Original Investigation

DRD2-related TaqIA polymorphism modulates motivation to smoke

Yantao Zuo, David G. Gilbert, Norka E. Rabinovich, Hege Riise, Rachel Needham, & Jodi I. Huggenvik

Abstract

Introduction: TaqIA polymorphism, a genetic variant associated with the expression level of dopamine D2 receptors in the brain, has been linked to various aspects of smoking behavior, including smoking prevalence, affective withdrawal symptoms, and smoking cessation outcome. However, its involvement in motivation to smoke cigarettes has not been elucidated.

Methods: The present study examined the possible differences in self-reported reasons to smoke and craving for smoking in 160 smokers participating in a clinical trial.

Results: Individuals with at least one A1 allele of the TaqIA polymorphism were more likely to report smoking for stimulating effects and to reduce negative affect compared with those lacking an A1 allele. The association of the A1 genotype with a higher probability and stronger motive to smoke to enhance cognitive functioning was evident in female but not in male smokers. Female A1 carriers also expected a greater likelihood of smoking for pleasure than those without an A1 allele. A1 subjects reported stronger craving for cigarettes during early days and the last phase of a 6-week abstinence period.

Discussion: These results support the idea that dopaminergic transmission plays an important role in the neurobiological basis of reasons for smoking and that the TaqIA variant is one of the genetic factors underlying individual differences in these aspects. These findings also have implications for improving treatment strategies to help individuals quit smoking by controlling their motivation to continue cigarette consumption.

Introduction

The mesolimbic dopamine (DA) system plays an important role in mediating the reinforcing effects of nicotine, like many other drugs of abuse. It is well documented in animal studies that nicotine increases DA release in the nucleus accumbens in the ventral striatum (Di Chiara & Imperato, 1988; Nisell, Nomikos, & Svensson, 1994). Both DA antagonists and lesions of the mesolimbic DA system reduce nicotine self-administration in rodents (Corrigall & Coen, 1991; Corrigall, Franklin, Coen, & Clarke, 1992). In human imaging studies, cigarette smoking has been shown to induce DA release in the ventral striatum (Brody et al., 2004); nicotine also activates brain areas in the dopaminergic pathways (Stein et al., 1998). Besides its involvement in acute rewarding effects of nicotine, neuroadaptive changes in the mesolimbic system may also be underlying sensitized response and tolerance to nicotine. Previous exposure to nicotine is found to potentiate DA release from the nucleus accumbens stimulated by acute nicotine (Schoffelmeer, De Vries, Wardeh, van de Ven, & Vanderschuren, 2002). In contrast to its effect on phasic DA activity, a recent study shows that chronic nicotine consumption leads to marked decrease in tonic DA activity, as indicated by lower D2 receptor density in the ventral striatum in smokers (Fehr et al., 2008). The finding suggests that low DA activity associated with chronic smoking could result in decreased sensitivity of reward circuits to natural reinforcers and the maintaining of nicotine dependence and persistent vulnerability to relapse from abstinence. Together, the aforementioned evidence supports the critical role of the mesolimbic DA system in motivated nicotine and tobacco intake behavior. Therefore, it is not surprising that genetic factors that regulate DA neurotransmission are primary targets for numerous studies on individual

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differences in the development and treatment of nicotine addiction (Munafò, Clark, Johnstone, Murphy, & Walton, 2004).

