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Dopamine system genes are associated with orienting bias among healthy individuals

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ABSTRACT

Healthy individuals display subtle orienting bias, manifested as a tendency to direct greater attention toward one hemispace, and evidence suggests that this bias reflects an individual trait, which may be modulated by asymmetric dopamine signaling in striatal and frontal regions. The current study examined the hypothesis that functional genetic variants within dopaminergic genes (DAT1 3′ VNTR, dopamine D2 receptor Taq1A (rs1800497) and COMT Val158Met (rs4680)) contribute to individual differences in orienting bias, as measured by the greyscales paradigm, in a sample of 197 young healthy Israeli Jewish participants. For the Taq1A variant, homozygous carriers of the A2 allele displayed significantly increased leftward orienting bias compared to the carriers of the A1 allele. Additionally, and as previously reported by others, we found that bias towards leftward orienting of attention was significantly greater among carriers of the 9-repeat allele of the DAT1 3′ VNTR as compared to the individuals who were homozygous for the 10-repeat allele. No significant effect of the COMT Val158Met on orienting bias was found. Taken together, our findings support the potential influence of genetic variants on inter-individual differences in orienting bias, a phenotype relevant to both normal and impaired cognitive processes.

1. Introduction

The two hemispheres of the healthy mammalian brain show asymmetry at functional, structural and neurochemical levels (Toga & Thompson, 2003; Ocklenburg & Güntürkün, 2012). Although neurochemical asymmetries have been studied less extensively than structural asymmetries, a considerable body of evidence points to the existence of asymmetries within the dopaminergic system in animals (for review, see Glick & Shapiro (1985)) and in the human brain (Larisch et al., 1998; Vernaleken et al., 2007; Laakso et al., 2000; van Dyck et al., 2002; Hietala et al., 1999). Previous studies have shown that the direction of dopaminergic asymmetry varies between individuals (Larisch et al., 1998; Tomer, Goldstein, Wang, Wong, & Volkow, 2008; Tomer et al., 2013; Tomer et al., 2014) and has behavioral correlates in animals (Glick & Carlson, 1989; Glick, Jerussi, & Fleisher, 1976; Glick & Shapiro, 1985; Shapiro, Glick, & Hough, 1986; Thiel & Schwarting, 2001) and humans (Martin-Soelch et al., 2011; Tomer et al., 2008, 2013, 2014).

One of the behavioral correlates of asymmetrical activation of the two hemispheres is orienting, or the direction of attention in space, where relatively greater activation of one hemisphere results in orienting towards the contralateral space (Kinsbourne, 1970; Nash, McGregor, & Inzlicht, 2010). Individual differences in orienting bias (also referred to as spatial bias or spatial attention bias) are well documented in animals, reflecting asymmetries in dopaminergic brain circuits, such that orienting is contralaterally to the striatum with greater dopaminergic activity (Glick et al., 1976; Glick & Shapiro, 1985). Evidence from human subjects also supports the role of dopamine in orienting bias (Slagter, Davidson, & Tomer, 2010; Lee, Harris, Atkinson, & Fowler, 2001; Geminiani, Bottini, & Sterzi, 1998) and indicates that healthy subjects display a consistent bias in orienting towards one hemispace, the direction and magnitude of which varies between individuals (Tomer, 2008). Notably, individual differences in the direction and magnitude of the orienting bias among individuals have been found to be strongly associated with the pattern of asymmetric binding of dopamine D2/3 receptors in the putamen, temporal and the frontal cortex (Tomer et al., 2013).

Polymorphic variants within genes that encode elements of DA neurotransmission may partially regulate DA tone by modulating

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the available amount of neurotransmitter and receptor number that contribute to background DA neuron firing (Zhong et al., 2009). Thus, these polymorphisms may regulate, at least to some degree, behaviors that are modulated by asymmetric subcortical DA signaling, such as orienting bias. Indeed, previous studies reported that the variable number of tandem repeats (VNTR) within the 3′ untranslated region of the SLC6A3 gene, which encodes the dopamine transporter (DAT) were associated with orienting bias among ADHD affected children (Bellgrove et al., 2005a; Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005b; Bellgrove et al., 2008), healthy children (Bellgrove et al., 2007) and healthy adults (Greene, Robertson, Gill, & Bellgrove, 2010; Newman, O'Connell, Nathan & Bellgrove, 2012). Although most studies reported that reduced leftward bias was associated with the 10-repeat allele in children with ADHD (Bellgrove et al., 2005a, 2005b) and healthy children (Bellgrove et al., 2007) as well as healthy adults (Newman et al., 2012), an association between rightward bias and the 9-repeat allele has also been reported among healthy young adults (Greene et al., 2010). In the latter study, increased rightward bias was also associated with the presence of two copies of the T allele of the promoter C-1021T variant of the dopamine beta-hydroxylase (DBH) gene, although this finding is based on a very small number of subjects. To our knowledge, the contribution of other dopamine-related genes to orienting bias has not been reported.

