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ORIGINAL ARTICLE

Stress-induced cigarette craving: effects of the *DRD2 Taq*I RFLP and *SLC6A3* VNTR polymorphisms

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ABSTRACT
Animal models have long implicated dopamine in stress-induced craving for a variety of addictive substances. However, translational studies of dopamine, stress and craving in humans are lacking. Based on the animal literature, this study's objective was to test the hypothesis that cigarette smokers carrying specific variants in dopamine-related genes would have heightened levels of cigarette craving following exposure to a laboratory stressor. Cigarette craving induced by controlled exposure to a laboratory stressor was assessed in healthy adult smokers ($n = 108$) recruited by advertisement. Significantly stronger stress-induced cigarette craving was found for individuals carrying either the *DRD2* (D2 dopamine receptor gene) A1, or the *SLC6A3* (dopamine transporter gene) nine-repeat allelic variants. Stress-induced craving was markedly higher for those carrying both alleles, compared to those with neither, consistent with the separate biological pathways involved (receptor, transporter). Findings provide strong support for the possibility that dopamine involvement in stress-induced craving well established in animal models also applies to humans, and suggest a potential genetic risk factor for persistent smoking behavior.
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INTRODUCTION

Cigarette smoking is one of the most preventable causes of morbidity and mortality. Despite the widely recognized risks, about one-third of people continue to smoke worldwide.[1] According to estimates from the US, while a majority of smokers attempt to quit, only 5–15% maintain abstinence over a 1-year interval, even with pharmacological and psychological interventions.[2] Quantitative genetic studies of mono- and dizygotic twins have demonstrated that this persistent smoking behavior has a considerable genetic component.[3]

Consistent with this possibility, research over the past decade has identified specific genetic polymorphisms in the dopamine system that are predictive of smoking behavior, in particular, as well as other types of substance abuse. For example, an early study by Blum *et al*[4] found that the presence of the *Taq*I RFLP A1 allele of the D2 dopamine receptor gene (*DRD2*) predicted severe alcoholism. Subsequent studies have replicated these findings (see Noble[5] for a review), and have extended them to other addictive behaviors, including psychostimulant use[6] and cigarette smoking (eg, Comings *et al*,[7] Bierut *et al*,[8] and Spitz *et al*[9]; see

Noble[10] for a review). Some studies, however, have failed to replicate these findings,[11,12] while others have suggested that the magnitude of relations between the A1 allele and addictions may vary by sample characteristics (eg, gender[13,14]). Consistent with relations between the A1 allele and substance abuse, numerous molecular studies (see Noble[10] for a review) have shown that the presence of the A1 allele is associated with reduced D2 receptor density, and lower brain dopaminergic function. These basal deficits, in turn, are thought to increase the incentive salience of drug use in the presence of triggers (eg, stress) that might be related to acute phasic increases in dopamine levels and may help explain observed relations between A1 and addictions.[10,15]

Other studies have identified relations between a nine-repeat variable number of tandem repeats (VNTR) sequence on the dopamine transporter gene (*SLC6A3*) and substance abuse. For example, studies by Sander *et al*[16,17] found that the presence of this nine-repeat allele was associated with severe alcohol problems. On the other hand, Lerman *et al*[18] have reported that the absence of the nine-repeat allele was related to smoking status and shorter quit durations. Another study found that nine-repeat status was not related to smoking status,[19] while a third study[20] found that the presence of the nine-repeat allele was related to smoking status using a stricter definition of 'never smoking'. Similarly, there is some inconsistency in the literature regarding the function of this VNTR, with some reports suggesting that it is not functional in itself (eg, Martinez *et al*[21]). Several recent studies, however, have demonstrated that the nine-repeat allele enhances transcription of the dopamine transporter protein (eg, Michelaugh *et al*[22]), which might result in overly efficient clearing of synaptic dopamine, and thus lower basal availability. Similar to the *DRD2*-A1 allele, the nine-repeat allele might thus enhance the incentive salience of drug use in the presence of triggers that might be related to acute increases in dopamine levels. On balance, some, but not all, studies have found that the *DRD2*-A1 and *SLC6A3* nine-repeat alleles are related to substance abuse in general, and smoking behavior in particular.

