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 behavioral disorders. The dopamine system has been hypothesized to contribute to variations in sensation seeking between different individuals, and both experimental and observational studies in humans and nonhuman animals provide evidence for the involvement of the dopamine system in sensation-seeking behavior. In this study, we took a candidate-system approach to genetic association analysis of sensation-seeking behavior. We analyzed single-nucleotide polymorphisms (SNPs) from a number of dopaminergic genes. Using 273 SNPs from eight dopamine genes in a sample of 635 unrelated individuals, we examined the aggregate effect of SNPs that were significantly associated with sensation-seeking behavior. Multiple SNPs in four dopamine genes accounted for significant variance in sensation-seeking behavior between individuals. These results suggest that multiple SNPs, aggregated within genes that are relevant to a specific neurobiological system, form a genetic-risk score that may explain a significant proportion of observed variance in human traits such as sensation-seeking behavior.

Sensation seeking is a personality trait that is of great significance in public health, as the trait is specifically associated with behavioral disorders that have high social costs, especially substance-use disorders. Among individuals with substance-use disorders, greater sensation seeking is associated with an earlier age of onset of substance use and abuse, increased poly-substance use, a greater number of symptoms, and more severe functional impairment (Ball, Carroll, & Rounsaville, 1994). Increased sensation-seeking behavior is also associated with an increased treatment dropout rate and poorer treatment outcome (Staiger, Kambouropoulos, & Dawe, 2007).

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

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The trait of sensation seeking therefore represents a promising endophenotypic indication of externalizing problems (Benjamin, Ebstein, & Belmaker, 2001; Gottesman & Gould, 2003; Krueger, Markon, Patrick, Benning, & Kramer, 2007). A theory-driven, candidate-neurogenetic system approach can be used to link genetic polymorphisms with specific behavioral phenomena. Sensation seeking would be an important target phenotype in this type of study, as the trait has a demonstrable neurobiological basis in humans (Joseph, Liu, Jiang, Lynam, & Kelly, 2009). The dopaminergic system has long been hypothesized to underlie individual variation in sensation seeking (Zuckerman, 1984), and recent studies support this hypothesis. The increased availability of the dopamine D2 receptor (*DRD2*) and the dopamine D3 receptor (*DRD3*) in the nucleus accumbens is negatively associated with impulsivity (a trait similar to the disinhibition scale within sensation seeking) in a rodent model (Dalley et al., 2007). In addition, the increased availability of dopamine D2 receptors in the ventral midbrain is negatively associated with novelty seeking (a trait similar to the experience-seeking scale of sensation seeking) in humans (Zald et al., 2008). A pharmacological study in humans also suggests that dopamine stimulation increases nicotine craving in individuals who score highly on the experience-seeking scale of sensation seeking (Netter, Hennig, & Roed, 1996).

Candidate-gene studies provide some evidence of a link between sensation-seeking behavior and specific polymorphisms in genes involved in the dopaminergic system. In the catechol-O-methyltransferase (*COMT*) gene, a commonly examined functional single-nucleotide polymorphism (SNP), rs4680 (also known as Val158Met), has been associated with sensation-seeking behavior (although the association was specific to females; Lang, Bajbouj, Sander, & Gallinat, 2007). A gene-gene interaction effect on sensation seeking has been demonstrated between the rs1800497 SNP, also known as DRD2 Taq1A or C32806T—located in the ankyrin repeat and kinase-domain-containing 1 (*ANKK1*) gene—and the commonly studied variable-number-of-tandem-repeats (VNTR) polymorphism (48 base pairs that repeat a variable number of times) in the dopamine D4 receptor (*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 infants' visual exploratory behavior and adolescents' novelty-seeking behavior (Laucht, Becker, & Schmidt, 2006). However, as in many other traits and diseases, the 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).

The sensation-seeking trait is an appealing target for human genetic research, as it is a continuous trait that confers risk of developing externalizing disorders and increasing the severity of these disorders. Candidate-gene studies of sensation seeking (and personality traits in general) have tended to focus on a small number of polymorphisms within a single gene (Ebstein, 2006), the individual effects on behavioral traits of SNPs from multiple genes (Heck et al., 2009), or the aggregate effects on behavioral traits of single polymorphisms from each of several genes (Beaver, 2009). The advent of dense, whole-genome SNP genotyping means that far more genetic variation can be captured than in earlier candidate-gene studies. However, the use of whole-genome data incurs a considerable statistical cost, by exacting a heavy penalty in the form of *p*-value corrections to account for multiple testing.

