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Association of *BDNF* and *COMT* genotypes with cognitive processing of anti-smoking PSAs

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Anti-smoking public service announcements (PSAs) often use persuasive arguments to attempt to influence attitudes about smoking. The persuasiveness of a PSA has previously been associated with factors that influence the cognitive processing of its message. Genetic factors that influence cognitive processing might thus affect individuals' responses to the persuasive arguments presented in PSAs. In the present study, we examined polymorphisms in the genes encoding brain-derived neurotrophic factor (*BDNF* Val66Met) and catechol-O-methyltransferase (*COMT* Val158Met), which affect cognitive processing in the prefrontal cortex, to identify genetic factors associated with self-reported outcomes of message processing, perceived effectiveness and quitting intentions among smokers viewing PSAs. A total of 120 smokers viewed sets of four PSAs that varied with respect to features of argument strength (AS) and message sensation value. We observed significant associations of *BDNF* genotype with central processing, narrative processing, perceived effectiveness of the anti-smoking PSAs and participant quitting intentions; the *BDNF* Met allele was associated with lower scores on all these measures. Central processing acted as a mediator of the association of genotype with quitting intentions and perceived effectiveness. There was a significant interaction of *COMT* genotype by AS in the model of narrative processing, such that individuals homozygous for the *COMT* Val allele reported higher narrative processing in the high-AS condition but not in the low-AS condition. To our knowledge, this is the first study to identify genetic factors associated with cognitive processing of anti-smoking PSAs.

Keywords: BDNF, cognitive processing, COMT, genetics, public service announcements

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Tobacco smoking is the leading preventable cause of death worldwide (World Health Organization 2009). Anti-smoking advertising campaigns using public service announcements (PSAs) have been employed in efforts to decrease smoking prevalence (Biener *et al*. 2000; Messer *et al*. 2007; Siegel 1998). Anti-smoking PSAs often use persuasive arguments to influence public attitudes about smoking, and features affecting cognitive processing of the arguments influence the perceived persuasiveness of PSAs (Biener *et al*. 2000; Leshner & Cheng 2009; Strasser *et al*. 2009). Functional magnetic resonance imaging (fMRI) has shown activation in regions of the prefrontal cortex (PFC) associated with memory encoding in response to effective persuasive arguments (Fal *et al*. 2010b). Further, activation in the PFC in response to persuasive messages predicts behavior change (Falk *et al*. 2010a). Indeed, the accuracy of recall of anti-smoking PSAs correlates with PFC activation (Langleben *et al*. 2009), and increases in PFC activation while viewing anti-smoking PSAs predict quitting success (Chua *et al*. 2011). Therefore, factors influencing cognitive processing in the PFC might influence the effectiveness of anti-smoking PSAs.

Dopamine is one of the primary neurotransmitters in the PFC, and regulation of dopamine levels is a key component of optimizing PFC function (Cools & D'Esposito 2011). Catechol-O-methyltransferase (COMT) degrades dopamine and is the primary regulator of dopamine levels in the PFC. A common polymorphism in the gene encoding COMT results in a valine to methionine substitution at codon 158 (Val158Met). The *COMT* Met allele is associated with reduced enzyme activity, leading to higher dopamine levels in the brain (Chen *et al*. 2004). *COMT* Met carriers outperform *COMT* Val homozygotes in tasks measuring working memory and PFC function (Egan *et al*. 2001; Goldberg *et al*. 2003). Furthermore, fMRI studies incorporating working memory tasks have shown greater increases in activation and less task-related deactivation in the PFC in *COMT* Val homozygotes at the same level of performance, a finding which has been interpreted as decreased neural efficiency in this group compared with *COMT* Met carriers (Bertolino *et al*. 2006; Pomarol-Clotet *et al*. 2010).