One possible reason for the mixed results in this literature may be the lack of experimental control over the multiplicity of factors that influence smoking behavior in real-world settings.[23] Similarly, the difficulty associated with establishing a meaningful operational definition of a complex behavior such as smoking could have a significant impact on results.[20] One approach to addressing this problem is to examine specific genetic influences on alternative, more tightly characterized smoking-related endophenotypes. One such candidate is stress-induced craving for cigarettes. The potential utility of examining genetic influences on this more ''proximal'' phenotype is also supported by research demonstrating a critical role of CNS dopamine pathways for stress-induced craving and drug seeking in animal models.[15] As one example, Shaham and Stewart[24] have demonstrated that stress-induced dopamine release correlates strongly with drug-seeking behavior in rats, and that this effect was attenuated with administration of dopamine antagonists.[25] Similarly, Buczek *et al*[26] found that, in rats, administration of an acute stressor induced high levels of nicotine-seeking behavior.

Consistent with these animal models, as reviewed by Sinha,[27] stress and associated cigarette-craving reactions in humans have been identified, both by clinical accounts and by empirical studies, to be strong predictors of persistent smoking, as well as other substance abuse.[28,29] That is, exposures to acute stressors throughout the day are thought to trigger repeated experiences of high levels of craving, which may make it particularly difficult for people who are trying to quit smoking and to stay abstinent.

Based on the literature reviewed above, the present study used an experimental model of stress-induced craving in humans, to test the hypothesis that smokers who are carriers of the *DRD2 Taq*I RFLP A1 (D2 dopamine receptor) or the *SLC6A3* VNTR nine-repeat (dopamine transporter) polymorphisms would exhibit heightened levels of cigarette craving after exposure to a classic laboratory stressor.[28] We further hypothesized that smokers found to be carriers of both the receptor and transporter polymorphisms would exhibit the strongest stress-induced craving reactions.

METHOD

Overview

To test the study hypotheses, 108 current smokers were genotyped for the *DRD2* and *SLC6A3* polymorphisms. All underwent a laboratory psychological stress session, during which time they were exposed to guided mental imagery of both stressful and neutral stimuli. Measures of stress and cigarette craving were taken immediately before and after each imagery session. A factorial analysis of variance was used to assess effects of genotype on stress-induced cigarette craving.

Participants

Smokers ($n = 108$) were recruited by advertisement from the East Harlem community in New York City to participate in a research study. Participants had to: speak English, be at least 23 years old (to increase the likelihood of recruiting regular daily smokers), have no previous or current cancer, cardiovascular disease, emphysema, or other smoking-related illnesses, not be currently attempting to quit smoking, and report no history of treatment for other substance abuse. All participants provided informed consent prior to participation in the study, and all study procedures were approved by the Mount Sinai Medical Center's Institutional Review Board.

Measures

Background questionnaires

Participants completed background questionnaires assessing demographic information (age, gender, ethnic background, education level, income level) and smoking history (cigarettes per day, years of smoking). In addition, participants completed the Fagerstrom Test of Nicotine Dependence

(FTND), a standardized index of habit strength, and the Minnesota Nicotine Withdrawal Questionnaire (MNWQ). Both instruments have been used extensively in the literature and have established psychometric properties.[30,31]

Outcome measures

As a measure of cigarette craving, participants completed a five-item 0–100 craving questionnaire. Consistent with previous recommendations,[32] the items assessed craving using a variety of descriptors, including 'urge', 'desire', and 'craving'. The instrument has been employed in a number of laboratory craving-induction studies (eg, Hutchison *et al*[33]), and was highly reliable in the current sample (Chronbach's alpha = 0.96). As a brief measure of psychological distress, participants completed a one-item visual analog scale, on which they were asked to rate their anxiety levels by striking a mark along a 100 mm line anchored on opposite ends by 'not at all anxious' and 'as anxious as can be'.[34] As these measures were administered four times, immediately before and immediately after both the stress and neutral imagery (see below), brief assessments were necessary to limit participant burden and to maximize the likelihood of obtaining responses while participants were 'in the moment'. Both of these measures have demonstrated utility for rapid and repeated assessments under laboratory conditions.[33,34] Finally, participants completed a face-valid four-item 0–25 scale of imagery vividness (eg, how vivid were your images?) to assess how well they were able to image the stress and neutral stimuli.