In the study presented in this article, we combined the theory-driven, candidate-gene approach with the genotypic data available from genome-wide, high-throughput genotyping technology. From a pool of all SNPs located in dopamine genes (available from a dense-coverage, commercially available genotyping platform), we first selected SNPs that were individually associated with the sensation-seeking trait. We then fit nested regression models, in which sensation seeking was predicted by demographic covariates (Model 1) or by variables from Model 1 (as covariates) as well as all SNPs identified as significant in the individual association tests (Model 2). By comparing 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)?

Method

Participants

Participants were 635 unrelated individuals who had participated in the Study of Addiction: Genetics and Environment (SAGE; Bierut et al., 2010). Participants in our study were a subset of the SAGE participants, all of whom were drawn from a primary study of alcohol dependence, the Collaborative Study on the Genetics of Alcoholism (COGA; Reich et al., 1998) because these individuals had completed the Sensation Seeking Scale (Zuckerman, Eysenck, & Eysenck, 1978). Participants heard a thorough description of the study, after which written, informed consent was obtained from all the participants. The average age of our sample was 45.3 years (range: 22–77 years), 55.1% were female and 44.9% were male, 18.9% were of self-reported African ancestry and 8.2% were of self-reported Hispanic ancestry, and 65.2% met the criteria for a lifetime alcohol-dependence diagnosis (according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision, or DSM–IV–TR; American Psychiatric Association, 2000).

Measures

Participants were administered Zuckerman's Sensation Seeking Scale Form V (SSS-V; Zuckerman et al., 1978). In the SSS-V, four 10-item subscale scores are summed to calculate

an overall sensation-seeking score for each participant. The four 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 overall sensation-seeking score obtained from these four subscale scores is reliable (in terms of internal consistency) in both American males (Cronbach's α = .84) and females (α = .85; Zuckerman et al., 1978). We analyzed the total sensation-seeking score, rather than its subscales, to obtain 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 (Illumina, Inc., San Diego, CA). The median missing-data (or missingness) 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 the assessment of population structure, missing call rates, Mendelian errors, duplication errors, gender and chromosomal anomalies, hidden relatedness, batch effects, and Hardy-Weinberg disequilibrium. Samples identified as duplicates, related subjects, or outliers were removed. A total of 948,142 SNPs remained available for analysis following this data-cleaning procedure (Bierut et al., 2010).

Gene and SNP selection

Dopamine-related genes were identified through a search of the relevant candidate-gene literature. Only genes located on autosomal (i.e., nonsex) chromosomes that have definite and direct effects on the dopaminergic system were included in the analysis. SNPs in each of these genes (identified from the Database of Single Nucleotide Polymorphisms, 2008; or dbSNP, 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.[1]

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 et al. (2006). Two major principal components emerged, corresponding to European versus African ancestry (PC1) and Hispanic versus non-Hispanic ancestry (PC2). Treating ancestry as a covariate assumes that although minor (i.e., less common) allele frequencies may differ between races, the biological impact of SNPs does not (Ioannidis, Ntzani, & Trikalinos, 2004). Although ideally we would model ethnicities separately to explore this potential difference, our sample size prevented this approach. PC1 and PC2 were used as covariates in our analyses, along with age (as in earlier SAGE analyses, this was coded in quartiles as three dummy codes, 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, or 2 to indicate the number of minor alleles present for a particular individual. We did not control for alcohol-dependence case status for our main analyses, because sensation seeking and similar traits are significantly linked to alcohol-use behaviors (e.g., Slutske et al., 2002), and including the trait as a covariate may eliminate meaningful variance (Meehl, 1971).

