



Divergence of an association between depressive symptoms and a dopamine polygenic score in Caucasians and Asians

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Abstract

A recent study reported a negative association between a putatively functional dopamine (DA) polygenic score, indexing higher levels of DA signaling, and depressive symptoms. We attempted to replicate this association using data from the Duke Neurogenetics Study. Our replication attempt was made in a subsample of 520 non-Hispanic Caucasian volunteers (277 women, mean age 19.78 ± 1.24 years). The DA polygenic score was based on the following five loci: rs27072 (*SLC6A3/DAT1*), rs4532 (*DRD1*), rs1800497 (*DRD2/ANKK1*), rs6280 (*DRD3*), and rs4680 (*COMT*). Because the discovery sample in the original study consisted mostly of Asian participants, we also conducted a post hoc analysis in a smaller subsample of Asian volunteers ($N=316$, 179 women, mean age 19.61 ± 1.32 years). In the primary sample of non-Hispanic Caucasians, a linear regression analysis controlling for sex, age, socioeconomic status (SES), body mass index, genetic ancestry, and both early and recent life stress, revealed that higher DA polygenic scores were associated with higher self-reported symptoms of depression. This was in contrast to the original association of higher DA polygenic scores and lower depressive symptoms. However, the direction of the association in our Asian subsample was consistent with this original finding. Our results also suggested that compared to the Asian subsample, the non-Hispanic Caucasian subsample was characterized by higher SES, lower early and recent life stress, and lower depressive symptoms. These differences may have contributed to the observed divergence in associations. Collectively, the current findings add to evidence that specific genetic associations may differ between populations and further encourage explicit modeling of race/ethnicity in examining the polygenic nature of depressive symptoms and depression.

Keywords Dopamine · Depressive symptoms · Depression · Polygenic score · Genes · Ethnicity · Asians · Caucasians

Introduction

Multiple lines of evidence implicate dopamine (DA) signaling in the pathophysiology of depression [1, 2]. Accordingly, two recent genome-wide association studies (GWAS) have implicated common sequence variation in DA-related genes in depression [3, 4]. Consistent with this literature, Pearson-Fuhrhop et al. [5] reported a significant association between depressive symptoms and a putatively functional DA polygenic score consisting of common polymorphisms across five different DA-related genes. Specifically, they

found that higher DA polygenic scores were significantly associated with lower depressive symptoms. As higher DA polygenic scores putatively index higher in vivo DA signaling, the direction of their reported association is consistent with some earlier research linking relatively low DA with depressive symptoms, such as anhedonia and amotivation [6, 7].

The current study represents our attempt to replicate the association between higher DA polygenic scores and lower depressive symptoms in the Duke Neurogenetics Study (DNS). To avoid population stratification biases and achieve maximum statistical power, we focused our analyses on the largest ethnic subsample in the DNS, non-Hispanic Caucasians ($N=520$). However, as the original association reported by Pearson-Fuhrhop et al. [5] emerged from a discovery sample ($N=273$) with a preponderance of Asian participants (49%), we also present findings from an exploratory

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post hoc analysis in a small subsample of 316 students of Asian descent.

Methods and materials

Participants

Study participants included a subset of individuals having completed the DNS, which was designed to identify biomarkers of risk for psychopathology amongst 18- to 22-year-old full-time university students. Participants were recruited through posted flyers on the Duke University campus and through a Duke University listserv. All procedures were approved by the Institutional Review Board of the Duke University Medical Center, and participants provided informed consent before study initiation. All participants were free of the following study exclusions: (1) medical diagnoses of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease, or lifetime history of psychotic symptoms; (2) use of psychotropic, glucocorticoid, or hypolipidemic medication; and (3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension).

Our primary sample consisted of 520 self-reported non-Hispanic Caucasian participants (277 women, mean age 19.78 ± 1.24 years) from the DNS for whom there were complete data on genotypes, depressive symptoms, and all covariates. Exploratory post hoc analyses were performed on a smaller Asian subsample ($N=316$, 179 women, mean age 19.61 ± 1.32 years) from the DNS, also with complete data on study variables.

