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Association of genetic ancestry with striatal dopamine D2/D3 receptor availability

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Abstract

Despite ethnic differences in allele frequencies of variants in dopaminergic genes associated with dopamine D2/D3 receptor availability (D2R), no study to date has investigated the relationship between genetic ancestry and striatal D2R. Here, we show that ancestry informative markers significantly predict dorsal striatal D2R in 117 healthy ethnically diverse residents of the New York metropolitan area using Positron Emission Tomography (PET) with [^{11}C]raclopride (p<0.0001), while correcting for age, sex, BMI, education, smoking status, and estimated socioeconomic status (ZIP codes). Effects of ethnicity on D2R were not driven by variation in dopaminergic candidate genes. Instead, candidate gene associations with striatal D2R were diminished when correcting for ancestry. These findings imply that future studies investigating D2 receptor genes should covary for genetic ancestry or study homogeneous populations. Moreover, ancestry studies on human neurobiology should control for socioeconomic differences between ethnic groups.

Keywords

ancestry; dopamine; dopamine receptor; ethnicity; genetic ancestry; positron emission tomography

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Conflict of Iinterest

The authors declare no competing financial interests.

Introduction

Three-dimensional cortical geometry [1], cortical surface and total brain volume have been shown to be associated with genetic ancestry [2, 3]; which is consistent with a strong association between ancestry and the shape of cranial bones in humans [4]. Thus, studies investigating genetic markers in human brain development may have to correct for genetic ancestry or self-reported ethnicity.

Individual differences in striatal dopamine D2/D3 receptor (D2R) expression have been implicated in motivated behaviors, movement, and neuropsychiatric diseases such as schizophrenia [5–8]. D2R availability may be influenced by both environmental and genetic factors. Environmental factors that have been shown to influence D2R in monkeys and humans include social status and perceived social support [9–13]. In addition, repeated exposure to drugs of abuse, including alcohol and nicotine, has been associated with decreased striatal D2R [14], as well as morbid obesity [15]. Similarly, aging [16, 17], sleep deprivation [18–20], BMI [21, 22] and education [11] have been linked with reduced striatal D2R availability. Genetics are also likely to influence D2R; directly or by modulating environmental factors that affect striatal D2R expression. In monozygotic and dizygotic twins, variability in D2R availability was recently found to be a highly heritable trait (i.e., narrow sense heritability = 0.67) [23]. Several polymorphisms have been associated with D2R availability and dopamine function in PET studies, including *ANKK1* variant rs1800497, which is 10 kb downstream from *DRD2* (Taq1A), *DRD2* variants rs1079597 (Taq 1B), rs1076560, and rs6277 [24], *DRD3* rs6280, *COMT* 34680, *OPRM1* rs1799971, *DAT* SLC6A3; among others (meta-analyzed in [25]). Of these, the association between Taq1A with striatal D2R availability was most frequently observed; however these are all individually small studies and null findings have also been reported [2526]. Despite known ethnic differences in allele frequencies of these genetic variants [27], it currently remains unknown whether D2R availability is associated with genetic ancestry and whether single gene findings may be driven or influenced by ancestry.

Here we investigated whether genetic ancestry predicts striatal D2R availability as measured with positron emission tomography (PET) and [^{11}C]raclopride in 117 healthy volunteers with mixed ethnic background, while correcting for the potential confounding factors of age, sex, BMI, education, smoking status, and estimated socioeconomic status based on individuals' ZIP codes. We further tested whether the effect of genetic ancestry on D2R availability was mediated by polymorphisms in candidate genes previously associated with striatal D2R availability, which are known to have ethnic differences in allele frequencies.

Materials and Methods

Participants

PET [^{11}C]raclopride images and DNA of 120 healthy individuals (age: 18–49) were selected from our Brookhaven National Laboratory PET database. Participants resided in the New York metropolitan area and served as healthy volunteers in previous [^{11}C]raclopride PET studies [19, 28–31] (see Supplementary Material S1 for PET protocol information). In addition, all participants provided written informed consent agreeing to provide a blood sample to

assess genetic effects on PET data. The genetics study was approved by the Committee on Research in Human Subjects at Stony Brook University (IRB net number 289072). For all PET studies, healthy volunteer exclusion criteria were: present or past history of substance use disorders other than nicotine and tobacco, present or past history of neurological or psychiatric disease including seizures, high levels of anxiety, panic attacks, psychosis; current medical illness that may affect brain function; current or past history of cardiovascular disease; head trauma with loss of consciousness > 30 minutes; urine positive for psychoactive drugs; history of vascular headaches. Due to missing data for education years (n=1) and participants' ZIP codes (n=2), we proceeded with 117 healthy individuals for further analyses (22 female; 9 smokers, 4 past smokers). Table 1 provides participants' demographics.

