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Disrupted-in-Schizophrenia 1 (DISC1) functional polymorphisms and D₂/D₃ receptor availability: a [¹¹C]-(+)-PHNO imaging study

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Abstract

The Disrupted-in-Schizophrenia 1 (DISC1) protein has been implicated in a range of biological mechanisms underlying chronic mental disorders such as schizophrenia. Schizophrenia is associated with abnormal striatal dopamine signalling, and all antipsychotic drugs block striatal

dopamine $D_{2/3}$ receptors ($D_{2/3}$ Rs). Importantly, the DISC1 protein directly interacts and forms a protein complex with the dopamine D_2 receptor (D_2 R) that inhibits agonist-induced D_2 R internalization. Moreover, animal studies have found large striatal increases in the proportion of D_2 R receptors in a high affinity state (D_2^{highR}) in DISC1 rodent models. Here, we investigated the relationship between the three most common polymorphisms altering the amino-acid sequence of the DISC1 protein (Ser704Cys (rs821616), Leu607Phe (rs6675281) and Arg264Gln (rs3738401)) and striatal $D_{2/3}$ R availability in 41 healthy human volunteers, using [^{11}C]-(+)-PHNO positron emission tomography. We found no association between DISC1 polymorphisms and $D_{2/3}$ R availability in the striatum and D_2 R availability in the caudate and putamen. Therefore, despite a direct interaction between DISC1 and the D_2 R, none of its main functional polymorphisms impact striatal $D_{2/3}$ R binding potential, suggesting DISC1 variants act through other mechanisms.

Introduction

The *Disrupted-in-Schizophrenia 1* (*DISC1*) gene was originally identified at the breakpoint of a balanced t(1;11) (q42;q14.3) translocation in a Scottish family with a high-prevalence of psychiatric disorder¹⁻³. Evidence for a link between *DISC1* and mental disorders such as psychotic and affective disorders emerged from the follow-up of families displaying rare *DISC1* mutations in large family-based studies and association studies⁴⁻⁹. DISC1 protein may be a useful molecule for investigating biological mechanisms underlying mental disorders^{10,11}. Among its neuronal functions, DISC1 is a scaffold protein involved in neuro-signaling and signal transduction, through a wide range of protein interactions^{12,13}.

The DISC1 protein is known to form a protein complex with the dopamine D_2 receptor (D_2 R)¹⁴. The DISC1- D_2 R complex, which formation is induced by D_2 R stimulation, is involved in the regulation of D_2 R internalization and downstream behavioural effects of D_2 signaling^{14,15}. It has been shown that the DISC1- D_2 R complex inhibits agonist-induced D_2 R internalization, whilst its disruption prevents amphetamine-induced locomotor hyperactivity seen in an artificial DISC1 model with a point mutation in exon 2 (*Disc1*-L100P model)¹⁴. The D_2 R exists in two interconverting states, a low-affinity (μM) and a high-affinity (nM) state¹⁶. A switch from D_2 low-affinity to D_2 high-affinity has been described in schizophrenia^{17,18}, with recent evidence showing a higher proportion of D_2 high-affinity receptors (D_2^{highR}) in the putamen of antipsychotic-naïve patients¹⁹. Interestingly, two animal studies investigated the effect of DISC1 on the D_2^{highR} using [^3H]-domperidone binding challenged with dopamine^{20,21}. Both studies found large striatal D_2^{highR} increases compared to wild-type controls: 113% in the *Disc1* L100P model²⁰ and 80% in a full-length DISC1-overexpressing rat model²¹. This increase in proportion D_2^{highR} levels has been suggested as a putative mechanism for the increased locomotor sensitivity to amphetamine seen in the two *DISC1* models, and also consistently reported in other *DISC1* models^{17,20-22}. However, it is noteworthy that divergent findings have been found in $D_{2/3}$ R availability and dopamine D_1 and D_2 receptor levels in rodent studies²². Therefore, the question of whether DISC1 variants are associated with alterations in striatal D_2 R or $D_{2/3}$ R availability remains unanswered, and to our knowledge no study has yet investigated it in humans.

