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# COGNITIVE NEUROSCIENCE

# The influence of dopamine-related genes on perceptual stability

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#### Abstract

Bistable perception is the spontaneous and automatic alternation between two different perceptual states that occurs when sensory information is ambiguous. Perceptual alternation rates are robust within individuals but vary substantially between individuals. Slowed perceptual switching has been consistently reported in patients with bipolar disorder (BPD) and has been suggested as a trait marker for this disease. Although genetic factors have been implicated in both BPD and bistable perception, the underlying biological mechanisms that mediate the observed perceptual stability in BPD remain elusive. Here, we tested the effect of two variable number tandem repeat (VNTR) polymorphisms in DRD4 and DAT1 (SLC6A3), both candidate genes for BPD with functional impact on dopaminergic neurotransmission, on bistable perception in a cohort of 108 healthy human subjects. The BPD risk allele DRD4-2R was significantly associated with slow perceptual switching. There was no effect of DAT1 genotype on bistable perception. Our findings indicate that genetic differences in dopaminergic neurotransmission linked to BPD also account for interindividual variability in bistable perception, thus providing a genetic basis for perceptual stability as a trait marker of BPD.

# Introduction

Ambiguous sensory information induces spontaneous alternations between two conscious perceptual states. These alternations between differing perceptual interpretations are commonly referred to as bistable perception and are evoked by various ambiguous stimuli such as figures that involve ambiguity in depth-ordering of visual patterns or binocular rivalry. An interesting feature of bistable perception is that the rate of perceptual alternations is rather stable within individuals (George, 1936; Pettigrew & Miller, 1998; Miller et al., 2003) but highly variable between individuals (Kleinschmidt et al., 2012). This inter-individual variability in perception has recently been linked to variability in brain structure using magnetic resonance imaging, showing that switch rates during bistable perception are related to focal grey matter differences in parietal cortex and to differences in structural connectivity between brain regions (Kanai et al., 2010, 2011; Genç et al., 2011). Moreover, recent twin and association studies have demonstrated a substantial genetic contribution to the switching dynamics in bistable perception. Additive genetic effects have been shown to account for 52% of inter-individual variability in perceptual rivalry (Miller et al., 2010; Kondo et al., 2011; Shannon et al., 2011).

An intriguing example of the variability in perceptual alternations across individuals has been initially reported by Hunt & Guilford

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(1933), who found that, in patients with bipolar disorder (BPD), switches between the two alternative perceptual states occur less frequently than in healthy individuals. This increased perceptual stability has been consistently replicated in euthymic patients with BPD, whereas bistable perception is unaltered in other psychiatric conditions (Eysenck, 1952; Philip, 1953; Pettigrew & Miller, 1998; Miller et al., 2003; Krug et al., 2008; Nagamine et al., 2009). Given the high heritability of BPD (McGuffin et al., 2003; Kieseppa, 2004), Ngo et al. (2011) have further proposed perceptual switch rates in bistable perception as an endophenotype for BPD. Endophenotypes are subclinical traits that are assumed to be linked more closely to the pathophysiology of complex psychiatric disorders such as BPD than the full-blown disorder itself (Gottesman & Gould, 2003; Puls & Gallinat, 2008). Along these lines, investigating the potential BPD endophenotype of perceptual stability in healthy individuals offers a powerful approach for studying the neurobiological bases of BPD in the absence of confounding factors such as medication. Here, we exploited this suggested BPD endophenotype of perceptual stability as a model for systematically addressing the biological mechanisms and thus the specific genetic substrate underlying inter-individual differences in bistable perception.

We hypothesised that polymorphisms in dopamine-related candidate genes for BPD might account for inter-individual differences in bistable perception in healthy individuals. Dopaminergic neurotransmission seems to play a crucial role in the neurobiology of both bistable perception and BPD, as indicated by evidence from pharmacological and functional neuroimaging studies (Phillipson & Harris, 1984; Calvert *et al.*, 1988; Cousins *et al.*, 2009; Anand *et al.*, 2011). Genetic differences in dopamine neurotransmission have been associated with BPD, with the dopamine receptor D4 (DRD4) and the dopamine transporter 1 (DAT1) (SLC6A3) being considered the most promising dopamine-associated candidate genes (Muglia *et al.*, 2002; Ohadi *et al.*, 2007; Serretti & Mandelli, 2008; Pinsonneault *et al.*, 2011). Both DRD4 and DAT1 harbor variable number tandem repeat (VNTR) polymorphisms that functionally impact dopamine neurotransmission (Asghari *et al.*, 1995; Miller & Madras, 2002; VanNess *et al.*, 2005). To probe whether dopaminergic neurotransmission provides a link between bistable perception and BPD, we investigated the effect of the VNTR polymorphisms in DRD4 and DAT1 on perceptual phase durations of a rotating sphere with ambiguous rotation direction.

