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Dopamine transporter genotype predicts attentional asymmetry in healthy adults

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ABSTRACT

A number of recent studies suggest that DNA variation in the dopamine transporter gene (DAT1) influences spatial attention asymmetry in clinical populations such as ADHD, but confirmation in non-clinical samples is required. Since non-spatial factors such as attentional load have been shown to influence spatial biases in clinical conditions, here we sought to determine whether any association between DAT1 genotype and spatial bias might be moderated by non-spatial attentional load. Healthy adults were asked to react to sudden onset peripheral targets while demand on non-spatial attention was manipulated via a central task. Participants were genotyped for a DAT1 variable number of tandem repeat (VNTR) polymorphism. The 10-repeat allele of this variant is a replicated susceptibility allele for ADHD and has been shown to associate with spatial bias. As expected, an overall leftward asymmetry/pseudoneglect was observed when the data were averaged across the entire sample. When data were stratified by DAT1 genotype, individuals lacking homozygosity for the 10-repeat DAT1 allele (non-10/10) showed a pronounced leftward bias that was significantly different from zero. In line with past reports from children with ADHD, this leftward bias was attenuated in individuals who were homozygous for the DAT1 10-repeat allele (10/10), suggestive of relatively weaker right hemisphere dominance for spatial attention. This effect of DAT1 genotype on spatial bias was not modulated by non-spatial attention load. These data confirm in healthy adult participants both the existence and the direction of the relationship previously reported between DAT1 genotype and spatial bias in children with ADHD. These data add to a growing body of evidence showing that spatial attentional asymmetry is a stable quantitative trait, with individual differences in this trait significantly predicted by common DNA variation in the DAT1 gene.

1. Introduction

In many circumstances humans can shift, or orient, their attention from one area of space to another with little cost to perception and with no discernable advantage for processing stimuli in one visual field over the other. Decades of neuropsychological research however has shown that systematic biases, or asymmetries, of attention do exist in humans (Bowers & Heilman, 1980; Bradshaw, 1989). For example, a subtle processing advantage favouring the left side of space for judgments of size, brightness and numerosity of visual stimuli has been observed across healthy samples (Nicholls, Bradshaw, & Mattingley, 1999). When humans are required to detect targets presented in either the left or right visual fields, a processing advantage exists such that left targets are on average responded to more quickly than comparable targets on the right (Dodds et al., 2008; O'Connell, Schneider, Hester, Mattingley, & Bellgrove, 2010). Although this asymmetry for left targets is evident when data are averaged across individuals, considerable variation in the direction and extent of bias exists between individuals and is influenced by a number of personality traits including novelty seeking and approach and avoidance behaviours (Garner et al., 2012; Tomer, 2008a). These data suggest that spatial biases might reflect a stable, trait-like phenomenon that varies in the normal population. The neurophysiological origins of these asymmetries have been primarily investigated in animals where individual differences in orienting preferences are linked to inter-hemispheric differences in striatal dopamine levels (Maisonnette, Huston, Brandao, & Schwarting, 1998; Shapiro, Glick, & Hough, 1986; Zimmerberg, Glick, & Jerussi, 1974). For example, rodents preferentially orient away from, or contralateral to, the striatum with elevated dopamine content (Zimmerberg et al., 1974).

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Although the attentional asymmetries of the normal population are subtle, dramatic asymmetries of attention are also observed following acquired damage to the right cerebral hemisphere in humans. Typically, lesions of the right hemisphere (RH) induce left spatial neglect, in which the ability to detect and act upon contralesional stimuli is impaired. In neglect the attentional deficit due to RH damage is asymmetrical in that it occurs for the visual field that is contralateral to the lesion but not for the visual field that is ipsilateral to the lesion (Driver & Mattingley, 1998). Importantly, left neglect can also arise from lesions to a number of sub-cortical regions, including the striatum and basal ganglia (Karnath, Himmelbach, & Rorden, 2002), that receive strong dopamine inputs. Consistent with animal studies that have reported spatial inattention following lesions of the ascending dopaminergic pathways (Iversen, 1984), treatment with dopamine agonists has been shown to reduce the extent of inattention in human subjects (Fleet, Valenstein, Watson, & Heilman, 1987).