Another potential influence on PFC function is brain-derived neurotrophic factor (BDNF). BDNF is involved in synaptic transmission and plasticity and has been shown to influence hippocampal-dependent learning and memory (Savitz *et al*. 2006). The *BDNF* Val66Met polymorphism affects intracellular trafficking of pro-BDNF and secretion of the mature peptide (Egan *et al*. 2003); carriers of the *BDNF* Met allele show reduced hippocampal activity during memory encoding and retrieval tasks (Hariri *et al*. 2003; Hashimoto *et al*. 2008) and perform worse than *BDNF* Val homozygotes on a measure of PFC function (Rybakowski *et al*. 2003). Furthermore,

Schofield *et al*. (2009) found that *BDNF* Met homozygotes showed delays in P300 latency in response to task-relevant target stimuli, which suggests an effect of this polymorphism on selective information processing.

On the basis of the demonstrated associations of *COMT* and *BDNF* with working memory and cognitive processing in the PFC, and the role of cognitive processing and PFC activity in the perceived effectiveness of PSAs, we investigated associations of *COMT* and *BDNF* genotype with self-reported message processing, perceived effectiveness and quitting intentions among smokers after viewing sets of PSAs. We hypothesized that we would see reduced processing and perceived effectiveness of PSAs and lower intentions to quit smoking among individuals carrying the *COMT* Val or *BDNF* Met alleles, which have been associated with decreased PFC function. We classified PSAs according to message sensation value (MSV) and argument strength (AS), two factors shown to influence individual responses to PSAs (Strasser *et al*. 2009), and examined interactions between genotype, MSV and AS on outcomes.

Methods

Selection of anti-tobacco PSAs

PSA selection and study design were described previously (Strasser *et al*. 2009). Briefly, 569 cigarette smoking PSAs were acquired from several state and national health authorities. Three trained raters viewed each PSA for content and identified a subset of 99 PSAs that (1) promoted seeking smoking cessation treatment or portrayed the negative consequences of continuing to smoke, (2) targeted adults and (3) were 30 s in duration. These PSAs were rated for MSV features using a scoring template (visual range = 0–10, audio range = 0–5 and content range = 0–5) based on work by Morgan *et al*. (2003).

To classify PSAs by AS, trained raters viewed the PSAs to generate a single statement reflecting the central argument (or arguments) of each PSA (e.g. 'If the health harms of smoking are not enough to get you to quit, consider quitting for your children and those you love', and 'Although you may think smoking helps you cope, if you don't soon quit you will eventually die'). Next, we conducted a shopping mall intercept survey of 300 current smokers to collect ratings of the transcribed central arguments from which an overall AS score was created for each PSA by taking the mean of the 36–38 individual scores recorded for each PSA (Zhao *et al*. 2011).

Four groups of PSAs were then created from the existing collection of 99 PSAs: (1) high MSV–high AS, (2) high MSV–low AS, (3) low MSV–high AS and (4) low MSV–low AS. PSAs exceeding 1 SD from the mean on each of the two dimensions were selected for use in the present study; 16 PSAs met this criterion (four in each group).

Participant selection

Smokers responding to recruitment flyers and advertisements participated in an initial telephone contact at which eligibility was determined. A total of 199 eligible individuals completed a single 90-min session. After giving informed consent, participants provided an exhaled breath carbon monoxide sample (Vitalograph, Lenexa, KS, USA) for biochemical verification of smoking status and a saliva sample for genotyping. Of these 199 participants, 122 self-identified as European American [EA, selected to reduce potential bias because of population stratification (Palmatier *et al*. 1999; Petryshen *et al*. 2010)]. Of these, genotype data (*BDNF* rs6265 and *COMT* rs4680) were collected from 120 participants. Genotypes were classified as Val/Val vs. */Met for both *BDNF* rs6265 and *COMT* rs4680 based on previous research showing significant cognitive differences between Val homozygotes and Met carriers for both genes (Colzato *et al*. 2010; Hariri *et al*. 2003; Loughead *et al*. 2009; Schofield *et al*. 2009).