# Materials and methods

#### Participants

One hundred and twelve healthy volunteers aged 18-44 years (mean  $\pm$  SD age, 25.08  $\pm$  4.59 years; 54 men), with normal or corrected-to-normal vision, gave informed written consent to participate in the study, which was approved by the Ethics committee of the Charité University Berlin and was in accordance with the ethical standards of the 1964 Declaration of Helsinki. None of the participants reported a past history of psychiatric problems, neurological diseases or head injury as determined by screening in a telephone interview. To further ensure the exclusion of individuals with psychiatric disorders the Structured Clinical Interview for DMS-IV-Axis I was performed with all participants prior to participation. One participant was excluded from further analysis due use of to psychoactive medication. Three further participants were excluded because they did not perform the behavioral task as instructed, leaving a sample of 108 healthy participants. The majority of participants were of self-identified Caucasian descent (96% of the cohort), rendering confounding effects due to population stratification unlikely.

# Bistable perception task

The kinetic-depth effect initially described by Wallach & O'Connell (1953) was used to create a dot-kinematogram that appears as a rotating sphere that is perceptually ambiguous with respect to its three-dimensional structure and therefore its rotation direction. This virtual sphere was rotating around a central vertical axis (diameter 4.1° of visual angle, rotation speed 60°/s or 1/6 cycles per second). Four-hundred and fifty randomly distributed yellow squares ('dots'; maximum size  $0.2^{\circ} \times 0.2^{\circ}$  of visual angle) were projected onto the surface of a virtual sphere and displayed with a central white cross for fixation (size 0.2° of visual angle) on a black background. Animation frames were updated every 40 ms, and a sequence of 200 frames (8000 ms) was looped repeatedly to produce continuous motion. Dot lifetime was 25 display frames (1000 ms). The sphere was framed by a white square (size 4.2° of visual angle). In order to stabilise three-dimensional appearance, the dot density around the fixation cross was reduced.

Visual stimuli were presented using Matlab (MathWorks Inc.) and Cogent 2000 toolbox (http://www.vislab.ucl.ac.uk/cogent.php). Participants viewed the stimulus from a distance of 60 cm through a mirror stereoscope, as the present experiment was part of a larger study in which the mirror stereoscope was used to produce stereoscopic vision. In the experiment reported here, no stereoscopic image cues were used. Through the mirror stereoscope the identical stimulus was presented to both eyes using a desktop screen (resolution 1024  $\times$  768 pixels), yielding binocular fusion. A chin-rest was used to minimise head movements.

Each of the five experimental blocks comprised 4 min of continuous stimulus presentation. Observers reported switches of the rotation direction of the ambiguous sphere by pressing one of three keys on a computer keyboard. They were instructed to press the leftor the right-arrow key according to the perceived motion direction of the sphere's front surface, and the down-arrow key in cases of unclear perceptual states. Participants were instructed to report each reversal as rapidly as possible.

During the whole experiment participants' eye movements were recorded using a video-based eye tracker (sampling rate 250 Hz, spatial resolution 0.05°; Cambridge Research Systems, UK).