Procedure

After providing informed consent, participants donated 5 ml of blood (double-blinded) for genotyping and completed background questionnaires. They then participated in a classic laboratory stress-induced craving paradigm,[28] which included imaginal exposure to both neutral (changing a light bulb) and stressful (going to a dentist) stimuli. Briefly, participants were asked to close their eyes and imagine as vividly as possible the two separate scenarios, which were read to them by an examiner. The scenarios (neutral, stress) were read for 60 s and were followed by 30 s of 'quiet time', during which the participants were instructed to continue to imagine the scenes. The neutral scene was always administered first and the stress imagery second, to avoid carryover effects noted in pilot studies. To further control carryover, participants viewed a nature video for 5 min between the two imagery scenes. Immediately before and after exposure to each imagery scene, participants completed the stress and craving scales. In addition, after each of the imagery scenes, participants completed the vividness scale. All participants smoked one of their own cigarettes immediately before the study session was begun, to reduce the variability in initial deprivation levels and to avoid acute ceiling effects in craving at the 'baseline' assessment point (pre-imagery). Pilot data indicated that, without this instruction to smoke prior to the session, by the time participants completed the questionnaires and reached the stress paradigm (about 20 min), many had levels of craving nearing the top of the 0–100 scale. After completing the study, participants were reimbursed $50 for their time and thanked for their participation.

Data analysis

To assess for genotype, leukocyte DNA was isolated from blood samples using the Puregene DNA isolation kit (Gentra Systems, Minneapolis, MN, USA). The two loci evaluated were genotyped by previously described PCR methodologies using published primer sequences;[35,36]

SLC6A3: 5′-TGTGGTGTAGGGAACGGCCTGA-3′,
5′-CTTCTTGGAGGTCACGGCTCAA-3′,

and

DRD2: 5′-CCGTCGACGGCTGGCCAAGTTGTCTA-3′,
5′-CCGTCGACCCTTCCTGAGTGTCATCA-3′.

Amplification was performed under standard conditions and PCR products resolved by electrophoresis through 1.5% agarose gels with appropriate size standards and visualized by staining with ethidium bromide. *SLC6A3* alleles were resolved directly and ranged in size from 200 to 520 bp. *DRD2* allele amplicons were digested with 5 U of *Taq*I (New England Biolabs, Beverly, MA, USA) overnight, and the digestion products resolved by electrophoresis.

To examine the study hypotheses, pre–post imagery change scores, statistically correcting for baseline variability, were calculated as indices of distress and craving reactivity to the imagery conditions, following classic methods in the literature.[37,38] Change scores were used to avoid multiple comparisons, and their attendant inflation of Type I error probability, that would be necessitated in a repeated-measures approach.[38] These outcomes were then assessed using factorial analyses of variance (ANOVA), entering *DRD2* and *SLC6A3* genotype status (presence *vs* absence) as predictors. To formally test for gene–gene interactions, we also included a *DRD2* × *SLC6A3* interaction term. Since we were also interested in possible additive relations between these genotypes, we also performed planned comparisons of the four *DRD2* × *SLC6A3* subgroups. To control for the possible effects of population stratification, we included participants' ethnicity, as well as any other demographic variables found to be related to either group status or reactivity (age, education, and for the analysis of distress reactions, income as well; see below) in the ANOVA as covariates. In addition, to rule out the possibility that observed effects could be attributed to other smoking-related characteristics, we included participants' smoking variables (number of cigarettes smoked per day, number of years having smoked, FTND, MNWQ) as covariates as well. Finally, we included reactivity scores to the neutral imagery and the self-reported imagery 'vividness' scale as covariates, to rule out the possibility that differences may be due to imagery *per se*.

RESULTS

Sample characteristics

Mirroring the East Harlem catchment area of our medical center, the sample consisted of participants of several racial/ethnic backgrounds: 67% of participants reported being African-American, 22% Hispanic, 7.3% Caucasian, and 3.7% reported other ethnicities. Sixty-four percent of the sample was female, 53% had completed high school, and 47% reported household income levels of greater than $20 000/year. The mean age of the sample was $40.8 + 10.0$ years. Participants had smoked an average of $22.3 + 11.4$ cigarettes per day for an average of $21.6 + 10.6$ years.

