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Predicting sensation seeking from dopamine genes: A candidate system approach

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Abstract

Sensation seeking is a heritable personality trait that has been reliably linked to behavior disorders. The dopamine system has been hypothesized to contribute to individual differences in sensation seeking, and both experimental and observational studies in humans and non-human animals provide evidence for this relationship. We present here a candidate-system approach to genetic association analysis of sensation seeking, in which single nucleotide polymorphisms (SNPs) from a number of dopaminergic genes were analyzed. Using 273 SNPs from eight dopamine genes in a sample of 635 unrelated individuals, we examined the aggregate effects of those SNPs significantly associated with sensation seeking. Multiple SNPs in four dopamine genes accounted for significant variance in sensation seeking. These results suggest that aggregation of multiple SNPs within genes relevant to a specific neurobiological system into a “genetic risk score” may explain a nontrivial proportion of variance in human traits.

Keywords

sensation seeking; dopamine; candidate gene; association study

Sensation seeking is a personality trait of great importance to public health, in that it has been specifically associated with behavior disorders with high social costs, especially substance use disorders (Zuckerman & Neeb, 1979). Among individuals with substance use disorders, greater sensation seeking is associated with earlier age onset of use and abuse, more poly-substance use, a greater number of symptoms, and more severe impairment (Ball, Carroll, & Rounsaville, 1994). Higher sensation seeking levels are also associated with increased treatment drop-out rates and poorer treatment outcomes (Staiger, Kambouropoulos, & Dawe, 2007).

Heritability for sensation seeking ranges from 40% to 60% (Eysenck, 1983; Fulker, Eysenck, & Zuckerman, 1980; Hur & Bouchard, 1997; Koopmans, Boomsma, Heath, & van Doornen, 1995). Correlations among specific elements (facets) of sensation seeking are primarily accounted for by overlapping genetic factors (Hur & Bouchard, 1996; Koopmans, Boomsma, Heath, & van Doornen, 1995). Twin studies suggest no sex differences in the magnitude or nature of genetic effects on sensation seeking (Eysenck, 1983; Koopmans, Boomsma, Heath, & van Doornen, 1995). Further, behavioral undercontrol (similar to the disinhibition scale of sensation seeking) shares substantial genetic risk with alcohol dependence and conduct disorder (Slutske et al., 2002).

Sensation seeking therefore represents a promising endophenotypic aspect of externalizing problems (Benjamin, Ebstein, & Belmaker, 2001; Gottesman & Gould, 2003; Krueger, Markon, Patrick, Benning, & Kramer, 2007). It is also an important target phenotype for a theory-driven candidate neurogenetic system approach to linking molecular genetic polymorphisms with specific behavioral phenomena. Sensation seeking has a demonstrable neurobiological basis in humans (Joseph, Liu, Jiang, Lynam, & Kelly, 2009). The dopaminergic system has been long hypothesized to underlie individual variation in sensation seeking (Zuckerman, 1984), and recent research supports this hypothesis. A rodent model has demonstrated that availability of nucleus accumbens dopamine D2 and D3 receptors is negatively associated with impulsivity (similar to the disinhibition scale of sensation seeking; Dalley et al., 2007). A study in humans has shown a negative association

between ventral midbrain dopamine D2 receptor availability and novelty seeking (similar to the experience seeking scale of sensation seeking; Zald et al., 2008). A pharmacological study in humans also suggested that dopamine stimulation increases nicotine craving in individuals who score highly on the experience seeking scale of sensation seeking (Netter, Henning, & Roed, 1996).

