

# Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <http://orca.cf.ac.uk/125021/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

D'Ambrosio, Enrico, Dahoun, Tarik, Pardinas, Antonio F., Veronese, Mattia, Bloomfield, Michael A.P., Jauhar, Sameer, Bonoldi, Ilaria, Rogdaki, Maria, Froudish-Walsh, Sean, Walters, James T. R. and Howes, Oliver D. 2019. The effect of a genetic variant at the schizophrenia associated AS3MT/BORCS7 locus on striatal dopamine function: A PET imaging study. *Psychiatry Research: Neuroimaging* 291 , pp. 34-41. 10.1016/j.psychresns.2019.07.005 file

Publishers page: <http://dx.doi.org/10.1016/j.psychresns.2019.07.005>  
<<http://dx.doi.org/10.1016/j.psychresns.2019.07.005>>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



# The effect of a genetic variant at the schizophrenia associated AS3MT/BORCS7 locus on striatal dopamine function: a PET imaging study

Enrico D'Ambrosio<sup>a,b</sup>, Tarik Dahoun<sup>c,d,e</sup>, Antonio F. Pardiñas<sup>f</sup>, Mattia Veronese<sup>g</sup>, Michael A. P. Bloomfield<sup>c,h,i,j</sup>, Sameer Jauhar<sup>r<sup>a</sup>,k</sup>, Ilaria Bonoldi<sup>a,k</sup>, Maria Rogdaki<sup>a,c</sup>, Sean Froudish-Walsh<sup>l</sup>, James T.R. Walters<sup>f</sup>, Oliver D. Howes<sup>a,c,d,k\*</sup>

## Affiliations

- a. Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, SE5 8AF, UK
- b. Psychiatric Neuroscience Group, Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari 'Aldo Moro', Bari, Italy
- c. Psychiatric Imaging Group, MRC London Institute of Medical Sciences, Hammersmith Hospital, London, W12 0NN, UK
- d. Institute of Clinical Sciences, Faculty of Medicine, Imperial College London, Hammersmith Hospital, London, W12 0NN, UK
- e. Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, OX37 JX, UK
- f. MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK
- g. Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, SE5 8AF, UK
- h. Translational Psychiatry, Research Department of Mental Health Neuroscience, Division of Psychiatry, University College London, Maple House, 149 Tottenham Court Road, London W1T 7NF
- i. Clinical Psychopharmacology Unit, Research Department of Clinical, Educational & Health Psychology, University College London, 1-19 Torrington Place, London WC1E 7HB
- j. NIHR University College London Hospitals Biomedical Research Centre, Maple House, 149 Tottenham Court Road, London W1T 7DN
- k. South London and Maudsley NHS Trust, London, UK
- l. Center for Neural Science, New York University, New York, 10003, USA

**\* Corresponding Author:**

Professor Oliver D Howes

Box 67, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, SE5 8AF, UK; tel: +44 2083833446; e-mail: oliver.howes@kcl.ac.uk

**Abstract word count:** 200 words

**Manuscript word count:** 3377 words

**Number of figures:** 2

**Number of tables:** 1

## Abstract

One of the most statistically significant *loci* to result from large-scale GWAS of schizophrenia is 10q24.32. However, it is still unclear how this locus is involved in the pathoetiology of schizophrenia. The hypothesis that presynaptic dopamine dysfunction underlies schizophrenia is one of the leading theories of the pathophysiology of the disorder. Supporting this, molecular imaging studies show evidence for elevated dopamine synthesis and release capacity. Thus, altered dopamine function could be a potential mechanism by which this genetic variant acts to increase the risk of schizophrenia. We therefore tested the hypothesis that the 10q24.32 region confers genetic risk for schizophrenia through an effect on striatal dopamine function. To this aim we investigated the *in vivo* relationship between a GWAS schizophrenia-associated SNP within this locus and dopamine synthesis capacity measured using [<sup>18</sup>F]-DOPA PET in healthy controls. 92 healthy volunteers underwent [<sup>18</sup>F]-DOPA PET scans to measure striatal dopamine synthesis capacity (indexed as  $K_i^{cer}$ ) and were genotyped for the SNP rs7085104. We found a significant association between rs7085104 genotype and striatal  $K_i^{cer}$ . Our findings indicate that the mechanism mediating the 10q24.32 risk locus for schizophrenia could involve altered dopaminergic function. Future studies are needed to clarify the neurobiological pathway implicated in this association.

**Key words:** schizophrenia; 10q24.32; psychosis; dopamine synthesis capacity; PET; striatum; imaging

# 1 Introduction

Large-scale Genome-Wide Association Studies (GWAS) have identified a number of common genetic variations conferring risk for schizophrenia in human populations (Pardiñas et al., 2018; Ripke et al., 2014, 2013, 2011). Nevertheless, it remains challenging to assign the association signal at risk loci to specific genes or mechanisms, which is a requirement if genetic findings are to help elucidate the pathophysiology of the disorder. In this sense it is important to identify methods to investigate the biological pathways linked to risk loci and thus help identify potential pharmacological targets (Birnbaum and Weinberger, 2017; Schubert et al., 2014).

One of the best supported genome-wide significant loci from large-scale GWAS of schizophrenia is the 10q24.32 region (Duarte et al., 2016; Pardiñas et al., 2018; Ripke et al., 2014). Potential specific molecular mechanisms of genetic risk related to this locus have been recently identified. In particular, increased expression of BLOC-1 related complex subunit 7 (BORCS7) and of a novel arsenite methyltransferase isoform, namely AS3MT<sup>d2d3</sup>, have been found in the brains of patients with schizophrenia relative to controls (Li et al., 2016b). In the general population, the full isoform of arsenite methyltransferase is involved in arsenic metabolism (Sumi and Himeno, 2012), and arsenic toxicity has been implicated in central nervous system (CNS) dysfunction (Tyler and Allan, 2014) and psychosis (Ratnaike, 2003). However, the AS3MT<sup>d2d3</sup> isoform lacks arsenite methyltransferase activity (Li et al., 2016b); therefore a different, and still unknown, mechanism is likely to be implicated in the biological process leading to risk for schizophrenia.

The hypothesis that dopamine dysfunction underlies schizophrenia is one of the leading theories of the pathophysiology of the disorder (Abi-Dargham et al., 2000; Davis et al., 1991; Heinz et al., 2003;

Heinz and Schlagenhauf, 2010; Howes et al., 2015, 2012; Howes and Kapur, 2009; Laruelle and Abi-Dargham, 1999) and is supported by findings from genetic studies of the disorder through genome-wide significant association at a locus implicating the DRD2 dopamine receptor (Pardiñas et al., 2018; Ripke et al., 2014). Molecular imaging studies show evidence for presynaptic striatal dopamine dysfunction, in particular increased striatal dopamine synthesis and release capacity, in patients with schizophrenia (Abi-Dargham et al., 2009; Hietala et al., 1999; Howes et al., 2013, 2009; Jauhar et al., 2017a; Kumakura et al., 2007; Meyer-Lindenberg et al., 2002; Mizrahi et al., 2012; Reith et al., 1994) with a large effect size on meta-analysis (Cohen  $d = 0.79$ ) (Howes et al., 2012). Moreover, increased dopamine synthesis capacity is also reported in individuals at increased clinical risk of schizophrenia (Egerton et al., 2013; Howes et al., 2011a), as well as in first-degree relatives of patients with schizophrenia (Huttunen et al., 2008), and linked to transition to the disorder (Howes et al., 2011b). Thus, altered dopamine synthesis capacity could be a potential mechanism by which genetic variation acts to increase risk of schizophrenia.

Our study aimed to test the hypothesis that the association signal at the 10q24.32 locus confers genetic risk for schizophrenia through an effect on striatal dopamine function. We therefore investigated the *in vivo* relationship between the GWAS schizophrenia-associated SNP rs7085104 (the top expression quantitative trait locus (eQTL) for *AS3MT* and *BORCS7* (Li et al., 2016b)) and dopamine synthesis capacity, measured using [<sup>18</sup>F]-DOPA positron emission tomography (PET) in healthy controls. We hypothesised that carriers of the rs7085104 risk allele (A) would show increased striatal dopamine synthesis capacity relative to controls who did not carry the risk allele.

## 2 Methods

### 2.1 Participants

We studied 92 healthy volunteers (demographics in Table 1). Inclusion criteria were: minimum age 18 years, good physical health with no history of major medical condition and capacity to give written informed consent. Exclusion criteria were: history of significant head trauma, history of neurological disorder, presence of any significant medical disorder or treatment, pregnancy or breastfeeding, a diagnosis of past or current psychiatric disorders using the Structured Clinical Interview for DSM-IV (SR et al., 1996) including alcohol or any other substance dependence or abuse, a family history of any psychotic disorder in first- or second- degree relatives. PET data from some participants have been included in previous publications (Bloomfield et al., 2014a, 2014b; Dahoun et al., 2018; Froudast-Walsh et al., 2017; Jauhar et al., 2017b).