This study examined whether three *DISC1* single nucleotide polymorphisms (Ser704Cys (rs821616), Leu607Phe (rs6675281) and Arg264Gln (rs3738401)) are associated with altered D₂R and/or D_{2/3}R availability in humans. We focused on the Ser704Cys, Leu607Phe and Arg264Gln as they are the most common *DISC1* polymorphisms altering the *DISC1* amino-acid sequence and therefore the *DISC1* protein itself. As non-synonymous missense variants, the polymorphisms result in amino acids changes of respectively serine (A) to cysteine (T) at codon 704 in exon 11 (Minor Allele Frequency (MAF) for cysteine 0.31-0.33), leucine (C) to phenylalanine (T) at codon 607 in exon 9 (MAF for phenylalanine 0.12-0.14) and arginine (G) by glutamine (A) at codon 264 in exon 2 (MAF for glutamine 0.28)²³⁻²⁵. Ser704Cys, Leu607Ph and Arg264Gln have all been shown to have biological impacts on cellular signaling transduction pathways such as extracellular signal-regulated protein Kinases 1 and 2 (ERK1/2) and Wnt signaling^{26,27}. All three polymorphisms have also been associated with an increased risk for psychosis and also with the severity of positive psychotic symptoms in some studies^{23,28-41}. However it should be acknowledged that the involvement of the *DISC1* gene in schizophrenia is debated^{10,42,43} and that these *DISC1* polymorphisms have not been linked to schizophrenia⁴⁴⁻⁴⁶ or any other psychiatric disorder^{47,48} in Psychiatric Genomics Consortium Genome-Wide Association Studies. We hypothesized that the serine (rs821616), leucine (rs6675281) and arginine (rs3738401) alleles would be associated with increased striatal D₂R availability, in accordance with the alleles expressed on the *DISC1* protein in the full-length human *DISC1*-overexpressing model²¹. We used Positron Emission Tomography (PET) to measure D_{2/3}R availability in 41 healthy participants using the high-affinity D_{2/3}R ligand [¹¹C]-(+)-4-propyl-9-hydroxynaphthoxazin (PHNO). The PET ligand [¹¹C]-(+)-PHNO measures the non-displaceable binding potentials (*BP_{ND}*) of D_{2/3}R in the brain^{49,50}. As a full agonist, [¹¹C]-(+)-PHNO may preferentially bind to D₂^{high} compared with D₂^{low} receptors⁵¹. Moreover, although the relative D₂R:D₃R binding fraction of [¹¹C]-(+)-PHNO in the striatum varies between sub-regions, [¹¹C]-(+)-PHNO *BP_{ND}* has been shown to be largely due to binding to D₂ receptors in the caudate and putamen, allowing us to selectively quantify D₂R availability in addition to striatum D_{2/3}R availability⁵²⁻⁵⁴. We first examined the striatum in accordance with the findings from the rodent studies^{20,21}, and then its caudate and putamen subdivisions⁵² in order to focus on D₂ rich striatal regions.

Materials and Methods

Participants

The study was approved by the institutional review board and local research ethics committee (15/LO/0011 and 12/LO/1955). Participants were recruited via online advertisement and in the newspaper. All participants gave informed written consent to take part in the study after its full description. The inclusion criteria for the study were 1) age above 18 years; 2) capacity to give written informed consent. The exclusion criteria were 1) any current medical conditions, or history of medical condition (past minor self-limiting conditions were permitted); 2) history of a psychiatric disorder as determined by the Structured Clinical Interview for DSM-IV Axis 1 Disorders, Clinician Version (SCID-CV)⁵⁵; 3) history of substance abuse/dependence as determined by the Structured Clinical Interview for DSM-IV Axis 1 Disorders, Clinician Version (SCID-CV)⁵⁵; 4) history of head

injury with a loss of consciousness; 5) a family history of any psychiatric disorder in first- or second-degree relatives; 6) contraindications to positron emission tomography (PET) scanning (significant prior exposure to radiation, pregnancy or breast feeding); 7) positive urine drug screen for cannabis as the drug has been shown to influence $D_{2/3}$ availability^{56,57}. All participants provided urine samples to screen for a drug use and pregnancy test in women prior to the scan.

Data acquisition

[¹¹C]-PHNO PET data acquisition—PET images were acquired using a Siemens Biograph HiRez XVI PET scanner (Siemens Healthcare, Erlangen, Germany). A low-dose computed tomography scan was first administered for attenuation and model-based scatter correction followed by the injection of a single intravenous bolus of 0.020-0.029 micrograms/kg [¹¹C]-(+)-PHNO. Dynamic emission data were acquired continuously for 90 minutes after the administration of the radiotracer. The dynamic images were then reconstructed using a filtered back-projection algorithm into 31 frames (8x15 seconds, 3x60 seconds, 5x120 seconds, 15x300 seconds) with a 128 matrix, a zoom of 2.6 and a transaxial Gaussian filter of 5mm.