Table 1. Genes From Which Single-Nucleotide Polymorphisms (SNPs) Were Chosen for Analyses

Gene	Chromosome location	Number of SNPs[a]	Role in dopamine (DA) system
DRD3 (dopamine receptor D3)	3q13.3	32	Codes D3 subtype of DA receptors
SLC6A3 (solute carrier family 6), also known as *DAT1* (dopamine transporter 1)	5p15.3	35	DA transporter that mediates reuptake of DA from the synapse
DRD1 (dopamine receptor D1)	5q35.1	9	Codes D1 subtype of DA receptors
DDC (dopa decarboxylase)	7p12.2	81	Codes a protein that converts L-3,4-dihydroxyphenylalanine (L-DOPA) to DA
DBH (dopamine β-hydroxylase)	9q34	37	Converts DA to norepinephrine
DRD4 (dopamine receptor D4)	11p15.5	4	Codes D4 subtype of DA receptors
DRD2 (dopamine receptor D2)	11q23	40	Codes D2 subtype of DA receptors
COMT (catechol-O-methyltransferase)	22q11.21	35	Affects degradation of catecholamines (including DA)

[a]This column indicates the number of SNPs available in the Study of Addiction: Genetics and Environment (SAGE) data from the Illumina Human IM Bead Chip, after application of quality-control procedures.

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 2 remained significant, at $p < 5 \times 10^{-12}$).

Association tests were initially run on each individual SNP (coded as 0, 1, or 2, according to the number of minor alleles for each SNP). We used R (an open-source statistical program; R Development Core Team, 2009) to perform a linear regression of the sensation-seeking score on each SNP and all covariates (i.e., PC1, PC2, age, and sex). We then 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 that reached significance. FDR controls the proportion of false-positive results expected from all tests declared significant. The following equation was used to estimate the proportion of null *p* values falling at or above test *i* in terms of *p*-value ranking and to determine FDR:

$$P_i \le (i/m) * \alpha \qquad (1)$$

In this equation, *i* denotes the rank order of the test (ranked in terms of ascending *p* values), *m* denotes the total number of independent tests, α is the *p* value cutoff for significance, and P_i is the *p* value for test *i* (Benjamini & Hochberg, 1995). We set our maximum FDR at .10, meaning that no more than 10% of the SNPs that were declared significant (using α = .05) were expected to be false positives. For our purposes, we set the value of *m* at 8, the number of genes included in our analyses.

Second, to account for linkage disequilibrium (LD, or the correlation between SNPs) in our heterogeneous sample, we estimated false positives by calculating 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 values the same as in the real association tests, in which the genotypes were not randomly assigned), 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* < .05 level in the individual-SNP association tests and that met the criterion FDR of < .10), we compared two statistical models of sensation-seeking behavior. The first (baseline) model regressed sensation seeking on the same standard covariates that were included in the initial association tests. The second model regressed sensation seeking on covariates and significant SNPs identified via 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 by the model (i.e., the R^2 value), (b) the model likelihoods, (c) Akaike's information criterion (AIC) from each model, and (d) the Bayesian information criterion (BIC) from each model (Table 2). AIC and BIC are information theoretic measures of goodness of model fit and account for model parsimony in evaluating fit. AIC and BIC are more conservative measures than a direct comparison of model likelihoods, requiring greater evidence of the predictive utility of additional predictor variables in order to show that a model has improved fit. Lower AIC and BIC values 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 behavior, controlling for demographic characteristics. Results for the individual-SNP association tests (for SNPs whose regression weights met *p* < .05) are reported in Table 3. (For results from all 273 association tests, see Table S1 in the Supplemental Material available online.) Twelve SNPs met the significance criteria for association with sensation seeking (*p* < .05 and FDR < .10). By comparison, only three SNPs in

Table 2. Comparison of the Model Predicting Sensation Seeking From Covariates Alone and the Model Predicting Sensation Seeking From Covariates and All Significant Single-Nucleotide Polymorphisms (SNPs)

Model	Number of SNPs	R^2	ΔR^2	−2LL	df	p	AIC	BIC
1. Covariates alone	0	27.9%	—	4,113.0	8	—	4,129.0	4,164.7
2. Covariates plus all significant SNPs	12	31.7%	3.9%	4,027.5	20	$< 4 \times 10^{-13}$	4,067.5	4,156.5

Note: R^2 indicates the proportion of variance in sensation seeking explained by the model; ΔR^2 indicates the additional variance explained by adding SNPs to the covariate model. The *p* value listed is the value obtained when comparing Model 2 with Model 1, and was estimated by the change in −2LL (−2 × the log likelihood of the regression model) on a chi-square distribution with *df* equal to the difference in *df*s between the models. Lower values of Akaike's information criterion (AIC) and the Bayesian information criterion (BIC) indicate better model fit to the data. All SNPs included in Model 2 met the following criteria in association tests: *p* < .05 and false discovery rate < .10.

