 2008); although non-replications have been reported (Bakker et al., 2003; Langley et al., 2005). Moreover, recent studies also suggest that DAT1 may mediate neuropsychological impairments in ADHD, notably for skills that require response variability and inhibition (Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005; Cornish et al., 2005), and sustained and spatial attention (Bellgrove et al., 2005, 2009; Loo et al., 2003). Regarding DAT1, however, there are several inconsistent findings of an effect on neuropsychological functioning in ADHD suggesting that this gene may have a moderating rather than direct influence on cognitive impairments (Kebir & Joober, in press). In contrast, no current studies have yet examined the direct association between DAT1 and RD, or between DAT1 and comorbid ADHD + RD. However, previous findings indicate measures of response inhibition load most closely with reading and *not* attention constructs in experimental studies (Purvis & Tannock, 2000) and in robust 'error-free' latent variable analysis (Savage, Cornish, Manly, & Hollis, 2006), indicating a potential important link between DAT1 and reading ability that has hitherto not been explored.

Using a quantitative trait loci (QTL) approach to investigate the link between DAT1 and RD, and having previously found an association between DAT1 and ADHD symptoms in the same sample (Cornish et al., 2005), in the present study we test the hypothesis that this association is not independent of reading disability, and that DAT1 would remain a strong predictor of reading ability after initial controls for variability in ADHD symptoms (based on teacher-ratings of attention problems, and extraneous measures; IQ, chronological age) (Model 1). In contrast, we hypothesized that DAT1 would not be a strong predictor of ADHD symptoms after parallel controls for reading ability and extraneous measures (Model 2).

2. Method

2.1. Participants

In the first stage of the study, we anonymously screened an epidemiological sample of 1776 6-to-11-year-old children from Central England (UK) for symptoms of ADHD using a teacher-rated behavioral questionnaire, the strengths and weaknesses of ADHD-symptoms and normal behavior scale (SWAN; Swanson, McStephen, Hay, & Levy, 2001). The SWAN scale is based on the 18 ADHD symptoms listed in the DSM-IV manual (American Psychiatric Association, 1994). Scoring for each item goes from a low level of problems (3, 2, 1) through average (0) to a high level (−1, −2, −3). Children's scores ranged from a minimum of −27 to a maximum of 27 for each sub-scale: Inattention (items 0–9) and hyperactivity/impulsivity (items 10–18). This scale allows for a normal distribution of the data and avoids potential psychometric flaws that are associated with skewed distributions. This is especially advantageous when selecting extreme high and low scorers for genetic association studies investigating qualitative trait loci (QTL), as in the present study.

Of the 1776 questionnaires, 92 were excluded from further analysis due to missing or incomplete responses. There were complete questionnaires on 872 boys and 812 girls. SWAN summary (total) scores were normally distributed; Boys: mean = 4.7, SD = 23.1, skewness = −0.11, kurtosis = −0.30; Girls: mean = −9.9, SD = 20.4, skewness = −0.24, kurtosis = −0.30). Because the distribution of SWAN total score in boys was shifted to the right compared to the distribution of scores for girls (such that 86% of the highest 10% SWAN ratings were for boys), only boys were included in the subsequent parts of this study. This produced a total of 126 participants made up of two groups: (1) 58 boys who were rated by teachers above the 90th percentile for Inattentive *and/or* hyperactivity/impulsivity sub-scale items on the SWAN questionnaire (mean SWAN score of 40.8; SD 1.56; age range 6–11 years; mean age 9 years 5 months); (2) 68 boys who were rated by teachers as below the 10th percentile for inattentive and/or hyperactivity/impulsivity sub-scale items on the SWAN questionnaire (mean SWAN score of −33.1; SD −1.63; age range 6–11 years; mean age 8 years 6 months). Each participant was also rated by the same class teacher using the *Conners' Teacher Rating Scale-Revised: Short version* (*CTRS-R:S*) (Conners, Sitarenios, Parker, & Epstein, 1998a) and by parents using the *Conners' Parent Rating Scale-Revised: Short version* (*CPRS-R:S*) (Conners, Sitarenios, Parker, & Epstein, 1998b). The ADHD index of the *CPRS-R:S* and *CTRS-R:S* contains 12 items that discriminate well between ADHD clinical cases and controls (Conners et al., 1998a, 1998b). High correlations between these two scales have previously been reported (Cornish et al., 2005) and the SWAN has demonstrated good psychometric properties in discriminating between children with and without ADHD (Young, Levy, Martin, & Hay, 2009). None of the children were receiving stimulant medication (e.g. methylphenidate or dexamphetamine). One child was African Caribbean, and one child was Cypriot.

2.2. DNA extraction and genotyping

Buccal cells were harvested in 10 ml sterile saline, and DNA was extracted by alkaline lysis of the cells, as described by Ferrie et al. (1992). The analyses were performed at the Department of Molecular Genetics, Nottingham City Hospital, Nottingham, England, and each individual was genotyped twice. This DNA procedure has been described in detail in Cornish et al. (2005). Genotyping was conducted on 119 out of the 126 eligible participants (boys scoring > 90th and < 90th percentile on the SWAN scale). DNA samples were unobtainable or incomplete from seven participants and these children were excluded from further analysis. Initial analysis was conducted using the three most common genotype groups: 10/10, (n = 62); 9/10 (n = 41), and 9/9 (n = 12). Further analysis was made combining the 9/10 genotype with 3/10, 8/10 and 11/10 to create a heterozygous 10-repeat allele group (n = 45).

2.3. Intellectual ability

All participants were tested (individually) on the *Wechsler Abbreviated Scale of Intelligence* (WASI; Wechsler, 1999). This test provides a composite IQ score based on four subtests tapping both verbal and performance domains.

2.4. Reading tests

The *Neale Analysis of Reading Ability* (2nd edition) (NARA, Neale, 1997) was used to measure reading. Children are asked to read aloud a series of graded fiction and non-fiction narratives as speedily and as accurately as possible. Children are also told in advance that they will be asked questions about the narratives they have read. The test provides an age-standardized score measure of *reading accuracy* (calculated by the number of reading errors to a discontinuation point of 14 errors in a single narrative), *rate* (based on words read per minute in each narrative) and *comprehension* (based on the accuracy of subsequent responses to questions about