Candidate gene studies provide some evidence of a relationship between specific polymorphisms in genes involved in the dopaminergic system and sensation seeking. A commonly examined functional single nucleotide polymorphism (SNP; rs4680, also known as Val158Met) in the *COMT* gene has been associated with sensation seeking (though the effect was specific to females; Lang, Bajbouj, Sander, & Gallinat, 2007). A gene-gene interaction effect on sensation seeking has been demonstrated between rs1800497 (also known as DRD2 Taq1A or C32806T) located in the gene *ANKK1* and the commonly studied variable-number-of-tandem-repeats (VNTR) polymorphism (48 base pairs that repeat a variable number of times) in the *DRD4* gene (Eisenberg, Campbell, MacKillop, Lum, & Wilson, 2007). This *DRD4* VNTR appears to be a developmentally stable predictor of experience seeking behaviors, and has been associated longitudinally with infant visual exploratory behavior and adolescent novelty seeking (Laucht, Becker, & Schmidt, 2006). However, as with many other traits and diseases, non-replication of specific candidate gene effects on sensation seeking and related traits is a common occurrence, and evidence for the involvement of any specific variant is typically modest at best (e.g. Heck et al., 2009).

As a continuous trait conferring risk for the development of externalizing disorders, and greater disorder severity, sensation seeking is an appealing target for human genetic research. Candidate gene studies of sensation seeking and personality traits more generally have previously focused on a small number of polymorphisms within a single gene (Ebstein, 2006), the individual effects of SNPs from multiple genes (Heck et al., 2009), or the aggregate effects of single polymorphisms from each of several genes (Beaver, 2009). The advent of dense whole-genome SNP genotyping allows us to capture far more genetic variation than has previously been captured by candidate gene studies. However, use of whole-genome data incurs a considerable cost, in the form of exacting a heavy penalty for multiple testing.

Here, we pursue an approach that combines the theory-driven candidate gene approach with the genotypic data available from genome-wide high-throughput genotyping technology. From all SNPs located in dopamine genes that were available from a dense-coverage commercially-available genotyping platform, we first selected those SNPs that were individually associated with sensation seeking. We then fit nested regression models, in which sensation seeking was predicted by 1) demographic covariates; or 2) variables from model 1 (covariates) and all SNPs identified as significant in the individual association tests. By comparing model fit statistics for these models, we addressed a specific research question. Does the aggregation of multiple SNPs within dopamine genes explain significant variance in sensation seeking, over and above that explained by demographic covariates (i.e. age, sex, and ancestry)?

Methods

Participants

Participants were 635 unrelated individuals who had participated in the Study of Addiction: Genetics and the Environment (SAGE; Bierut et al., under review; http://zork.wustl.edu/gei/). Participants in the current research were a subset of the SAGE sample, all of whom were drawn from a primary study of alcohol dependence (COGA; Reich et al., 1998) because these individuals had completed the Sensation Seeking Scale

(Zuckerman, 1978; Zuckerman, 1996). Written informed consent was obtained from all participants following thorough description of the study. The average age of our sample was 45.3 years (with a range of 22 to 77), 55.1% were female, 65.2% met criteria for a lifetime DSM-IV alcohol dependence diagnosis, and 18.9% and 8.2% self-reported African and/or Hispanic ancestry, respectively.

Measure

Participants were administered Zuckerman's Sensation Seeking Scale Form V (SSS-V; Zuckerman, 1978; Zuckerman, 1994). The SSS-V yields an overall Sensation Seeking score from four 10-item subscale scores. The subscales are Boredom Susceptibility (e.g. "When you can predict almost everything a person will do and say, he or she must be a bore."), Disinhibition (e.g. "I like wild 'uninhibited' parties."), Experience Seeking (e.g. "I often find beauty in the 'clashing' colors and irregular form of modern painting."), and Thrill/ Adventure Seeking (e.g. "I would like to try parachute jumping."). The total sensation seeking score has good reliability in both American males (Cronbach's $\alpha = 0.84$) and females ($\alpha = 0.85$; Zuckerman, 1979). Our analysis of the total sensation seeking score, rather than its subscales, provides generally greater measurement reliability, as well as a reduced number of statistical tests.