Several studies have demonstrated abnormal asymmetries of attention in children with ADHD, using both standard clinical tests of neglect that require visual search for targets amongst distracters (Chan et al., 2009; Sheppard, Bradshaw, Mattingley, & Lee, 1999; Voeller & Heilman, 1988), and spatial orienting paradigms (Bellgrove et al., 2009; Carter, Krener, Chaderjian, Northcutt, & Wolfe, 1995; Nigg, Swanson, & Hinshaw, 1997). Although subtle in comparison to the frank deficits of left spatial neglect, ADHD children have difficulty allocating visual attention to left-sided targets in response to cues (Bellgrove et al., 2009), and are slower to respond to left-sided targets (Nigg et al., 1997). Left-sided deficits have also been reported in the biological mothers of children with ADHD (Nigg et al., 1997). Importantly, left-sided inattention in ADHD may be ameliorated by psychostimulants such as methylphenidate (MPH) (Sheppard et al., 1999), implying a dopaminergic contribution to asymmetries of attention in ADHD.

A number of lines of evidence suggest that lateralised attentional mechanisms can also be modulated by non-spatial processes such as sustained attention and attentional capacity. For example, sustained attention for auditory stimuli predicts the severity of spatial bias in neglect patients (Robertson et al., 1997). Peers, Cusack, and Duncan, (2006) asked patients with right parietal lesions as well as patients with left parietal lesions to complete a spatial attention task whilst manipulating non-spatial attention load via the addition of a concurrent auditory task. The dual task condition elicited a rightward shift in perceptual bias in both left parietal and right parietal patients. These data suggest that non-spatial factors modulate the allocation of spatial attention

The effect of non-spatial load on spatial attention is consistent with our burgeoning understanding of the interaction between the right lateralised ventral attention network and the bilateral dorsal attention network. Specifically, modulations of the ventral attention network via manipulations of alertness, arousal and/or attentional capacity may modulate activity within the dorsal orienting network driving attention rightwards (Corbetta & Shulman, 2011). In light of evidence that the RH lateralisation of non-spatial attention may be driven by asymmetries in the modulation of catecholamine mechanisms (Corbetta, Patel, & Shulman, 2008; Posner & Petersen, 1990), it is plausible that the abnormal attention asymmetries seen in disorders of dopamine such as ADHD could be driven by right ventral network dysfunction leading to a secondary effect on the dorsal network and spatial attention.

Consistent with the animal literature pointing to a role for dopamine in spatial attention, a small number of human studies have reported that DNA variation in dopamine genes accounts for significant individual differences in spatial asymmetry. Following observations that attentional asymmetry in ADHD can be normalized by MPH which inhibits the dopamine transporter, Bellgrove et al. tested whether variation in the dopamine transporter gene (DAT1) itself might relate to attentional asymmetry in ADHD. An association between the 10-repeat allele of a variable number of tandem repeat (VNTR) polymorphism within the DAT1 gene is one of the best replicated molecular genetic findings in ADHD (Hawi et al., 2003), with meta-analysis confirming that DAT1 is a susceptibility locus for ADHD (Gizer, Ficks, & Waldman, 2009). Bellgrove et al. (2005a), Bellgrove, Hawi, Kirley, Gill and Robertson (2005b) have demonstrated that asymmetries of attention in ADHD are related to the 10-repeat DAT1 allele, with left-sided inattention being most pronounced in 10-repeat DAT1 homozygotes (10/10 DAT1 genotype). Further, left-sided inattention also correlated with levels of inattentive symptomatology (Bellgrove et al., 2005a). Since the dopamine transporter is heavily expressed in the striatum (Krause, Dresel, Krause, la Fougere, & Ackenheil, 2003), and imaging studies show an effect of DAT1 genotype on striatal transporter densities (Cheon, Ryu, Kim, & Cho, 2005; Heinz et al., 2000), Bellgrove et al. hypothesised that the 10-repeat DAT1 allele is associated with overactive dopamine transporters, particularly within RH networks. This hypothesis is supported by molecular imaging in ADHD reporting increased transporter binding specifically in the right striatum (Spencer et al., 2007) and an fMRI study with typically developing childeren reporting a significant effect of DAT1 genotype on activation of the right striatum (Stollstorff et al., 2010). The associated reduction of synaptic dopamine in the RH may give rise to asymmetrical attentional impairment in ADHD.