# Working memory task

Dopamine-dependent working memory processes have been related to both bistable perception (Leopold, 1999; Sterzer & Rees, 2008; Sterzer et al., 2009) and BPD (Meyer-Lindenberg et al., 2002, 2005; Balanzá-Martínez et al., 2008). To test whether working memory might mediate the hypothesised link between bistable perception and dopaminergic neurotransmission, participants performed a standard working memory N-back task (Kirchner, 1958). Participants were presented with a sequence of numbers and were required to press a button when the number they saw equaled the number seen two numbers before (two-back condition). In the control condition, participants had to respond with a button press each time they saw the number zero (zero-back condition). Stimuli were presented using Matlab (MathWorks Inc.) and Cogent 2000 toolbox (http://www.vislab.ucl.ac.uk/cogent.php). White numbers (1-9) were displayed on a grey background for 500 ms with interstimulus durations of 900 ms. We used a standard block design with a randomised order of three blocks of the two-back and the zero-back conditions, respectively, each containing 44 trials and six hits. Working memory performance was calculated as d-prime: (Z(hit rate) - Z(false alarm rate)) in the two-back task, a measure that takes into account both hits and false alarms. Six participants were excluded from the analyses of working memory performance due to either not completing the task or to a hit rate of < 10% in the zero-back or two-back task.

#### Control for eye movements

Dopamine has been critically involved in the motor control of eye movements (e.g. Kato et al., 1995). To test for the possibility that differences in eye movements might underlie the hypothesised effect of dopaminergic genes on bistable perception, eye movements were recorded during the bistable perception task using a video-based eye tracker (MK2; High-Speed Camera, Cambridge Research Systems Ltd.; 100 Hz). Participants were instructed to maintain fixation throughout the experiment. To relate eye movements to bistable perception and genotype, a measure of fixation quality was calculated for each participant. The one-dimensional time courses of gaze positions were linearly de-trended. Gaze positions were then transformed into a two-dimensional histogram of their Helmholtz coordinates of a resolution  $1 \times 1$  arcmin and smoothed with a two-dimensional Gaussian kernel (full width at half maximum, six arcmin). Fixation quality was calculated as the area included by the contour line encompassing 95% of the eye positions. A smaller contour line area corresponds to better fixation whereas a larger area is indicative of larger overall eye movements. Participants in whom less than half of the gaze positions were tracked successfully were excluded from these control analyses.

# Genotyping

DNA was extracted from whole blood following a standard highsalt procedure. In the DRD4 the VNTR is characterised by 2-10 copies of a 48-bp repeat located in the third exon, with each repeat encoding for 12 amino acids. The VNTR in the 3' untranslated region of DAT1 is characterised by 3-11 repeats of a 40-bp sequence. Both polymorphisms were amplified using polymerase chain reaction (PCR) techniques with conditions previously published (Vandenbergh et al., 1992; Lichter et al., 1993). We used an ABI Capillary Electrophoresis Genetic Analyzer 3130 (Applied Biosystems, Foster City, CA, USA) for the fragment analysis of both VNTRs using the PCR product obtained with 5' fluorescently labeled primer with sequence previously published. Primers Fw 5' 6FAM-AGGACCCTCATGGCCTTG and Rv 5' GCGACTACG TGGTCTACTCG were used to obtain the VNTR fragment in DRD4. The VNTR in DAT1 was amplified using the following primers: Fw 5' NED-TGTGGTGTAGGGAACGGCCTGAG and Rv 5' CTTCCTGGAGGTCACGGCTCAAGG. Due to technical problems, genotyping could not be performed in four and three participants, respectively, for the DRD4-VNTR and the DAT1-VNTR.

#### Statistical analyses

Statistical analyses were conducted using SPSS Student version 14.0. and Matlab (MathWorks Inc.). Genepop 4.0.10 was used for testing whether genotype distribution was in Hardy-Weinberg equilibrium; ANCOVAS were not performed for low genotype frequencies (≤ 5%: DRD4-3R, -8R; DAT1-8R, -11R). To preclude confounding effects of demographic variables, we first analysed the influence of sex and age on genotype (chi-square test and ANOVA, respectively) and phenotype distributions (ANCOVA). When significant (P < 0.05), demographic variables were included as covariates in the main analyses of genotype associations using analysis of covariance (ANCOVA). As we tested the effects of five different genotypes (DAT1-9R and -10R; DRD4-2R, -4R and -7R) on mean perceptual phase durations, the alpha-level for statistical significance of P < 0.05 (two-tailed) was adjusted to P < 0.01 according to Bonferroni-correction for multiple comparisons. To estimate the effect size of the differences in mean phase durations between genotype-groups, Cohen's d was calculated as the difference between the means of groups divided by the pooled standard deviation (Kenny, 1987).