Genotyping

DNA was obtained from blood samples and genotyping was carried out at the Johns Hopkins University Center for Inherited Disease Research (CIDR) using the Illumina Human IM Bead Chip. The median missing call rate was less than 0.05%, with 95% of SNPs resulting in less than 1.4% missingness. Strict quality control procedures were implemented, including assessment of population structure, missing call rates, Mendelian errors, duplication errors, gender and chromosomal anomalies, hidden relatedness, batch effects, and Hardy-Weinberg disequilibrium. Duplicates, related subjects, and outliers were removed. A total of 948,142 SNPs passed this thorough cleaning procedure (Laurie et al., under review; http://www.genevastudy.org/).

Gene and SNP selection

Dopamine-related genes were identified from a search of the relevant candidate-gene literature. Only genes located on autosomal (i.e. non-sex) chromosomes that have definite and direct effects on the dopaminergic system were included. SNPs in each of these genes (identified from dbSNP; Database of Single Nucleotide Polymorphisms, build 129) that were available on the Illumina Human 1M Bead Chip were then selected. Functionality of each SNP was identified using dbSNP. A total of 273 SNPs were chosen for inclusion in our analyses. Table 1 reports the genes included in our analyses, the number of SNPs available in each gene from the SAGE genotype data, and the general function of each gene as it relates to dopamine. (Note. No SNPs from the DRD5 gene were included in our analysis, because the single SNP available in this gene on the Illumina 1M platform did not pass genotyping quality control procedures in the SAGE sample. In addition, our sample did not include genotyping of rs1800955, or a reasonable proxy, a SNP in DRD4 showing significant association with impulsivity-related personality traits in a recent meta-analysis by Munafò and colleagues, 2008.)

Analyses

To characterize ethnic heterogeneity in our sample, principal components were estimated based on the SAGE genome-wide data, using the procedure described by Price and colleagues (2006). Two major principal components emerged, corresponding to European vs. African ancestry (PC1) and Hispanic vs. non-Hispanic ancestry (PC2). Treating ancestry

as a covariate assumes that while minor (i.e. less common) allele frequencies may differ between races, the biological impact of SNPs does not (Ioannidis, Ntzani, & Trikalinos, 2004). While ideally we would model ethnicities separately to explore this, our sample size prevented this approach. PC1 and PC2 were used as covariates in our analyses, along with age (coded in quartiles as three dummy codes, as has been done in previous SAGE analyses, corresponding to ≤34, 35–39, and 40–44, with 45+ as the reference group), and sex (1 for males and 2 for females). SNPs were coded as 0/1/2 to indicate the number of minor alleles present for a given individual. We did not control for alcohol dependence case status for our main analyses, because sensation seeking is substantially related to alcohol use behaviors (Zuckerman, 1994), and including it as a covariate may eliminate meaningful variance (Meehl, 1971). Nevertheless, post-hoc analyses revealed that our pattern of results and conclusions did not change if alcohol dependence was included as a covariate in the aggregated SNP tests (i.e. the p-value reported in Table 3 remained significant at $p < 5 \times 10^{-12}$).

Association tests were initially run on each individual SNP (coded as 0, 1, or 2, representing the number of minor alleles), performing a linear regression in R (an open-source statistical program; R Development Core Team, 2009) of the sensation seeking score on that SNP and all covariates (i.e. PC1, PC2, age, and sex). We implemented two additional methods to ensure that any significant results were greater than chance. First, in addition to p-values, we calculated the false discovery rate (FDR) for each regression-weight p-value reaching significance. FDR controls the proportion of false-positive results expected from all those tests declared significant and is calculated as:

$$P_i \leq (i/m)^* \alpha \quad (1)$$

Where i is the rank order of the test (ranked in terms of ascending p-values), m is the total number of independent tests, α is the p-value cut-off for significance, and P_i is the p-value for test i (Benjamini & Hochberg, 1995). We set our maximum FDR at 0.10, interpreted as no more than 10% of the SNPs declared significant based on $p < 0.05$ would be false positives. For our purposes, we set the value of m to 8, the number of genes included in our analyses.