Although a number of studies have reported associations between spatial biases and DAT1 genotype in healthy children and adults, the direction of effects (leftward versus rightward bias) is inconsistent (Bellgrove et al., 2007; Greene, Robertson, Gill, & Bellgrove, 2010). Here we sought to clarify the relationship between DAT1 genotype and spatial biases in a healthy adult population. Further, given observations that non-spatial attentional load may influence behavioural and neural markers of spatial bias we sought to determine the influence of DAT1 genotype and non-spatial attentional load on spatial biases. We predicted an association between DAT1 genotype and spatial biases such that individuals homozygous for the 10-repeat DAT1 allele (10/10 DAT1 genotype) would display less RT advantage for left, relative to right, targets. In contrast, we predicted that individuals with one or no copies of the 10-repeat allele would display pseudoneglect, responding faster to left relative to right targets. Such a finding would add support for the notion that DAT1 harbours a quantitative trait locus for attentional asymmetry. Further, we tested the hypothesis that the relationship between DAT1 genotype and spatial bias is moderated by non-spatial attentional load, predicting the greatest effect of non-spatial load on the spatial bias of individuals homozygous for the 10-repeat DAT1 allele.

2. Method

2.1. Participants

Participants were 91 right-handed volunteers (53 female) of Caucasian descent. All reported normal or corrected to normal vision, no history of neurological or psychiatric disorder and no head injury resulting in loss of consciousness. Data from a subset ($N=45$) of these participants has been previously reported (O'Connell et al., 2010), however they were not analysed as a function of DAT1 genotype. Four participants were outliers for peripheral target detection rate, responding to fewer than 75% of peripheral targets, which suggests insufficient engagement with the task. These participants were excluded from further analysis. Two participants could not be included due to missing RT data. This left a final sample size of 85 participants (49 female) aged 18 to 47 ($M=23$).

2.2. Apparatus

2.2.1. Visual attention task

Full details of the visual attention task are described elsewhere (O'Connell et al., 2010). A schematic of a single trial is illustrated in Fig. 1.

Briefly, participants viewed a centrally presented rapid serial visual presentation (RSVP) stream for the occurrence of a designated probe item, while also monitoring peripheral locations for the appearance of a target. Peripheral targets were presented randomly (but with equal probability) in either left or right target locations (or not at all) at either 1200 ms or 2400 ms. Participants indicated their detection of the peripheral target via a speeded left mouse click with their right hand. Peers et al. (2006) found response hand had no effect on spatial bias using a similar paradigm. At the end of each trial participants were asked whether a central probe item was present and responded 'yes/no' via a non-speeded left or right mouse click, respectively.

The three experimental conditions (no report, low-load, and high-load) were completed in separate blocks. The only aspect of the experiment that differed between these conditions was the instructions regarding the central probe item. At the beginning of the no report condition, participants were instructed to simply fixate on the central RSVP stream and to monitor for peripheral targets. At the beginning of the low-load condition, participants were instructed that the probe item was any green character within the central stream. The target was relatively easy to identify here because it was defined by its unique colour (Treisman & Gelade, 1980). For the high-load condition, the probe item was any red letter within the central stream of red characters, requiring more attentional resources (than the low-load task) because the target was defined by a conjunction of features shared with the other characters (Treisman & Gelade, 1980). The central probe item appeared unpredictably in 50% of the trials (under low- and high-load) and its order of appearance within the RSVP stream was randomised. The onset of the central target never coincided with the peripheral target.