### 2.2 SNP Selection and Genotype determination

We chose rs7085104 as the sole polymorphism of interest for this study given cumulative evidence for its importance in the 10q24 associated region: (i) a recent finding implicating it as the top SNP eQTL for *AS3MT* and *BORCS7* (Li et al., 2016b), (ii) it was the index SNP at this locus in previous schizophrenia GWAS association (Ripke et al., 2013) and (iii) in a recent genome-wide methylation study rs7085104 was found to be a methylation QTL in human fetal brain for *AS3MT* (Hannon et al., 2015).

DNA was extracted from whole blood samples or cheek swabs using standard procedures (Freeman et al., 2003). Genotyping was performed at Cardiff University, using HumanCore Exome 1.1 arrays ("Psych-chip", Illumina, San Diego, California, USA). Genotype quality control (QC) was performed

according to standard parameters (Anderson et al., 2010). The variant of interest for our analysis, rs7085104, was directly genotyped and passed QC in all the subjects.

### **2.3 Population structure**

The top 10 principal components of the sample were generated using PC-AiR (Conomos et al., 2015) on the full set of genotypes, and included as covariates of no interest in all the analyses, in order to correct for population stratification.

Moreover, to confirm the robustness of the findings, the analyses were repeated in a sub-group of individuals of European ancestry. To this aim, each individual was assigned to a cluster (European, African, Asian) on the basis of their ancestry score (threshold for the attribution to a specific cluster: 0.7). Ancestry scores were calculated using ADMIXTURE (Alexander et al., 2009) (Version 1.3.0) with the Human Genome Diversity Panel (HGPD-CEPH) (Li et al., 2008) as a reference.

### **2.4 PET scanning**

[<sup>18</sup>F]-DOPA PET scans were used to measure striatal dopamine synthesis capacity (indexed as the influx rate constant  $K_i^{cer}$ ).

#### *2.4.1 Image acquisition*

Dynamic scans were acquired in three-dimensional mode (transaxial resolution of ~5 mm full width at half maximum ((NEMA), 2007) using three different PET scanners: one was a ECAT HR+ 962 PET scanner (CTI/Siemens, Knoxville, Tennessee) while the other two were Siemens Biograph HiRez XVI PET-CT scanners (Siemens Healthcare, Erlangen, Germany). Subjects were asked to refrain from eating and drinking (except water) for at least 12 hours before the scans. One hour before the scan, all participants received 400 mg entacapone, a peripheral catechol-o-methyl-transferase inhibitor which decreases the formation of radiolabelled metabolites that may cross the blood–brain barrier



(Cumming et al., 1993; Guttman et al., 1993), and 150 mg carbidopa, a peripheral aromatic acid decarboxylase inhibitor which reduces the peripheral metabolism of the tracer (Garnett et al., 1983). Approximately 150 MBq of radioactive [ $^{18}\text{F}$ ]-DOPA was administered by intravenous injection followed by 95 minutes of dynamic PET scan. PET data were reconstructed using filterback projection and corrected for tissue attenuation and scatter (full details are reported in (Bloomfield et al., 2014a, 2014b; Froudast-Walsh et al., 2017; Jauhar et al., 2017b)).

#### 2.4.2 Analysis of PET data

PET image analysis was performed as previously described (Dahoun et al., 2018). In summary, frames were realigned to a single reference frame, employing a mutual information algorithm (Studholme et al., 1996; Turkheimer et al., 1999). The transformation parameters were then applied to the corresponding attenuated-corrected dynamic images, creating a movement-corrected dynamic image, which was used in the analysis. Realigned frames were then summated to create an individual motion-corrected reference map for the brain tissue segmentation. The striatum was sub-divided into sub-regions as previously described (Howes et al., 2009; Martinez et al., 2003) to create a Region of Interest (ROI) map (Egerton et al., 2010). SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>) was used to normalize a tracer-specific ([ $^{18}\text{F}$ ]-DOPA) template together with the ROI map to each individual PET summation image (Howes et al., 2009). The striatal influx constant ( $K_i^{cer}$ ) was calculated relative to uptake in the reference region using a graphical approach adapted for a reference tissue input function (Howes et al., 2009). To control for effects of scanner model, PET scanners were included as covariates of no interest in all analyses.

## 2.5 Statistical analysis

ANOVA and  $\chi^2$  tests were used to compare demographics age and gender as functions of rs7085104 genotype. ANCOVA analyses were performed to explore the correlation between genotype and

dopamine synthesis capacity (fixed factor: rs7085104 genotype [three groups: GG, GA, AA, dependent variable:  $K_i^{cer}$ , covariates of no interest: age, gender, scanner, top 10 genetic principal components). Exploratory analyses were conducted using associative striatum, limbic striatum and sensorimotor striatum  $K_i^{cer}$  as dependent variables. All these were performed in SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Mac, Version 24.0.0.1 Armonk, NY: IBM Corp.). GraphPad Prism 7.02 (<http://www.graphpad.com/>) was used to plot the main results.

The R package RobustSNP (So and Sham, 2011) was used to confirm the genetic model suggested by the LSD post hoc analysis. The robust tests were performed including the same covariates of no interest used for the ANCOVAs.

### 3 Results

Demographic ( $\pm$  SD) and  $K_i^{cer}$  values included are reported in Table 1.

Genotype groups were in Hardy-Weinberg Equilibrium ( $X^2= 0.16, p= 0.69$ ) and did not differ in terms of age ( $p= 0.22$ ), sex ( $X^2= 0.86, p= 0.65$ ), PET scanner ( $X^2= 5.66, p= 0.23$ ) or tobacco smoking status ( $X^2= 0.94, p= 0.62$ ).

The frequency of the schizophrenia risk allele in our sample approximated that reported in the public NCBI database dbSNP (Sherry, 2001). Specifically, the risk allele (A) of rs7085104 had a reported frequency of 0.62 in the latter, while the frequency for our sample was 0.69.

We found a significant association between rs7085104 genotype and whole striatal  $K_i^{cer}$  ( $F(2,76)= 4.660, p= 0.012$ ) [Fig. 1]. LSD post-hoc analyses showed that risk allele carriers had significantly elevated  $K_i^{cer}$  compared to subjects with the genotype GG (GA vs GG,  $p= 0.003$ ; GA vs AA,  $p= 0.275$ ; AA vs GG,  $p= 0.020$ , Hedges'  $g= 0.957$ ), suggesting a dominant effect of A alleles. The RobustSNP association test confirmed the dominant model for this association ( $Z^{\text{Dominant Model}}= 2.337, p^{\text{Dominant Model}}= 0.019$ ).

The exploratory analyses in the striatal subdivisions revealed an effect of genotype on dopamine synthesis capacity for all the regions. Specifically, we found an effect of rs7085104 genotype on associative  $K_i^{cer}$  ( $F(2,76)= 4.075, p= 0.021$ ; LSD post-hoc contrasts: GA vs GG,  $p= 0.006$ ; GA vs AA,  $p= 0.424$ ; AA vs GG,  $p= 0.020$ ) [Fig. 2a], limbic  $K_i^{cer}$  ( $F(2,76)= 5.453, p= 0.006$ ; LSD post-hoc contrasts: GA vs GG,  $p= 0.001$ ; GA vs AA,  $p= 0.406$ ; AA vs GG,  $p= 0.007$ ) [Fig. 2b], and sensorimotor  $K_i^{cer}$  ( $F(2,76)= 4.100, p= 0.020$ ; LSD post-hoc contrasts: GA vs GG,  $p= 0.008$ ; GA vs AA,  $p= 0.126$ ; AA vs GG,  $p= 0.071$ ) [Fig. 2c]. RobustSNP association tests confirmed the dominant effect of A alleles on dopamine synthesis capacity for all the striatal subdivisions (associative  $K_i^{cer}$ :  $Z^{\text{Dominant Model}}= 2.217, p^{\text{Dominant Model}}=$

0.0266; limbic  $K_i^{cer} : Z^{\text{Dominant Model}} = 2.480, p^{\text{Dominant Model}} = 0.013$ ; sensorimotor  $K_i^{cer} : Z^{\text{Dominant Model}} = 2.345, p^{\text{Dominant Model}} = 0.019$ ).

The sensitivity analyses performed in the sub-group of individuals of European Ancestry confirmed the association of rs7085104 genotype with whole striatal  $K_i^{cer}$  ( $F(2,48) = 6.102, p = 0.004$ ) and all the striatal subdivisions: associative  $K_i^{cer}$  ( $F(2,48) = 4.835, p = 0.012$ ); limbic  $K_i^{cer}$  ( $F(2,48) = 6.935, p = 0.002$ ); and sensorimotor  $K_i^{cer}$  ( $F(2,48) = 6.091, p = 0.004$ ).