Socioeconomic Status

Characteristics of neighborhoods were assessed by mapping the subjects' addresses to the 2000 census tract boundaries (http://factfinder.census.gov) and used as a surrogate for socioeconomic status (SES). U.S. census tract boundaries are based on 4,000–6,000 persons, determined in collaboration with local committees to represent demographically homogeneous areas approximating neighborhoods [32]. Address matching was available for 117 participants from the New York metropolitan area. The variables "per capita household income" and "percent of occupied housing units that are occupied by the owner" were divided by the national average, and used for our regression model.

Ancestry Informative Markers (AIMs)

Ethnic origin for individual study subjects was characterized using a panel of 2500 ancestry-informative markers and individual comparison to the 51 worldwide populations represented in the Human Genome Diversity Cell Line Panel of the Human Genome Diversity Project (HGDP) and Centre d'Etude du Polymorphisme Humain (CEPH), which includes 1,051 individuals (http://www.cephb.fr/HGDP-CEPH-Panel). Genotyping for the study cohort was performed using the Illumina human OmniExpressExome array (Illumina, San Diego) and compared to data from the Human HapMap 550K array for the CEPH diversity panel.

Ancestry scores were calculated using Structure, version 2.2 (http://pritch.bsd.uchicago.edu/structure.html) where data for the CEPH diversity panel was run along with data for a single study subject so that the derived scores for each study participant were not influenced by others within that cohort [32, 33]. This "anchored" approach yields a stable factor structure interpretable in the context of worldwide genetic diversity and is unaffected by the addition of samples to the study cohort unlike factors derived by principal components analysis. The number of ethnic clusters (K) was defined by running the data with different K values and computing the probability of K=n. The six-factor solution was optimal for this marker set and closely replicates solutions found by Rosenberg, Pritchard [34] for the same 51 reference populations determined with short tandem repeat markers and SNPs [34, 35], and by the 186 SNP panel described [33], wherein all the non-Arabic African populations in the Human Genome Diversity Cell Line Panel are identified by a single African factor in this six-factor solution.

Multivariate Pillai's Trace analysis showed that in the current sample self-reported ethnicity strongly predicted genetic ancestry scores (V=1.28, $F_{(30, 550)}$=6.34, p<0.0001) (Supplementary Fig. 1). Separate univariate ANOVAs showed that self-reported ethnicity significantly predicted African ($F_{(5,116)}$=102.7, p<0.0001), European ($F_{(5,116)}$=142.9, p<0.0001), American ($F_{(5,116)}$=8.11, p<0.0001) and Asian ($F_{(5,116)}$=3.2, p=0.01) genetic ancestry scores, but not Far East Asia or Oceania (p>0.05).

PET imaging, processing and analyses

All [^{11}C]raclopride scans were performed on a Siemens, HR+ scanner (resolution 4.5 × 4.5 × 4.5 mm full width half-maximum, 63 slices) at the BNL PET Imaging Center. The procedures for subjects positioning and scanning protocols have been described previously [36, 37]. In short, emission scans were started immediately after injection of 4–8 mCi (specific activity 0.5–1.5 Ci/μM at end of bombardment or EOB). Twenty dynamic emission scans were obtained from time of injection up to 60 min and arterial sampling was used to quantify total carbon-11 and unchanged [^{11}C]raclopride in plasma. A total of n=62 participants (53%) received a placebo during PET scanning, whereas the other 55 (47%) were tested at a baseline condition. All placebo scans were done before active pharmacological intervention scans (i.e., methylphenidate challenges), thus participants had not been exposed methylphenidate prior to the placebo. D2R measures between the participants studied at baseline versus studied after placebo did not differ for any striatal region (all p>0.1). This indicates that in the healthy controls without prior experience with methylphenidate there were no effect of drug expectation when given placebo, justifying the integration of the data sets obtained under a baseline and a placebo condition.