To account for linkage disequilibrium (LD; the correlation between SNPs) in our heterogeneous sample, our second method for estimating false positives was to calculate the number of statistically significant associations observed when genotypes were randomly assigned to individuals (i.e., a permutation analysis). By randomly assigning intact genotypes to individuals (and keeping each individual's sensation seeking and covariate scores the same as in the real association tests), we were able to observe the number of false-positive results obtained when keeping allelic distributions and LD patterns in our sample intact.

Following the identification of all statistically significant SNPs (i.e. those that were significant at the two-tailed $p < 0.05$ level in the individual SNP association tests, and that met FDR < 0.10), we compared two models of sensation seeking. The baseline model regressed sensation seeking on the covariates included in the initial association tests. The second model regressed sensation seeking on covariates and those significant SNPs identified from our initial association tests. We evaluated the relative goodness-of-fit of these models to the raw data by comparing a) the total proportion of variance in sensation seeking explained, b) the model likelihoods, and c) the Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) from each model. AIC and BIC are information theoretic measures of goodness-of-model fit, and account for model parsimony

in evaluating fit. Relative to a comparison of model likelihoods, AIC and BIC are more conservative, requiring greater evidence of the predictive utility of additional predictor variables to show improved fit. Lower values of AIC and BIC indicate a relatively better fit to the data (Akaike, 1974; Schwarz, 1978).

Results

Tests for association between individual SNPs and sensation seeking

A total of 273 SNPs from eight dopamine-related genes were individually tested for association with sensation seeking, controlling for demographic characteristics. Results for the individual-SNP association tests (for those SNPs whose regression weights met $p<0.05$) are reported in Table 2. Table S1 in the supporting information available on-line presents results from all 273 association tests. Twelve SNPs met significance criteria for association with sensation seeking, as defined by $p < 0.05$ and FDR < 0.10. By comparison, only three SNPs in the randomized genotype condition (rs2042449 and rs9312866 in SLC6A3, and rs1611114 in DBH) were significant by chance (at $p < 0.05$), and none of these passed FDR criteria (i.e. the p-value of the top-ranked SNP was greater than its FDR value). Because the number of SNPs meeting $p < 0.05$ was substantially greater in the correct genotype tests than in the tests using randomly assigned genotypes, and because all of the SNPs in the correct genotype condition met FDR criteria, compared to none of the SNPs in the random genotype condition, we concluded that the implicated SNPs are likely true associations with sensation seeking, at least in the current data set.

Table 2 shows that eight of our twelve significant SNPs were located in *DDC*, and two were located in *COMT*. To examine whether these SNPs could be expected to explain unique variance in sensation seeking, we estimated the intercorrelations among all significant SNPs located within a single gene. In our sample, the two *COMT* SNPs (rs174699 and rs933271) had an r-squared value of 0.03, suggesting that linkage disequilibrium (LD, i.e., correlation between SNPs) was not responsible for the significant association of both with sensation seeking. Among the eight *DDC* SNPs significantly associated with sensation seeking, three (rs11575522, rs11575542, and rs11575543) were highly intercorrelated ($r^2 = 0.95–0.98$). Nevertheless, even including these highly intercorrelated SNPs, the median r-squared value among the significant *DDC* SNPs was 0.04, indicating that linkage disequilibrium was likely not driving the inclusion of a relatively large number of *DDC* SNPs in our aggregate score.

Predictive utility of aggregate SNPs

We examined the utility of including all SNPs that were significant in the initial association tests when predicting sensation seeking. Results from models comparing the utility of covariates to covariates plus all significant SNPs are presented in Table 3. The model that included dopamine-related SNPs fit significantly better than the covariates-only model (as indicated in Table 3 by $p < 4 \times 10^{-13}$ and the lower AIC and BIC of model 2 compared to model 1). Including the 12 significant SNPs explained 3.9% more variance (an average of 0.35% per exonic SNP, 0.31% per intronic SNP) in sensation seeking than the covariates-only models.