## 4 Discussion

We report for the first time an *in vivo* association between the schizophrenia-associated SNP rs7085104 and striatal dopamine synthesis capacity. Specifically, we found that the rs7085104 risk allele (A) carriers show higher striatal  $K_i^{cer}$  than the subjects homozygous for the G allele. It is not clear at present whether the possible dominant effect we have detected on dopamine synthesis capacity matches the observed effect of this SNP as a schizophrenia risk allele, since the latter has at the moment only been assessed by GWAS based on simple additive models (Pardiñas et al., 2018; Ripke et al., 2014, 2013). In order to resolve this, explicit modelling of dominance effects in large-scale schizophrenia samples would have to be performed, as has been explored in other psychiatric conditions (Leblond et al., 2019; Van der Auwera et al., 2018). At the moment, dominant effects are not currently considered to explain much of the variance of human complex traits in general, though they have been shown to exist at some particular loci (Zhu et al., 2015).

These results offer new insights into the biological mechanisms that could underlie the association of the locus 10q24.32 with schizophrenia. A genetic risk variant on chromosome 10q24.32 has recently been demonstrated to correlate with the expression of the gene *AS3MT* (Duarte et al., 2016). *AS3MT* codes for an arsenic methyltransferase (Lin et al., 2002; Sumi and Himeno, 2012). Since arsenic can result in CNS toxicity and neurological sequelae, including the development of psychosis (Ratnaike, 2003; Tyler and Allan, 2014), it has been speculated that dysregulation of arsenic metabolism mediates the relationship between this genetic locus and schizophrenia. However, Li and colleagues (Li et al., 2014) have demonstrated that the top GWAS SNP for this locus is not associated with the full-length isoform of the *AS3MT* transcript (*AS3MT<sup>full</sup>*) but with the isoform *AS3MT<sup>d2d3</sup>*, which lacks arsenite methyltransferase activity. Therefore, alterations in arsenic

metabolism may not explain the association between rs7085104 and schizophrenia. Our data suggest that the dopaminergic pathway is involved in this association.

The rs7085104 SNP might impact dopamine synthesis capacity through its association with the expression of *BORCS7* (Li et al., 2016b). Specifically, the risk genotype (A) is associated with upregulation of this protein, which forms one of the subunits of BLOC-one-related complex (BORC). BORC in turn makes up subunits of lysosome-related organelles complex 1 (BLOC-1), which has been shown to be involved in modulation of dopaminergic neurotransmission (Iizuka et al., 2007; Nagai et al., 2010).

There is accumulating evidence to support the longstanding neurodevelopmental hypothesis of adult-onset psychiatric disorders and in particular schizophrenia (Birnbaum et al., 2015; Howes and Murray, 2014; Jaffe et al., 2014; Weinberger, 1987). Therefore, it is noteworthy that the expression of *AS3MT*<sup>d2d3</sup> and *BORCS7* is up-regulated in early neuronal differentiation (Li et al., 2016b). In consideration of the fact that human dopaminergic innervation is also present in the early phases of neurodevelopment (Money and Stanwood, 2013; Zecevic and Verney, 1995), it can be speculated that the genetic variant examined in our study exerts its effect on the dopaminergic system early in the neurodevelopment, increasing risk for schizophrenia (Hannon et al., 2015).

Our study was conducted in healthy subjects; therefore, future work should focus on patients with schizophrenia and other major psychiatric disorders. Supporting this assertion of broader implications of 10q24.32 in serious mental illness, rs7085104 and two other SNPs in linkage disequilibrium (rs7914558 ( $D' = 0.956$ ;  $r^2 = 0.689$  in Europeans) and rs11191580 ( $D' = 1$ ;  $r^2 = 0.178$  in Europeans)) within this chromosomal region are also associated with bipolar disorder, major depressive disorder, schizophrenia, autism spectrum disorder, and attention deficit-hyperactivity disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Li et al., 2016a;

Psychiatric GWAS Consortium Bipolar Disorder Working Group et al., 2011; Ripke et al., 2011). In this context, it is noteworthy that expression of *AS3MT*<sup>d2d3</sup> is elevated in patients not only with schizophrenia but also major depression when compared with healthy subjects. Dopamine dysregulation, namely elevated dopamine synthesis capacity, has been demonstrated in patients with bipolar disorder with psychosis as well as in schizophrenia (Jauhar et al., 2017a). It could be speculated that the mediator of the association of this locus with major psychiatric disorders is the dopaminergic system.

### *Strengths and Limitations*

Since there is evidence of increased striatal dopamine synthesis capacity in schizophrenia (Howes et al., 2012), the increased striatal dopamine synthesis capacity of the risk allele carriers could explain the association of this genetic variant with schizophrenia (Ripke et al., 2014).

However, it should be considered that association does not necessarily imply causality. Pre-clinical studies are needed to clarify the mechanism that links the genetic risk given by polymorphisms within 10q24.32-33 with dysregulation in the dopaminergic system. Moreover, in consideration of the small proportion of subjects with the genotype GG for the SNP rs7085104 and of the fact that some imaging studies based on a candidate gene approach have shown contradictory findings (Bogdan et al., 2017), replications with a higher number of subjects are needed. Nevertheless, to our knowledge, this study is one of the largest PET studies of association of a genetic variant with dopamine function (Dahoun et al., 2018; Gluskin and Mickey, 2016; Laakso et al., 2005; Shumay et al., 2017; Wiers et al., 2017; Wu et al., 2012).

We note that, for the SNP described herein, the allele associated with increased schizophrenia risk is the most common allele in the general population. Whilst risk alleles for disorders are generally

minor alleles (Kido et al., 2018), this is not always the case and several risk alleles identified by GWAS have frequencies higher than 50% in the general population (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Mulle, 2012). This is in line with the evidence that schizophrenia is a polygenic disorder; and many common variants contribute to risk and protection, each with small effects (Weinberger, 2019). These small effects have likely enabled a proportion of these risk variants to become highly represented in the general population as a consequence of genetic drift or balancing selection (Owen et al., 2016; Pardiñas et al., 2018).

A relevant limitation was the use of data from three different PET scanners. However, to control for this, PET scanners were included as covariates of no interest in all the analyses. Anyway, there was no difference in the genotype distribution across the three scanners. Furthermore, some participants were smokers; however, groups did not differ for smoking status and dopamine synthesis capacity is not altered in moderate smokers (Bloomfield et al., 2014a); and it is not clear if even heavy smoking has a significant effect on dopamine synthesis capacity (Ashok et al., 2019).

Our sample was not homogeneous for ethnicity, thus genetic principal components were included as covariates in all the analyses, in order to correct for population stratification. However, a recent GWAS has shown an association of common genetic variants within the locus 10q24.32 with schizophrenia in the Han Chinese population (Yu et al., 2016). Moreover, a variable number tandem repeat (VNTR) in the first exon of AS3MT is associated with AS3MT<sup>d2d3</sup> mRNA expression not only in Caucasian subjects but also in African Americans (Li et al., 2014). This would indicate that the association of this locus with schizophrenia is ethnicity-independent.

### *Implications*



Studies such as this can help move from a genomic region of association to highlighting potential mechanisms through which candidate SNPs within the region are acting to increase the risk for schizophrenia. Our study can be considered a step towards translation of one of the most statistically significant findings in the genetics of schizophrenia, the association of the locus 10q24.32, towards the identification of novel treatment targets in line with recent proposals (Birnbaum & Weinberger, 2017; Schubert et al., 2014).

The modest effect size of the association between rs7085104 and dopamine synthesis capacity is in line with the fact that the risk for schizophrenia conferred by each of the schizophrenia GWAS-significant loci is relatively small (Ripke et al., 2014). In this regard, the contribution of this SNP to the variation in the striatal  $K_i^{cer}$  - as can be deduced from the difference between the subjects homozygous for the risk variant and the individuals homozygous for the G allele (Hedges'  $g = 0.957$ ) - is in line with the effect size of the association of AS3MT<sup>d2d3</sup> expression with diagnosis of schizophrenia (effect size = 0.813 (Li et al., 2016b)). However, given the modest sample size of G homozygotes in our study, our effect size estimate should be considered as preliminary and warrants replication. Moreover, in view of the fact the risk allele is common in the general population, it is important to note that other genetic and environmental factors, such as psychosocial stressors, cannabis use, and obstetric complications are likely to combine to lead to schizophrenia (Birnbaum and Weinberger, 2017; Howes et al., 2017).

#### **4.1 Conclusions**

The results from the present work indicate that the mechanism mediating the 10q24.32 risk locus for schizophrenia could involve altered dopaminergic function. Future studies are needed to clarify the neurobiological pathway implicated in this association.