Structural MRI acquisition—The PET spatial pre-processing pipeline required a high resolution structural magnetic resonance imaging (MRI) scan for each subject. MR images were acquired on a Siemens MAGNETOM Verio 3T MRI scanner and a 32-channel phased-array head-coil. A high-resolution T1-weighted volume was acquired for PET coregistration using a Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence with parameters from the Alzheimer's Disease Research Network (ADNI-GO; 160 slices x240x256, TR=2300ms, TE=2.98ms, flip angle=9°, 1mm isotropic voxels, bandwidth=240Hz/pixel, parallel imaging (PI) factor=2)⁵⁸.

PET analysis

PET images were analysed using MATLAB version 2015B and an automatic analysis pipeline implemented in MIAKAT (MIAKAT release 4.2.6, www.miakat.org)⁵⁹. The ICBM152 high-resolution structural MRI template in Montréal Neurologic Institute (MNI) space was non-linearly warped to the high-resolution T₁-weighted MRI of each participant using Statistical Parametric Mapping (SPM8) (Wellcome Trust Centre for Neuroimaging). The deformation parameters were applied to the CIC atlas which defines the anatomical extents of the striatum, caudate and putamen and a whole cerebellum ROI in MNI space⁵³. The application of deformation parameters brings the ROIs into the native space of each subject's MRI scan. The MRI and ROIs were then downsampled to the PET resolution (2 mm). A frame-by-frame registration process on a single frame of reference was used for motion correction for dynamic PET images. Individual averaged PET images were then co-registered to their respective MRIs using rigid body co-registration. Regional time activity curves (TAC) were obtained by applying individual parcellations to the realigned dynamic images. Our outcome measure of interest was non-displaceable binding (BP_{ND}) of [¹¹C]-(+)-PHNO:

$$BP_{ND} = \frac{f_{ND} B_{avail}}{K_D}$$

where B_{avail} is the proportion of $D_{2/3}R$ s available to be bound by PHNO (i.e. the fraction of receptors not bound by endogenous synaptic dopamine), f_{ND} is the free fraction of PHNO in the brain and $1/K_D$ the affinity of ligand for the target. BP_{ND} was obtained by kinetic modelling with a simplified reference tissue model^{60,61}, using the whole cerebellum as a reference region due its low content in dopaminergic neurons^{62,63}.

Genetic analysis

Genomic DNA was extracted from blood using standard methods⁶⁴. Genotyping of the rs821616 A>T, rs6675281 A>G, rs3738401 A>G polymorphisms was performed using the Illumina Infinium™ CoreExome-24 PsychArray version 1.1 BeadChip Kit (<https://emea.illumina.com>). The genotype frequencies did not significantly deviate from Hardy–Weinberg equilibrium for the rs821616 SNP ($\chi^2=1.636$, $p=0.200$), the rs3738401 SNP ($\chi^2=0.573$, $p=0.449$) and the rs6675281 SNP ($\chi^2=0.124$, $p=0.724$).

Statistical analysis

Statistical Package for the Social Sciences SPSS version 24 was used for all statistical analysis (IBM, Armonk, N.Y.). Independent t test and Mann-Whitney test were used to compare age and injected dose respectively. Participants were divided into two groups for each polymorphism. For rs821616 (Ser704Cys), serine homozygotes (AA) were compared to cysteine homozygotes (TT) and heterozygotes (AT). For rs6675281 (Leu607Phe), leucine homozygotes (CC) were compared to phenylalanine homozygotes (TT) and heterozygotes (TC). For rs3738401 (Arg264Gln), arginine homozygotes (GG) were compared to glutamine homozygotes (AG) and heterozygotes (AA). LDlink⁶⁵ was used to map linkage disequilibrium for the three polymorphisms based on the 1000 genomes phase 3 (version 5) data⁶⁶. Planned-independent t-tests were used to test for an effect of the DISC1 polymorphisms rs821616 (Ser704Cys) and rs3738401 (Arg264Gln) on mean $D_{2/3}R$ availability in the striatum, caudate and putamen. As age has been shown to affect [¹¹C]-(+)-PHNO signal⁶⁷ and subjects were not matched for age for rs6675281 (Leu607Phe), univariate analysis of covariance (ANCOVAs) were used for this polymorphism, with the rs6675281 (Leu607Phe) genotype as the independent variable, $D_{2/3}R$ binding potential for the striatum, the caudate and putamen respectively as the dependent variables, and age entered as covariate. Effect sizes are reported as corrected Cohen's d and partial η^2 . An alpha threshold was set at a 0.05 (two-tailed) for significance for all statistical comparisons.