Table 3. Single-Nucleotide Polymorphisms (SNPs) Significantly Associated With Sensation Seeking According to Individual SNP Tests

SNP	Gene	Chromosome location of SNP	Gene position on chromosome (base pairs)	SNP function	Allele	MAF	b	z	p	FDR
rs11575551	*DDC*	7	50,493,757	UTR-3′	C	.03	−3.266	−2.756	.006	.006
rs11575522	*DDC*	7	50,502,889	intron	A	.05	−2.185	−2.581	.010	.013
rs11575542	*DDC*	7	50,498,481	missense	A	.05	−2.125	−2.512	.012	.019
rs11575543	*DDC*	7	50,498,363	intron	T	.05	−2.170	−2.506	.012	.025
rs3829897	*DDC*	7	50,597,258	intron	T	.42	−0.896	−2.456	.014	.031
rs7876027	*DBH*	9	135,504,360	intron	G	.07	1.688	2.335	.020	.038
rs174699	*COMT*	22	18,334,458	intron	C	.06	−1.748	−2.290	.022	.044
rs10278338	*DDC*	7	50,597,764	intron	T	.34	−0.842	−2.277	.023	.050
rs11575552	*DDC*	7	50,493,740	UTR-3′	C	.02	−3.118	−2.250	.024	.056
rs933271	*COMT*	22	18,311,407	intron	C	.32	−0.827	−2.127	.033	.063
rs12669770	*DDC*	7	50,597,382	intron	A	.33	−0.732	−1.984	.047	.069
rs2975284	*SLC6A3*	5	1,485,552	intron	T	.01	−2.902	−1.970	.049	.075

Note: See Table 1 for descriptions of gene functions. *DDC* refers to the dopa decarboxylase gene, *DBH* to the dopamine β-hydroxylase gene, *COMT* to the catechol-O-methyltransferase gene, and *SLC6A3* to the solute carrier family 6 gene; UTR-3′ refers to an SNP located in an untranslated region (UTR) at the 3′ end of the gene that may affect the stability, localization, or efficiency of messenger RNA translation of the gene. Intron refers to a noncoding SNP; missense refers to a missense mutation, in which each allele produces a different amino acid; and G, C, A, and T refer to guanine, cytosine, adenine, and thymine, respectively. The alleles listed are minor alleles (i.e., the less frequently occurring nucleotides), for which the regression effect, *b*, is reported. The table reports the *z* score for each regression coefficient, calculated as *b*/*SE*(*b*); the two-tailed *p* value for *b* is also given. MAF = minor-allele frequency; FDR = false discovery rate (see Equation 1 in the Method section). All SNPs in Table 3 met the following criteria in association tests: *p* < .05 and FDR < .10.

the randomized-genotype condition (rs2042449 and rs9312866 in the dopamine transporter gene, or *SLC6A3*, and rs1611114 in dopamine β-hydroxylase, or *DBH* gene) were significant by chance (at *p* < .05), and none of these passed the FDR criterion (i.e., the *p* value of the top-ranked SNP was greater than its FDR value). Because the number of SNPs meeting the *p*-value criterion was substantially greater in the correct-genotype tests than in the tests using randomly assigned genotypes, and because all SNPs in the correct-genotype condition met the FDR criterion (and no SNPs in the random-genotype condition met the FDR criterion), we concluded that the implicated SNPs are likely to have true associations with sensation seeking, at least in the current data set.