## **Acknowledgements**

This research was supported by Medical Research Council (grant MC-A656-5QD30), Maudsley Charity (grant 666), the US Brain & Behavior Research Foundation, Wellcome Trust (grant 094849/Z/10/Z to Professor Howes), the National Institute for Health Research Biomedical Research Centre at South London and Maudsley National Health Service Foundation Trust, King's College London. Dr Jauhar is supported by a Sim Fellowship, from the Royal College of Physicians, Edinburgh. Dr Veronese is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. Dr Dahoun was supported by a EU-FP7 MC-ITN IN-SENS grant (grant number 607616) and by the National Institute for Health Research (NIHR) at Oxford Health NHS Foundation Trust. Dr Bloomfield is supported by a UCL Excellence Fellowship and by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

We acknowledge the Cardiff University MRC CNGG Core Team, especially Lucinda Hopkins and Lesley Bates, for laboratory sample management and genotyping of the healthy volunteer sample.

We would like to thank Prof. D.R. Weinberger for his helpful comments and suggestions.

## **Financial Disclosures and conflict of interests**

Professor Howes has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organised by Astra-Zeneca, Autifony, BMS, Eli Lilly, Heptares, Janssen, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand and Roche. Neither Professor Howes nor his family have been employed by or have holdings/a financial stake in any biomedical company.

Dr D'Ambrosio reported no biomedical financial interests or potential conflicts of interest.

Dr Dahoun reported no biomedical financial interests or potential conflicts of interest.

Dr Pardiñas reported no biomedical financial interests or potential conflicts of interest.

Dr Veronese reported no biomedical financial interests or potential conflicts of interest.

Dr Bloomfield reported no biomedical financial interests or potential conflicts of interest.

Dr Jauhar reported no biomedical financial interests or potential conflicts of interest.

Dr Bonoldi reported no biomedical financial interests or potential conflicts of interest.

Dr Rogdaki reported no biomedical financial interests or potential conflicts of interest.

Dr Froudish-Walsh reported no biomedical financial interests or potential conflicts of interest.

Professor Walters reported no biomedical financial interests or potential conflicts of interest.

**Table 1**

***Demographic characteristics of the sample***

**Figure 1**

***Effect of AS3MT rs7085104 on whole striatum  $K_i^{cer}$***

**Figure 2**

***Exploratory analyses: effect of AS3MT rs7085104 on  $K_i^{cer}$  in the different striatal subdivisions***

## References

- (NEMA), N.E.M.A., 2007. Performance Measurements of Positron Emission Tomographs. Rosslyn, VA: NEMA. Stand. Publ. NU 2-2007.
- Abi-Dargham, A., Rodenhiser, J., Printz, D., Zea-Ponce, Y., Gil, R., Kegeles, L.S., Weiss, R., Cooper, T.B., Mann, J.J., Van Heertum, R.L., Gorman, J.M., Laruelle, M., 2000. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc. Natl. Acad. Sci. U. S. A.* 97, 8104–8109. <https://doi.org/10.1073/pnas.97.14.8104>
- Abi-Dargham, A., van de Giessen, E., Slifstein, M., Kegeles, L.S., Laruelle, M., 2009. Baseline and Amphetamine-Stimulated Dopamine Activity Are Related in Drug-Naïve Schizophrenic Subjects. *Biol. Psychiatry* 65, 1091–1093. <https://doi.org/10.1016/j.biopsych.2008.12.007>
- Alexander, D.H., Novembre, J., Lange, K., 2009. Fast Model-Based Estimation of Ancestry in Unrelated Individuals. *Genome Res.* 19, 1655–64. <https://doi.org/10.1101/gr.094052.109>
- Anderson, C.A., Pettersson, F.H., Clarke, G.M., Cardon, L.R., Morris, A.P., Zondervan, K.T., 2010. Data quality control in genetic case-control association studies. *Nat. Protoc.* 5, 1564–1573. <https://doi.org/10.1038/nprot.2010.116>
- Ashok, A.H., Mizuno, Y., Howes, O.D., 2019. Tobacco smoking and dopaminergic function in humans: a meta-analysis of molecular imaging studies. *Psychopharmacology (Berl)*. <https://doi.org/10.1007/s00213-019-05196-1>

- Birnbaum, R., Jaffe, A.E., Chen, Q., Hyde, T.M., Kleinman, J.E., Weinberger, D.R., 2015. Investigation of the prenatal expression patterns of 108 schizophrenia-associated genetic loci. *Biol. Psychiatry* 77, e43–e51. <https://doi.org/10.1016/j.biopsych.2014.10.008>
- Birnbaum, R., Weinberger, D.R., 2017. Genetic insights into the neurodevelopmental origins of schizophrenia. *Nat. Rev. Neurosci.* <https://doi.org/10.1038/nrn.2017.125>
- Bloomfield, M.A., Pepper, F., Egerton, A., Demjaha, A., Tomasi, G., Mouchlianitis, E., Maximen, L., Veronese, M., Turkheimer, F., Selvaraj, S., Howes, O.D., 2014a. Dopamine function in cigarette smokers: an [(1)(8)F]-DOPA PET study. *Neuropsychopharmacology* 39, 2397–2404. <https://doi.org/10.1038/npp.2014.87>
- Bloomfield, M.A.P., Morgan, C.J.A., Egerton, A., Kapur, S., Curran, H.V., Howes, O.D., 2014b. Dopaminergic function in cannabis users and its relationship to cannabis-induced psychotic symptoms. *Biol. Psychiatry* 75, 470–478. <https://doi.org/10.1016/j.biopsych.2013.05.027>
- Bogdan, R., Salmeron, B.J., Carey, C.E., Agrawal, A., Calhoun, V.D., Garavan, H., Hariri, A.R., Heinz, A., Hill, M.N., Holmes, A., Kalin, N.H., Goldman, D., 2017. Imaging Genetics and Genomics in Psychiatry: A Critical Review of Progress and Potential. *Biol. Psychiatry* 82, 165–175. <https://doi.org/10.1016/j.biopsych.2016.12.030>
- Conomos, M.P., Miller, M.B., Thornton, T.A., 2015. Robust Inference of Population Structure for Ancestry Prediction and Correction of Stratification in the Presence of Relatedness. *Genet. Epidemiol.* 39, 276–293. <https://doi.org/10.1002/gepi.21896>
- Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013. Identification of risk loci with

shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* 381, 1371–9. [https://doi.org/10.1016/S0140-6736\(12\)62129-1](https://doi.org/10.1016/S0140-6736(12)62129-1)

Cumming, P., Leger, G.C., Kuwabara, H., Gjedde, A., 1993. Pharmacokinetics of plasma 6-[<sup>18</sup>F]fluoro-L-3,4-dihydroxyphenylalanine ([<sup>18</sup>F]Fdopa) in humans. *J Cereb Blood Flow Metab* 13, 668–675. <https://doi.org/10.1038/jcbfm.1993.85>

Dahoun, T., Pardiñas, A.F., Veronese, M., Bloomfield, M.A.P., Jauhar, S., Bonoldi, I., Froudust-Walsh, S., Nosarti, C., Korth, C., Hennah, W., Walters, J., Prata, D., Howes, O.D., 2018. The effect of the DISC1 Ser704Cys polymorphism on striatal dopamine synthesis capacity: an [<sup>18</sup>F]-DOPA PET study. *Hum. Mol. Genet.* 27, 3498–3506. <https://doi.org/10.1093/hmg/ddy242>

Davis, K.L., Kahn, R.S., Ko, G., Davidson, M., 1991. Dopamine in schizophrenia: A review and reconceptualization. *Am. J. Psychiatry* 148, 1474–1486. <https://doi.org/10.1176/ajp.148.11.1474>

Duarte, R.R.R., Troakes, C., Nolan, M., Srivastava, D.P., Murray, R.M., Bray, N.J., 2016. Genome-wide significant schizophrenia risk variation on chromosome 10q24 is associated with altered cis-regulation of BORCS7, AS3MT, and NT5C2 in the human brain, in: *Am J Med Genet B Neuropsychiatr Genet.* pp. 806–814. <https://doi.org/10.1002/ajmg.b.32445>

Egerton, A., Chaddock, C.A., Winton-Brown, T.T., Bloomfield, M.A., Bhattacharyya, S., Allen, P., McGuire, P.K., Howes, O.D., 2013. Presynaptic striatal dopamine dysfunction in people at ultra-high risk for psychosis: findings in a second cohort. *Biol Psychiatry* 74, 106–112. <https://doi.org/10.1016/j.biopsych.2012.11.017>