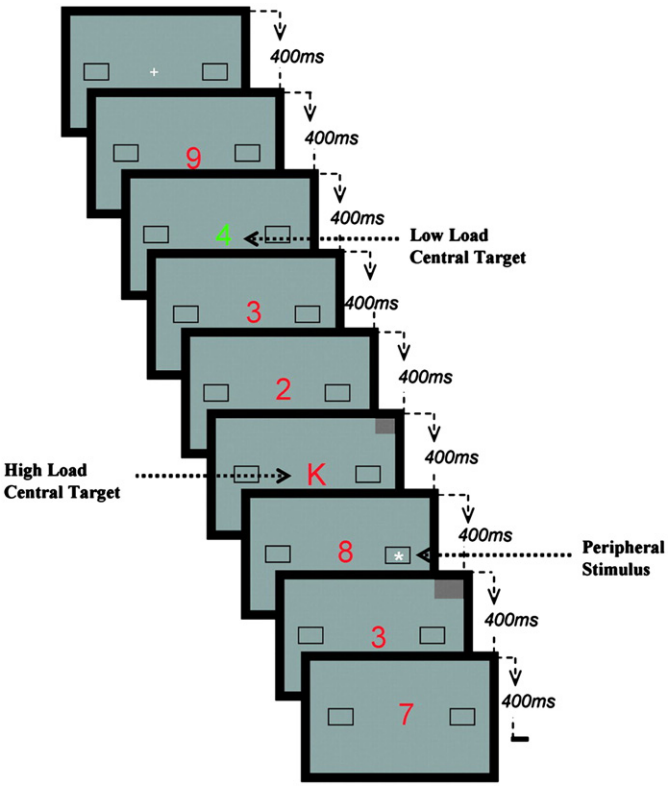

Fig. 1. A single trial from the visual attention task. Participants fixated on the central stream searching for a designated probe item, while simultaneously monitoring the periphery for a brief stimulus that could appear to the right or left. Non-spatial attentional load was manipulated across three conditions: a no report condition, low-load (central target: any green item) and high-load (central target: red letter). Participants indicated detection of the peripheral target with a speeded mouse click. With respect to the central task participants were asked whether a probe item was present (for high and low-load) in the stimulus stream and responded yes/no with a non-speeded left or right mouse click, respectively, at the end of each trial. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.3. Procedure

Participants were seated comfortably with their head supported by a chin rest ensuring a consistent viewing distance of 50 cm. Although continuous EEG was recorded, only behavioural data are reported herein. Before beginning each condition, participants read on-screen instructions and the task was explained verbally. Participants were instructed to maintain central fixation and avoid blinking or moving their eyes during each trial, but were encouraged to blink and move in the short breaks between each trial, if desired. Both speed and accuracy of responses to the peripheral target detection task were emphasised. When participants had mastered a practice session, they were left alone in a dimly lit room to begin the task. Participants completed the three load conditions in one session. The order of completion for the three conditions was counterbalanced. Each condition comprised 300 trials and participants received a 5 min rest period every 100 trials. Each 100 trial block lasted approximately 12–13 min, but varied depending on how long the participant took to make the non-speeded central target present/absent judgements at the end of each trial. During the third break, participants were asked to provide a small (2 mL) saliva sample for DNA extraction.

2.4. Genotyping

Saliva was collected from each participant for DNA extraction using Oragene DNA self-collection kits (DNAgenotek, Ottawa, ON, Canada). DNA was extracted following the protocol provided by Oragene DNA. Participants were genotyped for the VNTR polymorphism located in the 3′ untranslated region (UTR) of the DAT1 gene. Polymerase chain reaction (PCR) amplification was conducted using the following primers (20 pmol/μL each): forward: 5′ TGTGGTGTAGG GAACGGCCT-GAG-3′; reverse 5′ CTTCCTGGAGGTCACGGCTCAAGG-3′. The 25 μL PCR solutions each contained 11.3 μL of H_2O, 2.5 μL of PCR buffer (Hot FirePol buffer B2 from Solis BioDyne), 2 μL of $MgCl_2$ at 25 mM, 4 μL of dNTP mix (dATP, dCTP, dGTP, and dTTP), 3 μL of DNA at 20 ng/μL, 1 μL of forward primer at 20 pmol/μL, 1 μL of reverse primer at 20 pmol/μL, 0.2 μL of Taq Polymerase (Hot FirePol Taq from Solis BioDyne).

The following cycling protocol was run in a Bio-Rad Tetrad 2 Peltier Thermal Cycler: initial denaturation at 95 °C for 12 min, followed by 35 cycles of denaturation at 95 °C for 30 s, annealing at 60 °C for 30 s and extension at 72 °C for 30 s. A final 5 min extension at 72 °C was used. Gel electrophoresis was run at 100 V for 60 min, in 2% agarose gels containing SYBR safe gel stain and a 100 bp ladder. The amplification products were visualised using a Bio-Rad Gel Doc XR. The observed genotype frequencies for the 3′ UTR VNTR were consistent with Hardy Weinberg Equilibrium, $\chi^2 = .015$, $p = .902$.