Allele frequencies for the two genes can be found in Table 1. With 'carriers' defined as participants who tested positive for the presence of the allelic variants (eg, Blum *et al*[4] and Lerman *et al*[18]), whether homozygous or heterozygous (ie A1/A1; A1/A2), we found that 59.3% of the sample ($n = 64$) carried the *DRD2*-A1 allele ($n = 14$ homozygous), while 40.7% ($n = 44$) did not (ie, A2/A2). For the *SLC6A3* VNTR allele, 30.5% of the sample ($n = 33$) carried the nine-repeat allele ($n = 4$ homozygous), while the remaining 69.4% ($n = 75$) did not. Genotype frequencies in this sample demonstrated Hardy–Weinberg equilibrium.

To assess the possibility of genotype differences in background variables, we compared the demographic and smoking characteristics by each genotype. As shown in Table 2, *SLC6A3*–9 repeat carriers were marginally significantly older, and smoked an average of five more cigarettes per day than noncarriers. *DRD2*-A1 carriers were marginally significantly more likely to report lower education levels than noncarriers. There were no other differences between groups on background variables.

We then examined relations between background variables and our dependent measures, distress and craving. Results (see Table 3) revealed modest correlations between education, income and FTND, and distress, as well as cigarettes per day and craving. As expected, the stress imagery vividness scale was modestly related to both distress and craving reactions.

Table 1 Allele frequencies

Allele	*2*n	*Frequency*	*Heterozygosity*	
			Expected	*Observed*
*DRD2-Taq*I RFLP			0.46	0.46
A1	78	0.36		
A2	138	0.64		
SLC6A3-VNTR				
3	4	0.02	0.38	0.34
8	5	0.02		
9	37	0.17		
10	165	0.76		
11	5	0.02		

$2n$ = number of alleles.

Genotype effects on distress reactions

Preliminary analyses confirmed that the laboratory stressor induced significant psychological distress reactions (raw mean $\Delta = 21.7 \pm 4.2$); $t_{107} = 5.2$, $P < 0.0001$. For distress reactions, results of the factorial ANCOVA revealed no significant main effects (Figure 1) of *DRD2*-A1 carrier status; $F_{1/106} = 0.1$, $P < 0.74$, or *SLC6A3*-9R carrier status; $F_{1/106} = 0.04$, $P < 0.84$, and no gene–gene interaction; $F_{1/106} = 0.3$, $P < 0.60$, suggesting that all groups were comparably distressed by the stress imagery.

Genotype effects on craving reactions

Preliminary analyses confirmed that the laboratory stressor induced significant craving reactions (raw mean $\Delta = 14.3 \pm 4.0$); $t_{107} = 3.6$, $P < 0.0006$. Consistent with the primary study hypothesis, the factorial ANCOVA revealed a significant effect of carrier status on stress-induced craving reactions. As depicted in Figure 2, carriers of the *DRD2* (receptor) A1 allele exhibited stress-induced craving reactions that were more than twice the magnitude of those of noncarriers; $F_{1/106} = 4.2$, $P < 0.05$.

Carriers of the *SLC6A3* (transporter) nine-repeat allele exhibited craving reactions four times greater than noncarriers; $F_{1/106} = 9.1$, $P < 0.005$ (Figure 2). As baseline craving levels and reactivity to neutral imagery were entered as covariates (see above), the genetic effects observed here appear to be specific to the stress-induced craving phenomenon. Thus, carrier status selectively impacted stress-induced craving, not stress-induced distress responses, consistent with a role for CNS dopamine pathways in relapse to drug seeking in animals.[15]

The formal interaction between *DRD2*-A1 and *SLC6A3*-9R carrier statuses was not significant; $F_{1/106} = 0.8$, $P < 0.38$. Gene–gene interactions were thus not supported. Hypothesized additive relations for carriers of both polymorphisms (which are thought to have distinct biological effects) were supported by planned contrasts of the four genotype subgroups ($-/-$, $+/-$, $-/+$, $+/+$). Consistent with our hypothesis, individuals who carried both the *DRD2* (D2 receptor) A1 and *SLC6A3* (transporter) nine-repeat variants exhibited the highest stress-induced craving reactions, reaching levels that were more than a dozen times higher than carriers of neither variant ($t_{107} = 3.7$, $P < 0.0005$), while carriers of one of the two variants had intermediate craving reactions (see Figure 3).