Table 3 shows that 8 of our 12 significant SNPs were located in the *DDC* gene, which encodes dopa decarboxylase (aromatic L-amino acid decarboxylase), and 2 were located in the *COMT* gene, which encodes catechol-O-methyltransferase. To examine whether these SNPs could explain unique variance in sensation-seeking behavior, we estimated the intercorrelations among all significant SNPs located within a single gene. In our sample, the 2 *COMT* SNPs (rs174699 and rs933271) had an r^2 value of .03, which strongly suggested that LD (i.e., correlation between SNPs) was not responsible for the significant association of both SNPs with sensation seeking. Among the 8 *DDC* SNPs significantly associated with sensation seeking, 3 (rs11575522, rs11575542, and rs11575543) were highly intercorrelated (r^2 = .95−.98). Nevertheless, even including these highly intercorrelated SNPs, the median r^2

value among the significant *DDC* SNPs was .04, which indicated that LD probably was 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 in the prediction of sensation seeking of including all SNPs that were significant according to the initial association tests. Results from models comparing the utility of covariates with the utility of covariates plus all significant SNPs are presented in Table 2. The model that included dopamine-related SNPs fit significantly better than the covariates-only model (as indicated by the *p* value in Table 2, $< 4 \times 10^{-13}$, as well as by the lower AIC and BIC values for Model 2 compared with Model 1). The addition of the 12 significant SNPs (in Model 2) explained 3.9% more variance (an average of 0.35% per exonic SNP, and 0.31% per intronic SNP) in sensation seeking than the covariates-only model (Model 1).

To illustrate the influence of all significantly associated SNPs on the total sensation-seeking score, we calculated a genetic-risk score (e.g., 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 (i.e., 0, 1, or 2), multiplied by that SNP's regression weight from the aggregate SNP model. The genetic risk score was calculated as follows:

$$(SNP_1 \text{ minor alleles} * b_1) + (SNP_2 \text{ minor alleles} * b_2) + \ldots + (SNP_{12} \text{ minor alleles} * b_{12})$$

Figure 1 illustrates the correlation ($r = .20$, $p < 2 \times 10^{-8}$) between the calculated genetic-risk score and the residualized overall sensation-seeking score[2] (after accounting for age, sex, and ancestry; both the genetic-risk score and the residual sensation-seeking score were standardized to a mean of 0 and a standard deviation of 1 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 estimate of the population effect size, this correlation represents a nontrivial 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 nontrivial effect in the context of the candidate-gene and genome-wide association literatures, where effect sizes for single genetic polymorphisms are typically small (e.g., Plomin, Haworth, & Davis, 2009).

Discussion

We implemented a multivariate approach to investigate the aggregate effect of SNPs in dopamine genes (part of 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 from eight dopamine genes, and conducted initial association analyses to identify individual SNPs significantly associated with sensation seeking ($p < .05$, FDR < .10). We then estimated the variance in sensation-seeking
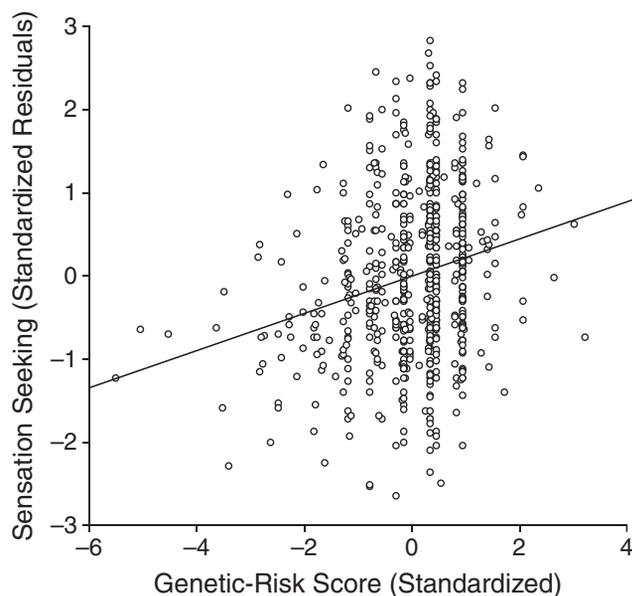
Fig. 1. Scatter plot and least squares regression line illustrating the additive effects of 12 single-nucleotide polymorphisms from four dopamine-related genes (standardized as a genetic-risk score) in predicting the sensation-seeking trait ($r = .20$, $p < 2 \times 10^{-8}$), after accounting for demographic covariates.