Results

Forty-two subjects underwent a [¹¹C]-(+)-PHNO PET scan and a structural Magnetic Resonance Imaging scan. One subject was excluded due to positive urine drug screen result for cannabis. This resulted in the final inclusion of 41 subjects (16 females, mean age/year (SD)=25.51 (6.58)). Demographics, scans parameters and PET results are shown in Table 1, with the mean $D_{2/3}R$ binding potentials for the DISC1 Ser704Cys (rs821616), Leu607Phe

(rs6675281) and Arg264Gln (rs3738401) polymorphisms for the striatum caudate, and putamen respectively. The polymorphisms have all been reported to be in linkage equilibrium ($\chi^2=0.48$, $p=0.493$ for rs821616 and rs6675281), ($\chi^2=0.46$, $p=0.496$ for rs821616 and rs3738401) and ($\chi^2=1.84$, $p=0.175$ for rs6675281 and rs3738401). The T carriers and CC homozygotes of the rs6675281 group were not matched for age (mean age (SD) respectively 30.10 (10.08) and 24.03 (4.25), $p=0.009$). Age was therefore included as a covariate for this polymorphism as age has been shown to be linearly related to [^{11}C]-(+)-PHNO signal⁶⁷. There was no effect of rs821616 ($t(39)=-0.204$, $p=0.839$, corrected Cohen's $d=0.06$), rs6675281 ($F(1,38)=1.166$, $p=0.287$, partial $\eta^2=0.03$) or rs3738401 ($t(39)=0.971$, $p=0.338$, corrected Cohen's $d=0.30$) genotype on $D_{2/3}\text{R}$ binding potential in the striatum (Figure 1). To avoid a masking effect by the $D_3\text{R}$, we also examined the caudate and putamen sub-regions, as these regions have negligible $D_2\text{R}/D_3\text{R}$ fraction⁵³. There was no effect of rs821616 ($t(39)=-1.022$, $p=0.313$, corrected Cohen's $d=0.32$), rs6675281 ($F(1,38)=0.352$, $p=0.557$, partial $\eta^2=0.01$) or rs3738401 ($t(39)=0.767$, $p=0.448$, corrected Cohen's $d=0.24$) genotypes on $D_2\text{R}$ binding potential in the caudate (Figure 2). There was no effect of rs821616 ($t(39)=0.121$, $p=0.905$, corrected Cohen's $d=0.04$), rs6675281 ($F(1,38)=1.217$, $p=0.277$, partial $\eta^2=0.03$) and rs3738401 ($t(39)=0.935$, $p=0.355$, corrected Cohen's $d=0.29$) genotypes on $D_2\text{R}$ binding potential in the putamen (Figure 3).

Discussion

This study examined for the first time whether the three most common missense variants of the *DISC1* gene Ser704Cys, Leu607Phe and Arg264Gln have an effect on $D_{2/3}\text{R}$ availability in the striatum, or $D_2\text{R}$ availability in the caudate and putamen, using [^{11}C]-(+)-PHNO PET in 41 healthy participants. Our results showed that none of these polymorphisms were associated with significant alterations of [^{11}C]-(+)-PHNO signal in any of these regions of interest in humans.

Our results are not in line with the rodent studies showing 1) increased $D_2\text{R}$ availability in the artificial point mutation *Disc1* model and *DISC1*-overexpressing rat model using [^3H]domperidone binding challenged with dopamine^{20,21}; and 2) increased striatal $D_{2/3}\text{R}$ availability using [^{11}C]-raclopride, increased $D_2\text{R}$ availability in the medial part of the right rostral striatum using [^3H]-spiperone autoradiography and increased $D_2\text{R}$ levels using real-time PCR in the *hDISC1* model⁶⁸. However, our results are consistent with other rodent studies. For example, no significant differences in striatal $D_2\text{R}$ levels were found in the *DISC1*-overexpressing model using [^3H]-raclopride autoradiography ($D_{2/3}\text{R}$)²¹, in the *hDISC1* model using [^3H]-spiperone autoradiography ($D_2\text{R}$) (lateral part of the right rostral striatum)⁶⁸ or [^{11}C]-raclopride autoradiography ($D_{2/3}\text{R}$)⁶⁹, and in the *Disc1* 2–3 model using real-time polymerase chain reaction⁷⁰. The variable effects on D_2 highlights that *DISC1*'s interactions with D_2 are complex.