Standard questionnaires (Lerman *et al*. 1997) were administered at the beginning of the session to assess demographics, smoking history and nicotine dependence (Fagerström test for nicotine dependence, which includes current smoking rate; Heatherton *et al*. 1991). Four PSAs were then presented through a 17-in computer monitor using MediaLab Research Software (Empirisoft, New York, NY, USA) with the participant seated in a comfortable chair approximately 1 m away. Each participant viewed one of the four sets of PSAs classified by MSV and AS. After viewing the PSAs, participants completed measures of cognitive processing, narrative processing and sensory processing of the PSAs (Andrews *et al*. 1990; Chaudhuri & Buck 1995; Palmgreen *et al*. 2002); affective response to the PSAs (Batra & Holbrook 1990; Chaudhuri & Buck 1995); perceived effectiveness of the PSA; recognition of content (Everett & Palmgreen 1995) and intentions to quit smoking (Fishbein *et al*. 2001; Norman *et al*. 1999; Yzer *et al*. 2003). Items measuring processing were accompanied by response scales ranging from 1 (not at all) to 7 (very much), and assessed thinking about the central message of the PSA (cognitive processing; five items, e.g. 'Overall, how much did the PSA make you think about arguments for quitting smoking?'), the story told by the PSA (narrative processing; three items, e g., 'Overall, how much did you pay attention to the characters in the PSA?') and the sensory qualities of the PSA (sensory processing; three items, e g., 'Overall, how much did you pay attention to the PSA's sound tracks?'). Perceived effectiveness was measured by four sets of seven items (one set for each PSA) accompanied by response scales running from 1 (strongly disagree) to 5 (strongly agree). Intentions to quit were measured using two items accompanied by four-point response scales. Affective response was measured using four sets of 12 items (one set for each PSA) assessing emotional response to the PSA (e.g. 'Did the PSA make you feel sad?') accompanied by response scales ranging from 1 (not at all) to 7 (extremely). For each construct described above (cognitive processing, narrative processing, sensory processing, perceived effectiveness, intentions to quit and affective response), participant responses were averaged across all items measuring that construct to generate a summary score, which was used for analysis. Recognition was assessed using five items; for purposes of analysis, a dichotomous recognition variable was used (answered all five items correctly vs. answered at least one item incorrectly).

Descriptive statistics were obtained for all variables. One-way ANOVAS (analysis of variances) were used to test for differences across genotype groups in demographics, smoking history, quitting intentions, processing, perceived PSA effectiveness and recognition. Linear regression models of quitting intentions, perceived effectiveness, message processing as well as affective response and a logistic regression model of the dichotomized recognition measure were then performed. The predictors were age, nicotine dependence (continuous), education (college graduate = 1, non-college graduate = 0), MSV (low = 0, high = 1), AS (low = 0, high = 1) and the dichotomous versions of *BDNF* Val66Met (Val/Val = 0 and */Met = 1) and *COMT* Val158Met (*/Met = 0 and Val/Val = 1). The two-way interactions of the genotype variables with MSV and AS were also included. All predictors were entered as a block, after which nonsignificant ($P > 0.05$) interaction terms were allowed to drop out.

We investigated the possibility that the association of *BDNF* genotype with quitting intentions and perceived effectiveness was mediated by central processing using the method originally proposed by Baron and Kenny (1986) and applied to tobacco prevention research by MacKinnon *et al*. (2002). Using this method, mediation is shown when (1) the predictor is significantly associated with both the outcome and the mediator and (2) in a regression of outcome on predictor and mediator, the mediator is significantly associated with the outcome (which should reduce, or render nonsignificant, the effect of the predictor). To accomplish this, regression models of quitting intentions and perceived effectiveness were performed using *BDNF* genotype and central processing as predictors.

Results

Demographics

In the final sample of 120 smokers, 69 (57.5%) were male and 40 (33.3%) graduated college. Mean age was 41.52 years (SD = 12.49), mean number of cigarettes smoked each day at baseline was 23.25 (SD = 16.06) and mean score at baseline on nicotine dependence was 5.13 (SD = 2.49).