behavior between individuals that was explained by demographic covariates alone (Model 1) and by these covariates plus all significantly associated SNPs (Model 2). Increased variance explained and improved model-fit statistics (Table 2) 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 LD (i.e., correlated) with ungenotyped functional variants, these proportions of variance may be underestimates of 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 ($N = 635$) and our lack of a sample in which to replicate our findings. However, our sample was demographically diverse, with an overrepresentation of individuals meeting the criteria for alcohol dependence, a disorder in which sensation seeking may be a particularly relevant risk factor. Our genotypic data provided a more thorough coverage of genetic variation in the candidate genes examined in our study, in comparison to the coverage of genetic variation in other sensation-seeking-related association studies (Beaver, 2009; Ebstein, 2006; Heck et al., 2009). We also 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 demonstrated an overall nontrivial aggregate effect (Cohen, 1992) of dopaminergic SNPs on sensation seeking, and enabled us to predict sensation-seeking scores more accurately than if we had relied on covariates alone.

Conclusion

Our results indicated that dopamine genes are associated with sensation-seeking behavior at the system level, that is, at the level of multiple SNPs in multiple dopamine genes. Our systems-approach study accounts for nontrivial variance: 3.9% of the variance in sensation seeking (corresponding to a correlation of .20) was explained using only 12 SNPs. Given a 58.3% heritability of sensation-seeking behavior (Fulker et al., 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 may be an overestimate. Nevertheless, model-fit indices demonstrated that significant independent variance was accounted for by the inclusion of multiple SNPs.

The lack of evidence for LD accounting for our detection of multiple SNPs within both the *COMT* and *DDC* genes associated with sensation seeking suggests that dopamine-related

candidate genes contain multiple variants that affect sensation seeking, rather than a single variant of relatively large effect that is simply being "tagged" by surrounding SNPs (because of inter-SNP correlations, i.e., LD). The apparent overrepresentation of significant SNPs located in the gene *DDC*, which catalyzes the decarboxylation of L-3,4-dihydroxyphenylalanine (DOPA) to dopamine, in the individual association tests might imply that dopamine production has greater relevance to sensation-seeking behavior than dopamine-receptor characteristics do. Although our data support this conclusion, replication of our results in future research is necessary. Further research should also examine genes associated with other candidate systems, such as serotonin-related genes (e.g., Heck et al., 2009), which have also been implicated in the etiology of sensation seeking and associated traits.

Our model of aggregating multiple SNP effects 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., Plomin et al., 2009). The construction of theory-driven genetic-risk scores (as in the candidate-system approach demonstrated here) is a promising avenue for predicting phenotypic variation. Future work should focus on refining calculation of the genetic-risk score, by using larger samples that would allow for greater accuracy in SNP selection and cross-validation of results.

Acknowledgments

Declaration of Conflicting Interests

L.J. Bierut and S. Saccone are listed as inventors on the patent "Markers for Addiction" (U.S. 20070258898), which covers the use of certain single-nucleotide polymorphisms in determining the diagnosis, prognosis, and treatment of addiction. L.J. Bierut acted as a consultant for Pfizer, Inc., in 2008. All other authors report no competing interests.

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Supplemental Material

Additional supporting information may be found at http://pss.sagepub .com/content/by/supplemental-data

Notes

1. No SNPs from the dopamine receptor D5 (*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 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 (Munafò, Yalcin, Willis-Owen, & Flint, 2008).
2. 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—Disinhibition: $r = .19$, $p = 8 \times 10^{-7}$; Boredom Susceptibility: $r = .18$, $p = 7 \times 10^{-6}$; Thrill/Adventure Seeking: $r = .14$, $p = 4 \times 10^{-4}$; Experience Seeking: $r = .12$, $p = 2 \times 10^{-3}$. These correlations were within the range of those reported for the total sensation-seeking score (i.e., $r = .20$). A reasonable conclusion is that the dopaminergic genetic-risk score explained variance in general sensation seeking, rather than variance in only a specific subscale.

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