2.5. Analysis

Peripheral target RTs (ms) were analysed using a $3 \times 2 \times 2$ mixed model ANOVA, with central load (no report vs. low-load vs. high-load) and target side (left vs. right) as within subjects factors and DAT1 genotype group (non-10/10 DAT1 vs. 10/10 DAT1) as the between subjects factor. Age was included as a covariate in the ANOVA to control for the significant difference in age between the DAT1 genotype groups (see Table 1). Due to the relatively low number of participants with zero copies of the 10-repeat allele (7%), those with zero or one copy of the 10-repeat allele (non-10/10 DAT1 group; 40 participants) were compared to those carrying two copies of the 10-repeat allele (10/10 DAT1 group; 45 participants) (see Bellgrove et al., 2005a for a similar approach). The non-10/10 DAT1 group comprised 34 participants with a 9/10 genotype, 5 participants with a 9/9 genotype and 1 participant with a 3/3 genotype. Gender was evenly distributed across the genotype groups (see Table 1). Greenhouse-Geisser corrections were used throughout the analysis where sphericity was violated. All follow-up tests were performed after the ANOVA using Bonferroni adjusted pairwise comparisons.

3. Results

3.1. Central task load manipulation check

Central target detection rates were analysed as a function of central load (low- vs. high-load; no target detection was required in the no report condition) to verify that the central task increased attentional demands at fixation. There was a main effect of central load on detection rates, $F(1, 84) = 45.01$, $p < 001$, whereby detection rates were significantly greater under low-load ($M = 97\%$, $SE = 0.30$) than under high-load ($M = 94\%$, $SE = 0.54$).

3.2. DAT1 genotype predicts asymmetry in peripheral target detection response times

Peripheral target response times were filtered to accept trials where participants correctly identified whether there was a central probe item or not (for the low- and high-load conditions). The RT distributions were normally distributed as a function of load, target-side and DAT1 genotype. Levene's test indicated the data met the assumptions of homogeneity of variances.

The mixed model ANOVA, covarying for age, revealed a significant main effect of central task load, $F(2, 164)=3.39$, $p=.036$, $\eta^2=.04$, indicating that peripheral target RTs were slower in the high-load condition ($M=510$ ms, $SE=7.5$) than low-load condition ($M=493$ ms, $SE=7.6$,) ($p<.001$), which were in turn were slower than the no report condition ($M=408$ ms, $SE=5.9$), ($p<.001$). This main effect of central load was not modified by target-side or DAT1 genotype. Crucially however, there was a significant DAT1 × target-side interaction, $F(1, 82)=5.31$, $p=.024$, $\eta^2=.06$. This interaction was driven by a significant simple effect of target-side within the non-10/10 DAT1 group (see Fig. 2).

The non-10/10 DAT1 group had significantly faster RTs for left targets ($M=468$ ms, $SE=9.4$) than right targets ($M=475$ ms, $SE=9.9$) ($p<001$), whereas no asymmetry existed for the 10/10 DAT1 group ($p=.372$). This confirms the existence of a significant leftward attentional bias (pseudoneglect) in the non-10/10 DAT1 group only. There were no significant RT differences between non-10/10 and 10/10 DAT1 groups within each level of target-side ($ps>.845$). It should also be noted that there was no evidence for a DAT1 × load × target-side interaction in the RT data ($p=.172$).

To further understand the spatial asymmetry effect reported above, an RT asymmetry index was derived using the following formula:

$$\text{RTasymmetryindex} = \frac{(\text{lefttargetRT})-(\text{righttargetRT})}{(\text{meanleftandrighttargetRT})}$$

This index gives negative values when RTs are faster for left relative to the right targets (leftward bias), positive values when the opposite is true (rightward bias), and a value of zero when there is no spatial bias. Crucially, Pearson's correlation indicated no relationship between age and RT asymmetry ($r=-.17$, $p=.121$) and an independent samples t-test revealed no significant gender effect on the RT asymmetry, $t(83)=.198$, $p=.844$. A one sample t-test demonstrated that RT asymmetry over the entire sample was significantly less than zero and thus left biased, $t(84)=-3.01$, $p=.003$. This confirms the presence of a subtle leftward spatial bias across the population under study. The equivalent test on the sub-sample of participants carrying a non-10/10 genotype indicated a significant leftward bias, $t(39)=-3.34$, $p=.002$, while the RT asymmetry of the 10/10 DAT1 group was not different from zero, $t(44)=-0.66$, $p=.515$ (see Fig. 3).