The differences observed with the rodent studies could be due to the three human variants having different biological effects compared to the *DISC1* models in which significant effects on D_2 levels were found. Among the *DISC1* models used, only the short interfering RNA knockdown or knockout models (*hDISC1* model) should have loss of function phenotypes whereas all others could have either loss of function, gain of function or

combined phenotypes at the same time. Notwithstanding this, as highlighted above, there is still inconsistency amongst the animal loss of function models (*hDISC1* model). In summary, the DISC1 rodent models are not the same between one another, and not the same as the DISC1 human variants which could explain the discrepancies between the results observed in the literature. The point mutations associated with the variants might also not encompass the binding site with the D₂R. Despite the description of the direct interaction between DISC1 and D₂R¹⁴, its biophysical characterization and the exact site(s) of the DISC1 protein involved remain unknown.

Limitations

This study has several limitations. First, although our sample size is relatively large for human PET studies (N=41), a type II error could account for the observed results, although our sample had more than 80% power to detect a main effect of Cohen's $d=1$ with $\alpha=0.05$ (two-tailed), corresponding to a percent difference between groups of 13% for the striatum. Nevertheless our effect size estimates indicate that, if there is an effect it is likely to be small (Cohen's d values from 0.01 to 0.32), and, as such, an effect is unlikely to be clinically significant on its own if it is present. Increased D₂R binding potential have been found with large effect sizes (Cohen's $d>2$) in the artificial point mutation *Disc1* model and DISC1-overexpressing rat model^{20,21}. However, it should be noted that human variants are likely to have much smaller effects. Second, while some studies report that [¹¹C]-(+)-PHNO binds specifically to D₂^{high}R as opposed to D₂^{low}R⁵¹, other studies present opposing results (Seeman, 2012). Therefore, [¹¹C]-(+)-PHNO PET imaging may be unable to adequately distinguish between high vs low variants of D₂Rs, further diminishing our power to detect a specific effect of DISC1 polymorphisms on D₂^{high}R. Third, the heterogeneous ancestry of the sample should also be acknowledged as a limitation since genetic ancestry has been associated with striatal dopamine D_{2/3}R availability⁷¹. However, the groups for each polymorphism were matched for the different ethnicities ($p=0.586$ for Ser704Cys, $p=0.588$ for Leu607Phe and $p=0.140$ for Arg264, Table 1).

Implications

Our results did not show an effect of the Ser704Cys, Leu607Phe and Arg264Gln polymorphisms on availability of D_{2/3}Rs in the striatum, or D₂Rs in the caudate and putamen regions, with no indication of difference between groups. We therefore have not found evidence that the associations between these polymorphisms and psychotic and other mental disorders (Ser704Cys²⁸⁻³⁶, Leu607Phe³⁷⁻⁴⁰, and Arg264Gln^{23,29,41}) are likely mediated by altered striatal D_{2/3}R availability.

However, statistical epistasis between the DISC1 polymorphisms and other genes involved in the D₂R signaling pathway affecting D₂R cannot be ruled out, as well as effects of other DISC1 variants on the D₂R. Likewise, environmental factors such as exposure to psychosocial stress may also interact with the polymorphisms to affect dopamine function and mediate risk for schizophrenia and other mental illnesses⁷². The DISC1 Ser704Cys, Leu607Phe and Arg264Gln polymorphisms could increase risk of psychotic and others disorders through effect on prefrontal or hippocampal structure and function²⁵, other neurotransmitters such as glutamate⁷³, or alterations in other components of the dopamine

system such as the dopamine receptor (DAT)²¹ or presynaptic dopamine synthesis capacity and release. We have recently shown association between the serine allele of Ser704Cys and increased striatal dopamine synthesis capacity in healthy participants⁷⁴. Interestingly, recent studies indicate the t(1;11) translocation may increase the risk of psychosis through various other mechanisms, including altered DNA methylation⁷⁵, regulation of N-methyl-D-aspartate receptors (NMDAR) motility⁷⁶ and/or⁷⁶ added effects of the translocation and a variable subset of potential phenotypic polymorphisms⁷⁷. Future studies should aim at clarifying how the DISC1 protein interacts with the D₂R and whether the DISC1 Ser704Cys, Leu607Phe and Arg264Gln polymorphisms affect D₂R availability in clinical populations.