Genotype distribution

The genotype distribution for *BDNF* Val66Met was 75 (62.5%) Val/Val, 40 (33.3%) Val/Met and 5 (4.2%) Met/Met. For *COMT* Val158Met the distribution was 29 (24.2%) Met/Met, 72 (60.0%) Val/Met and 19 (15.8%) Val/Val. Both genotypes were in Hardy–Weinberg equilibrium. For hypothesis testing, both *BDNF* and *COMT* genotypes were dichotomized as Val/Val vs. */Met. Characteristics of demographics did not differ by *BDNF* genotype; however, there were differences in smoking rate and nicotine dependence by *COMT* genotype (Table 1). No differences were found in the distribution of genotypes across the study conditions.

Genetic associations with self-report outcomes

In the multivariate models, *BDNF* genotype was associated significantly with quitting intentions ($\beta = -0.31$, $t(112\ \text{df}) = -3.38$, $P = 0.001$), perceived effectiveness ($\beta = -0.32$, $t(112\ \text{df}) = -3.76$, $P < 0.001$), central processing ($\beta = -0.29$, $t(112\ \text{df}) = -3.31$, $P = 0.001$) and narrative processing ($\beta = -0.19$, $t(111\ \text{df}) = -2.02$, $P = 0.046$); as shown in Fig. 1, the reduced-function *BDNF* Met allele was associated with lower scores on all of these measures . There were no significant main effects of *COMT* genotype; however, there was a significant interaction of *COMT* genotype by AS in the model of narrative processing ($\beta = 0.27$, $t(111\ \text{df}) = 2.02$, $P = 0.046$), indicating that the *COMT* Val/Val genotype was associated with higher narrative processing scores in the high-AS condition, but not in the low-AS condition (where a trivial difference in the opposite direction was observed). Neither *BDNF* nor *COMT* genotype contributed to the models of sensory processing, affective response or recognition.

As described earlier, to test the possibility that central processing might mediate the effect of *BDNF* genotype on perceived effectiveness and quitting intentions, additional regression models of perceived effectiveness and quitting intentions were performed using *BDNF* genotype and central processing as predictors. As shown in Table 2, in both of the models, the effect of central processing was highly significant, and the effect of *BDNF* genotype was reduced, becoming nonsignificant ($\beta = -0.10$, $t(117\ \text{df}) = -1.79$, $P = 0.076$) in the model of perceived effectiveness.

Discussion

We report a significant association of *BDNF* Val66Met genotype with central processing, narrative processing and perceived effectiveness of the PSAs used in this study, and with quitting intentions; the reduced-function *BDNF* Met allele was associated with lower scores on all these measures. We have shown that central processing acts as a mediator of the effect of *BDNF* genotype on quitting intentions and perceived effectiveness; these results are independent upon nicotine dependence.

The *BDNF* Val66Met polymorphism affects intracellular trafficking and secretion of the mature BDNF peptide; the reduced-function *BDNF* Met allele impacts measures of memory encoding and retrieval, selective information processing, and general PFC function (Egan *et al*. 2003; Hariri *et al*. 2003; Rybakowski *et al*. 2003; Schofield *et al*. 2009). Delays in information processing and difficulties in memory encoding may negatively affect an individual's ability to follow and process the central message of a PSA, especially given that the short duration of the PSA requires this information to be processed quickly. It is possible that an individual who experiences more difficulty in processing the central argument may not find the PSA to be effective or persuasive, and thus the PSA would have little effect on quitting intentions.

The *BDNF* Val66Met polymorphism has also been shown to influence emotional response and emotional decision making (Gasic *et al*. 2009; Kang *et al*. 2010), and it is possible that the effects we have shown could be influenced by emotional processing of the PSAs used in the study. We did not see an association between *BDNF* genotype and affective response to the PSAs, and therefore we believe that the associations of this polymorphism with quitting intentions and perceived effectiveness in our study are primarily mediated by differences in cognitive processing between *BDNF*