Current and lifetime DSM-IV axis I or select axis II disorders (antisocial personality disorder and borderline personality disorder) were assessed with the electronic Mini International Neuropsychiatric Interview [8] and Structured Clinical Interview for the DSM-IV axis II subtests [9]. Of the 520 non-Hispanic Caucasians included in our analyses, 117 individuals had at least one DSM-IV diagnosis. Of the 316 Asian participants, 42 individuals had at least one DSM-IV diagnosis. Importantly, neither current nor lifetime diagnosis was an exclusion criterion, as the DNS sought to establish broad variability in multiple behavioral phenotypes related to psychopathology. However, no participants, regardless of diagnosis, were taking any psychoactive medication during or at least 14 days prior to their participation.

Socioeconomic status (SES)

We controlled for possible SES effects using the “social ladder” instrument [10], which asks participants to rank themselves relative to other people in the United States (or their origin country) on a scale from 0 to 10, with people who are

best off in terms of money, education, and respected jobs, at the top (10) and people who are worst off at the bottom (0).

Genetic ancestry

To further minimize the risk of population stratification, an analysis of identity-by-state of whole-genome single nucleotide polymorphisms (SNPs) was performed in PLINK [11]. Multidimensional scaling was done separately for the two subgroups included in the current analyses (i.e., non-Hispanic Caucasians and Asians), and the first two components for each group were used in each respective analysis as covariates.

Depressive symptoms

The 20-item Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depressive symptoms in the past week [12]. All items were summed to create a total depressive symptoms score.

Life stress

We controlled for the effects of early life stress using the Childhood Trauma Questionnaire [CTQ; 13], and of stress during the year prior to study participation using the Life Events Scale for Students [LESS; 14]. All items from the CTQ were summed to create a total score of early life stress. For the LESS, we summed the 38 negatively valenced items for a total score of recent stress [as described in 15, 16].

Body mass index (BMI)

BMI was calculated based on the height and weight of the participants ($\text{pounds/inches}^2 \times 703$). We included BMI as a covariate because it is a known risk factor for depression [17].

Genotyping

DNA was isolated from saliva using Oragene DNA self-collection kits (DNA Genotek) customized for 23andMe (www.23andme.com). Genotyping was done through 23andMe which uses the services/labs of the National Genetics Institute (NGI), a CLIA-certified clinical laboratory and subsidiary of Laboratory Corporation of America. One of the two different Illumina arrays with custom content was used to provide genome-wide SNP data, the HumanOmniExpress ($N=524$) or HumanOmniExpress-24 [$N=276$; 18–20]. We performed a K-means analysis based on the first two multidimensional scaling components of the Asian participants, dividing them into two subgroups. Hardy–Weinberg equilibrium (HWE) tests were performed in PLINK

[11] on the created Asian groups and on the non-Hispanic Caucasians separately. All SNPs were in HWE ($p > 0.05$).

Dopamine polygenic scores

As per the strategy of Pearson-Fuhrhop et al. [5], we derived a DA polygenic score for each participant based on the following five loci: rs27072 (*SLC6A3/DAT1*), rs4532 (*DRD1*), rs1800497 (*DRD2/ANKK1*), rs6280 (*DRD3*), and rs4680 (*COMT*). Scoring details are provided in Table 1. Of note, we used a putatively functional SNP in *SLC6A3/DAT1* instead of the variable number tandem repeat (VNTR) used in the original study, because VNTRs were not genotyped in our sample.

Statistical analyses

Descriptive statistics and univariate analyses of variance were conducted using SPSS version 24. Mplus version 7 [21] was used to conduct a linear regression analysis with

participants' sex (coded as 0 = males, 1 = females), age, two genetic ancestry principal components, SES, BMI, and both early and recent life stress, as covariates. Maximum likelihood estimation with bias-corrected bootstrapping (set to 10,000) was used in all models to generate non-symmetric 95% confidence intervals (CIs).

Results

Allele frequencies and descriptive statistics for the non-Hispanic Caucasian and Asian subsamples are presented in Tables 1 and 2, respectively. The allele frequencies are comparable to those observed in the 1000 genomes sample for Europeans and East Asians.