To illustrate the influence of all significantly associated SNPs on the total sensation seeking score, we calculated a “genetic risk score” (Evans, Visscher, & Wray, in press; Purcell et al., 2009; Wray, Goddard, & Visscher, 2007), defined for each individual as the sum of the number of minor alleles at each associated SNP multiplied by that SNPs regression weight from the aggregate SNP model. That is:

$$(SNP_1 \text{ minor alleles}, i.e.\ 0/1/2^{*}B_1)+(SNP_2 \text{ minor alleles}^{*}B_2)+\ldots+(SNP_{12} \text{ minor alleles}^{*}B_{12}) \quad (2)$$

Figure 1 illustrates the correlation ($r = 0.20$; $p < 2 \times 10^{-8}$) between this genetic risk score and the residualized total sensation seeking score[1] (after accounting for age, sex, and ancestry; both the genetic risk score and the residual sensation seeking score were standardized to a mean of zero and a standard deviation of one to increase interpretability). With the caveat that calculating the genetic risk score in the same sample used to identify significant SNPs may represent an optimistic population effect size estimate, this correlation represents a non-trivial effect in the behavioral sciences (e.g. Cohen, 1992) and is notable in the context of the effect sizes of accepted physical and mental health associations (e.g. aspirin and heart attack survival; chemotherapy and breast cancer survival; lead exposure and childhood IQ; nicotine patch use and smoking cessation; Meyer et al., 2001). This is also a non-trivial effect in the context of the candidate gene and genome-wide association literatures, where effect sizes for single genetic polymorphisms are typically small (Maher, 2008).

Discussion

We implemented a multivariate approach to investigating the effects of SNPs in dopamine genes, a theoretically implicated neurobiological system, on sensation seeking, a personality trait associated with costly outcomes, such as substance use disorders. Working with data from 635 individuals, we selected 273 SNPs covering eight dopamine genes, and conducted initial association analyses to identify individual SNPs significantly associated (at $p<0.05$, FDR < 0.10) with sensation seeking. We then estimated the variance in sensation seeking explained by 1) demographic covariates; and 2) all significantly associated SNPs. Increased variance explained and improved model fit statistics (see Table 3) indicated that aggregated SNPs from dopamine genes explained significant variation between individuals in sensation seeking, even when controlling for demographic characteristics. Despite our relatively dense coverage of these selected genes, not all possible SNPs (or other genetic variants) were included on our genotyping platform. To the extent that the genotyped SNPs are not themselves functional, but are instead in linkage disequilibrium (i.e. correlated) with ungenotyped functional variants, these proportions of variance may be underestimates compared to the true variance in sensation seeking explainable by these dopamine genes.

Strengths and weaknesses

The primary weakness of this study was its modest sample size, and our lack of a sample in which to examine replication of our findings. However, our sample was demographically diverse, with an overrepresentation of individuals meeting criteria for alcohol dependence, a disorder where sensation seeking may be a particularly relevant risk factor. Our genotypic data provided more thorough coverage of genetic variation in the candidate genes examined here than in previous association studies related to sensation seeking (Beaver, 2009; Ebstein, 2006; Heck et al., 2009), and we made use of our additional genomic data by taking a systems approach and considering the aggregate effect of numerous SNPs in multiple genes associated with dopamine. This approach resulted in significant improvement in our ability

[1]We conducted post hoc analyses to examine the generality of the genetic risk score across sensation seeking subscales. Each subscale was residualized over all covariates and then correlated with the overall genetic risk score. Pearson correlations were 0.19, 0.18, 0.14, and 0.12 for disinhibition, boredom susceptibility, thrill and adventure seeking, and experience seeking, with p-values of 8×10^{-7}, 7×10^{-6}, 4×10^{-4}, and 2×10^{-3}, respectively. These correlations were within the range of those reported for the total sensation seeking score (i.e., r = 0.20). A reasonable conclusion is that the dopaminergic genetic risk score explained variance in general sensation seeking, rather than variance in only a specific subscale.

to predict sensation seeking scores, beyond the prediction afforded by covariates, with an overall non-trivial aggregate effect (Cohen, 1992) of SNPs on sensation seeking.