Table 1: Demographics by genotype

	BDNF Val66Met			*COMT* Val158Met		
Variable	Val/Val ($n = 75$)	Val/Met ($n = 40$)	Met/Met ($n = 5$)	Val/Val ($n = 19$)	Val/Met ($n = 72$)	Met/Met ($n = 29$)
Age, M (SD)	40.96 (12.67)	42.62 (12.60)	41.00 (10.20)	38.16 (12.65)	43.43 (12.51)	38.97 (11.82)
Female, *N* (%)	32 (42.7)	15 (37.5)	4 (80.0)	10 (52.6)	26 (36.1)	15 (51.7)
College graduate, *N* (%)	25 (33.3)	15 (37.5)	0 (0.0)	7 (36.8)	23 (31.9)	10 (34.5)
Cigarettes/day, M (SD)	22.09 (14.51)	25.95 (19.23)	19.00 (7.42)	16.05* (7.79)	25.94* (19.32)	21.28* (7.30)
Nicotine dependence, M (SD)	5.03 (2.64)	5.42 (2.23)	4.40 (2.41)	3.79† (1.99)	5.26† (2.63)	5.69† (2.19)

*F for difference across these three means = 3.26, $P = 0.042$.
†F for difference across these three means = 3.74, $P = 0.027$.

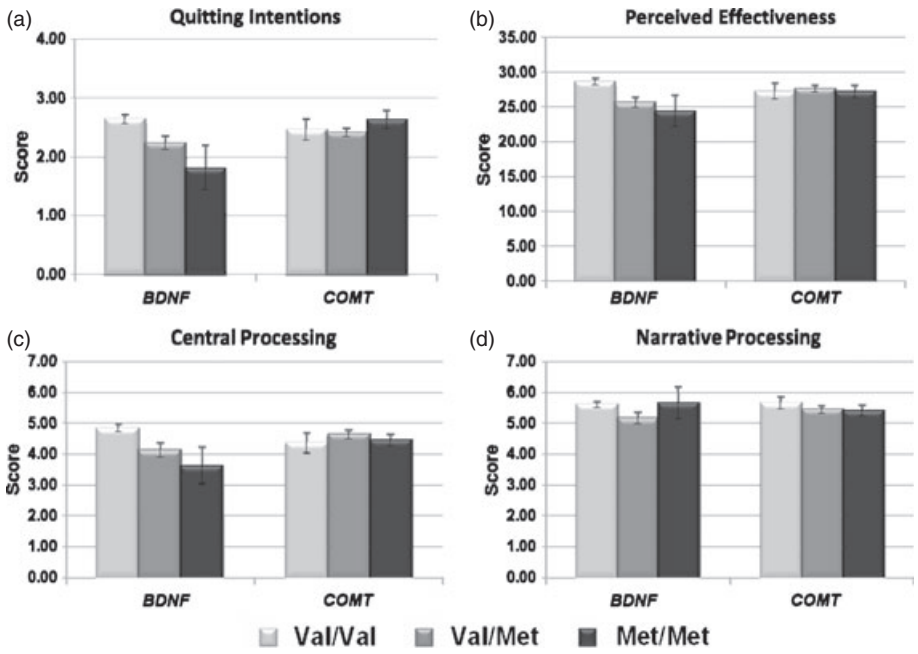

Figure 1: Association of outcome measures with genotype. Results are presented as mean scores ± SE. In the multivariate models, the dichotomous *BDNF* genotype (Val/Val vs. */Met) was significantly associated with quitting intentions ($\beta = -0.31$, $P = 0.001$), perceived effectiveness ($\beta = -0.32$, $P < 0.001$), central processing ($\beta = -0.29$, $P = 0.001$) and narrative processing ($\beta = -0.19$, $P = 0.046$).

Table 2: Results of regression models testing mediation of the effect of *BDNF* Val66Met genotype on quitting intentions and perceived effectiveness by central processing

	Effect of *BDNF* Val66Met			Effect of central processing		
Outcome	β	t	P	β	t	P
Quitting intentions	−0.18	−2.12	0.037	0.41	4.81	<0.001
Perceived effectiveness	−0.10	−1.79	0.076	0.80	14.97	<0.001

Val/Val homozygotes and Met carriers. However, future studies which more closely examine the influence of *BDNF* Val66Met on emotional response to PSAs may be of interest.