DA polygenic scores and depressive symptoms

Of the covariates, only early life stress ($b = 0.24$, $SE = 0.046$, $p < 0.001$; CI 0.15–0.33) and recent life stress ($b = 0.67$,

Table 1 The putatively functional single nucleotide polymorphisms included in the dopamine polygenic score

Gene	SNP and allele coding	Target allele frequency	Functional associations
<i>DRD1</i>	rs4532 C = 1, T = 0	Non-Hispanic Caucasians-0.366 Asians-0.224	While there may be some indication of the functionality of rs4532 through its high linkage disequilibrium with rs686 [39], it was coded based on the association of the G allele with dopamine-related phenotypes, such as treatment resistance in schizophrenia [40] and shorter time to hallucinations in Parkinson's disease patients [41]
<i>DRD2</i>	rs1800497 G(A2) = 1, A(A1) = 0	Non-Hispanic Caucasians-0.803 Asians-0.625	The T allele has been associated with reduced striatal DRD2 binding in postmortem tissue [42, 43] and with a blunted striatal response to reward [44]
<i>DRD3</i>	rs6280 C = 1, T = 0	Non-Hispanic Caucasians-0.309 Asians-0.319	The C allele has been associated with higher DRD3 dopamine affinity and intracellular signaling in human embryonic kidney cells [45]. Additionally, it has been associated with increased reward-related DA release in a PET study [46]
<i>COMT</i>	rs4680 A = 1, G = 0	Non-Hispanic Caucasians-0.502 Asians-0.292	The A (Met) allele has been associated with lower COMT activity [47] and higher ventral striatum activity [48]
<i>SLC6A3/DAT1</i>	rs27072 T = 1, C = 0	Non-Hispanic Caucasians-0.183 Asians-0.278	The T allele has been associated with a loss of function and lower DAT activity [49]

The "target allele" is the allele coded as 1

Table 2 Descriptive statistics for the main study variables

	Non-Hispanic Caucasians (N = 520)			Asians (N = 316)		
	Minimum	Maximum	Mean (SD)	Minimum	Maximum	Mean (SD)
Age	18	22	19.78 (1.24)	18	22	19.61 (1.32)
SES	2	10	7.34 (1.43)	2	10	6.93 (1.47)
Early life stress	25	74	31.33 (7.17)	25	76	35 (8.50)
Recent life stress	0	18	2.49 (2.30)	0	16	2.17 (2.40)
Body mass index	16.3	39.15	22.29 (2.83)	16.3	35.44	21.80 (2.68)
Depressive symptoms	0	43	8.96 (7.14)	0	52	10.70 (8.75)
Dopamine score	1	9	4.33 (1.37)	0	8	3.4 (1.57)

SE = 0.15, $p < 0.001$; CI 0.39–0.96), significantly predicted depressive symptoms; so, that higher stress levels were associated with higher depressive symptoms. The DA polygenic score significantly and positively predicted depressive symptoms ($b = 0.43$, SE = 0.20, $p = 0.03$; CI 0.05–0.82; Fig. 1a). The R^2 of the model was 0.166. Comparing the R^2 of the model with the DA polygenic score to the R^2 of a model without it indicated that the variance explained by the polygenic score was small ($R^2 = 0.007$).

Exploratory post hoc analyses in the Asian subsample

Since Pearson-Fuhrhop et al. [5] used a discovery sample with a majority of Asian participants, we also examined the association in a smaller Asian subsample as a post hoc analysis. Descriptive statistics for the Asian participants are presented in Table 2. Comparisons of the non-Hispanic Caucasian and Asian participants on the main study variables pointed to many differences between the groups. Non-Hispanic Caucasians were more likely to have a higher SES [$F(1, 834) = 15.47$, $p < 0.001$], less likely to experience

early life stress [$F(1, 834) = 44.65$, $p < 0.001$], more likely to have a higher BMI [$F(1, 834) = 6.21$, $p = 0.013$], less likely to experience depressive symptoms [$F(1, 834) = 9.92$, $p = 0.002$], somewhat more likely to experience recent stress [$F(1, 834) = 3.74$, $p = 0.054$], and somewhat more likely to be older [$F(1, 834) = 3.74$, $p = 0.054$]. Lastly, the non-Hispanic Caucasian participants had higher DA polygenic scores than the Asian participants [$F(1, 834) = 67.93$, $p < 0.001$], suggesting differences in allele frequencies between populations.