4. Discussion

Systematic biases of spatial attention exist when averaged at a population level but vary considerably between individuals both in terms of the direction and extent of spatial bias. Here we sought to determine whether DNA variation in the dopamine transporter gene (DAT1) could account for significant individual differences in spatial bias and further whether any genetically-driven spatial bias could be modulated by non-spatial task factors, such as attentional load. Consistent with a wealth of previous data from visual attention tasks, participants on average responded more quickly to targets presented in the left, compared to right, hemi-field, confirming the existence of pseudoneglect. Individual differences in attentional asymmetry were evident and were significantly predicted by allelic variation in the DAT1 gene. Specifically, individuals homozygous for the 10-repeat DAT1 allele showed no systematic attentional asymmetry, whereas individuals who were not homozygous at this locus displayed a pronounced leftward attentional asymmetry. These effects were not modulated by the imposition of a non-spatial processing load at fixation.

These data support the view that spatial bias is a trait-like phenomenon whose variation in the normal population is partly driven by individual differences in dopamine functioning. Tomer (2008a) recorded strong test-retest reliability in the direction and magnitude of spatial bias in a sample of healthy adults ($r=.722$, $p<001$), suggesting that the degree of spatial bias within an individual is a relatively stable trait over time. Similarly to the current study, a leftward asymmetry was present when the perceptual measure of spatial bias employed by Tomer (2008a) was averaged across individuals, but subsets of individuals

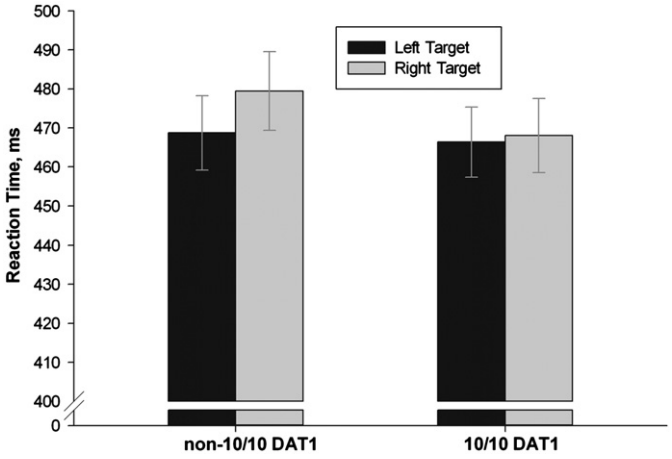

Fig. 2. Mean peripheral target RT as a function of target-side and DAT1 genotype group. The non-10/10 DAT1 group displayed significantly faster responses to left than right peripheral targets, whereas those with the 10/10 genotype showed no significant asymmetry between response times for left and right targets. Error bars reflect the standard error of the mean.

Table 1
Genotype specific demographics. Gender did not differ significantly between genotype groups. There was however a significant age difference between genotype groups.

	DAT1 genotype group		
	Non-10/10 DAT1 ($n=40$)	10/10 DAT1 ($n=45$)	Significance test
Gender, female, no. (%)	25 (62.5%)	24 (53.3%)	$\chi^2=.73$, $p=.393$
Age, M (SD)	25.4 (8.2)	22.1 (4.9)	$t(61.97)=2.2$, $p=.032$ [a]

[a] Equal variances not assumed.