Of genetic variants linked to functioning of the mesolimbic system in relation to drug abuse, one of the most widely studied is the dopamine type-2 receptor (*DRD2*)-related TaqIA polymorphism. Residing within the coding region of the ankyrin repeat and kinase domain containing 1 (*ANKK1*) gene and located near the 3' end of the *DRD2* gene (Neville, Johnstone, & Walton, 2004), the TaqIA polymorphism has repeatedly shown association with *DRD2* expression. Individuals with at least one A1 allele appear to have up to 40% fewer striatal *DRD2* receptors relative to those carrying the A2/A2 allele (Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991; Ritchie and Noble, 2003). Compared with A2/A2 genotype, TaqIA A1 variant has been associated with an increased electroencephalography slowing during smoking abstinence (Gilbert et al., 2004), with less improvement in negative affect withdrawal symptoms by antidepressants (Cinciripini et al., 2004; David et al., 2003), and with more short-lived attenuation of affective symptoms by nicotine replacement therapy (NRT; Gilbert et al., 2009). In contrast, comprehensive reviews of many studies suggest that main effects of this genotype on smoking cessation have been elusive (Munafò, Timpson, David, Ebrahim, & Lawlor, 2009; Munafò et al., 2004). The most robust findings associated with this genetic variant are pharmacogenetic. Specifically, the A1 genotype has been reported to be linked with better NRT treatment outcome (e.g., Yudkin et al., 2004) while the A2/A2 carriers are repeatedly found to be more responsive to antidepressants (Cinciripini et al.; David, Strong, et al., 2007). Moreover, some studies suggest that effects of TaqIA Genotype $\times$ Treatment interactions on smoking cessation may be modulated by factors such as sex (Yudkin et al.) and craving (David, Brown, et al., 2007). There is also a lack of strong support for the link of this polymorphism to crude measures of smoking behavior such as smoking initiation, smoking persistence, and smoking rate (Munafò, Timpson, et al.). Taken together, existing data raise the possibility that the TaqIA variants may be more closely related to some specific aspects rather than broadly defined phenotypes of smoking behavior. Despite the extensive data on the association of TaqIA variants with *DRD2* receptor densities and on the important role of the mesolimbic DA system in nicotine addiction, little research has been conducted to examine the involvement of this polymorphism in motivation to smoke, which is crucial to a fuller understanding of how this genetic factor contributes to nicotine addiction and individual response to treatments. A recent study indicates that smokers with A1 allele experienced greater "liking" for cigarette smoking, had shorter latency to first puff, and took more puffs under experimentally induced negative mood as compared with positive mood, while non-A1 carriers did not exhibit such behavior patterns (Perkins et al., 2008). It remains unknown whether this genetic variance contributes to other aspects of smoking motivation, in particular during abstinence.

Craving has been posited as one of the motivational factors for smokers to maintain smoking behavior and for former smokers to lapse/relapse after abstinence (Killen & Fotmann, 1997; Shiffman et al., 1997). It is generally agreed among researchers that craving, under certain conditions, is directly related to relapse (Drummond, 2001). Besides craving, reasons for smoking are another reflection of smokers' motivation to smoke (Gilbert, Sharpe, Ramanaiah, Detwiler, & Anderson, 2000; Joffe, Lowe, & Fisher, 1981; Tate & Stanton, 1990).

The mesolimbic DA system has been implicated in the rewarding (Corrigall et al., 1992; Di Chiara & Imperato, 1988; Wise & Rompré, 1989), psychomotor (Clarke, Fu, Jakubovic, & Fibiger, 1988; Wise & Bozarth, 1987), cognitive (Koob & Le Moal, 2001; Levin & Simon, 1998; Maskos et al., 2005), and affective effects of nicotine (Cinciripini et al., 2004; David et al., 2003; Gilbert, 1995; Gilbert et al., 2004; Koob & Le Moal). The present study examined the association of TaqIA polymorphism with self-reported motivations to smoke and craving in habitual smokers prior and subsequent to quitting smoking. Based on the known involvement of DA in drug craving (Berridge, 2007; Robinson & Berridge, 1993; Wise, 1988), we predicted that A1 relative to A2/A2 carriers would experience stronger craving both prior to and during smoking abstinence and would report smoking more for pleasure seeking, psychomotor stimulation, cognitive enhancement, and negative affect reduction. Given recent evidence for interactions between this gene variant and sex on smoking behavior (Munafò, Johnstone, Murphy, & Aveyard, 2009; Munafò, Timpson, et al., 2009), sex effects and the interactions on motivation to smoke were also investigated.