- Egerton, A., Demjaha, A., McGuire, P., Mehta, M.A., Howes, O.D., 2010. The test-retest reliability of 18F-DOPA PET in assessing striatal and extrastriatal presynaptic dopaminergic function. *Neuroimage* 50, 524–531. <https://doi.org/10.1016/j.neuroimage.2009.12.058>
- Freeman, B., Smith, N., Curtis, C., Hockett, L., Mill, J., Craig, I.W., 2003. DNA from buccal swabs recruited by mail: Evaluation of storage effects on long-term stability and suitability for multiplex polymerase chain reaction genotyping. *Behav. Genet.* 33, 67–72. <https://doi.org/10.1023/A:1021055617738>
- Froudust-Walsh, S., Bloomfield, M.A.P.P., Veronese, M., Kroll, J., Karolis, V.R., Jauhar, S., Bonoldi, I., McGuire, P.K., Kapur, S., Murray, R.M., Nosarti, C., Howes, O., 2017. The Effect Of Perinatal Brain Injury On Dopaminergic Function And Hippocampal Volume In Adult Life. *bioRxiv* 6, 1–20. <https://doi.org/10.7554/eLife.29088>
- Garnett, E.S., Firnau, G., Nahmias, C., 1983. Dopamine visualized in the basal ganglia of living man. *Nature*. <https://doi.org/10.1097/00004728-198402000-00054>
- Gluskin, B.S., Mickey, B.J., 2016. Genetic variation and dopamine D2 receptor availability: a systematic review and meta-analysis of human in vivo molecular imaging studies. *Transl. Psychiatry* 6, e747. <https://doi.org/10.1038/tp.2016.22>
- Guttman, M., Leger, G., Reches, A., Evans, A., Kuwabara, H., Cedarbaum, J.M., Gjedde, A., 1993. Administration of the new COMT inhibitor OR-611 increases striatal uptake of fluorodopa. *Mov Disord* 8, 298–304. <https://doi.org/10.1002/mds.870080308>
- Hannon, E., Spiers, H., Viana, J., Pidsley, R., Burrage, J., Murphy, T.M., Troakes, C., Turecki, G.,



- O'Donovan, M.C., Schalkwyk, L.C., Bray, N.J., Mill, J., 2015. Methylation QTLs in the developing brain and their enrichment in schizophrenia risk loci. *Nat. Neurosci.* 19, 48–54.  
<https://doi.org/10.1038/nn.4182>
- Heinz, A., Romero, B., Gallinat, J., Juckel, G., Weinberger, D.R., 2003. Molecular brain imaging and the neurobiology and genetics of schizophrenia. *Pharmacopsychiatry* 36, 152–157.
- Heinz, A., Schlagenhauf, F., 2010. Dopaminergic dysfunction in schizophrenia: Salience attribution revisited. *Schizophr. Bull.* 36, 472–485. <https://doi.org/10.1093/schbul/sbq031>
- Hietala, J., Syvälahti, E., Vilkmann, H., Vuorio, K., Rääköläinen, V., Bergman, J., Haaparanta, M., Solin, O., Kuoppamäki, M., Eronen, E., Ruotsalainen, U., Salokangas, R.K.R., 1999. Depressive symptoms and presynaptic dopamine function in neuroleptic-naive schizophrenia. *Schizophr. Res.* 35, 41–50. [https://doi.org/10.1016/S0920-9964\(98\)00113-3](https://doi.org/10.1016/S0920-9964(98)00113-3)
- Howes, O., Bose, S., Turkheimer, F., Valli, I., Egerton, A., Stahl, D., Valmaggia, L., Allen, P., Murray, R., McGuire, P., 2011a. Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis: a PET study. *Mol Psychiatry* 16, 885–886.  
<https://doi.org/10.1038/mp.2011.20>
- Howes, O., McCutcheon, R., Stone, J., 2015. Glutamate and dopamine in schizophrenia: an update for the 21st century. *J Psychopharmacol* 29, 97–115.  
<https://doi.org/10.1177/0269881114563634>
- Howes, O.D., Bose, S.K., Turkheimer, F., Valli, I., Egerton, A., Valmaggia, L.R., Murray, R.M., McGuire, P., 2011b. Dopamine synthesis capacity before onset of psychosis: a prospective

[18F]-DOPA PET imaging study. *Am J Psychiatry* 168, 1311–1317.

<https://doi.org/10.1176/appi.ajp.2011.11010160>

Howes, O.D., Kambeitz, J., Kim, E., Stahl, D., Slifstein, M., Abi-Dargham, A., Kapur, S., 2012. The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch Gen Psychiatry* 69, 776–786. <https://doi.org/10.1001/archgenpsychiatry.2012.169>

Howes, O.D., Kapur, S., 2009. The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophr Bull* 35, 549–562. <https://doi.org/10.1093/schbul/sbp006>

Howes, O.D., McCutcheon, R., Owen, M.J., Murray, R.M., 2017. The Role of Genes, Stress, and Dopamine in the Development of Schizophrenia. *Biol. Psychiatry* 81, 9–20. <https://doi.org/10.1016/j.biopsych.2016.07.014>

Howes, O.D., Montgomery, A.J., Asselin, M.C., Murray, R.M., Valli, I., Tabraham, P., Bramon-Bosch, E., Valmaggia, L., Johns, L., Broome, M., McGuire, P.K., Grasby, P.M., 2009. Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Arch Gen Psychiatry* 66, 13–20. <https://doi.org/10.1001/archgenpsychiatry.2008.514>

Howes, O.D., Murray, R.M., 2014. Schizophrenia: An integrated sociodevelopmental-cognitive model. *Lancet* 383, 1677–1687. [https://doi.org/10.1016/S0140-6736\(13\)62036-X](https://doi.org/10.1016/S0140-6736(13)62036-X)

Howes, O.D., Williams, M., Ibrahim, K., Leung, G., Egerton, A., McGuire, P.K., Turkheimer, F., 2013. Midbrain dopamine function in schizophrenia and depression: a post-mortem and positron emission tomographic imaging study. *Brain* 136, 3242–3251. <https://doi.org/10.1093/brain/awt264>

- Huttunen, J., Heinimaa, M., Svirskis, T., Nyman, M., Kajander, J., Forsback, S., Solin, O., Ilonen, T., Korkeila, J., Ristkari, T., McGlashan, T., Salokangas, R.K., Hietala, J., 2008. Striatal dopamine synthesis in first-degree relatives of patients with schizophrenia. *Biol Psychiatry* 63, 114–117. <https://doi.org/10.1016/j.biopsych.2007.04.017>
- lizuka, Y., Sei, Y., Weinberger, D.R., Straub, R.E., 2007. Evidence That the BLOC-1 Protein Dysbindin Modulates Dopamine D2 Receptor Internalization and Signaling But Not D1 Internalization. *J. Neurosci.* 27, 12390–12395. <https://doi.org/10.1523/JNEUROSCI.1689-07.2007>
- Jaffe, A.E., Shin, J., Collado-Torres, L., Leek, J.T., Tao, R., Li, C., Gao, Y., Jia, Y., Maher, B.J., Hyde, T.M., Kleinman, J.E., Weinberger, D.R., 2014. Developmental regulation of human cortex transcription and its clinical relevance at single base resolution. *Nat. Neurosci.* 18, 154–161. <https://doi.org/10.1038/nn.3898>
- Jauhar, S., Nour, M.M., Veronese, M., Rogdaki, M., Bonoldi, I., Azis, M., Turkheimer, F., McGuire, P., Young, A.H., Howes, O.D., 2017a. A Test of the Transdiagnostic Dopamine Hypothesis of Psychosis Using Positron Emission Tomographic Imaging in Bipolar Affective Disorder and Schizophrenia. *JAMA Psychiatry*. <https://doi.org/10.1001/jamapsychiatry.2017.2943>
- Jauhar, S., Veronese, M., Rogdaki, M., Bloomfield, M., Natesan, S., Turkheimer, F., Kapur, S., Howes, O.D., 2017b. Regulation of dopaminergic function: an [<sup>18</sup>F]-DOPA PET apomorphine challenge study in humans. *Transl. Psychiatry* 7. <https://doi.org/doi:10.1038/tp.2016.270>
- Kido, T., Sikora-Wohlfeld, W., Kawashima, M., Kikuchi, S., Kamatani, N., Patwardhan, A., Chen, R., Sirota, M., Kodama, K., Hadley, D., Butte, A.J., 2018. Are minor alleles more likely to be risk

alleles? BMC Med. Genomics 11, 1–11. <https://doi.org/10.1186/s12920-018-0322-5>

Kumakura, Y., Cumming, P., Vernaleken, I., Buchholz, H.-G., Siessmeier, T., Heinz, A., Kienast, T., Bartenstein, P., Grunder, G., 2007. Elevated [18F]Fluorodopamine Turnover in Brain of Patients with Schizophrenia: An [18F]Fluorodopa/Positron Emission Tomography Study. *J. Neurosci.* 27, 8080–8087. <https://doi.org/10.1523/JNEUROSCI.0805-07.2007>

Laakso, A., Pohjalainen, T., Bergman, J., Kajander, J., Haaparanta, M., Solin, O., Syvalahti, E., Hietala, J., 2005. The A1 allele of the human D2 dopamine receptor gene is associated with increased activity of striatal L-amino acid decarboxylase in healthy subjects. *Pharmacogenet. Genomics* 15, 387–391.