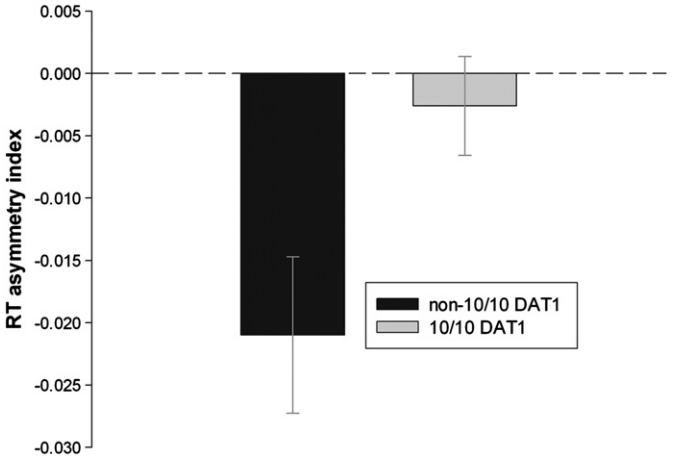

Fig. 3. Mean RT asymmetry index as a function of DAT1 genotype. Negative values indicate leftward spatial bias, zero indicates no bias. The non-10/10 DAT1 group had a significantly left-biased RT asymmetry, whereas the 10/10 group did not differ from zero, indicating no systematic spatial bias. Error bars reflect the standard error of the mean.

consistently showed no spatial bias or showed a consistent rightward asymmetry. Here we confirm that one substrate of such individual differences in spatial bias is DNA variation in the DAT1 gene.

Evidence from both healthy and clinical populations indicates a modulatory influence of non-spatial factors such as sustained attention, alertness, and attentional load, on spatial biases (Bellgrove, Dockree, Aimola, & Robertson, 2004; Dodds et al., 2008; Manly, Dobler, Dodds, & George, 2005; Peers et al., 2006; Pérez et al., 2009; Robertson, Mattingley, Rorden, & Driver, 1998). A prominent neuroanatomical model (Corbetta & Shulman, 2011) proposes that this modulation arises through a right lateralised ventral network for non-spatial attention (Coull, Frackowiak, & Frith, 1998; Pardo, Fox, & Raichle, 1991; Sturm et al., 2004; Sturm & Willmes, 2001; Paus et al., 1997; Sturm and Willmes, 2001; Culham et al., 2001; Schwartz et al., 2005; Vuilleumier et al., 2008) that regulates inter-hemispheric rivalry in the bilateral dorsal network for spatial attention orienting (Corbetta, Patel, & Shulman, 2008; Husain & Nachev, 2007). In contrast to our hypothesis, we did not find any modulation of the association between DAT1 genotype and spatial bias by non-spatial attentional load. These data suggest that DAT1 may have a greater influence on the dorsal attention networks that are responsible for spatial orienting than on the right lateralised ventral attention networks.

A number of lines of evidence support the notion that individual differences in spatial asymmetry are related to dopamine functioning. First, DAT1 genotype has been related to personality traits that have a putative dopaminergic substrate, such as novelty seeking and impulsivity (Colzato, van den Wildenberg, Van der Does, & Hommel, 2010; Forbes et al., 2007; Kazantseva, Gaysina, Malykh, & Khusnutdinova, 2009; Van Gestel et al., 2002). Second, traits such as novelty seeking which are related to spatial asymmetry (Tomer, 2008a) have also been linked to a hemispheric asymmetry in dopamine functioning (Huang et al., 2010; Tomer, & Aharon-Peretz, 2004; Tomer, Goldstein, Wang, Wong, & Volkow, 2008b). Third, abnormal spatial asymmetries of attention are found in other disorders of dopamine such as schizophrenia (Maruff, Hay, Malone, & Currie, 1995) and Parkinson's disease. Patients with Parkinson's disease with predominant RH dopamine depletion show leftward inattention that is qualitatively similar to that seen in patients with acquired right hemisphere lesions and neglect (Ebersbach et al., 1996; Lee et al., 2001). Moreover, dopamine agonist therapy has been shown to reduce leftward inattention in both neglect (Fleet et al., 1987; Geminiani, Bottini, & Sterzi, 1998; Mukand et al., 2001) and ADHD where much evidence points to a dopaminergic pathophysiology (Nigg et al., 1997; Sheppard et al., 1999) and abnormal RH function (Booth et al., 2005; Silk, Vance, Rinehart, Bradshaw, & Cunnington, 2008; Sowell et al., 2003; Vance et al., 2007).

