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

Corinde E. Wiers¹, Par C. Towb¹, Colin A. Hodgkinson², Pei-Hong Shen², Clara Freeman¹, Gregg Miller¹, Elsa Lindgren¹, Ehsan Shokri-Kojori¹, Şükrü Barış Demiral¹, Sunny Kim¹, Dardo Tomasi¹, Hui Sun², Gene-Jack Wang¹, David Goldman², and Nora D. Volkow¹,³

¹Laboratory of Neuroimaging, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda 20892, Maryland ²Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda 20852, Maryland ³National Institute on Drug Abuse, National Institutes of Health, Bethesda 20892, Maryland

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 [¹¹C]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
Introduction

Three-dimensional cortical geometry, cortical surface and total brain volume have been shown to be associated with genetic ancestry, which is consistent with a strong association between ancestry and the shape of cranial bones in humans. 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. 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. In addition, repeated exposure to drugs of abuse, including alcohol and nicotine, has been associated with decreased striatal D2R, as well as morbid obesity. Similarly, aging, sleep deprivation, BMI, and education 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). 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, DRD3 rs6280, COMT 34680, OPRM1 rs1799971, DAT SLC6A3; among others (meta-analyzed in ). 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. Despite known ethnic differences in allele frequencies of these genetic variants, 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 [11C]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 [11C]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 [11C]raclopride PET studies (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. 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. 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 for the same 51 reference populations determined with short tandem repeat markers and SNPs, and by the 186 SNP panel described, 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 $[^{11}\text{C}]$raclopride scans were performed on a Siemens, HR+ scanner (resolution $4.5 \times 4.5 \times 4.5$ 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. In short, emission scans were started immediately after injection of 4–8 mCi (specific activity $0.5–1.5 \text{ Ci}/\mu\text{M}$ 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 $[^{11}\text{C}]$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 ($\text{BP}_{\text{ND}}$) for hand-drawn caudate, putamen and ventral striatum (VS) regions of interest (ROIs) using a procedure previously described. 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 $\text{BP}_{\text{ND}}$ measures, which corresponds to $B_{\text{max}}/K_d - 1$ and reflects D2R availability.

**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. 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 availability 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, cortical surface and total brain volume, 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. 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. An association has been found between a polymorphism in AKTI, a gene acting
downstream of D2R, and tardive dyskinesia present in African Americans but not in
Caucasians. 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): 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. 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. Future D2R imaging genetic studies should
thus correct for genetic ancestry, e.g., or study populations that are relatively
homogenous and hence not subject to the problem of unrecognized stratification.

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. 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. From studies in animals we have
learned that higher-ranking cynomolgus monkeys and rats have higher levels of
D2R in striatum than subordinate ones, and SES has been shown to be correlated with
striatal D2R in humans. 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. 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.
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 to N=84), 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.

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.

**Acknowledgments**

The work was supported by the National Institutes of Health Intramural Research Program (Y1AA-3009 to NDV). We thank Dr. Richard Cooper and Dr. Eliseo Pérez-Stable for helpful comments and suggested literature.

**References**

1. Fan CC, Bartsch H, Schork AJ, Chen CH, Wang Y, Lo MT, et al. Modeling the 3D geometry of the cortical surface with genetic ancestry. Current biology : CB. 2015; 25(15):1988–1992. [PubMed: 2616778]
2. Bakken TE, Dale AM, Schork NJ. A geographic cline of skull and brain morphology among individuals of European Ancestry. Human heredity. 2011; 72(1):35–44. [PubMed: 21849792]
3. Pfefferbaum A, Rohlfing T, Pohl KM, Lane B, Chu W, Kwon D, et al. Adolescent Development of Cortical and White Matter Structure in the NCANDA Sample: Role of Sex, Ethnicity, Puberty, and Alcohol Drinking. Cerebral cortex. 2016; 26(10):4101–4121. [PubMed: 26408800]
4. Reyes-Centeno H, Ghiroto S, Detroit F, Grimaud-Herve D, Barbujani G, Harvati K. Genomic and cranial phenotype data support multiple modern human dispersals from Africa and a southern route into Asia. Proceedings of the National Academy of Sciences of the United States of America. 2014; 111(20):7248–7253. [PubMed: 24753576]
5. Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. Pharmacological reviews. 2011; 63(1):182–217. [PubMed: 21303898]
6. Heinz A, Schlagenhauf F. Dopaminergic dysfunction in schizophrenia: salience attribution revisited. Schizophrenia bulletin. 2010; 36(3):472–485. [PubMed: 20453041]
7. Volkow ND, Gur RC, Wang GJ, Fowler JS, Moberg PJ, Ding YS, et al. Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. The American journal of psychiatry. 1998; 155(3):344–349. [PubMed: 9501743]
8. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III--the final common pathway. Schizophrenia bulletin. 2009; 35(3):549–562. [PubMed: 19325164]
9. Morgan D, Grant KA, Gage HD, Mach RH, Kaplan JR, Prioleau O, et al. Social dominance in monkeys: dopamine D2 receptors and cocaine self-administration. Nature neuroscience. 2002; 5(2):169–174. [PubMed: 11802171]