Conclusions

Our results indicated that dopamine genes are associated with sensation seeking at the system level, that is, at the level of multiple SNPs in multiple dopamine genes. This systems approach had the ability to account for nontrivial variance; 3.9% (corresponding to a correlation of 0.20) of the variance in sensation seeking was explained using only 12 SNPs. Given a heritability of sensation seeking of 58.3% (Fulker & Eysenck, 1980), we were able to account for 6.6% of the heritable variance in sensation seeking. However, our sample was not of sufficient size to allow for cross-validation, and so this effect size estimate may be reduced when replication is attempted. Nevertheless, model fit indices demonstrated that significant independent variance was accounted for by the inclusion of multiple SNPs.

The lack of evidence for linkage disequilibrium accounting for our detection of multiple SNPs within both the *COMT* and *DDC* genes associated with sensation seeking suggests that dopamine-related candidate genes likely contain multiple markers that affect sensation seeking, rather than a single SNP (or other individual unit of genetic variation) of relatively large effect which is simply being “tagged” (due to inter-SNP correlations, i.e., linkage disequilibrium) by surrounding SNPs. The apparent overrepresentation of significant SNPs located in the gene *DDC* in the individual association tests might imply the relevance of production over receptor characteristics in sensation seeking. While our current results suggest this conclusion, it would require replication in future research before being considered a reliable finding. Future research should also include genes corresponding with other candidate systems, such as serotonin-related genes (e.g. Heck et al., 2009), that have also been implicated in the etiology of sensation seeking and associated traits.