In the Asian subsample, similar to the primary non-Hispanic Caucasian subsample, early and recent life stress were significant predictors of depressive symptoms (early life stress: $b = 0.33$, SE = 0.072, $p < 0.001$, CI 0.20–0.48; recent life stress: $b = 0.54$, SE = 0.17, $p < 0.001$, CI 0.21–0.90). However, in contrast to the non-Hispanic Caucasian subsample, SES also significantly predicted depressive symptoms ($b = -0.80$, SE = 0.29, $p = 0.006$, CI -1.39 to -0.24), so that individuals from lower SES experienced higher levels of depressive symptoms. Lastly, in the Asian subsample, the association between the DA polygenic scores and depressive symptoms was significant and negative ($b = -0.68$, SE = 0.34, $p = 0.047$; CI -1.38 to -0.021), so that higher DA polygenic scores predicted lower levels of depressive symptoms (Fig. 1b). The R^2 of the model was 0.214. Comparing the R^2 of the model with the DA polygenic score to the R^2 of a model without it indicated that the variance explained by the polygenic score was small ($R^2 = 0.012$).

The effect of each SNP is presented in Table 3 for both the non-Hispanic Caucasian and Asian subsamples. In the non-Hispanic Caucasian subsample, the SNP in the *SLC6A3/DAT1* gene (rs27072) was significant ($b = 1.62$, SE = 0.63, $p = 0.01$; CI 0.50–3.001), explaining 0.015 of the variance. In the Asian subsample, the SNP in the *DRD1* gene (rs4532) was significant ($b = -1.83$, SE = 0.80, $p = 0.022$; CI -3.49 to -0.36), explaining 0.013 of the variance.

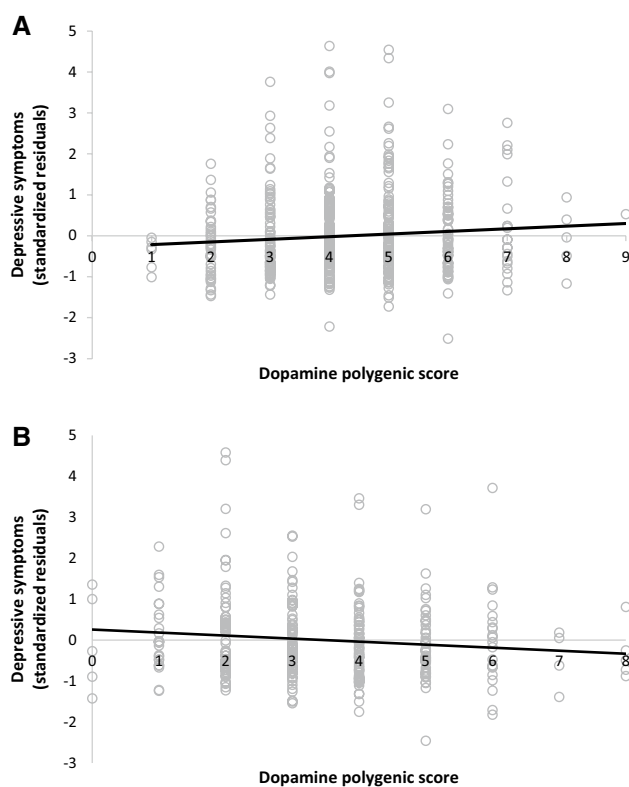


Fig. 1 Dopamine polygenic scores are differentially associated with depressive symptoms in **a** non-Hispanic Caucasians and **b** Asians. To better depict the linear regression described in the text, the standardized residuals of depressive symptoms, as assessed by the CES-D, are shown (controlling for sex, age, two multidimensional scaling ancestry components, SES, BMI, and early and recent life stress)

Discussion

In the current study, we attempted to replicate earlier work by Pearson-Fuhrhop et al. [5], reporting an association between higher DA polygenic scores and lower levels of depressive symptoms. While we did find a significant association between DA polygenic scores and depressive symptoms in our primary sample of non-Hispanic Caucasians, it was in the opposite direction to the one reported in the original study: higher DA polygenic scores were associated with higher depressive symptoms. However, the pos hoc analysis in our smaller subsample of Asian participants revealed an association consistent with that of the original report: higher DA polygenic scores were associated with lower depressive symptoms. When each SNP was examined separately, there

Table 3 The effect of each single nucleotide polymorphism on depressive symptoms as estimated with the CES-D

	Non-Hispanic Caucasians			Asians		
	<i>b</i>	SE	<i>p</i> value	<i>b</i>	SE	<i>p</i> value
rs1800497	0.458	0.511	0.371	−0.467	0.702	0.506
rs4532	−0.364	0.394	0.355	−1.827	0.8	0.022
rs6280	0.224	0.423	0.596	0.6	0.732	0.413
rs4680	0.503	0.392	0.199	−1.19	0.668	0.075
rs27072	1.621	0.627	0.01	−0.878	0.661	0.184