There may be a number of potential mechanisms by which DNA variation in the DAT1 gene influences spatial bias. Evidence from both in vitro measures of gene expression (Fuke, 2001; VanNess et al., 2005) and in vivo measures of transporter densities (Cheon et al., 2005; Heinz et al., 2000) converge to suggest that the DAT1 10-repeat allele, or other DNA variants that it tags, are functionally related to DAT density and dopamine availability. The DAT1 10-repeat allele may influence hemispheric dopamine asymmetry by increasing dopamine transporter density within the RH relative to the LH. The relatively increased reuptake of dopamine in the RH (Ciliax et al., 1999) may decrease activation in RH attention networks, weakening the orienting bias of the RH, relative to the left, thus driving attention rightward. Indeed, Stollstorff et al. (2010) recorded significantly greater right caudate nucleus activation in healthy children who were not carrying the 10/10 genotype compared to those with the 10/10 genotype, although the sample size was small for a genetic association study ($N=20$). Molecular imaging in ADHD suggests increased transporter binding in the right striatum compared to control participants (Spencer et al., 2007). Although the 10-repeat DAT1 allele is an established susceptibility allele for ADHD (Gizer et al., 2009; Maher, Marazita, Ferrell, & Vanyukov, 2002) and children with ADHD display abnormal attentional asymmetry which is predicted by DAT1 genotype (Bellgrove et al., 2005a,b, 2009), no study has yet linked DAT1 genotype, spatial biases and molecular imaging markers of dopamine such as transporter binding. Nevertheless, the current data add to a growing body of evidence that common DNA variation in the DAT1 gene drives individual differences in spatial asymmetry. Future studies in both healthy and clinical (e.g., ADHD) populations will need to determine whether this association is underpinned by objective evidence of a hemispheric asymmetry in dopamine functioning.

One may contend that an alternative explanation for the association between DAT1 genotype and spatial bias is that DAT1 genotype influences post-perceptual motor processing, rather than attentional processes per se (Miller, 1988). This would seem reasonable in light of evidence that dopamine affects sensorimotor processing (e.g., Rammsayer & Stahl, 2006) and ablation of ascending dopaminergic projections in rodents gives rise to a contralateral sensory-motor deficit (Iversen, 1984; Shapiro, Glick, & Camarota, 1987). However, associations between DAT1 genotype and spatial biases have also been found using perceptual measures of spatial bias that are not sensitive to differences in post-perceptual motor processing. For example DAT1 genotype was shown to associate with spatial bias as measured by the Landmark Task (Bellgrove et al., 2005a), which is a perceptual measure that does not require a speeded motor response. The consistency of reported associations across tasks suggests that DAT1 genotype is in fact related to visuospatial processing rather than merely post-perceptual motor processes.

The direction of the DAT1 effect herein is consistent with evidence from a variety of spatial attention paradigms in ADHD and healthy children (Bellgrove et al., 2008, 2007, 2005a,b, 2009). However, these results conflict with Greene et al. (2010), in which healthy adults carrying the relatively rare 9/9 DAT1 genotype showed significantly more rightward-bias on the landmark task when compared to a larger group of participants carrying either the 9/10 or 10/10 genotype. That study however reported an overall

rightward bias across the whole sample in contrast to the leftward pseudoneglect that is typically reported for visuospatial tasks, and was seen in the current study. Given this inconsistency and considering that the direction of Greene et al.'s DAT1 effect is in direct contrast with both previous research and the current findings, the balance of evidence suggests that the 10/10 genotype, rather than the 9/9 genotype, is associated with relative leftward inattention.

Here we show that the direction of the relationship between DAT1 genotype and spatial bias, which has been previously reported in children, is also evident in adulthood. Those with the 10/10 DAT1 genotype did not show the typical preference for left target detection, suggesting a genetically-driven attenuation of the RH dominance for spatial processing. By contrast, individuals without the 10/10 DAT1 genotype displayed a pronounced leftward bias that is typical of the phenomenon of pseudoneglect. These data add to a growing body of evidence suggesting that attentional asymmetry is a quantitative trait, with individual differences in the direction and extent of asymmetry predicted by dopamine system genes. Molecular imaging work that is able to precisely define the neural substrates of these relationships will help to delineate a susceptibility mechanism for disorders such as ADHD, where the 10-repeat DAT1 allele confers risk and has been associated with abnormal asymmetries of attention.

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