We calculated regional measures of non-displaceable binding (BP_{ND}) for hand-drawn caudate, putamen and ventral striatum (VS) regions of interest (ROIs) using a procedure previously described [38]. ROIs had the same size and shape across subjects. The ratio of the distribution volume in striatal regions was computed to that in the cerebellum was computed to obtain BP_{ND} measures, which corresponds to Bmax/Kd – 1 and reflects D2R availability [39].

Statistical analyses

Multiple linear regression was used to predict D2R availability, independently for caudate, putamen and VS, as a function of the independent AIMs (IBM, Armonk, New York). Covariates were: age, sex, BMI, education, smoking status (9 smokers, 4 past smokers), and ZIP code's consensus tracts "per capita income" and "housing units occupied per owner" as estimates of socioeconomic status. Table 2 provides zero-order Pearson correlations between all variables in the regression models.

Results

African and European ancestry differentially predict D2R in Caudate and Putamen

The following six genetic ancestry scores were obtained: Africa, Europe, Asia, Far East Asia, Oceania, America. Since African and European ancestry scores explained 93% of

variance (other scores explained <5%, Table 1), we performed regression analyses for African and European ancestry only.

Regression models showed that African and European ancestry significantly predicted striatal D2R availability in dorsal but not ventral striatum. That is, African ancestry negatively predicted D2R availability in bilateral caudate (β =−0.30, $t_{(107)}$=−4.14, p<0.0001) and putamen (β=−0.33, $t_{(107)}$=−4.74, p<0.0001), but not VS (β=0.03, $t_{(107)}$=0.37, p=0.71) (Fig. 1; Supplementary Table 1).

European ancestry, however, positively predicted availability in Caudate: β=0.29, $t_{(107)}$=4.01, p<0.0001; Putamen: β=0.33, $t_{(107)}$=4.67, p<0.0001; but not in VS: (β=−0.03, $t_{(107)}$=−0.31, p=0.75) (Fig. 2; Supplementary Table 2).

Age predicted D2R in both models for all 3 striatal ROIs (all p<0.0001; Supplementary Table 1 and 2), which is in line with previous studies [16, 17]. There were no other significant predictors of D2R, although Per capita income and Housing units occupied per owner reached trend levels for D2R Caudate and D2R Putamen (p<0.09).

Candidate genes associated with genetic ancestry did not mediate effects on D2R

Candidate genes *ANKK1* Taq 1A, *DRD2* SNPs, rs6277, rs6274, rs6278, and rs1076560, *DRD3* rs6280, *COMT* rs4680, *OPRM1* rs1799971 and *Leptin* rs12706832 were associated with African and European ancestry scores (Table 3). However, none of the candidate genes predicted D2R availaiblity when corrected for multiple comparisons. Therefore, effects of African ancestry on striatal D2R availability in caudate and putamen were not mediated by known candidate gene variants.

Discussion

Our data indicate a strong association between striatal D2R availability and genetic ancestry in a healthy human population of mixed ancestry from the New York metropolitan area. Specifically, we show that African genetic ancestry negatively predicts striatal D2R availability in the caudate and putamen, whereas European genetic ancestry was a positive predictor of D2R in these striatal areas. There were no effects for the VS. Effects were both present without covariates, as well as when corrected for the potential confounding factors age sex, BMI, education, smoking status, and estimated socioeconomic status. In the current study, however, the only significant predictors of striatal D2R were age (ventral and dorsal striatum) and ethnicity (dorsal striatum only). Although genetic ancestry has previously been associated with cortical geometry [1], cortical surface and total brain volume [2, 3], this study is the first in reporting an association between genetic ancestry and striatal D2R.

If replicated, the findings reported here may have implications for pharmacological treatment targeting D2R, and ethnic differences in psychopharmacological responses have been previously described [40, 41]. For example, evidence exists that vulnerability attributed to genetic ancestry is seen in long term use of antipsychotic D2R antagonists, with increased risk of tardive dyskinesia in African Americans when compared to Caucasian Americans [42–44]. An association has been found between a polymorphism in *AKT1*, a gene acting

downstream of D2R, and tardive dyskinesia present in African Americans but not in Caucasians [45]. However, evidence for an ethnic association with tardive dyskinesia is preliminary and in need of further clinical and neurobiological investigation.