Methods

Participants

Detailed description of subjects participating in the study was reported in a separate paper (Gilbert et al., 2009). In brief, smokers wanting to quit were recruited in a Midwestern university community from 1998 through 2004. Exclusion criteria included smoking fewer than 7 cigarettes/day for the past 2 years, use of psychoactive drugs or medications other than alcohol and caffeine, alcohol use in excess of 28 alcoholic drinks per week, age less than 18 or greater than 50 years, and uncorrected visual impairment. Upon completion of the baseline phase of the study, 80% of the participants were randomly assigned to the quit group and the rest were assigned to the group that continued to smoke. Those in the quit group were assigned (50:50 chance) to the nicotine (NP) or placebo (PP) patch group in a double blind manner. Completion of the study resulted in earning \$500 minus any penalties for smoking. Penalties for the first to the third cigarette were \$10, \$25, and \$50, respectively, with a maximum total of \$85 for three or four cigarettes. Participants were excluded from the study without payment for smoking more than four cigarettes total over the abstinence period. Financial incentive resulted in a high percentage of individuals that completed the study. Among them, 73 (81%) in the NP group and 68 (84%) in the PP group maintained abstinent status, defined as smoking four or fewer cigarettes total across the 45-day period. The number of cigarettes smoked during the quit period was estimated by a combination of self-report, carbon monoxide concentration (8+ parts per million), plasma or salivary cotinine (20+ ng/ml), and plasma nicotine (1.5+ ng/ml). If self-report and biochemical indicators differed, the indicator suggesting that the greater number of cigarettes was taken as the number of cigarettes smoked. Of the 38 assigned to the smoke group, 33 (87%) fulfilled the requirements, including continuing to smoke. To avoid ethnic admixture, only the data from the Caucasian subjects ($N = 160$) were analyzed in this report. Table 1 summarized basic demographic, smoking characteristics, genotype, and group assignment status. There were no significant differences in gender, age, nicotine dependence, and group assignment ratios between subjects with and without TaqIA A1 allele.

Table 1. Descriptives of subjects with and without TaqIA A1 allele

	A1 carriers (<i>n</i> = 97)	A2/A2 carriers (<i>n</i> = 63)
Gender (male)	43 (44.3%)	30 (47.6%)
Age	27.4 ± 9.2 years	25.3 ± 7.5 years
FTND	4.6 ± 2.2	4.8 ± 2.2
Pack-year	11.1 ± 9.9	9.9 ± 9.6
Cases in each treatment group:		
Nicotine patch	39 (40.2%)	26 (41.3%)
Placebo patch	41 (42.3%)	23 (36.5%)
Smoke	17 (17.5%)	14 (22.2%)

Note. *M* ± *SD* are reported for age, FTND, and pack-year. FTND = Fagerström Test for Nicotine Dependence.

Genotyping

The TaqIA polymorphism was assessed by restriction fragment length polymorphism as described by Gilbert et al. (2005). For statistical purposes, the genotypes were classified as either A1 allele carriers (A1/A2 and A1/A1) or non-A1 (homozygous A2/A2 alleles) carriers. The allele frequencies (63 [39.4%] A2/A2, 94 [58.8%] A1/A2, and 3 [1.9%] A1/A1) for the gene deviated somewhat from the Hardy–Weinberg equilibrium, $\chi^2(1, N = 160) = 4.305, p = .035$. This deviation was verified by conducting blinded reanalysis of the samples.

Questionnaires

Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991). The FTND is a widely used and validated measure of nicotine dependence.

Horn–Waingrow Reasons for Smoking Scale (HWRSS; Horn & Waingrow, 1966). This 23-item questionnaire was used to assess six reasons to smoke, including stimulation, habit, negative affect reduction, sensory motor, psychological addiction, and pleasure.

Smoking Motivation Questionnaire (SMOQ; Gilbert et al., 2000). Subjects separately rated their desire (urge or craving), probability of smoking, and motives (reasons) for smoking in 55 situations. Responses were scored in four categories, including cognitive enhancement, negative affect reduction, pleasure enhancement, and weight–appetite control.

The Shiffman Withdrawal Questionnaire (SWQ; Shiffman, 1979). Participants rated their typical/average state across the preceding 72 hr. Only the craving subscale scores for the Shiffman Withdrawal Questionnaire (SWQ) were analyzed in this report.

Procedure

Phase 1 was a 2-week baseline during which participants smoked at their usual rate and attended biweekly monitoring sessions. Phase 1 ended with random assignment to treatment groups. Phase 2 included late afternoon monitoring sessions on the first day of abstinence (or corresponding day in the smoke group), at Day 3 of abstinence, and then every 72 hr across 44 days after quitting. FTND, HWRSS, SMOQ, and prequit SWQ craving measures were collected during Phase 1. SWQ craving ratings continued at 72-hr intervals throughout Phase 2. To conform to the 3-day timeframe

for the rest of sessions, craving at Day 1 of abstinence was excluded from the current analysis.