#### Results

# Bistable perception

The average mean  $\pm$  SEM perceptual phase duration during bistable perception of the ambiguous sphere was 9.92  $\pm$  0.45 s. As expected, mean phase durations varied widely across participants (range 3.0–24.5 s). The distribution of perceptual phase durations did not differ significantly from a gamma distribution (l = 0.52, r = 1.90; P = 0.46; Kolmogorov–Smirnov test), as previously reported for bistable phenomena (e.g. Levelt, 1967; Borsellino *et al.*, 1972). An ANCOVA with the independent variables sex and age revealed a significant main effect of age ( $F_{104} = 9.72$ , P = 0.002), but no significant effect of sex ( $F_{104} = 1.88$ , P = 0.173) nor a sex × age interaction ( $F_{104} = 1.05$ , P = 0.308) on mean phase duration. Therefore, age was included as a covariate of no interest in all subsequent genotype analyses.

#### Gene effects on bistable perception

Allele and genotype frequencies in our sample were similar to previously published data (Chang *et al.*, 1996; Bertolino *et al.*, 2006). Genotype data were obtained for the DAT1 VNTR and the DRD4 VNTR multiallelic variants, with highest frequencies for the 9 and 10 repeat allele as commonly observed for the DAT1 VNTR (10R, 0.781; 9R, 0.200; 8R, 0.005; 11R, 0.014); and the 4, 7 and 2 repeat alleles for the DRD4 variant (4R, 0.668; 7R, 0.154; 2R, 0.111; 8R, 0.005; 3R, 0.009). For both markers, genotype distribution did not differ significantly from Hardy–Weinberg Equilibrium (P > 0.05). There were no significant differences of age, sex or ethnicity between the genotype groups (Table 1).

To examine the effect of DAT1 and DRD4 VNTRs on the temporal dynamics of bistable perception we performed an ANCOVA with dominant genotype models for the most frequent (> 5%) repeat alleles as independent variables and mean phase durations as dependent variable. As there was a significant main effect of age on mean phase duration (see above), age was entered as a covariate of no interest. Results for the DRD4 VNTR revealed a significant main effect for the DRD4-2R ( $F_{101} = 7.08$ , P = 0.009; Fig. 1B), but no effect for DRD4-7R ( $F_{101} = 0.00$ , P = 0.999) nor for the DRD4-4R  $(F_{101} = 0.32, P = 0.574)$ . The mean  $\pm$  SEM phase durations were on average 34% longer in DRD4-2R carriers than in DRD4-2R noncarriers (12.47  $\pm$  1.19 vs. 9.29  $\pm$  0.49 s), indicating that the DRD4-2R allele was associated with slowed perceptual switching. The effect size of this result equals to d = 0.69 (Cohen's d), indicating a medium (d = 0.5) to large (d = 0.8) effect (Kenny, 1987). After exclusion of three potential outliers that deviated > 2.5 SD from the mean, the main effect for the DRD4-2R remained significant ( $F_{98} = 7.12$ , P = 0.009) and, again, mean phase durations were longer in DRD4-2R carriers than in DRD4-2R non-carriers (on average 32%; Fig. 1B). For the DAT1 VNTR, none of the two most frequent repeat alleles demonstrated a significant main effect on mean phase durations in our sample (DAT1-9R,  $F_{102} = 0.26$ , P = 0.610; DAT1-10R,  $F_{102} = 0.007$ , P = 0.932).

#### Working memory and bistable perception

As working memory processes have been associated with both bistable perception (Leopold, 1999; Sterzer *et al.*, 2009) and BPD (Meyer-Lindenberg *et al.*, 2002, 2005; Balanzá-Martínez *et al.*, 2008), we next investigated whether working memory performance might mediate the observed association between the DRD4-2R and perceptual switch rates. We found no significant correlation between

TABLE 1. Statistics of the relationships of DRD4-VNTR and DAT1-VNTR to demographic variables

Genotype	n	Demographic variables						
		Age			Sex		Ethnicity	
		F	df	Р	$\chi^2$	Р	$\chi^2$	Р
DRD4								
DRD4-2R	104	0.33	102	0.564	1.85	0.173	0.93	0.335
DRD4-4R	104	3.02	102	0.085	0.42	0.514	0.65	0.421
DRD4-7R	104	0.44	102	0.510	0.01	0.923	1.61	0.205
DAT1								
DAT1-9R	105	0.13	103	0.719	0.22	0.642	1.59	0.207
DAT1-10R	105	2.35	103	0.128	1.08	0.301	0.24	0.625