Inclusion of covariates in these analyses provided confirmation that differences in stress-induced craving were not due to any variability in demographic factors, smoking variables, or standardized indices of dependence or withdrawal. To provide further confirmation that the observed effects could not be attributed to race/ethnicity differences in the sample (stratification), we compared stress-induced craving reactions of the predominant groups in this sample (African American *vs* Hispanic *vs* other), and found that they did not differ; $F_{2/105} = 0.6$, $P > 0.50$. In addition, results were comparable with and without inclusion of other demographic characteristics (ie, gender, income), further indicat-

Table 2 Demographic and smoking characteristic by genotype

Variable (% or mean ± std. err.)	*DRD2-A1 carrier status*		*SLC6A3-9R carrier status*	
	Negative (n = 44)	*Positive (n = 64)*	*Negative (n = 75)*	*Positive (n = 33)*
Age	39.1 ± 1.3	41.8 ± 1.3	39.5 ± 1.1[a]	43.5 ± 1.9[a]
Gender (% female)	61.4	65.6	66.7	57.5
Race/ethnicity				
% African American	63.6	68.8	72.0	54.6
% Hispanic	25.0	20.3	18.7	30.3
%Other	11.4	10.9	9.3	15.1
Education[b]				
% did not complete HS	20.4	23.4	18.7	30.3
% completed HS	18.2	39.1	30.7	30.3
% completed some college	31.8	20.3	25.3	24.2
% completed college or >	29.6	17.2	25.3	15.2
Income				
% < 10 K/year	25.0	32.8	29.3	30.3
% 10–19.9 K/year	18.2	29.7	26.7	21.2
% 20–39.9 K/year	36.4	25.0	30.7	27.3
% > 40 K/year	20.4	12.5	13.3	21.2
Cigarettes/day	22.7 ± 1.8	22.1 ± 1.4	20.8 ± 1.3[c]	25.8 ± 2.1[c]
Years of smoking	21.4 ± 1.5	21.6 ± 1.4	21.5 ± 1.1	21.4 ± 2.2
FTND	5.6 ± 0.3	5.6 ± 0.3	5.7 ± 0.3	5.4 ± 0.3
MNWQ	19.1 ± 1.1	18.7 ± 1.0	19.7 ± 0.9	16.8 ± 1.2
Baseline distress	30.1 ± 5.0	41.0 ± 7.2	36.0 ± 5.8	37.8 ± 7.8
Baseline craving	53.7 ± 5.9	52.3 ± 5.1	51.1 ± 4.6	57.1 ± 7.2
Vividness				
Stress imagery	19.6 ± 0.8	19.5 ± 0.8	19.6 ± 0.7	19.2 ± 1.0
Neutral imagery	19.2 ± 0.7	18.5 ± 0.7	18.8 ± 0.6	18.8 ± 0.8

[a]Values marginally differ at $P < 0.10$.
[b]Marginally associated with *DRD2*-A1 status, $P < 0.08$.
[c]Values differ at $P < 0.05$.

Table 3 Bivariate correlations between sample characteristics and stress-reactivity scores

Variable	*Distress*	*Craving*
Age	0.02	−0.10
Gender	−0.09	0.00
Ethnicity (Af. Am. *vs* other)	−0.11	0.06
Education[a]	0.22**	0.06
Income[a]	0.30**	0.01
Cigarettes/day	−0.09	−0.16*
Years of smoking	−0.03	−0.08
FTND	−0.20**	0.00
MNWQ	−0.10	−0.02
Vividness		
Stress imagery	0.21*	0.31***
Neutral imagery	0.13	0.06

[a]Spearman rank coefficients: *$P < 0.10$, **$P < 0.05$, ***$P < 0.005$.

ing that the effects were not due to variability in sample demographics.