Participants received an abbreviated form of the American Lung Association smoking cessation program. Nicoderm or placebo patches of corresponding size were as follows: 21 mg for the first 17 days of abstinence, 14 mg for Days 18–26, and 7 mg for Days 27–38. The final assessment of mood 1 week after going off the patch was chosen to characterize rebound effects. Individuals were instructed to replace patches immediately upon waking each morning. Consent approved by the institutional review board was signed by each participant.

Data analysis

T tests were used for continuous variables and chi-square statistics for categorical variables to compare differences in subject characteristics. Genotype × Sex analyses of variance were conducted to compare group means on various prequit motivational measurements. Because the sample size allowed adequate power to detect medium but not small effect size often seen for genetic association studies, uncorrected *p* values were reported with additional indication of those effects that would survive Bonferroni correction for multiple comparisons across the subscales within a category (e.g., the four desire subscales on the SMOQ). Pearson correlations were calculated among those motivational variables to evaluate their convergent and discriminant validity.

To characterize how individual differences in genotype predict trajectories of craving during abstinence across 44 days, hierarchical linear modeling (HLM; Raudenbush & Bryk, 2002) was used to perform growth curve analyses for change scores of SWQ craving relative to prequit levels. Specifically, a two-level model was fitted, where a level-1 submodel describes how each individual's craving changed across 15 monitoring sessions over time and a level-2 submodel relates interindividual differences in craving trajectories to predictors including individual genotypes, treatment, sex, the interaction of genotypes and treatment, the interaction of genotypes and sex, and other control personal variables such as age, FTND scores, and prequit craving levels. To obtain a more parsimonious representation from each multilevel model, level-2 fixed effect parameters that were not significant according to the single parameter hypothesis test (*z*-statistic but labeled as *t* ratio in HLM) or did not account for significant variance according to the model deviance statistic were removed sequentially from the initial model (for more details about this approach, see Supplementary Material and Gilbert et al., 2009). Because of statistical power limitations associated with the small sample size of the smoke group, we limited analysis at this step to the two abstinence groups (*n* = 129).

Results

Correlations between motivational measurements

For each of the four categories of the SMOQ (cognitive enhancement, negative affect, pleasure, and weight control), subjects' report of desire, probability, and motive for smoking was correlated at moderate to high levels (*r* = .56–.87), indicating that desire, probability, and motive measure interrelated aspects of motivation to smoke. Overall, scores on the motive (reason) for smoking subscales of the SMOQ and similar measurements of the HWRSS were only modestly correlated. There

Table 2. Group means on the subscales of SMOQ, HWRSS, and SWQ between TaqIA genotypes and sexes