Laruelle, M., Abi-Dargham, A., 1999. Dopamine as the wind of the psychotic fire: new evidence from brain imaging studies. *J. Psychopharmacol.* 13, 358–371.  
<https://doi.org/10.1177/026988119901300405>

Leblond, C.S., Cliquet, F., Carton, C., Huguet, G., Mathieu, A., Kergrohen, T., Buratti, J., Lemièrre, N., Cuisset, L., Bienvenu, T., Boland, A., Deleuze, J.-F., Stora, T., Biskupstoe, R., Halling, J., Andorsdóttir, G., Billstedt, E., Gillberg, C., Bourgeron, T., 2019. Both rare and common genetic variants contribute to autism in the Faroe Islands. *npj Genomic Med.* 4, 1.  
<https://doi.org/10.1038/s41525-018-0075-2>

Li, J.Z., Absher, D.M., Tang, H., Southwick, A.M., Casto, A.M., Ramachandran, S., Cann, H.M., Barsh, G.S., Feldman, M., Cavalli-Sforza, L.L., Myers, R.M., 2008. Worldwide Human Relationships Inferred from Genome-Wide Patterns of Variation. *Science (80-. )*. 319, 1100 LP – 1104.  
<https://doi.org/10.1126/science.1153717>

- Li, L., Chang, H., Peng, T., Li, M., Xiao, X., 2016a. Evidence of AS3MT<sup>d2d3</sup>-Associated Variants within 10q24.32-33 in the Genetic Risk of Major Affective Disorders. *Mol. Neuropsychiatry* 2, 213–218. <https://doi.org/10.1159/000452998>
- Li, M., Jaffe, A.E., Straub, R.E., Tao, R., Shin, J.H., Wang, Y., Chen, Q., Li, C., Jia, Y., Ohi, K., Maher, B.J., Brandon, N.J., Cross, A., Chenoweth, J.G., Hoepfner, D.J., Wei, H., Hyde, T.M., McKay, R., Kleinman, J.E., Weinberger, D.R., 2016b. A human-specific AS3MT isoform and BORCS7 are molecular risk factors in the 10q24.32 schizophrenia-associated locus. *Nat Med* 22, 649–656. <https://doi.org/10.1038/nm.4096>
- Li, M., Tao, R., Jaffe, A.E., Zhang, F., Chen, D., Kleinman, J.E., Hyde, T.M., Shin, J.H., Weinberger, D.R., 2014. A human-specific isoform of AS3MT regulated by a human-unique variation explains susceptibility to psychiatric illness. *Neuropsychopharmacology* 39, S397–S398.
- Lin, S., Shi, Q., Brent Nix, F., Styblo, M., Beck, M.A., Herbin-Davis, K.M., Hall, L.L., Simeonsson, J.B., Thomas, D.J., 2002. A novel S-adenosyl-L-methionine:arsenic(III) methyltransferase from rat liver cytosol. *J. Biol. Chem.* 277, 10795–10803. <https://doi.org/10.1074/jbc.M110246200>
- Martinez, D., Slifstein, M., Broft, A., Mawlawi, O., Hwang, D.-R.R., Huang, Y., Cooper, T., Kegeles, L., Zarahn, E., Abi-Dargham, A., Haber, S.N., Laruelle, M., 2003. Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: amphetamine-induced dopamine release in the functional subdivisions of the striatum. *J Cereb Blood Flow Metab* 23, 285–300.
- Meyer-Lindenberg, A., Miletich, R.S., Kohn, P.D., Esposito, G., Carson, R.E., Quarantelli, M., Weinberger, D.R., Berman, K.F., 2002. Reduced prefrontal activity predicts exaggerated

striatal dopaminergic function in schizophrenia. *Nat Neurosci* 5, 267–271.

<https://doi.org/10.1038/nn804>

Mizrahi, R., Addington, J., Rusjan, P.M., Suridjan, I., Ng, A., Boileau, I., Pruessner, J.C., Remington, G., Houle, S., Wilson, A.A., 2012. Increased stress-induced dopamine release in psychosis. *Biol Psychiatry* 71, 561–567. <https://doi.org/10.1016/j.biopsych.2011.10.009>

Money, K.M., Stanwood, G.D., 2013. Developmental origins of brain disorders: roles for dopamine. *Front. Cell. Neurosci.* 7, 1–14. <https://doi.org/10.3389/fncel.2013.00260>

Mulle, J.G., 2012. Schizophrenia genetics: Progress, at last. *Curr. Opin. Genet. Dev.* 22, 238–244. <https://doi.org/10.1016/j.gde.2012.02.011>

Nagai, T., Kitahara, Y., Shiraki, A., Hikita, T., Taya, S., Kaibuchi, K., Yamada, K., 2010. Dysfunction of dopamine release in the prefrontal cortex of dysbindin deficient sandy mice: An in vivo microdialysis study. *Neurosci. Lett.* <https://doi.org/10.1016/j.neulet.2009.12.071>

Owen, M.J., Sawa, A., Mortensen, P.B., 2016. Schizophrenia. *Lancet* 388, 86–97.

Pardiñas, A.F., Holmans, P., Pocklington, A.J., Escott-Price, V., Ripke, S., Carrera, N., Legge, S.E., Bishop, S., Cameron, D., Hamshere, M.L., Han, J., Hubbard, L., Lynham, A., Mantripragada, K., Rees, E., MacCabe, J.H., McCarroll, S.A., Baune, B.T., Breen, G., Byrne, E.M., Dannlowski, U., Eley, T.C., Hayward, C., Martin, N.G., McIntosh, A.M., Plomin, R., Porteous, D.J., Wray, N.R., Caballero, A., Geschwind, D.H., Huckins, L.M., Ruderfer, D.M., Santiago, E., Sklar, P., Stahl, E.A., Won, H., Agerbo, E., Als, T.D., Andreassen, O.A., Bækvad-Hansen, M., Mortensen, P.B., Pedersen, C.B., Børglum, A.D., Bybjerg-Grauholm, J., Djurovic, S., Durmishi, N., Pedersen,

M.G., Golimbet, V., Grove, J., Hougaard, D.M., Mattheisen, M., Molden, E., Mors, O., Nordentoft, M., Pejovic-Milovancevic, M., Sigurdsson, E., Silagadze, T., Hansen, C.S., Stefansson, K., Stefansson, H., Steinberg, S., Tosato, S., Werge, T., Collier, D.A., Rujescu, D., Kirov, G., Owen, M.J., O'Donovan, M.C., Walters, J.T.R., 2018. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat. Genet.* <https://doi.org/10.1038/s41588-018-0059-2>

Psychiatric GWAS Consortium Bipolar Disorder Working Group, P., Ripke, S., Scott, L.J., Andreassen, O.A., Cichon, S., Craddock, N., Edenberg, H.J., Nurnberger, J.I., Rietschel, M., Blackwood, D., Corvin, A., Flickinger, M., Guan, W., Mattingsdal, M., McQuillin, A., Kwan, P., Wienker, T.F., Daly, M., Dudbridge, F., Holmans, P.A., Lin, D., Burmeister, M., Greenwood, T.A., Hamshere, M.L., Muglia, P., Smith, E.N., Zandi, P.P., Nievergelt, C.M., McKinney, R., Shilling, P.D., Schork, N.J., Bloss, C.S., Foroud, T., Koller, D.L., Gershon, E.S., Liu, C., Badner, J.A., Scheftner, W.A., Lawson, W.B., Nwulia, E.A., Hipolito, M., Coryell, W., Rice, J., Byerley, W., McMahon, F.J., Schulze, T.G., Berrettini, W., Lohoff, F.W., Potash, J.B., Mahon, P.B., McInnis, M.G., Zöllner, S., Zhang, P., Craig, D.W., Szelenberger, S., Barrett, T.B., Breuer, R., Meier, S., Strohmaier, J., Witt, S.H., Tozzi, F., Farmer, A., McGuffin, P., Strauss, J., Xu, W., Kennedy, J.L., Vincent, J.B., Matthews, K., Day, R., Ferreira, M.A., O'Dushlaine, C., Perlis, R., Raychaudhuri, S., Ruderfer, D., Hyoun, P.L., Smoller, J.W., Li, J., Absher, D., Thompson, R.C., Meng, F.G., Schatzberg, A.F., Bunney, W.E., Barchas, J.D., Jones, E.G., Watson, S.J., Myers, R.M., Akil, H., Boehnke, M., Chambert, K., Moran, J., Scolnick, E., Djurovic, S., Melle, I., Morken, G., Gill, M., Morris, D., Quinn, E., Mühleisen, T.W., Degenhardt, F.A., Mattheisen, M., Schumacher, J., Maier, W., Steffens, M., Propping, P., Nöthen, M.M., Anjorin, A., Bass, N., Gurling, H., Kandaswamy, R., Lawrence, J., McGhee, K., McIntosh, A., McLean, A.W., Muir,