Conclusions

The three most common DISC1 polymorphisms Ser704Cys, Leu607Phe and Arg264Gln are not associated with significant alterations in striatal D_{2/3}R or D₂R availability in healthy volunteers. This indicates the mechanism mediating associations between these variants and psychotic disorders is unlikely to involve altered D₂ availability.

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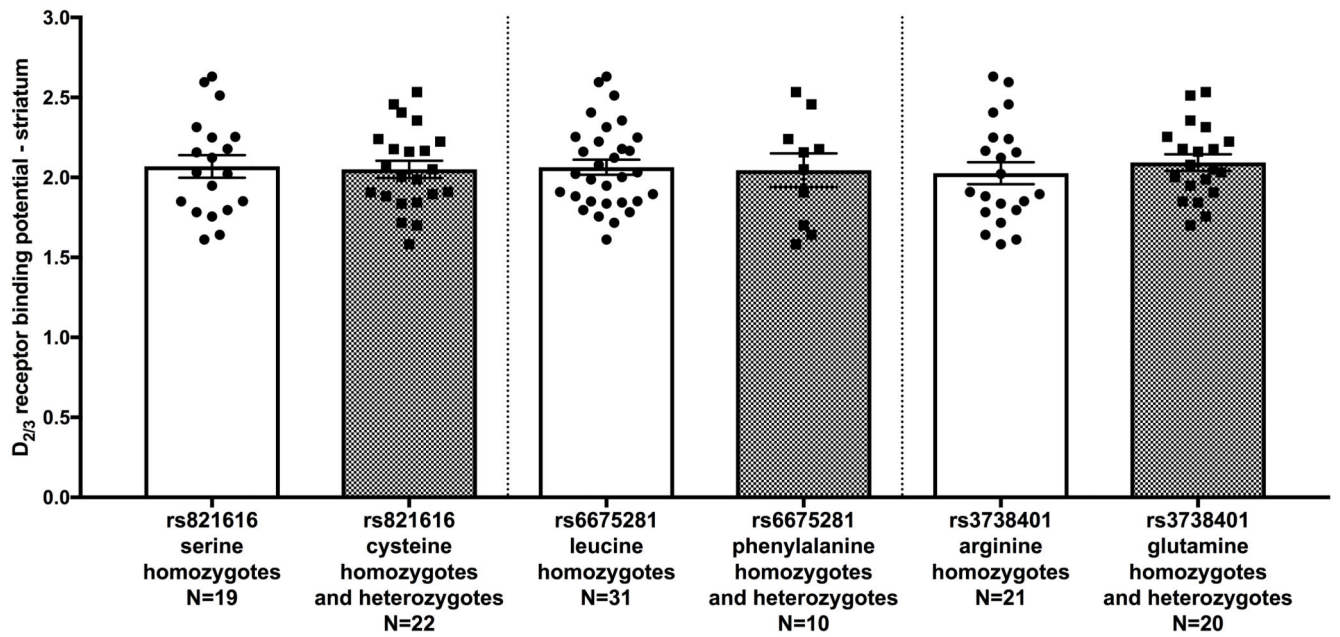


Figure 1.
Ser704Cys, Leu607Phe and Arg264Gln and dopamine $D_{2/3}$ receptor binding potentials in the striatum