	Male (<i>n</i> = 73)		Female (<i>n</i> = 87)		Significant effects ^a
	A1 (<i>n</i> = 43)	A2/A2	A1 (<i>n</i> = 54)	A2/A2	
SMOQ desire					
Cognitive enhancement	42.3 ± 1.3	40.9 ± 1.5	44.9 ± 1.1	41.3 ± 1.4	
Negative affect	94.3 ± 2.3	92.2 ± 2.8	99.8 ± 2.1	96.9 ± 2.7	Sex, <i>p</i> = .043
Pleasure	22.5 ± 0.7	24.0 ± 0.9	23.7 ± 0.7	23.5 ± 0.8	
Weight control	19.3 ± 1.2	20.7 ± 1.4	24.9 ± 1.0	23.3 ± 1.3	Sex, <i>p</i> = .001 ^b
SMOQ probability					
Cognitive enhancement	81.3 ± 2.9	83.5 ± 3.5	91.2 ± 2.6	73.8 ± 3.3	Genotype × Sex, <i>p</i> = .002 ^b ; genotype, <i>p</i> = .015
Negative affect	187.0 ± 6.8	184.0 ± 8.1	199.5 ± 6.1	174.4 ± 7.8	
Pleasure	46.4 ± 1.7	49.3 ± 2.1	49.9 ± 1.5	43.3 ± 2.0	Genotype × Sex, <i>p</i> = .011 ^b
Weight control	34.2 ± 2.9	36.9 ± 3.5	46.9 ± 2.6	43.7 ± 3.3	Sex, <i>p</i> = .002 ^b
SMOQ motive					
Cognitive enhancement	79.3 ± 3.9	78.5 ± 4.7	89.9 ± 3.5	71.6 ± 4.5	Genotype × Sex, <i>p</i> = .037; genotype, <i>p</i> = .023
Negative affect	165.5 ± 4.41	154.5 ± 8.4	186.6 ± 6.3	159.1 ± 8.0	Genotype, <i>p</i> = .011 ^b
Pleasure	40.3 ± 2.3	40.6 ± 2.8	45.7 ± 2.1	40.2 ± 2.6	
Weight control	30.2 ± 3.2	33.3 ± 3.9	47.7 ± 2.9	41.2 ± 3.7	Sex, <i>p</i> < .001 ^b
HWRSS					
Stimulation	5.7 ± 0.4	4.8 ± 0.4	6.2 ± 0.3	4.6 ± 0.4	Genotype, <i>p</i> = .002 ^b
Habit	6.2 ± 0.4	6.4 ± 0.5	5.4 ± 0.4	5.5 ± 0.5	
Negative affect reduction	15.2 ± 0.6	14.7 ± 0.7	16.2 ± 0.5	15.5 ± 0.7	
Sensory motor	5.0 ± 0.4	6.4 ± 0.5	4.5 ± 0.3	4.7 ± 0.4	Genotype, <i>p</i> = .042; sex, <i>p</i> = .01
Psychological addiction	9.6 ± 0.4	10.1 ± 0.5	10.2 ± 0.4	10.3 ± 0.5	
Pleasure	5.8 ± 0.2	5.8 ± 0.3	6.1 ± 0.2	6.3 ± 0.2	Sex, <i>p</i> = .046
SWQ					
Craving ^c	−0.2 ± 0.1	−0.1 ± 0.2	.2 ± 0.1	0 ± 0.2	

Note. *M* ± *SEMs* are reported. SMOQ = Smoking Motivation Questionnaire; HWRSS = Horn–Waingrow Reasons for Smoking Scale; SWQ = Shiffman Withdrawal Questionnaire.

^aSignificant effects are defined as uncorrected *p* < .05.

^b*p* < .05 after Bonferroni corrections.

^cMean *z*-scores are reported for prequit craving ratings on SWQ.

was a relatively high correlation ($r = .37$) between cognitive enhancement scores of the SMOQ and stimulation subscale scores of the HWRSS, suggesting that these two subscales capture on somewhat overlapping constructs. Similarly, ratings on the negative affect subscale of the SMOQ moderately correlated with the negative affect reduction subscale and the psychological addiction subscale of the HWRSS ($r = .42$ and $.35$, respectively). The latter could indicate a relatively closer association between smoking to cope with negative affect, among other reasons to smoke, and psychological addiction to smoking. As for craving measurements, prequit craving scores on the SWQ were modestly correlated with the four desire subscales on the SMOQ ($r = .17$ – $.40$). Among them, there was a relatively closer link between SWQ craving scores and desire for smoking as measured by the pleasure subscale of the SMOQ ($r = .40$). In short, these correlational results demonstrated that various measurements used in this study convergently measured both common and different motivations to smoke. Therefore, it is of value to collectively use them to examine the influence of TaqIA polymorphism on different aspects of smoking motivation.

Effects of TaqIA genotypes on prequit motivation to smoke

As shown in Table 2, there were significant genotype effects with or without interactions with sex on mean scores of some of the SMOQ measurements. Specifically, individuals with A1 alleles scored higher than non-A1 carriers on probability and motive to smoke for cognitive enhancement. However, the differences were manifest exclusively in female participants. Female smokers with A1 alleles also expected a higher probability of smoking for pleasure than those non-A1 carriers, but this was not the case for men. Additionally, A1 carriers in both men and women reported stronger motives to smoke in negative affect–charged situations. Although female smokers had higher scores on desire, probability, and motive to smoke for weight control, no genotype effects were observed in this regard. Independent of genotypes, female smokers tended to score higher than males on desire for smoking when experiencing negative affect. Of the HWRSS subscales, genotype was associated with only smoking for stimulation, with A1 carriers having higher scores than A2/A2 individuals (mean 6.0 vs. 4.7). A1 smokers tended to score lower on smoking for sensory–motor effects than those of A2/A2 genotype. While male

A1 smokers were less likely than their A2/A2 counterparts to attribute smoking to sensory-motor effects, women scored higher on smoking for pleasure on the HWRSS. In contrast to the SMOQ, genotype effects were not found for the negative affect reduction subscale of the HWRSS. No effects of genotype or sex were found for prequit craving (Table 2).