FIG. 1. Temporal dynamics of bistable perception and dominant genetic models for the DRD4-2R. (A) Schematic illustration of the behavioral experiment. Bistable perception was induced by continuous presentation of a dot kinematogram that can be perceived as a sphere either rotating leftward or rotating rightward. During the stimulus presentation participants reported perceptual reversals via key presses. (B) Mean phase durations of participants grouped according to 2R-DRD4-VNTR genotypes, with DRD-2R carriers (N = 19) and DRD-2R non-carriers (N = 85). Solid lines indicate the average mean phase duration in each genotype group and dashed lines indicate average mean phase durations in genotype groups after exclusion of potential outliers that deviated > 2.5 SD from the entire group mean (grey dots). Two-tailed ANCOVAS revealed a significant main effect of 2R-DRD4-VNTR genotypes for all participants (P = 0.009) and without outliers (P = 0.007).

working memory performance measured as the *d*-prime in the twoback task and mean phase duration in the bistable perception task (r = 0.03, P = 0.729, Pearson's correlation, N = 105). There was a trend-wise main effect of DRD4-2R genotype on working memory performance in our sample ( $F_{99} = 3.17$ , P = 0.078). However, there was still a significant main effect for the DRD4-2R on mean phase duration when the two-back *d*-prime was added as a covariate ( $F_{97} = 8.89$ , P = 0.004), indicating that working memory performance did not account for the observed association of the DRD4-2R allele with mean phase duration.

# Eye movements, bistable perception and genotype

Dopaminergic neurotransmission has been consistently implicated in the control of eye movements (e.g. Kato *et al.*, 1995). To investigate the possibility that the found association of DRD4 genotype and perceptual stability was mediated by inter-individual differences in eye movements, we analysed the eye tracking data recorded during the bistable perception task. Valid eye tracking data for the entire experiment could be obtained for 53 participants. In this sub-sample, fixation quality was not significantly correlated with mean phase duration (r = 0.16, P = 0.24; product–moment correlation), suggesting that inter-individual differences in eye movements were not related to perceptual stability. Furthermore, fixation quality did not differ between DRD4-2R genotype groups ( $F_{52} = 0.44$ ; P = 0.51), rendering it further unlikely that the reported difference in perceptual stability between DRD4-2R carriers and DRD4-2R non-carriers was mediated by differences in eye movements.

# Discussion

In the present study we sought to elucidate the neurobiological basis for the inter-individual differences in bistable perception by utilising the well-established association of BPD with its potential endophenotype of slowed perceptual switches during bistable perception. To test whether genetic differences in dopaminergic neurotransmission might provide the neurobiological link between BPD and bistable perception, we selected two functional multiallelic VNTR polymorphisms in the most promising dopamine-related BPD candidate genes DAT1 and DRD4 (Serretti & Mandelli, 2008), and examined genotype effects on the temporal dynamics of bistable perception in healthy participants. Carriers of the DRD4-2R showed slower perceptual switching than did non-carriers, with a medium to large effect size, whereas the presence of the ancestral allele DRD4-4R or the DRD4-7R did not have a significant effect on bistable perception. Although this single finding awaits replication and should therefore be regarded as preliminary, it is noteworthy that a large-scale meta-analysis previously revealed an increased incidence of the DRD4-2R in patients with BPD, which was not found for the DRD4-7R or the DRD4-4R (López León et al., 2005). Consequently, our finding of an exclusive association of the DRD4-2R allele with prolonged mean phase duration is in agreement with the well-established finding of slowed perceptual switching in patients with BPD (Hunt & Guilford, 1933; Pettigrew & Miller, 1998; Krug et al., 2008; Nagamine et al., 2009).