While we did not see a main effect of *COMT* Val158Met genotype on the primary outcomes of the study, we did note a significant interaction of *COMT* genotype by AS in the model of narrative processing; individuals homozygous for the *COMT* Val allele reported higher narrative processing in the high-AS condition, but not in the low-AS condition. The *COMT* Val allele encodes the normally functioning protein; dopamine levels in the PFC of *COMT* Val homozygotes are lower than in *COMT* Met allele carriers. Most studies of the *COMT* Val158Met polymorphism have focused on deficits in working memory in *COMT* Val homozygotes (Egan *et al*. 2001; Goldberg *et al*. 2003). However, a recent study suggests that the rapid regulation of dopamine levels in the *COMT* Val homozygotes may afford greater cognitive flexibility; *COMT* Val/Val individuals were faster and more efficient than *COMT* Met carriers in a task-switching paradigm (Colzato *et al*. 2010). It is therefore possible that *COMT* Val homozygotes in our study were able to more rapidly shift cognitive resources toward processing information in a PSA if the argument was strong enough to warrant consideration.

Generally, the effects of AS on the outcomes in our models were not as great as we expected. This could be due to the fact that the PSAs selected for this study were actual PSAs designed for, and used in, anti-smoking campaigns. Because no anti-smoking campaign would intentionally use extremely weak arguments as an intervention, the observed variation in AS across PSAs (while validated; Zhao *et al*. 2011) was relatively limited.

A limitation of this study is that we rely on accurate self-assessment of cognitive processing; our measures are not direct or objective measurements of cognitive processing. Despite this, we have no reason to suspect differences in self-report based on genotype, so the likelihood of bias is low, and the measures used here have shown good construct validity in previous research (Andrews *et al*. 1990; Chaudhuri & Buck 1995; Palmgreen *et al*. 2002). Another limitation is that time since last cigarette was not controlled. Nicotine administration is known to improve attention (Heishman *et al*. 2010) and nicotine withdrawal syndrome includes cognitive deficits (Leventhal *et al*. 2010); inconsistent levels of nicotine withdrawal among our participants may have added to error variance. However, in real-life situations smokers may view PSAs at any time; therefore, our findings may more closely reflect a real-world effect. Finally, our sample consisted entirely of non-treatment seeking smokers viewing ads with a smoking cessation theme. Chronic nicotine exposure has been shown to alter levels of BDNF (Bhang *et al*. 2010; Czubak *et al*. 2009), which may alter the degree to which *BDNF* genotype influences cognitive

processing. Furthermore, some anti-smoking PSAs employ different themes, such as smoking prevention or emphasizing the dangers of second-hand smoke, and are directed toward other groups (adolescents who have not started smoking or non-smokers). Therefore, our results may not apply to all anti-smoking PSAs or target audiences.

In conclusion, we have shown a significant association of *BDNF* Val66Met genotype with self-report outcomes of cognitive processing independent upon nicotine dependence, and a significant interaction of *COMT* Val158Met genotype by AS on narrative processing. Our findings are particularly interesting in light of recent studies suggesting an association between *BDNF* and *COMT* genotypes and smoking. The *BDNF* Met allele has been associated with increased risk of smoking initiation and nicotine dependence (Beuten *et al*. 2005; Lang *et al*. 2007; Novak *et al*. 2010), although not in all populations (Montag *et al*. 2008); the *COMT* Val allele has been associated with smoking status (Nedic *et al*. 2010) and decreased quit rates in smoking cessation studies (Colilla *et al*. 2005), possibly mediated by an increased susceptibility to cognitive symptoms following nicotine abstinence (Loughead *et al*. 2009). Given these associations, further consideration of genetic influences on cognitive processing of anti-smoking PSAs may be useful to increase PSA effectiveness for the target population. Moreover, our research may have broader implications concerning health messaging in at-risk populations. Future research into genotype associations with response to other health-behavior messages (e.g. healthy eating for obese populations) may provide valuable insights for public health campaigns.

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