Effects of TaqIA genotypes in predicting craving during abstinence

To examine associations of genotype with craving across the 6-week abstinence period, genotype, patch type, Genotype $\times$ Patch Type, sex, and Genotype $\times$ Sex were initially entered as main predictors, with age, FTND scores, and prequit baseline craving as control variables in the HLM level-2 models. Only the TaqIA genotype, prequit craving, and age were significant predictors of parameters of postquit craving trajectories in the final model ($p = .006$, $p < .001$, and $p = .038$, respectively; see Table S1 in Supplementary Material). The A1 genotype was associated with greater curvature of craving trajectories. As shown in Figure 1, relative to A2/A2 individuals, A1 smokers reported stronger craving for smoking during very early abstinence and the later phase of the study. In addition, baseline craving contributed to the prediction of craving levels during abstinence, with higher baseline scores associated with greater decreases in postquit craving levels relative to individual baseline. Age was related to the slope of time courses of craving in that older individuals tended to experience strong craving immediately after quitting, followed by a steeper decline of craving over time. Although the effects of patch type on craving trajectories were not significant, there was a notable tendency ($p < .15$) for nicotine patches to reduce craving relative to placebo patches over 44 days of smoking abstinence. No effects involving sex were found on postquit craving.

Discussion

In this study, *DRD2*-related TaqIA polymorphism was related to reported motivation to smoke during both smoking and abstinence periods. A1 carriers were more likely than those with

A2/A2 genotype to report smoking for psychomotor stimulation and to reduce negative affect. In female smokers, the A1 individuals scored higher than A2/A2 carriers in expected probability and motive to smoke for cognitive enhancement. Female A1 subjects also reported a greater likelihood to smoke for pleasure than those of the A2/A2 genotype. Moreover, A1 carriers, regardless of sex, experienced more craving in early and later phases of a 6-week abstinence period, representing continued vulnerability to lapse and relapse.

Effects on smoking for stimulation and cognitive enhancement

One major finding from this study is that the A1 allele is linked to enhanced motives for smoking in situations associated with a desire for stimulation. In female but not in male subjects, A1 carriers were also more inclined to attribute their reasons for smoking to obtaining cognition-enhancing effects. Nicotine has long been recognized as having psychostimulant-like action through activation of the mesolimbic DA pathway, a property closely related to its positive reinforcing effect (Wise & Bozarth, 1987). Nicotine increases locomotor activity in rats (Iwamoto, 1984). It also boosts psychomotor performance in humans, particularly when fatigue and boredom are factors in performance (Wesnes & Warburton, 1983). Besides nicotine's well-known arousing effects in general (Gilbert, 1995), recent studies increasingly emphasize its effects in enhancing cognitive function in both animal models and humans (Levin, McClernon, & Rezvani, 2006). Effects of addictive drugs, including nicotine, on cognitive functioning have been thought to be mediated by the cortico-striatal-thalamic circuitry, and the DA neurotransmission is an important modulator of this network (Brody, 2006; Koob & Le Moal, 2001). The present data highlight a need for detailed investigations of how the TaqIA polymorphism regulates functions of and connectivity among specific brain sites in this network which lead to individual differences in cognitive enhancement-related craving (Brody; Wang et al., 2007). In view of recent data that indicate female A1 carriers are less likely to maintain abstinence after NRT (Munafò, Johnstone, et al., 2009), the current finding of heightened motivation to smoke for cognitive enhancement in these individuals is interesting and calls for further studies to see if this aspect of smoking motivation contributes to the poorer treatment outcome, especially in women.