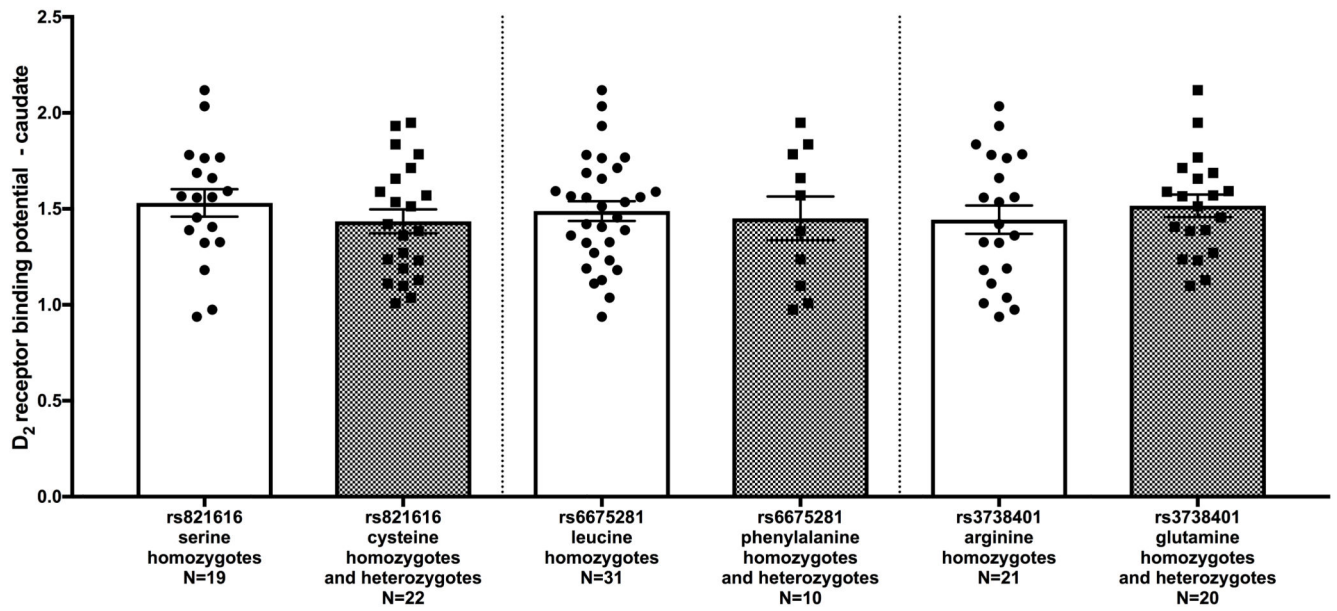


Figure 2.
Ser704Cys, Leu607Phe and Arg264Gln and dopamine D₂ receptor binding potentials in the caudate

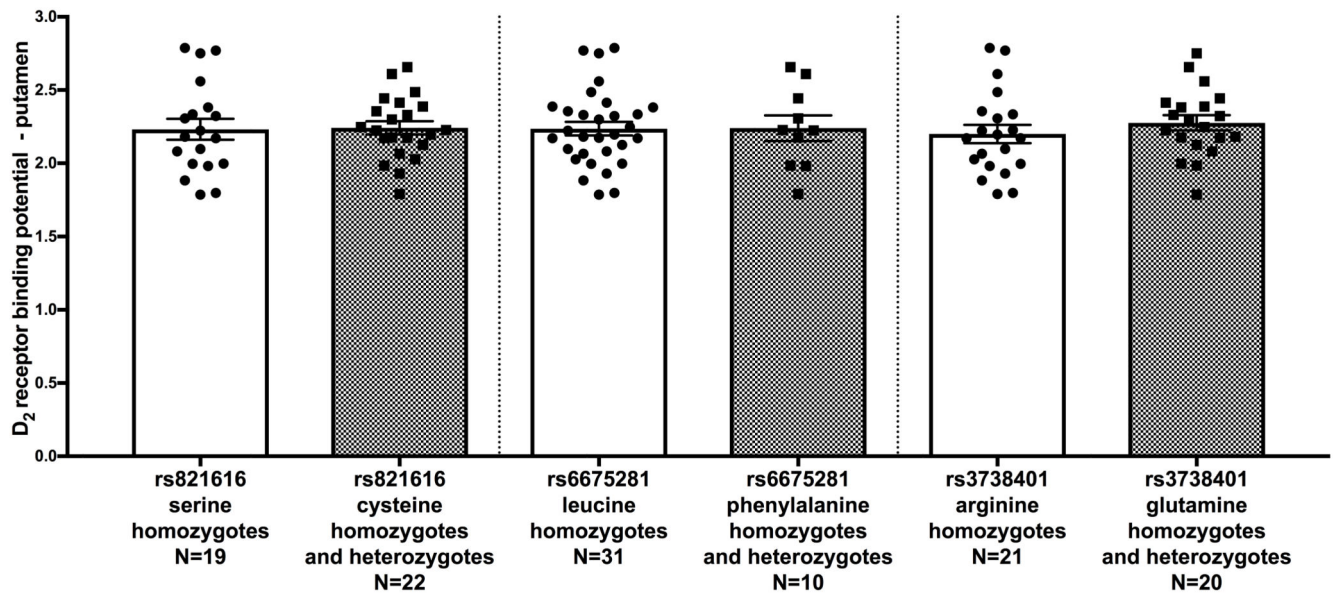


Figure 3.
Ser704Cys, Leu607Phe and Arg264Gln and dopamine D₂ receptor binding potentials in the putamen