*mol Psychiatry.* Author manuscript; available in PMC 2018 May 07.
10. Grant KA, Shively CA, Nader MA, Ehrenkaufer RL, Line SW, Morton TE, et al. Effect of social status on striatal dopamine D2 receptor binding characteristics in cynomolgus monkeys assessed with positron emission tomography. Synapse. 1998; 29(1):80–83. [PubMed: 9552177]

11. Martinez D, Orlowksa D, Narendran R, Slifstein M, Liu F, Kumar D, et al. Dopamine type 2/3 receptor availability in the striatum and social status in human volunteers. Biological psychiatry. 2010; 67(3):275–278. [PubMed: 19811777]

12. Nader MA, Nader SH, Czoty PW, Riddick NV, Gage HD, Gould RW, et al. Social dominance in female monkeys: dopamine receptor function and cocaine reinforcement. Biological psychiatry. 2012; 72(5):414–421. [PubMed: 22503110]

13. Wiers CE, Shokri-Kojori E, Cabrera E, Cunningham S, Wong C, Tomasi D, et al. Socioeconomic status is associated with striatal dopamine D2/D3 receptors in healthy volunteers but not in cocaine abusers. Neuroscience letters. 2016; 617:27–31. [PubMed: 26828302]

14. Volkow ND, Morales M. The Brain on Drugs: From Reward to Addiction. Cell. 2015; 162(4):712–725. [PubMed: 26276628]

15. Volkow ND, Baler RD. NOW vs LATER brain circuits: implications for obesity and addiction. Trends in neurosciences. 2015; 38(6):345–352. [PubMed: 25959611]

16. Volkow ND, Logan J, Fowler JS, Wang GJ, Gur RC, Wong C, et al. Association between age-related decline in brain dopamine activity and impairment in frontal and cingulate metabolism. The American journal of psychiatry. 2000; 157(1):75–80. [PubMed: 10618016]

17. Ishibashi K, Ishii K, Oda K, Kawasaki K, Mizusawa H, Ishiwata K. Regional analysis of age-related decline in dopamine transporters and dopamine D2-like receptors in human striatum. Synapse. 2009; 63(4):282–290. [PubMed: 19116949]

18. Wiers CE, Shumay E, Cabrera E, Shokri-Kojori E, Gladwin TE, Skarda E, et al. Reduced sleep duration mediates decreases in striatal D2/D3 receptor availability in cocaine abusers. Translational psychiatry. 2016; 6:e752. [PubMed: 26954979]

19. Volkow ND, Tomasi D, Wang GJ, Telang F, Fowler JS, Logan J, et al. Evidence that sleep deprivation downregulates dopamine D2R in ventral striatum in the human brain. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2012; 32(19):6711–6717. [PubMed: 22573693]

20. Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Wong C, et al. Sleep deprivation decreases binding of [11C]raclopride to dopamine D2/D3 receptors in the human brain. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2008; 28(34):8454–8461. [PubMed: 18716203]

21. Dang LC, Samanez-Larkin GR, Castrellon JJ, Perkins SF, Cowan RL, Zald DH. Associations between dopamine D2 receptor availability and BMI depend on age. NeuroImage. 2016; 138:176–183. [PubMed: 27208860]

22. Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, et al. Brain dopamine and obesity. Lancet. 2001; 357(9253):354–357. [PubMed: 11210998]

23. Borg J, Cervenka S, Kuja-Halkola R, Matheson GJ, Jonsson EG, Lichtenstein P, et al. Contribution of non-genetic factors to dopamine and serotonin receptor availability in the adult human brain. Molecular psychiatry. 2016; 21(8):1077–1084. [PubMed: 26821979]

24. Smith CT, Dang LC, Buckholtz JW, Tetreault AM, Cowan RL, Kessler RM, et al. The impact of common dopamine D2 receptor gene polymorphisms on D2/3 receptor availability: C957T as a key determinant in putamen and ventral striatum. Translational psychiatry. 2017; 7(4):e1091. [PubMed: 28398340]