Effects on smoking for negative affect reduction

A1 carriers also were more likely than those with the A2/A2 genotype to attribute smoking to dealing with negative affect as assessed by the SMOQ but not by the HWRSS. As indicated by a modest correlation ($r = .42$), the two measures may index different aspects of negative affect-related smoking motivation. If validated in future studies, our finding with the SMOQ suggests that the A1 allele may constitute a genetic vulnerability to negative affect-triggered smoking. Negative affect has been related to smoking as a form of self-medication (Markou, Kosten, & Koob, 1998; Pomerleau, 1986) and lapse/relapse after quitting smoking (Gilbert, Crauthers, Mooney, & McClernon, 1999; Shiffman & Waters, 2004). Smoking abstinence also leads to prominent affective symptoms such as irritability, anxiety, and depression (Hughes, Gust, Skoog, Keenan, & Fenwick, 1991). These symptoms are predictors of craving after smoking cessation (Doherty,

Figure 1. TaqIA polymorphism affected craving for cigarettes across 44 days of smoking abstinence. Craving changes are normalized to prequit baseline. Dark lines show values that were predicted from the final hierarchical linear model. Gray lines show observed group means, with SEMs omitted for graphic clarity.

Kinnunen, Militello, & Garvey, 1995). The present results are in agreement with a recent study by Perkins et al. (2008), who found that, relative to A2/A2 smokers, A1 carriers took more puffs, had shorter latencies to smoking, and reported increased cigarette liking during negative mood relative to positive mood.

Effects on postquit craving

The finding that craving during abstinence was influenced by the TaqIA genotype, while that prior to quitting was not, could have important implications. Smoking could mask the genetic effects on craving. When brain reward function is decreased during smoking cessation (Epping-Jordan, Watkins, Koob, & Markou, 1998), the genetically predisposed vulnerability to smoke may manifest as stronger urges for A1 carriers to smoke for positive reinforcement. It is interesting to note that nicotine patches had only a weak effect in attenuating craving in this study. This is in contrast with significant craving suppression outcome observed with nicotine patch in previous studies (e.g., Shiffman & Ferguson, 2008; Tiffany, Cox, & Elash, 2000; Transdermal Nicotine Study Group, 1991). It is not clear what factors might have contributed to this discrepancy. One source could be that participants in the current study intended to quit smoking and their motivation was likely enhanced by the large financial incentive to maintain abstinence. Smoking expectancy has been shown to affect prefrontal brain response to smoking cues (McBride, Barrett, Kelly, Aw, & Dagher, 2006; Wilson, Sayette, Delgado, & Fiez, 2005), and the opportunity to smoke in the near future results in stronger reported cravings to smoke in response to smoking cues (Carter & Tiffany, 2001). Thus, financially motivated commitment to abstinence may have reduced subjective cigarette craving as well as perceived effects of nicotine patches on urges to smoke. This is an important possibility that deserves further investigation. It should be noted that nicotine patch treatment significantly reduced negative affective symptoms during smoking cessation in this study (Gilbert et al., 2009), indicating that other factors could have attenuated the craving-suppressing effects of NRT.

Craving has been thought to be one key motivational factor for former smokers to lapse/relapse after abstinence (Drummond, 2001; Killen & Fotmann, 1997; Shiffman et al., 1997). In relation to recent evidence for female A1 carriers being less likely to be abstinent after NRT (Munafò, Johnstone, et al., 2009), our observation that A1 carriers experienced stronger craving for smoking not only during initial days of abstinence but also persistently during the last 2-week+ phase of the 6-week study period suggests that the link between the A1 genotype and poorer smoking cessation outcome may be, at least partially, mediated by craving. However, more work is needed to answer this question, as the overall evidence supporting the association of the TaqIA polymorphism and smoking behavior including treatment outcome remains equivocal (for a review, see Munafò, Timpson, et al., 2009). From yet another perspective, unlike broad measures of smoking behavior such as smoking status, smoking rate, and abstinence rate, which presumably are determined by multiple factors including multiple genes, craving can be viewed as a more specific phenotype that is closely related to the TaqIA polymorphism. The current finding highlights the possibility that this genetic variant may be mostly associated with treatment outcome in cases where craving is a crucial trigger for relapse.