DISCUSSION

Taken together, the results of this study provide the first evidence in the literature that smokers carrying specific polymorphisms related to dopamine function in the CNS have higher stress-induced craving responses. These findings provide strong support for the possibility that dopaminergic pathways are involved in stress-induced craving, consistent with relapse to drug seeking in animal models. Moreover, polymorphisms for presynaptic (transporter) and postsynaptic (D2 receptor) elements in dopamine pathways were found to have an additive impact on stress-induced craving. These results suggest a possible behavioral mechanism underlying previously observed relations between these genetic polymorphisms and persistent smoking behavior in survey studies.

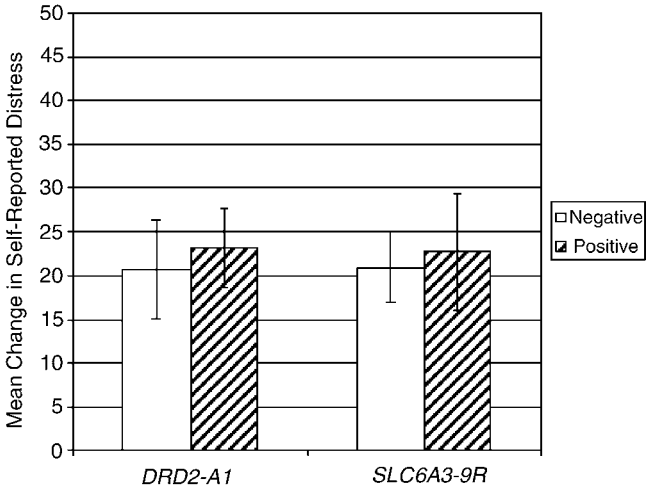

Figure 1 Covariate-adjusted mean distress reactions to stress imagery grouped by *DRD2-A1* and *SLC6A3-9R* carrier statuses. Groups did not differ significantly.

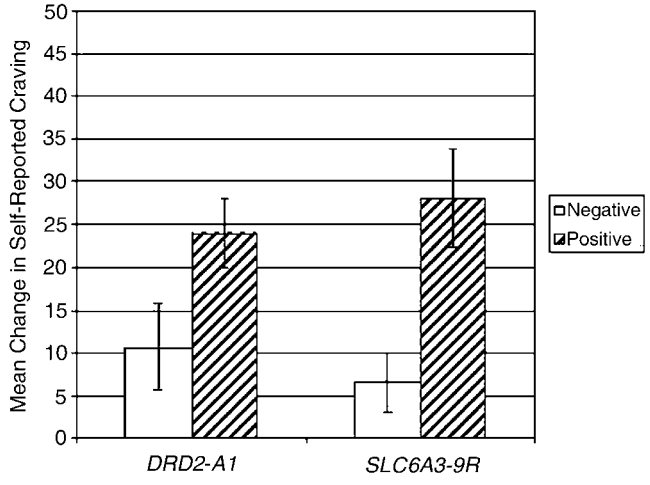

Figure 2 Covariate-adjusted mean craving reactions to stress imagery grouped by *DRD2-A1* and *SLC6A3-9R* carrier statuses. Groups differed significantly.

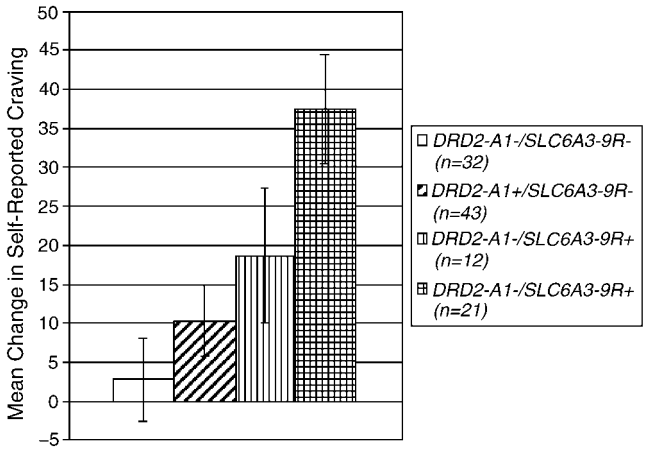

Figure 3 Covariate-adjusted mean craving reactions to stress imagery subgrouped by combined *DRD2-A1* and *SLC6A3-9R* carrier statuses. Genotypes did not formally interact statistically; their effects were additive, with +/+ subgroup evidencing markedly higher craving reactions than −/−, while +/− and −/+ subgroups fell in between.