W.J., Pickard, B.S., Breen, G., St. Clair, D., Caesar, S., Gordon-Smith, K., Jones, L., Fraser, C., Green, E.K., Grozeva, D., Jones, I.R., Kirov, G., Moskvina, V., Nikolov, I., O'Donovan, M.C., Owen, M.J., Collier, D.A., Elkin, A., Williamson, R., Young, A.H., Ferrier, I.N., Stefansson, K., Stefansson, H., Porgeirsson, P., Steinberg, S., Gustafsson, Ó., Bergen, S.E., Nimgaonkar, V., Hultman, C., Landén, M., Lichtenstein, P., Sullivan, P., Schalling, M., Osby, U., Backlund, L., Frisé, L., Langstrom, N., Jamain, S., Leboyer, M., Etain, B., Bellivier, F., Petursson, H., Sigurdsson, E., Müller-Mysok, B., Lucae, S., Schwarz, M., Schofield, P.R., Martin, N., Montgomery, G.W., Lathrop, M., Óskarsson, H., Bauer, M., Wright, A., Mitchell, P.B., Hautzinger, M., Reif, A., Kelsoe, J.R., Purcell, S.M., 2011. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat. Genet.* 43, 977–83. <https://doi.org/10.1038/ng.943>

Ratnaik, R.N., 2003. Acute and chronic arsenic toxicity. *Postgrad. Med. J.* 79, 391 LP – 396. <https://doi.org/10.1136/pmj.79.933.391>

Reith, J., Benkelfat, C., Sherwin, A., Yasuhara, Y., Kuwabara, H., Andermann, F., Bachneff, S., Cumming, P., Diksic, M., Dyve, S.E., Etienne, P., Evans, A.C., Lal, S., Shevell, M., Savard, G., Wong, D.F., Chouinard, G., Gjedde, A., 1994. Elevated dopa decarboxylase activity in living brain of patients with psychosis. *Proc. Natl. Acad. Sci. U. S. A.* 91, 11651–4. <https://doi.org/10.1073/pnas.91.24.11651>

Ripke, S., Dushlaine, C.O., Chambert, K., Moran, J.L., Anna, K., Akterin, S., Bergen, S., Collins, A.L., Crowley, J.J., Kim, Y., Lee, S.H., Magnusson, P.K.E., Sanchez, N., Eli, A., Williams, S., Wray, N.R., Xia, K., Bettella, F., Anders, D., Hougaard, D.M., Kendler, K.S., Lin, K., Morris, D.W., Milovancevic, M., Posthuma, D., Powell, J., Richards, A.L., Consortium, C., Bramon, E., Corvin,



A.P., Donovan, M.C.O., Hultman, M., Sullivan, P.F., 2013. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat. Genet.* 45, 1–26.

<https://doi.org/10.1038/ng.2742>. Genome-wide

Ripke, S., Neale, B.M., Corvin, A., Walters, J.T.R., Farh, K.-H., Holmans, P. a., Lee, P., Bulik-Sullivan, B., Collier, D. a., Huang, H., Pers, T.H., Agartz, I., Agerbo, E., Albus, M., Alexander, M., Amin, F., Bacanu, S. a., Begemann, M., Belliveau Jr, R. a., Bene, J., Bergen, S.E., Bevilacqua, E., Bigdeli, T.B., Black, D.W., Bruggeman, R., Buccola, N.G., Buckner, R.L., Byerley, W., Cahn, W., Cai, G., Campion, D., Cantor, R.M., Carr, V.J., Carrera, N., Catts, S. V., Chambert, K.D., Chan, R.C.K., Chen, R.Y.L., Chen, E.Y.H., Cheng, W., Cheung, E.F.C., Ann Chong, S., Robert Cloninger, C., Cohen, D., Cohen, N., Cormican, P., Craddock, N., Crowley, J.J., Curtis, D., Davidson, M., Davis, K.L., Degenhardt, F., Del Favero, J., Demontis, D., Dikeos, D., Dinan, T., Djurovic, S., Donohoe, G., Drapeau, E., Duan, J., Dudbridge, F., Durmishi, N., Eichhammer, P., Eriksson, J., Escott-Price, V., Essioux, L., Fanous, A.H., Farrell, M.S., Frank, J., Franke, L., Freedman, R., Freimer, N.B., Friedl, M., Friedman, J.I., Fromer, M., Genovese, G., Georgieva, L., Giegling, I., Giusti-Rodríguez, P., Godard, S., Goldstein, J.I., Golimbet, V., Gopal, S., Gratten, J., de Haan, L., Hammer, C., Hamshere, M.L., Hansen, M., Hansen, T., Haroutunian, V., Hartmann, A.M., Henskens, F. a., Herms, S., Hirschhorn, J.N., Hoffmann, P., Hofman, A., Hollegaard, M. V., Hougaard, D.M., Ikeda, M., Joa, I., Julià, A., Kahn, R.S., Kalaydjieva, L., Karachanak-Yankova, S., Karjalainen, J., Kavanagh, D., Keller, M.C., Kennedy, J.L., Khrunin, A., Kim, Y., Klovins, J., Knowles, J. a., Konte, B., Kucinskas, V., Ausrele Kucinskiene, Z., Kuzelova-Ptackova, H., Kähler, A.K., Laurent, C., Lee Chee Keong, J., Hong Lee, S., Legge, S.E., Lerer, B., Li, M., Li, T., Liang, K.-Y., Lieberman, J., Limborska, S., Loughland, C.M., Lubinski, J., Lönnqvist, J., Macek Jr, M., Magnusson, P.K.E., Maher, B.S., Maier, W., Mallet, J., Marsal, S., Mattheisen, M.,

Mattingsdal, M., McCarley, R.W., McDonald, C., McIntosh, A.M., Meier, S., Meijer, C.J.,  
Melegh, B., Melle, I., Mesholam-Gately, R.I., Metspalu, A., Michie, P.T., Milani, L., Milanova,  
V., Mokrab, Y., Morris, D.W., Mors, O., Murphy, K.C., Murray, R.M., Myin-Germeys, I., Müller-  
Myhsok, B., Nelis, M., Nenadic, I., Nertney, D. a., Nestadt, G., Nicodemus, K.K., Nikitina-Zake,  
L., Nisenbaum, L., Nordin, A., O’Callaghan, E., O’Dushlaine, C., O’Neill, F.A., Oh, S.-Y., Olincy,  
A., Olsen, L., Van Os, J., Endophenotypes International Consortium, P., Pantelis, C.,  
Papadimitriou, G.N., Papiol, S., Parkhomenko, E., Pato, M.T., Paunio, T., Pejovic-Milovancevic,  
M., Perkins, D.O., Pietiläinen, O., Pimm, J., Pocklington, A.J., Powell, J., Price, A., Pulver, A.E.,  
Purcell, S.M., Quested, D., Rasmussen, H.B., Reichenberg, A., Reimers, M. a., Richards, A.L.,  
Roffman, J.L., Roussos, P., Ruderfer, D.M., Salomaa, V., Sanders, A.R., Schall, U., Schubert,  
C.R., Schulze, T.G., Schwab, S.G., Scolnick, E.M., Scott, R.J., Seidman, L.J., Shi, J., Sigurdsson,  
E., Silagadze, T., Silverman, J.M., Sim, K., Slominsky, P., Smoller, J.W., So, H.-C., Spencer, C. a.,  
Stahl, E. a., Stefansson, H., Steinberg, S., Stogmann, E., Straub, R.E., Strengman, E.,  
Strohmaier, J., Scott Stroup, T., Subramaniam, M., Suvisaari, J., Svrakic, D.M., Szatkiewicz,  
J.P., Söderman, E., Thirumalai, S., Toncheva, D., Tosato, S., Veijola, J., Waddington, J., Walsh,  
D., Wang, D., Wang, Q., Webb, B.T., Weiser, M., Wildenauer, D.B., Williams, N.M., Williams,  
S., Witt, S.H., Wolen, A.R., Wong, E.H.M., Wormley, B.K., Simon Xi, H., Zai, C.C., Zheng, X.,  
Zimprich, F., Wray, N.R., Stefansson, K., Visscher, P.M., Trust Case-Control Consortium, W.,  
Adolfsson, R., Andreassen, O. a., Blackwood, D.H.R., Bramon, E., Buxbaum, J.D., Børglum,  
A.D., Cichon, S., Darvasi, A., Domenici, E., Ehrenreich, H., Esko, T., Gejman, P. V., Gill, M.,  
Gurling, H., Hultman, C.M., Iwata, N., Jablensky, A. V., Jönsson, E.G., Kendler, K.S., Kirov, G.,  
Knight, J., Lencz, T., Levinson, D.F., Li, Q.S., Liu, J., Malhotra, A.K., McCarroll, S. a., McQuillin,  
A., Moran, J.L., Mortensen, P.B., Mowry, B.J., Nöthen, M.M., Ophoff, R. a., Owen, M.J.,