Our model of aggregating multiple SNP effects from across genes within a single system is consistent with an additive model of genetic influence (the model of genetic influence employed for heritability estimates of sensation seeking; Fisher, 1918). The aggregation of multiple SNP effects into a genetic risk score is also well-aligned with current thinking on the nature of genetic influence on complex continuous traits. It is likely that numerous (e.g., thousands of) genetic polymorphisms, each with a small effect, contribute to the wide variation in observable human traits (e.g. Maher, 2008). The construction of theory-driven genetic risk scores (as in the candidate system approach demonstrated here) provides a promising direction for predicting phenotypic variation. Future work should focus on refining the genetic risk score, by using larger samples that would allow for greater accuracy in SNP selection and cross-validation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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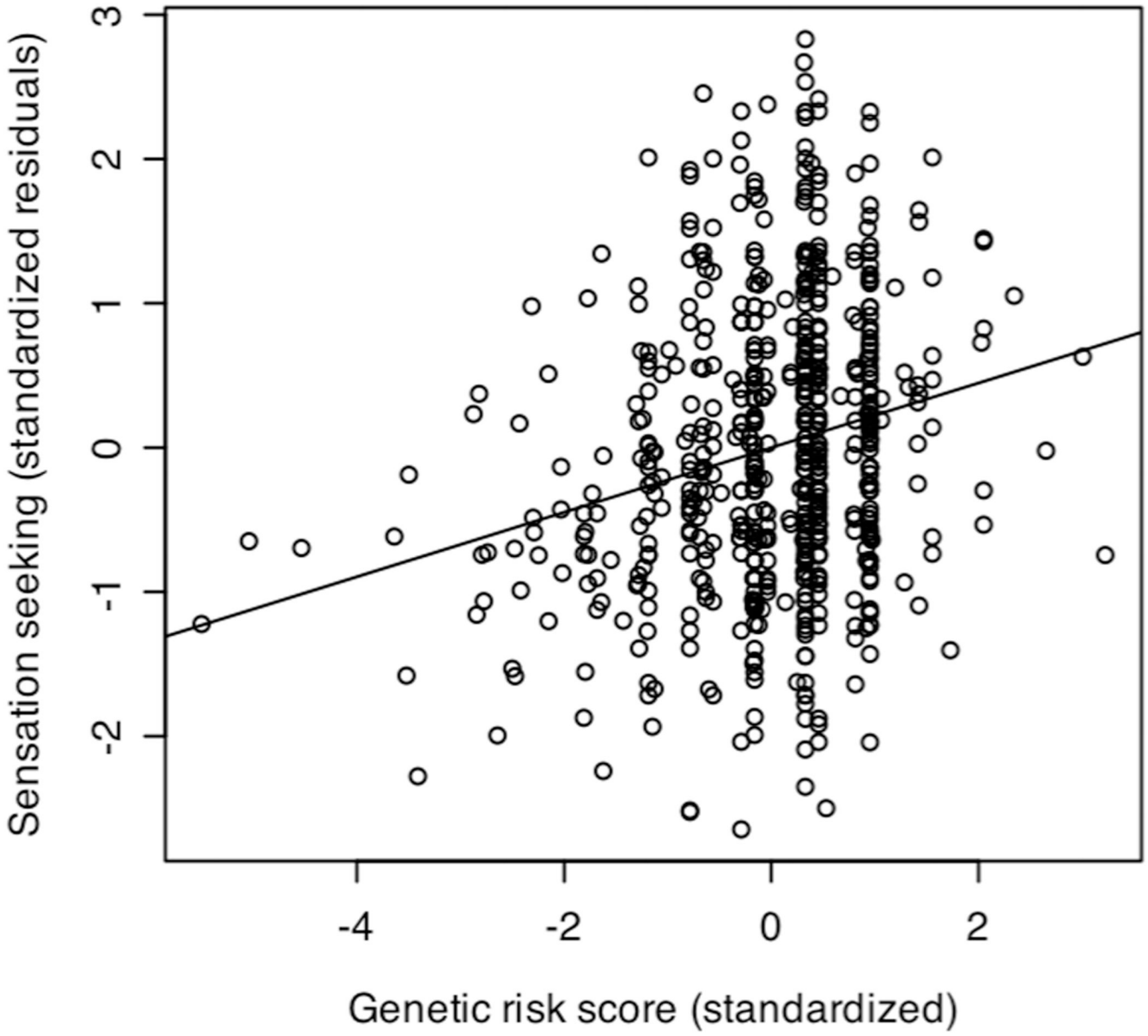

Figure 1.
Scatterplot and least-squares regression line for additive effects of twelve SNPs from four dopamine-related genes predicting sensation seeking ($r = 0.20$; $p < 2 \times 10^{-8}$), after accounting for demographic covariates.

Table 1

Genes from which SNPs were chosen for analyses.

Gene	Location	SNPs	Role in Dopamine (DA)
DRD3	3q13.3	32	codes D3 subtype of DA receptors
SLC6A3 (a.k.a. *DAT1*)	5p15.3	35	DA transporter that mediates reuptake of DA from the synapse
DRD1	5q35.1	9	codes D1 subtype of DA receptors
DDC	7p12.2	81	codes a protein that converts L-DOPA to DA
DBH	9q34	37	converts DA to norepinephrine
DRD4	11p15.5	4	codes D4 subtype of DA receptors
DRD2	11q23	40	codes D2 subtype of DA receptors
COMT	22q11.21	35	affects degradation of catecholamines (including DA)

Note. Location = chromosome location of the gene; SNPs = number of single nucleotide polymorphisms in that gene available in the SAGE data from the Illumina Human IM Bead Chip following quality control procedures; *DRD3* = dopamine receptor D3; *SLC6A3* = solute carrier family 6 (*DAT1* = dopamine transporter 1); *DRD1* = dopamine receptor D1; *DDC* = dopa decarboxylase; *DBH* = dopamine beta-hydroxylase; *DRD4* = dopamine receptor D4; *DRD2* = dopamine receptor D2; *COMT* = catechol-O-methyltransferase; L-DOPA = L-3,4-dihydroxyphenylalanine.