The use of a well-defined phenotype in a controlled laboratory context may have contributed to the strong results observed here, in comparison to the relatively mixed results on the relation between these genotypes and smoking behavior more generally. Indeed, a complex behavior such as smoking is likely to be multiply determined with different pathways being more or less important for different smokers or under different circumstances.[39] It is possible that these genes may be relevant predictors of real-world persistent smoking behavior only among smokers for whom stress-induced craving itself is the most salient predictor of persistence, whereas for other smokers (eg, those with low-stress lifestyles), this pathway may be less important. Results of the present study suggest the utility of employing more narrowly defined phenotypes under controlled conditions when attempting to determine CNS mechanisms underlying complex behavioral problems such as persistent smoking. Additional animal and human studies will be necessary to fully elucidate the CNS pathways linking genotype to stress-induced craving. Ultimately, such research may provide critical insights into the mechanisms responsible for the persistence of smoking and other addictions, as well as how to develop interventions targeted to individuals whose genotypes may make them susceptible.

It should be emphasized that we cannot formally rule out the possibility that the polymorphisms studied here, rather than having a direct impact, are in linkage disequilibrium with other genotypes that, in turn, may more directly affect stress-induced craving. Recent attempts to identify such genotypes in relation to smoking behavior more generally, however, have met with little success[40] The present results suggest the importance of examining potential additive effects, as well as gene–gene interaction, and other modifiers of genotype effects. As there could conceivably be modifying effects of race/ethnicity, the present findings from a sample of smokers of predominantly minority ethnicity need to be replicated in other samples to confirm the generalizability of effects. However, our results did not reveal the differences in stress-induced craving between racial/ethnic groups represented in the sample. The association between carrier status and stress-induced craving was significant with race/ethnicity included as a covariate. Thus, it is unlikely that the present findings are confounded by the participants' race/ethnicity, but larger studies will be required to explore the possible modifying effects more thoroughly.

Further studies of relations between dopamine polymorphisms and stress-induced craving exhibited in experimental models with humans may ultimately help in the

design and testing of novel pharmacogenetic approaches to smoking cessation, as well as other addictions. Consistent with this possibility, one study in the alcohol literature[41] found that administration of bromocriptine, which interacts with *DRD2*, was more effective in reducing craving and anxiety among alcoholics who carry the *DRD2*-A1 allele compared to noncarriers. Consistent with *DRD2*-A1 and *SLC6A3*-9R's association with lower basal CNS dopamine availability and increased stress-induced craving, administration of dopamine antagonists (eg, haloperidol) to smokers results in increases in cigarette smoking, while administration of agonists (eg, bromocriptine) decreases smoking behavior (eg, Caskey *et al*[42,43]), although craving, *per se*, was not formally assessed in these studies.

It should also be emphasized that, while these dopamine polymorphisms were found to be related to stress-induced cigarette craving, there are clearly other pathways to persistent smoking and the persistence of other addictive behaviors (eg, Swan[39]). Results of this study underscore the importance of continued characterization of the functions of *DRD2*-A1 and *SLC6A3*-9R, as well as other polymorphisms in the dopamine system not yet established to be associated with smoking variables (eg, other polymorphic loci at *DRD2*; loci at *DRD4*). Dopamine pathways have also been implicated in craving responses to smoking cues (eg, sight or smell of one's preferred brand of cigarette, seeing a billboard advertisement, etc,[15]) suggesting the importance of studies of the involvement of dopamine in craving triggered by stimuli other than stressors. Experimental studies of craving reactions induced by stress and by smoking cues under controlled laboratory conditions, as well as naturalistic investigation of craving reactions in the daily life of carriers of these dopamine polymorphisms may be important next steps in further elucidating the increasingly well-documented role of genetic factors in smoking behavior and addiction, more generally.

DUALITY OF INTEREST

None declared

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