We further showed that African and European ancestry was strongly associated with candidate genes previously associated with D2R (reviewed in: [25]): Taq 1A, *DRD2* SNPs rs6277, rs6274, rs6278, rs1076560, and *DRD3* rs6280, *COMT* rs4680, *OPRM1* rs1799971 and *Leptin* rs12706832; but not *DRD2* rs1079597 (Taq 1B). This was in line with allele frequencies in the NCBI 1000 genome dataset (https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes) and previous reports [27]. Nevertheless, in our sample only small associations were found between genotype and D2R for rs6277 (Caudate and Putamen), Taq1A (Caudate only), Taq 1B (VS only) and *OPRM1* (VS only), significance levels did not remain after correction for multiple comparisons. Exploratory tests showed that candidate gene associations were diminished when correcting for ancestry ($p>0.05$), whereas the strong association between genetic ancestry and striatal D2R availability were not driven by variation in *DRD2* candidate SNPs (all $p<0.0001$). Thus, previous effects of single genes on D2R availability in mixed population samples may have been largely a result of population structure, as this was often not controlled for. Five out of 25 PET D2R studies corrected for genetic ancestry or self-reported ethnicity [242526]. Future D2R imaging genetic studies should thus correct for genetic ancestry, e.g., [46, 47], or study populations that are relatively homogenous and hence not subject to the problem of unrecognized stratification [48].

Our findings may well have been a result of environmental exposures that are likely to differ between ethnic groups. Human genetic variation largely differs within - not between - human populations, and structural inequality in society largely explains racial differences in health status for common disease [49]. We attempted to correct for socioeconomic status, but could not do so extensively; since our measure of SES (i.e., average per capita income based on a person's ZIP code) was negatively associated with ancestry as well as positively with D2R, the problem of residual confounding arises [50]. From studies in animals we have learned that higher-ranking cynomolgus monkeys [9, 10, 12] and rats [51] have higher levels of D2R in striatum than subordinate ones, and SES has been shown to be correlated with striatal D2R in humans [11, 13]. Therefore, caution must be taken when interpreting the current results as a result of genetic ancestry, for they may have been influenced by social stressors known to differ between ethnic groups in the US such as perceived discrimination, social exclusion, childhood trauma, nutrition, general health and other factors [525354]. In our study, it is therefore not possible to disentangle the contribution of social factors known to influence D2R expression in the brain from intrinsic biological factors, as is the case in many studies where the intent is to determine causal explanations of disparities [55]. Further limitations include the limited sample size; while our sample comprised of 117 healthy participants is larger than any previous PET imaging genetics studies that assessed brain D2R as an outcome measure (ranging from N=12 [25] to N=84 [24]), it is nevertheless small compared to samples of behavioral genetic studies limiting our ability to detect diversity within ethnic subgroups.

In this study we corroborate an association between genetic ancestry and D2R availability in dorsal but not in ventral striatum. Since the dorsal striatum predominantly contains D2

receptors whereas the ventral striatum contains equivalent levels of D2 and D3 receptors, the differences in these regions might indicate that the association with D2R availability predominantly reflect D2 and not D3 receptors. However, it is also possible that the differences reflect greater sensitivity of dorsal rather than ventral striatal regions to environmental factors [56].

The findings have two major implications: (1) future studies investigating D2 receptor genes should include covariate adjustment for genetic ancestry, or study a homogeneous population; and (2) given significant SES differences between racial/ethnic groups in the USA, our results may be consistent with prior preclinical and human studies showing adverse effects of social stressors on striatal D2R. A more thorough evaluation of environmental correlates of ethnicity that potentially mediate its effects on striatal D2R is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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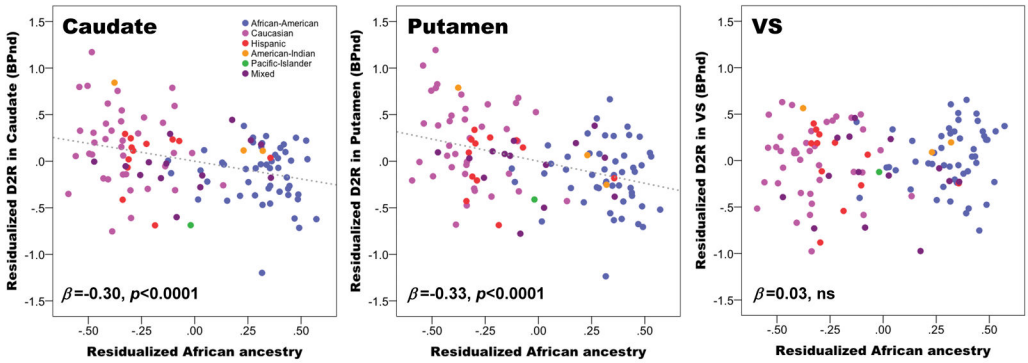

Figure 1.