In this study, we investigated the association of three functional polymorphisms of DA-regulating genes with orienting bias, a phenotype related to striatal dopamine asymmetry among healthy adults. In view of the above-mentioned finding regarding the role of the dopamine D2 receptor (DRD2) in orienting bias, we examined polymorphisms of the Taq1A (rs1800497) SNP, located near DRD2. Considering the inconsistent findings (reported above) relating orienting asymmetry in adults to the 3′ untranslated region of the VNTR of the DAT gene (DAT1), we also analyzed this variant. Lastly, we genotyped the Catechol-O-methyltransferase COMT exon variants Val/Met SNP (rs4680), which regulates the activity of the enzyme COMT (thus affecting DA availability).

2. Methods

2.1. Participants

Two hundred right-handed Jewish healthy adults (88 men, mean age: 25.3 ± 4.5) participated in this study. Only subjects without self-reported history of developmental disorders, head trauma or any psychiatric or neurological disease (including ADHD) were included. All had normal or corrected-to-normal visual acuity and were native Hebrew speakers. Subjects received monetary compensation for their time or credit points for participation. The study was approved by the institute's ethics committee, and all participants gave a written informed consent.

2.2. Grayscale task

Orienting bias was assessed using the computerized version of the greyscales task, a validated measure of orienting bias in healthy individuals (Nicholls, Bradshaw, & Mattingley, 1999), as described by Tomer et al. (2013). Briefly, this task requires participants to judge which of 2 brightness gradients (greyscales) appears darker overall. Each stimulus pair includes one greyscale shaded from black on the left to white on the right and one greyscale shaded in the reverse direction. The horizontal midlines of the stimuli are aligned with the center of the display screen, and the stimuli are aligned vertically (one above the other) such that choices (top vs. bottom) are orthogonal to the direction of the gradients, reducing the potential influence of response biases. Each pair of stimuli is presented on the screen until a response is made and maximally for 4 s. Following a practice block of 12 trials, a "test" block of 72 trials is presented, in which one stimulus is only slightly darker than the other. Without any notice or break, they then continue to complete a "bias" block of 72 trials in which the greyscales within a pair are identical in overall luminance, but left–right mirror reversed. Participants are asked to align their midlines with the center of the screen, and to press the up or down arrow key to indicate the top or bottom rectangle, respectively. Accuracy of response was stressed as important rather than speed, but participants were told to respond while the stimuli were present on the screen. Responses were categorized as either "left" or "right" according to whether participants selected the rectangle that was dark on its left or right side, respectively.

2.3. Genotyping

Participants provided buccal cells by rinsing their mouth with 20 ml of "Aquafresh" and then the mouthwash was poured into sterile tubes. The samples were stored at 4 °C, until DNA was extracted using the Master Pure kit (Epicentre, Madison WI). Genotyping was performed at the genetic laboratory of the S. Herzog Memorial Hospital Jerusalem, Israel. The VNTR of the DAT1 was characterized using the PCR amplification procedure with the following primers: F5′-TGTGGTGTAGGGAACGGCCTG-3′; R5′-CTTCCTGGAGGTCACGGCTCA-3′. PCR reactions were performed using 5 μl Master Mix (Thermo scientific), 2 μl primers (.5 μM), .6 μl Mg/Cl2 (2.5 mM), .4 μl DMSO 5% and 1 μl of water to total of 9 μl total volume and an additional 1 μl of genomic DNA was added to the mixture. All PCR reactions were employed on a Biometra T1 Thermocycler (Biometra, Güttingem, Germany). PCR reaction conditions are as follows: preheating step at 94.0 °C for 5 min, 34 cycles of denaturation at 94.0 °C for 30 s, reannealing at 55 °C for 30 s and extension at 72 °C for 90 s. The reaction proceeded to a hold at 72 °C for 5 min. All reaction mixtures were electrophoresed on a 3% agarose gel (AMRESCO) with ethidium bromide to screen for genotype. Both the Val158Met of the COMT gene (rs4680) and the DRD2 Taq1A (rs1800497) SNPs were genotyped using high resolution melt analysis (Liew et al., 2004) as previously described (Shalev et al., 2009). Quality control of genotyping was performed with additional genotyping of selected samples by the SNaPshot procedure.

2.4. Statistical analysis:

2.4.1. Assessment of orienting bias

Based on the behavioral data from the "bias" block, an asymmetry index (AI) was calculated for each subject: AI=(number of right responses−number of left responses)/total. The values of this index can vary between −1.0 and +1.0, with negative scores indicating a leftward bias and positive scores indicating a rightward bias. Participants were divided into bias groups (left bias and right bias), based on their AI. This latter categorical measure was used in the logistic regression analysis that examined the association between allele carriership status and left vs. right orienting bias, and for this analysis we excluded 3 participants who showed no bias. In order to keep the same sample for the analyses of both the categorical and continuous measures, we excluded these 3 participants from the analyses of the AI, and the Results section describes the results based on a sample of 197 participants. However, we also carried out the analyses of the continuous AI on the full sample including the 3 participants who did not show any bias (AI=.0). There were no differences between the analyses based on this sample [$n=200$], and the results reported below in Section 3.