- Palotie, A., Pato, C.N., Petryshen, T.L., Posthuma, D., Rietschel, M., Riley, B.P., Rujescu, D., Sham, P.C., Sklar, P., St Clair, D., Weinberger, D.R., Wendland, J.R., Werge, T., Daly, M.J., Sullivan, P.F., O'Donovan, M.C., 2014. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511, 421–427. <https://doi.org/10.1038/nature13595>
- Ripke, S., Sanders, A., Kendler, K., 2011. Genome-wide association study identifies five new schizophrenia loci. *Nat. ...* 43, 969–976. <https://doi.org/10.1038/ng.940>. Genome-wide
- Schubert, C.R., Xi, H.S., Wendland, J.R., O'Donnell, P., 2014. Translating human genetics into novel treatment targets for schizophrenia. *Neuron* 84, 537–541. <https://doi.org/10.1016/j.neuron.2014.10.037>
- Sherry, S.T., 2001. dbSNP: the NCBI database of genetic variation. *Nucleic Acids Res.* 29, 308–311. <https://doi.org/10.1093/nar/29.1.308>
- Shumay, E., Wiers, C.E., Shokri-Kojori, E., Kim, S.W., Hodgkinson, C.A., Sun, H., Tomasi, D., Wong, C.T., Weinberger, D.R., Wang, G.-J., Fowler, J.S., Volkow, N.D., 2017. New repeat polymorphism in the AKT1 gene predicts striatal dopamine D2/D3 receptor availability and stimulant-induced dopamine release in the healthy human brain. *J. Neurosci.* 37, 4982–4991. <https://doi.org/10.1523/JNEUROSCI.3155-16.2017>
- So, H.C., Sham, P.C., 2011. Robust association tests under different genetic models, allowing for binary or quantitative traits and covariates. *Behav. Genet.* 41, 768–775. <https://doi.org/10.1007/s10519-011-9450-9>
- SR, F.M.B., Gibbon, M., JBW, W., 1996. Structured Clinical Interview for DSM-IV Axis I Disorders,

Clinician Version (SCID-CV). Am. Psychiatr. Press Washington, DC.

Studholme, C., Hill, D.L., Hawkes, D.J., 1996. Automated 3-D registration of MR and CT images of the head. *Med Image Anal* 1, 163–175.

Sumi, D., Himeno, S., 2012. Role of Arsenic (+3 Oxidation State) Methyltransferase in Arsenic Metabolism and Toxicity. *Biol. Pharm. Bull.* 35, 1870–1875.

<https://doi.org/10.1248/bpb.b212015>

Turkheimer, F.E., Brett, M., Visvikis, D., Cunningham, V.J., 1999. Multiresolution analysis of emission tomography images in the wavelet domain. *J Cereb Blood Flow Metab* 19, 1189–1208. <https://doi.org/10.1097/00004647-199911000-00003>

Tyler, C.R., Allan, A.M., 2014. The Effects of Arsenic Exposure on Neurological and Cognitive Dysfunction in Human and Rodent Studies: A Review. *Curr. Environ. Heal. reports* 1, 132–147.

<https://doi.org/10.1007/s40572-014-0012-1>

Van der Auwera, S., Peyrot, W.J., Milaneschi, Y., Hertel, J., Baune, B., Breen, G., Byrne, E., Dunn, E.C., Fisher, H., Homuth, G., Levinson, D., Lewis, C., Mills, N., Mullins, N., Nauck, M., Pistis, G., Preisig, M., Rietschel, M., Ripke, S., Sullivan, P., Teumer, A., Völzke, H., Consortium, M.D.D.W.G. of the P.G., Boomsma, D.I., Wray, N.R., Penninx, B., Grabe, H., 2018. Genome-wide gene-environment interaction in depression: A systematic evaluation of candidate genes. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* 177, 40–49.

<https://doi.org/10.1002/ajmg.b.32593>

Weinberger, D.R., 2019. Thinking about schizophrenia in an era of genomic medicine. *Am. J.*

Psychiatry. <https://doi.org/10.1176/appi.ajp.2018.18111275>

Weinberger, D.R., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 44, 660–669.

Wiers, C.E., Towb, P.C., Hodgkinson, C.A., Shen, P.-H., Freeman, C., Miller, G., Lindgren, E., Shokri-Kojori, E., Demiral, Ş.B., Kim, S.W., Tomasi, D., Sun, H., Wang, G.-J., Goldman, D., Volkow, N.D., 2017. Association of genetic ancestry with striatal dopamine D2/D3 receptor availability. *Mol. Psychiatry* 1–6. <https://doi.org/10.1038/mp.2017.208>

Wu, K., O’Keefe, D., Politis, M., O’Keefe, G.C., Robbins, T.W., Bose, S.K., Brooks, D.J., Piccini, P., Barker, R.A., 2012. The catechol-O-methyltransferase Val<sup>158</sup>Met polymorphism modulates fronto-cortical dopamine turnover in early Parkinson’s disease: A PET study. *Brain* 135, 2449–2457. <https://doi.org/10.1093/brain/aws157>

Yu, H., Yan, H., Li, J., Li, Z., Zhang, X., Ma, Y., Mei, L., Liu, C., Cai, L., Wang, Q., Shi, Y., Li, T., Zhang, D., Yue, W., 2016. Common variants on 2p16.1, 6p22.1 and 10q24.32 are associated with schizophrenia in Han Chinese population. *Mol. Psychiatry* 1–7. <https://doi.org/10.1038/mp.2016.212>

Zecevic, N., Verney, C., 1995. Development of the catecholamine neurons in human embryos and fetuses, with special emphasis on the innervation of the cerebral cortex. *J. Comp. Neurol.* 351, 509–535. <https://doi.org/10.1002/cne.903510404>

Zhu, Z., Bakshi, A., Vinkhuyzen, A.A.E., Hemani, G., Lee, S.H., Nolte, I.M., van Vliet-Ostaptchouk, J.V., Snieder, H., Esko, T., Milani, L., Mägi, R., Metspalu, A., Hill, W.G., Weir, B.S., Goddard,

M.E., Visscher, P.M., Yang, J., 2015. Dominance Genetic Variation Contributes Little to the Missing Heritability for Human Complex Traits. *Am. J. Hum. Genet.* 96, 377–385.

<https://doi.org/https://doi.org/10.1016/j.ajhg.2015.01.001>

**Table 1**

**Demographic characteristics of the sample**

	<b>AA</b>	<b>GA</b>	<b>GG</b>	<b>Total</b>
<b>N</b>	43	41	8	<b>92</b>
<b>Age (yr ± SD)</b>	28.28 ± 8.34	31.17 ± 8.46	32.50 ± 12.47	<b>29.93 ± 8.84</b>
<b>Gender (male/female)</b>	26/17	21/20	5/3	<b>52/40</b>
<b>Ancestry cluster (EUR/AFR/ASI/other)</b>	31/9/0/3	27/7/2/5	6/0/1/1	<b>64/16/3/9</b>
<b>PET scanner (scanner 1/ scanner 2/ scanner 3)</b>	18/20/5	16/13/12	3/2/3	<b>37/35/20</b>
<b>Tobacco smoking status (non-smoker/smoker)</b>	36/7	31/10	6/2	<b>73/19</b>
<b><math>K_i^{cer}</math> (1/min) whole striatum (± SD)</b>	0.013 ± 0.001	0.013 ± 0.001	0.012 ± 0.001	<b>0.013 ± 0.001</b>
<b><math>K_i^{cer}</math> (1/min) associative striatum (± SD)</b>	0.013 ± 0.001	0.013 ± 0.001	0.012 ± 0.001	<b>0.013 ± 0.001</b>
<b><math>K_i^{cer}</math> (1/min) limbic striatum (± SD)</b>	0.013 ± 0.001	0.013 ± 0.001	0.012 ± 0.001	<b>0.013 ± 0.001</b>
<b><math>K_i^{cer}</math> (1/min) sensorimotor striatum (± SD)</b>	0.013 ± 0.001	0.014 ± 0.002	0.012 ± 0.001	<b>0.013 ± 0.001</b>