Table 2

SNPs significantly associated with sensation seeking ($p < 0.05$ and FDR < 0.10) from individual SNP tests.

SNP	Gene	Chr	Pos (bp)	Function	Allele	MAF	B	Z	p	FDR
rs11575551	DDC	7	50,493,757	UTR-3'	C	0.03	−3.266	−2.756	0.006	0.006
rs11575522	DDC	7	50,502,889	Intron	A	0.05	−2.185	−2.581	0.010	0.013
rs11575542	DDC	7	50,498,481	Missense	A	0.05	−2.125	−2.512	0.012	0.019
rs11575543	DDC	7	50,498,363	Intron	T	0.05	−2.170	−2.506	0.012	0.025
rs3829897	DDC	7	50,597,258	Intron	T	0.42	−0.896	−2.456	0.014	0.031
rs7876027	DBH	9	135,504,360	Intron	G	0.07	1.688	2.335	0.020	0.038
rs174699	COMT	22	18,334,458	Intron	C	0.06	−1.748	−2.290	0.022	0.044
rs10278338	DDC	7	50,597,764	Intron	T	0.34	−0.842	−2.277	0.023	0.050
rs11575552	DDC	7	50,493,740	UTR-3'	C	0.02	−3.118	−2.250	0.024	0.056
rs933271	COMT	22	18,311,407	Intron	C	0.32	−0.827	−2.127	0.033	0.063
rs12669770	DDC	7	50,597,382	Intron	A	0.33	−0.732	−1.984	0.047	0.069
rs2975284	SLC6A3	5	1,485,552	Intron	T	0.01	−2.902	−1.970	0.049	0.075

Note. SNP = single nucleotide polymorphism in the regression equation; Gene = gene location of the SNP (see Table 1 for gene function descriptions); Chr = chromosome location of the SNP; Pos (bp) = position on the chromosome (in base pairs) of the SNP; Function = SNP function; UTR-3' = SNP located in an untranslated region (UTR) at the 3' end of the gene that may affect the stability, localization, and/or efficiency of messenger RNA (mRNA) translation of the gene; Intron = non-coding SNP; Missense = missense mutation, in which each allele produces a different amino acid; Allele = minor allele (i.e. less frequent nucleotide) for which the regression effect, B, is reported; MAF = minor allele frequency; B = regression coefficient for the effect of the SNP; Z = z-score for the regression coefficient (calculated as B / std.error(B)); p = two-tailed p-value for B; FDR = False Discovery Rate (see Equation 1 in text).

Table 3

Comparisons between models predicting sensation seeking from 1) only covariates; and 2) covariates and all SNPs meeting $p < 0.05$ and FDR < 0.10 in the association tests.

Model	SNPs	R^2	ΔR^2	−2LL	df	p	AIC	BIC
1. Covariates only	0	27.9%		4113.0	8		4129.0	4164.7
2. All significant SNPs	12	31.7%	3.9%	4027.5	20	$< 4 \times 10^{-13}$	4067.5	4156.5

Note. SNPs = number of single nucleotide polymorphisms included in the model; R^2 = proportion of variance in the dependent variable explained by the covariates and any SNPs included in that regression model; ΔR^2 = additional variance explained by adding SNPs (model 2) to the covariate model (model 1); −2LL = −2 times the log-likelihood of the regression model; df = degrees of freedom in the regression model; p = the p-value when comparing model 2 to model 1, estimated by the change in −2LL on a chi-square distribution with df equal to the difference in dfs between the models; AIC = Akaike's Information Criterion, where lower values indicate better model fit to the data; BIC = Bayesian Information Criterion, where lower values indicate better model fit to the data.