African ancestry negatively predicted D2R availability in the caudate and putamen (p<0.0001), but not ventral striatum (VS); corrected for age, sex, BMI, education, smoking status and estimated socioeconomic status based on individuals' ZIP codes (per capita income and housing units occupied by owner).

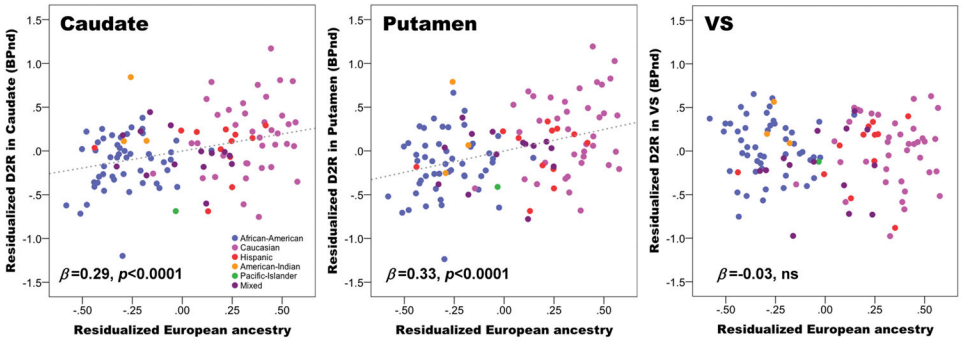

Figure 2.

European ancestry positively predicted D2R availability in the caudate and putamen (p<0.0001), but not ventral striatum (VS); corrected for age, sex, BMI, education, smoking status and estimated socioeconomic status based on individuals' ZIP codes (per capita income and housing units occupied by owner).

Table 1

Demographics, ancestry informative markers and striatal D2R availability in N=117 volunteers. Measures of D2R availability correspond to non-displaceable binding potential (BP_{ND}).

	Healthy Volunteers N=117		
Characteristic	**Mean**	**SD**	**Range**
Age, years	33.1	8.4	18–49
Years of education	14.2	2.1	9–20
BMI	25.4	3.1	18.5–31.2
Census tract: per capita income/national average	1.0	0.62	0.4–3.8
Census tract: housing units occupied by owner/national average	0.52	0.36	0.05–1.4
AIMs Africa	0.44	0.36	0.00–0.98
AIMs Europe	0.49	0.35	0.00–0.99
AIMs Asia	0.02	0.02	0.00–0.11
AIMs Far East Asia	0.01	0.02	0.00–0.13
AIMs Oceania	0.01	0.01	0.00–0.08
AIMs America	0.04	0.08	0.00–0.60
D2R Caudate	2.6	0.52	1.5–4.0
D2R Putamen	3.3	0.57	2.0–4.8
D2R VS [§]	2.9	0.45	1.8–4.0

Abbreviations: Aims = Ancestry informative markers; BMI = body mass index, D2R = Dopamine D2/D3 receptor availability, VS = ventral striatum

[§]In VS [^{11}C]raclopride reflects binding to both D2 and D3 receptors whereas in caudate and putamen it largely reflects binding to D2 receptors.

Table 2

Zero-order correlations between striatal D2R availability and all covariates added to the regression models.