Table 1
Demographics and PET parameters

		DISC1 Ser704Cys (rs821616)			DISC1 Leu607Phe (rs6675281)			DISC1 Arg264Gln (rs3738401)		
	Total	Serine homozygotes AA carriers	Cysteine homozygotes and heterozygotes (TT or AT carriers)	p value	Leucine homozygotes (CC carriers)	Phenylalanine homozygotes and heterozygotes (TC or TT carriers)	p value	Arginine homozygotes GG carriers	Glutamine homozygotes and heterozygotes (AG or AA carriers)	p value
Demographics										
Males, n (%)	25	9 (36%)	16 (64%)	0.097 ⁱⁱ	18 (72%)	7 (28%)	0.501 ⁱⁱ	14 (56%)	9 (34%)	0.444 ⁱⁱ
Females, n (%)	16	10 (62.5%)	6 (37.5%)		13 (81.3%)	3 (18.7%)		7 (43.8%)	11 (56.2%)	
Total n (%)	41	19 (46.3%)	22 (7 TT) (53.7%)		31 (75.6%)	10 (1 TT) (24.4%)		21 (51.2%)	20 (2 AA) (48.8%)	
Age, mean (SD)	25.51 (6.58)	25.32 (5.06)	25.7 (7.79)	0.862 ⁱ	24.03 (4.25)	30.10 (10.08)	0.009 ⁱ	25.19 (5.57)	25.85 (7.64)	0.753 ⁱ
White Caucasian, n (%)	26	11 (42.3%)	15 (57.7%)	0.586 ⁱⁱ	19 (73.1%)	7 (26.9%)	0.588 ⁱⁱ	11 (42.3%)	15 (57.7%)	0.140 ⁱⁱ
Black British, n (%)	12 (Black Africans n=11; Black Caribbean n=1)	7 (58.3%)	5 (41.7%)		9 (75%)	3 (25%)		9 (75%)	3 (25%)	
Mixed, n (%)	3 (East Asian: n=1; Mixed White Caucasian/South Asian n=1; Mixed White Caucasian/Central Asian n=1)	1 (33%)	2 (66%)		3 (100%)	0 (0%)		1 (33%)	2 (66%)	
PET parameters										
Radioactivity injected (MBq), mean (SD)	177.16 (47.36)	176.98 (51.31)	177.32 (44.90)	0.983 ⁱ	179.28 (48.02)	170.60 (47.13)	0.620 ⁱ	176.89 (51.68)	177.44 (43.72)	0.971 ⁱ
Mass Injected (µg), mean (SD)	1.57 (0.32)	1.56 (0.31)	1.58 (0.34)	0.792 ⁱ	1.57 (0.35)	1.58 (0.23)	0.881 ⁱ	1.57 (0.33)	1.58 (0.33)	0.939 ⁱ
D _{2/3} R BP _{ND} striatum, mean (SD)	2.05 (0.27)	2.05 (0.31)	2.04 (0.24)	0.839 ⁱ	2.05 (0.26)	2.05 (0.32)	0.287 ⁱⁱⁱ	2.01 (0.31)	2.09 (0.23)	0.338 ⁱ
D ₂ R BP _{ND} caudate, mean (SD)	1.48 (0.30)	1.53 (0.31)	1.43 (0.29)	0.313 ⁱ	1.49 (0.29)	1.45 (0.36)	0.557 ⁱⁱⁱ	1.44 (0.34)	1.52 (0.26)	0.448 ⁱ

	Total	DISC1 Ser704Cys (rs821616)			DISC1 Leu607Phe (rs6675281)			DISC1 Arg264Gln (rs3738401)		
		Serine homozygotes AA carriers	Cysteine homozygotes and heterozygotes (TT or AT carriers)	p value	Leucine homozygotes (CC carriers)	Phenylalanine homozygotes and heterozygotes (TC or TT carriers)	p value	Arginine homozygotes GG carriers	Glutamine homozygotes and heterozygotes (AG or AA carriers)	p value
D ₂ R <i>BP_{ND}</i> putamen, mean (SD)	2.24 (0.26)	2.23 (0.31)	2.24 (0.21)	0.905 ⁱ	2.23 (0.26)	2.24 (0.28)	0.277 ⁱⁱⁱ	2.20 (0.29)	2.28 (0.23)	0.355 ⁱ

ⁱIndependent t test

ⁱⁱPearson Chi-Square

ⁱⁱⁱANCOVA

D₂/3R *BP_{ND}*: dopamine D₂/3 receptor non-displaceable binding potential

MBq: megabecquerel

SD: standard deviation

µg: microgram