Effects on smoking for pleasure

Despite the well-established role of the mesolimbic DA system in acute positive reinforcing effects of nicotine as well as other drugs, we found significant differences in smoking for pleasure-seeking between only A1 carriers and A2/A2 female smokers, with the former group reporting a higher probability of smoking for this purpose. If validated in future studies, the lack of effects of the TaqIA variant on smoking for pleasure in men may provide some support for the incentive sensitization (IS) theory of drug craving (Berridge, 2007; Robinson & Berridge, 1993). Evidence favoring IS theory suggests that DA is neither necessary nor sufficient to mediate hedonic liking for sensory pleasures. Instead, the DA system is thought to contribute causally to IS, a process in which stimuli or cues associated with drug use are attributed incentive salience, that is, rewarding properties that make these stimuli attractive and wanted. With repeated drug exposures, the incentive values of the drug and related stimuli are progressively enhanced, and these enhancements appear to be mediated by dopaminergic activation in the striatum (Jentsch & Taylor, 1999). Dynamic activation of representation of drug or drug cues would trigger craving and drug-seeking behavior. From the perspective of this theory, cognitive challenges and negative emotions can be viewed as sensitized smoking-associated cues to induce urges to smoke. TaqIA A1 allele is likely to be an important factor in the DA system that causes strong incentive salience to be attributed to smoking and smoking-related stimuli. This would constitute an explanation for our findings on the association of TaqIA polymorphism with smoking for stimulation and negative affect reduction, in contrast with a lack of relationship between this genetic variant and smoking for pleasure-seeking in men. Although men are shown to have greater striatal DA release than women following psychostimulant challenges (Munro et al., 2006), specific mechanisms underlying the TaqIA Genotype $\times$ Sex interactions on smoking for pleasure and other motives have yet to be identified.

Independent of the genotypes, female smokers in this study scored significantly higher in desire, probability, and motive to smoke for weight control. These results are consistent with known sex differences in the association of smoking and weight control concerns (e.g., Park, 2009; Potter, Pederson, Chan, Aubult, & Koval, 2004).

Implications for smoking cessation interventions

Stronger motivation to smoke for cognitive enhancement and negative affect reduction associated with A1 allele may imply that A1 smokers, relative to their non-A1 counterparts, are more vulnerable to continued smoking behavior and relapse after attempted cessation and thus are in greater need for pharmacological and nonpharmacological interventions. The finding that the influence of DRD2-related TaqIA genetic predispositions on motivation to smoke can be detected on self-reported data has important implications for smoking cessation interventions. Given that genotyping-informed smoking cessation interventions are still far from common practice, professionals should be aware that at least some individuals reporting relatively stronger motivations to smoke for stimulation and negative affect reduction and/or more intense craving after smoking cessation may have genetically determined low dopaminergic tone and therefore need tailored help. Specifically, it is conceivable that

counselors and other mental health professionals can use the information to optimize strategies to help these smokers improve their cognitive-behavioral skills to cope with craving, especially in the face of poor cognitive performance and negative affect symptoms. In light of clinical evidence that A1 carriers benefit less from antidepressants for smoking cessation (Cinciripini et al., 2004; David, Strong, et al., 2007; David et al., 2003), exploring alternative or tailored pharmacological and behavioral interventions for these individuals is warranted.

Study limitations and future directions

Limitations of the study include study exclusion criteria, including drug use and educational status, as well as self-selection processes. Individuals with certain personality traits and genotypes may have been less likely than others to have participated in the study. For example, individuals homozygous for the *DRD2* A1 allele may have been less likely to be interested in the study or to have met the study selection criteria than those with only one A1 allele or those with two A2 alleles. Such a selection process may have been responsible for the slight, but statistically significant, tendency for there to be fewer homozygous A1 individuals in the study sample than predicted by Hardy–Weinberg equilibrium estimates. These and other study selection factors may limit the generalizability of the present findings. Nonetheless, the present study suggests that low *DRD2* density–related A1 allele carriers may have stronger motivation to smoke than individuals with the A2/A2 genotype both prior to and after smoking cessation. If replicated in studies with larger samples and using measurements other than self-reports, the data would provide new evidence for the involvement of the Taq1A polymorphism in altering neural substrates of smoking motivation. These findings also suggest that female A1 carriers may be especially vulnerable to continued smoking behavior. Better pharmacological and behavioral interventions tailored to meet the needs of A1 carriers may improve treatment success.

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Declaration of Interests

None declared.

Supplementary material

Supplementary Table 1 can be found at *Nicotine and Tobacco Research* online (<http://www.ntr.oxfordjournals.org/>).

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