	D2R Cau	D2R Put	D2R VS	Aims Africa	Aims Euro	Age	Sex	BMI	Edu	Current smoke	Ever smoke	Per capita $
D2R Caudate	1											
D2R Putamen	**.93*****	1										
D2R VS	**.52*****	**.60*****	1									
African ancestry	**−.31****	**−.34*****	−.05	1								
European ancestry	**.30****	**.33*****	.05	**−.97*****	1							
Age	**−.66*****	**−.66*****	**−.53*****	0.02	−.00	1						
Sex	.15	.14	.06	.12	−.12	**−.23***	1					
BMI	**−.29****	**−.26****	**−.20****	.06	−.09	**.39*****	**−.19***	1				
Education	−.03	−.03	−.02	.01	.06	.14	**.10**	−.08	1			
Current smoker	−.02	−.03	−.17	.11	−.09	−.02	.11	**−.20***	−.01	1		
Ever smoker	−.02	−.03	−.11	.09	−.08	−.03	.11	**−.20***	−.07	**.82*****	1	
Per capita income $	**.22***	**.22***	**.19***	**−.33*****	**.37*****	−.02	−.09	−.11	**.27****	**−.20***	**−.25****	1
Housing units occupied by owner	0.07	.06	.09	**−.35*****	**.36*****	−.03	**−.22***	−.17	.13	**−.19***	**−.26****	**.39*****

D2R = dopamine D2/D3 receptor availability (BP_{ND}) in Caudate, Putamen and Ventral Striatum (VS). Age in years, BMI = Body Mass Index. Sex = female (1) versus male (0). Current smoke = current smoker (1) versus non-smoker (0). Ever smoke = current or ex-smoker (1) versus never-smoker (0). Per capita income and Housing units occupied by owner were divided by the national average.

Significance levels in bold:

* $p<0.05$

** $p<0.01$

*** $p<0.001$

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Table 3

Candidate genetic polymorphisms and its associations with previously reported D2R availability, allele frequency in African American and Utah population (1000 genomes), genetic ancestry and striatal D2R availability (N=117)

	Association with D2R meta-analysis:[24]	**1000 genomes minor allele frequency African American/Utah**	**Allele freq (n)**	**Pearson's *r* African/ European ancestry**	**D2R Caudate β *d***	**D2R Putamen β^d**	**D2R VS β^d**
Taq 1A (*ANKK1* rs1800497)	A carriers lower D2R than GG	A=0.43/0.20	AA (5) [a] AG (52) GG (59)	−0.13/**0.19** *	**0.16** *	0.14	0.10
Taq 1B (*DRD2* rs1079597)	T carriers lower D2R than CC	T=0.21/0.14	TT (2) TC (27) CC (88)	0.18/−0.11	0.12	0.09	**0.17** *
DRD2 rs6274	-	C=0.24/0.01	CC (1) AC (19) AA (97)	**−0.43** ***/**0.42** ***	0.09	0.07	−0.09
DRD2 rs6277 (C957T)	A allele higher D2R than G carriers	A=0.15/0.50	AA (14) GA (38) GG (65)	**0.47** ***/**−0.49** ***	**−0.22** *	**−0.23** *	−0.08
DRD2 rs6278	-	A=0.09/0.14	AA (2) AC (20) CC (95)	**0.33** ***/**−0.26** **	0.09	0.07	0.13
DRD2 rs1076560	A carriers lower D2R than CC	A=0.11/0.14	AA (2) [b] AC (21) CC (92)	**0.29** **/**−0.22** **	0.09	0.07	0.12
DRD3 rs6280	No D2R difference	T=0.25/0.66	TT (28) CT (43) CC (46)	**0.49** ***/**−0.48** ***	−0.10	−0.09	−0.06
COMT rs4680	No D2R difference	A=0.27/0.46	AA (18) AG (55) GG (44)	**0.22** */**−0.21** *	−0.06	−0.02	−0.05
OPRM1 rs1799971	No D2R difference	G=0.05/0.15	GG (3) AG (18) AA (96)	**0.28** **/**−0.22** *	0.04	0.07	**0.28** **
Leptin rs12706832	No D2R difference	G=0.20/0.56	GG (17) AG (53) AA (47)	**0.47** ***/**−0.45** **	−0.13	−0.14	0.09

D2R = dopamine D2/D3 receptor availability (BP_{ND}) in Caudate, Putamen and Ventral Striatum (VS). Allele frequency = minor (−1), intermediate (0) and major (1).

Significance levels in bold:

* $p<.05$

** $p<.01$

*** $p<.001$

[a] n=116

[b] n=113

[c] n=109

[d] corrected for age, sex, BMI, education, smoking status, and ZIP code's consensus tracts "per capita income" and "housing units occupied per owner" as estimates of socioeconomic status.