The dopamine D1 receptor gene is associated with negative schizotypy in a non-clinical sample.

To The Editors:
The concept of a psychosis continuum, based on the notion that individual psychotic symptoms and subclinical schizotypic traits occur in the general population, has gained much support over recent years. Accumulating evidence suggests considerable overlap between schizotypy and schizophrenia, not simply at a phenomenological level but also in relation to cognitive, perceptual, neuropathological, psychopharmacological, environmental and genetic risk factors (Ettinger et al., 2014). In relation to psychopharmacological factors, the dopamine hypothesis of schizophrenia is longstanding and broadly suggests that positive symptoms may be partially attributable to changes in dopamine synthesis, release and a failure to regulate dopamine D2-like receptors, predominantly at a subcortical level, whereas, deficient dopaminergic transmission at D1 receptors in the prefrontal cortex (PFC) may contribute to the cognitive and negative symptoms of schizophrenia (Laruelle, 2014). The role of dopamine dysregulation in schizotypy is less established; however, there are pharmacological studies supporting a role for dopamine in schizotypy, as well as preliminary research linking polymorphisms in dopamine regulating genes to schizotypy (Colizzi et al., 2015; Grant et al., 2013; Taurisano et al., 2014). The DRD1 gene encodes the D1 subtype of dopamine receptor. One single nucleotide polymorphism (SNP), rs4532 (or Ddel), results in an A to G transition in the 5′ untranslated region (5′UTR) at bp-48 (A-48G) and has been described as a genuine, disease modifying risk allele in schizophrenia in a systematic meta-analysis (Allen et al., 2008).

We explored the association between rs4532 DRD1 and schizotypy in a non-clinical sample of 127 healthy adults (50% male; age \( M = 33.24 \) years, \( SD = 13.22 \)). Ethnicity was assessed using self-report (81% Caucasian; 12.5% Asian; 8% Hispanic; 4.7% ‘Other’). Exclusion criteria were current Axis I mental illness, neurological disorder or other serious medical condition, brain injury, current substance dependence or a first degree biological relative with psychosis. To assess schizotypy, participants completed the 104 item self-report Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) scale (Mason and Claridge, 2006). Subscale scores reflecting factors of schizophrenia were calculated: Unusual Experiences or positive schizotypy; Introvertive Anhedonia or negative schizotypy, and Cognitive
Disorganisation. Participants also donated a blood sample for genetic analyses. Informed written consent was provided in accordance with The Alfred Hospital ethics committee requirements.

DNA was extracted from whole blood using QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany) and SNP assays were designed using the Sequenom Assay Design Suite 1.0 software (Sequenom, San Diego CA). Genotyping for rs4532 (CC, CT, TT) was carried out using the MassARRAY system (Sequenom, San Diego CA) as per the manufacturer’s standard protocols. The MassArray platform relies on a primer extension reaction in combination with a mix of mass-tagged dideoxy-nucleotides (iPlex Gold chemistry) to generate a pool of oligo products that are analysed by chip-based matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF). Adherence to Hardy-Weinberg equilibrium and allele frequency were assessed to ensure validity of the results.

The relationships between genotype and demographic characteristics were analysed using one-way analysis of variance (ANOVA) or chi square tests as appropriate. O-LIFE subscale scores were entered into three separate ANCOVAs with DRD1 genotypes (CC, CT, TT) entered as an independent variable, and age, ethnicity and sex entered as covariates. Following bonferroni corrections, a p-value of 0.02 was considered significant.

The overall mean scores for the schizotypy subscales were: Unusual Experiences M= 5.83, SD= 5.10, range: 0 - 25; Introvertive Anhedonia M = 5.07, SD = 4.47, range: 0- 20; Cognitive Disorganisation M = 7.98, SD = 5.39, range: 0-20. Genotype-specific demographics indicated no significant group differences with respect to age F (2,124) =0.63, p=0.53, ethnicity χ² (6 N= 127) =5.68, p=.46 or sex χ²(2 N=127) =1.38, p=.50. ANCOVAs revealed a significant main effect for DRD1 rs4532 on Introvertive Anhedonia F(2,121)=4.81, p=.010, pη² = .074, but not Cognitive Disorganisation F(2,121)=1.84, p=.16, pη² = .029 or Unusual Experiences F(2,121)=0.32, p=.73, pη² = .005.

This is the first report of an association between the gene that encodes the dopamine D1 receptor and schizotypy. Importantly, this study revealed that the factors of schizotypy resembling the negative symptoms of schizophrenia are associated with the minor rs4532/C allele of 4532 SNP on the DRD1 gene. This finding extends previous research implicating the DRD1 SNP as a risk gene for schizophrenia (Allen et al., 2008; although we note that a
recent multi-stage genome wide association study that identified 108 schizophrenia associated genetic loci did not implicate *DRD1*, Schizophrenia Working Group of the Psychiatric Genomics, 2014), as well as research suggesting a role for dopamine in negative symptom schizotypy (Ettinger et al., 2013; Grant et al., 2013).

Previous research suggests that the major allele of *DRD1* (i.e. the T allele) increases gene expression, potentially via linkage disequilibrium with rs686 located in the 3’UTR (Huang et al., 2008). The minor rs4532/C allele (potentially associated with a decrease in D1 expression) has been associated with a large set of phenotypes including addictive behaviours (e.g. nicotine addiction; Huang et al., 2008). In relation to schizophrenia, the minor rs4532/C allele has been associated with treatment resistance (e.g. Ota et al., 2012).

Our findings that the minor rs4532/C allele of the *DRD1* gene is associated with increased scores on schizotypy factors that resemble negative symptoms in clinically diagnosable schizophrenia suggest that schizotypy is potentially linked to reduced D1 expression. This fits well with theories that dysregulation in dopaminergic transmission at D1 receptors in the PFC is associated with the negative symptoms of schizophrenia (Laruelle, 2014). For example, a D1-antagonist (SCH 39166) has been shown to significantly reduce negative symptoms without impacting positive symptoms in schizophrenia (Den Boer et al., 1995). Furthermore, a positron emission tomography study of D1 receptors in drug-free patients with schizophrenia revealed a reduction in D1 receptor binding in the PFC that correlated with negative symptom severity and cognitive deficits (Okubo et al., 1997). Hence, there is some evidence linking dopaminergic transmission at D1 receptors to the negative symptoms associated with schizophrenia.

These results should be interpreted with caution as they are limited by the small sample size, as well as the use of a single SNP. Furthermore, our mean schizotypy scores for the Unusual Experience and Cognitive Disorganisation subscales were lower than other published norms (e.g. Mason and Claridge, 2006). Nevertheless, these positive, albeit preliminary findings encourage further studies with larger sample sizes (with a broader range of schizotypy scores) to explore schizotypy-relevant correlates of the *DRD1* gene with greater coverage.

To our knowledge, this is the first study demonstrating an association between a polymorphism in the *DRD1* gene and schizotypy. The findings from this study add to the
growing body of evidence that schizotypy and schizophrenia share a common biological basis related to genetic susceptibility, as well as shared pathological processes in the sense of dysregulation of dopamine-functioning.
References


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