The DRD4-VNTR repeats (most common 2R, 4R and 7R) reside in exon 3 and encode a proline-rich protein domain within the third cytoplasmic loop of the DRD4 receptor. An impact on dopamine transmission of the different repeat alleles results from their different pharmacological potencies to inhibit cAMP formation upon dopamine binding: the receptor potency to inhibit cAMP formation upon dopamine binding is highest for DRD4-4R and lowest for DRD4-7R, while DRD4-2R is associated with an intermediate cAMP inhibition potency (Asghari *et al.*, 1995). It has been suggested that small differences in dopaminergic function affect cognitive functions along an inverted-U-shaped curve, as both insufficient and excessive dopaminergic signalling can impair cortical function (Meyer-Lindenberg *et al.*, 2002). A similar dose–effect relation might apply to bistable perception, as the same frontal brain areas have been suggested as being critically involved in both bistable perception and higher-order cognitive processes (Leopold, 1999; Sterzer *et al.*, 2009) and DRD4 is expressed at high levels in frontal cortex (Oak *et al.*, 2000). Thus, intermediate dopaminergic signalling, which results from the moderate inhibition potency mediated by DRD4-2R, may be critical for the stabilisation of perception, thereby giving rise to relatively slowed switching during bistable perception.

Although dopamine-dependent working memory processes involve a similar network of frontoparietal brain regions as bistable perception (Leopold, 1999; Sterzer *et al.*, 2009) and have been found to be impaired in BPD (Meyer-Lindenberg *et al.*, 2002, 2005; Balanzá-Martínez *et al.*, 2008), we found no evidence for working memory processes underlying the observed association between dopaminergic neurotransmission and bistable perception. There was no significant correlation between working memory performance and perceptual stability, and working memory performance did not account for the effect of DRD4 genotype on perceptual stability. Although these negative findings should be interpreted with care, they cast doubt on the notion that similar brain mechanisms might underlie working memory and bistable perception.

Dopaminergic neurotransmission plays a crucial role in the control of eye movements (e.g. Kato *et al.*, 1995). This raises the possibility that the reported effect of DRD4 genotype on bistable perception was mediated by inter-individual differences in eye movements or, more specifically, in the ability to maintain visual fixation. However, we found no indication of a relationship between the quality of visual fixation and DRD4 genotype or mean phase duration during bistable perception. It should be noted that these negative results stem from a smaller sub-sample and should therefore be treated with caution. Nevertheless, our current data do not provide any evidence that interindividual differences in eye movements do account for the found effect of DRD4 genotype and perceptual stability.

We found no effect of DAT1-VNTR genotype on the temporal dynamics of bistable perception. This VNTR polymorphism consists of a 40-bp sequence that most frequently occurs as 9 or 10 tandem repeat units. In contrast to the DRD4-VNTR, which resides directly in a coding region and is translated into a functional domain of the receptor protein, the DAT1-VNTR is located within the 3'-untranslated region. Therefore, functional impact is expected at the level of transcription efficiency, mRNA stability or subcellular localisation. However, evidence regarding the exact functional consequences of the DAT1-VNTR is inconclusive. Some functional in vitro and in vivo studies have related the DAT1-10R allele to greater gene expression and increased mRNA levels (Miller & Madras, 2002; VanNess et al., 2005) while others have associated the DAT1-9R allele with higher levels of striatal DAT1 availability (Jacobsen et al., 2000; Michelhaugh et al., 2001; van Dyck et al., 2005). Moreover, in vivo studies found no effect of the VNTR polymorphism on DAT1 density (Martinez et al., 2001), protein availability or function (Lynch et al., 2003; Mill et al., 2005). Given these discrepancies, the present negative findings for the DAT1 VNTR might be explained by additional functional polymorphisms in linkage disequilibrium to the VNTR (Ueno et al., 1999; Miller et al., 2001; Mill et al., 2005). A recent association and expression study with various polymorphisms within the DAT1 gene provided evidence for a functional SNP within the 3' untranslated region, which revealed an association with BPD in two independent cohorts (Pinsonneault et al., 2011). Future studies should investigate other functional polymorphisms within the dopamine transporter gene in relation to bistable perception to further explore its potential role in perceptual stability.

Taken together, our findings suggest that a functional polymorphism in dopamine receptor D4 gene previously implicated in BPD is associated with inter-individual differences in perceptual stability. They thus provide a promising starting point for further research on the role of dopamine signaling in the neurobiology of both BPD and perception, and pave the way for understanding endogenous mood oscillations in BPD and endogenous percept oscillations during bistable perception within a common framework.

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#### Abbreviations

ANCOVA, analysis of covariance; BPD, bipolar disorder; DAT1, dopamine transporter 1; DRD4, dopamine receptor D4; VNTR, variable number tandem repeat.

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