25. Gluskin BS, Mickey BJ. Genetic variation and dopamine D2 receptor availability: a systematic review and meta-analysis of human in vivo molecular imaging studies. Translational psychiatry. 2016; 6:e747. [PubMed: 26926883]

26. Eisenstein SA, Bogdan R, Love-Gregory L, Corral-Frias NS, Koller JM, Black KJ, et al. Prediction of striatal D2 receptor binding by DRD2/ANKK1 TaqIA allele status. Synapse. 2016; 70(10):418–431. [PubMed: 27241797]

27. Gelernter J, Goldman D, Risch N. The A1 allele at the D2 dopamine receptor gene and alcoholism. A reappraisal. JAMA : the journal of the American Medical Association. 1993; 269(13):1673–1677. [PubMed: 8095994]
28. Tomasi D, Wang GJ, Wang R, Caparelli EC, Logan J, Volkow ND. Overlapping patterns of brain activation to food and cocaine cues in cocaine abusers: association to striatal D2/D3 receptors. Human brain mapping. 2015; 36(1):120–136. [PubMed: 25142207]

29. Volkow ND, Tomasi D, Wang GJ, Logan J, Alexoff DL, Jayne M, et al. Stimulant-induced dopamine increases are markedly blunted in active cocaine abusers. Molecular psychiatry. 2014; 19(9):1037–1043. [PubMed: 24912491]

30. Wiers CE, Cabrera EA, Tomasi D, Wong CT, Demiral SB, Kim SW, et al. Striatal Dopamine D2/D3 Receptor Availability Varies Across Smoking Status. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2017

31. Volkow ND, Wang GJ, Telang F, Fowler JS, Alexoff D, Logan J, et al. Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. Proceedings of the National Academy of Sciences of the United States of America. 2014; 111(30):E3149–3156. [PubMed: 25024177]

32. Ducci F, Roy A, Shen PH, Yuan Q, Yuan NP, Hodgkinson CA, et al. Association of substance use disorders with childhood trauma but not African genetic heritage in an African American cohort. The American journal of psychiatry. 2009; 166(9):1031–1040. [PubMed: 19605534]

33. Enoch MA, Shen PH, Xu K, Hodgkinson C, Goldman D. Using ancestry-informative markers to define populations and detect population stratification. Journal of psychopharmacology. 2006; 20(4 Suppl):19–26.

34. Rosenberg NA, Pritchard JK, Weber JL, Cann HM, Kidd KK, Zhivotovsky LA, et al. Genetic structure of human populations. Science. 2002; 298(5602):2381–2385. [PubMed: 12493913]

35. Conrad DF, Jakobsson M, Coop G, Wen X, Wall JD, Rosenberg NA, et al. A worldwide survey of haplotype variation and linkage disequilibrium in the human genome. Nature genetics. 2006; 38(11):1251–1260. [PubMed: 17057719]

36. Volkow ND, Fowler JS, Wolf AP, Schlyer D, Shiue CY, Alpert R, et al. Effects of chronic cocaine abuse on postsynaptic dopamine receptors. The American journal of psychiatry. 1990; 147(6):719–724. [PubMed: 2343913]

37. Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Gifford A, et al. Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2 receptor levels. The American journal of psychiatry. 1999; 156(9):1440–1443. [PubMed: 10484959]

38. Wang GJ, Volkow ND, Fowler JS, Logan J, Abumrad NN, Hitzemann RJ, et al. Dopamine D2 receptor availability in opiate-dependent subjects before and after naloxone-precipitated withdrawal. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 1997; 16(2):174–182. [PubMed: 9015800]

39. Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL. Distribution volume ratios without blood sampling from graphical analysis of PET data. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 1996; 16(5):834–840.

40. Shu WY, Li JL, Wang XD, Huang M. Pharmacogenomics and personalized medicine: a review focused on their application in the Chinese population. Acta pharmacologica Sinica. 2015; 36(5):535–543. [PubMed: 25891088]

41. Taylor B, Moffett BS, Krenek M, Valdes SO, Kim J. Race contributes to beta-blocker efficacy in pediatric patients with arrhythmias. Pediatric cardiology. 2014; 35(4):641–644. [PubMed: 24247733]

42. Glazer WM, Morgenstern H, Doucette J. Race and tardive dyskinesia among outpatients at a CMHC. Hospital & community psychiatry. 1994; 45(1):38–42. [PubMed: 7907310]