Each linear regression model included sex, age, socioeconomic status, ancestry genetic components, BMI, and early and recent life stress as covariates

were specific loci that showed an independent significant effect on depressive symptoms, but these differed between our subsamples as well as between our study and the original study, indicating that individual SNP effects are less reliable, as replication studies of single candidate gene associations have previously shown [e.g., 22]. Lastly, the variance explained by the DA polygenic scores in both of our models (non-Hispanic Caucasians $R^2=0.007$, Asians $R^2=0.012$) was smaller than what was reported in the original discovery sample ($R^2=0.085$). Overestimating the true effect in discovery samples and finding smaller effect sizes in replication samples is a common observation usually explained as a regression to the mean [23].

The potential moderation of an association between DA polygenic scores and depressive symptoms is not inconsistent with the original report of Pearson-Fuhrhop et al. [5]. In that report, there was a successful replication, albeit with a DA polygenic score that only included three of the original variants, in a sample of 1267 adult Caucasians having a clinical diagnosis of non-psychotic MDD. However, a second replication attempt with a DA polygenic score comprising four of the original variants, in a sample of healthy 381 young adult Caucasians, was not successful. Thus, the link between DA polygenic scores and depressive symptoms may be moderated by clinical diagnosis and age. Indeed, the presence of a clinically significant disease has been shown to moderate the effect of DA-related genes [24]. Additionally, there is an age-related decline in DA signaling [25], which could contribute to differences in the effects of dopaminergic genes on behavior across development.

Our findings, although exploratory, further suggest that race/ethnicity may also moderate the link between DA polygenic scores and depressive symptoms. This observation is in line with previous findings demonstrating population differences in the effects of DA-related polymorphisms. For example, in a meta-analysis of 30 studies [26], the putatively functional 7-repeat allele of the dopamine receptor D4 exon III variable nucleotide tandem repeat was positively linked to attention deficit hyperactivity disorder (ADHD) in European Caucasian and South American samples, but negatively linked to ADHD in Middle-Eastern samples.

Similarly, the Met allele of the catechol-o-methyltransferase rs4680 has been associated with larger hippocampal volume in Caucasians [27], but smaller hippocampal volume in Han Chinese [28]. Theoretically, such differences can reflect variation in allele frequencies, linkage disequilibrium (LD) patterns, and/or non-genetic (e.g., cultural) effects. However, allele frequencies may be less likely to explain the current observed differences, because the effect in our non-Hispanic Caucasian subsample was not stronger, as may be expected, but reversed. It is possible that some of the examined SNPs only tag causal polymorphisms and consequently LD differences may affect the observed findings. Additionally, our two groups differed in stress levels and socioeconomic background, which suggest cultural and experience-related influences that could potentially moderate the genetic effects (e.g., through epigenetic modifications that affect gene expression [29] and/or through modifications of brain structure and function [30]). Indeed, previous studies have demonstrated that culture can act as a moderator of genetic influences [31, 32]. Nevertheless, as with any association study, replication across different age groups and populations, and in clinical and healthy samples is necessary.

Our study has several limitations. First, we were not able to directly assess the functionality of the DA polygenic score and establish links with in vivo DA signaling. Although previous studies have demonstrated the functionality of each individual SNP, research that validates the functionality of the polygenic score is needed. Second, the analysis in the Asian subsample was done post hoc and should be treated with caution. Third, we did not have a large sample of Asians nor were we able to examine other racial/ethnic groups. Fourth, the current polygenic score is limited to five SNPs and future studies may choose to extend it by implementing findings from open resources such as the Genotype-Tissue Expression project [33]. Notably, however, here we were specifically interested in attempting to replicate the finding of Pearson-Fuhrhop et al. [5]. Lastly, our findings should be viewed as tentative until further replication is reported.

In studies seeking mechanistic insight, polygenic scores similar to the one used in the current study may be preferable to either single candidate genes, which often fail to

replicate [e.g., 22], or to GWAS-based scores, which may explain more phenotypic variance, but are often limited in providing insight into the molecular mechanisms underlying the phenotype of interest [34]. If replicated, our results suggest that efforts to discover the biological mechanisms underlying depression and identify treatment targets should consider race/ethnicity as a moderator. Previous studies have indeed shown that racial/ethnic differences can affect treatment response to various diseases [35–38].

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Compliance with ethical standards

Conflict of interest The authors declare no competing financial or other interests.

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