43. Wonodi I, Reeves G, Carmichael D, Verovsky I, Avila MT, Elliott A, et al. Tardive dyskinesia in children treated with atypical antipsychotic medications. Movement disorders : official journal of the Movement Disorder Society. 2007; 22(12):1777–1782. [PubMed: 17580328]

44. Tenback DE, van Harten PN, van Os J. Non-therapeutic risk factors for onset of tardive dyskinesia in schizophrenia: a meta-analysis. Movement disorders : official journal of the Movement Disorder Society. 2009; 24(16):2309–2315. [PubMed: 19645070]

Mol Psychiatry. Author manuscript; available in PMC 2018 May 07.
45. Zai CC, Romano-Silva MA, Hwang R, Zai GC, Deluca V, Muller DJ, et al. Genetic study of eight AKT1 gene polymorphisms and their interaction with DRD2 gene polymorphisms in tardive dyskinesia. Schizophrenia research. 2008; 106(2–3):248–252. [PubMed: 18838251]

46. Mickey BJ, Sanford BJ, Love TM, Shen PH, Hodgkinson CA, Stohler CS, et al. Striatal dopamine release and genetic variation of the serotonin 2C receptor in humans. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2012; 32(27):9344–9350. [PubMed: 22764241]

47. Burghardt PR, Love TM, Stohler CS, Hodgkinson C, Shen PH, Enoch MA, et al. Leptin regulates dopamine responses to sustained stress in humans. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2012; 32(44):15369–15376. [PubMed: 23115175]

48. Tiihonen J, Rautiainen MR, Ollila HM, Repo-Tiihonen E, Virkkunen M, Palotie A, et al. Genetic background of extreme violent behavior. Molecular psychiatry. 2015; 20(6):786–792. [PubMed: 25349169]

49. Oyama S, Terry SF. Epigenetics and Racial Health Inequities. Genetic testing and molecular biomarkers. 2016; 20(9):483–484. [PubMed: 27636025]

50. Kaufman JS, Cooper RS, McGee DL. Socioeconomic status and health in blacks and whites: the problem of residual confounding and the resiliency of race. Epidemiology (Cambridge, Mass). 1997; 8(6):621–628.

51. Jupp B, Murray JE, Jordan ER, Xia J, Fluharty M, Shrestha S, et al. Social dominance in rats: effects on cocaine self-administration, novelty reactivity and dopamine receptor binding and content in the striatum. Psychopharmacology. 2015

52. Cooper RS, Kennelly JF, Durazo-Arvizu R, Oh HJ, Kaplan G, Lynch J. Relationship between premature mortality and socioeconomic factors in black and white populations of US metropolitan areas. Public health reports (Washington, DC : 1974). 2001; 116(5):464–473.

53. Cooper RS, Kaufman JS, Ward R. Race and genomics. The New England journal of medicine. 2003; 348(12):1166–1170. [PubMed: 12646675]

54. Cooper RS. Race in biological and biomedical research. Cold Spring Harbor perspectives in medicine. 2013; 3(11)

55. Kaufman JS, Cooper RS. Seeking causal explanations in social epidemiology. American journal of epidemiology. 1999; 150(2):113–120. [PubMed: 10412955]

56. Kogler L, Muller VI, Chang A, Eickhoff SB, Fox PT, Gur RC, et al. Psychosocial versus physiological stress - Meta-analyses on deactivations and activations of the neural correlates of stress reactions. NeuroImage. 2015; 119:235–251. [PubMed: 26123376]
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).
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}).

| Characteristic                          | Healthy Volunteers N=117 |
|-----------------------------------------|--------------------------|
|                                         | 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 [11C]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 Caudate | D2R Putamen | 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 (BPND) 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:

* $p<0.05$

** $p<0.01$

*** $p<0.001$
| 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:**  

| 1000 genomes minor allele frequency African American/Utah | Allele freq (n) | Pearson’s r African/European ancestry | D2R Caudate βd | D2R Putamen βd | D2R VS βd |
|---|---|---|---|---|---|
| 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 |

**Notes:**

- D2R = dopamine D2/D3 receptor availability (BPND) 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

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

Significance levels in bold:

* p<.05
\[ p < .01 \]
\[ *** \ p < .001 \]

\[ a \text{ } n=116 \]
\[ b \text{ } n=113 \]
\[ c \text{ } n=109 \]

\[ d \text{ corrected for age, sex, BMI, education, smoking status, and ZIP code’s consensus tracts “per capita income” and “housing units occupied per owner” as estimates of socioeconomic status.} \]