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Individual differences in positivity offset and negativity bias: Gender-specific associations with two serotonin receptor genes

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Abstract

Individual differences in the evaluation of affective stimuli, such as the positivity offset and negativity bias may have a biological basis. We tested whether two SNPs (*HTR2A*; 102T>C and *HTR1A*; 1019C>G) related to serotonin receptor function, a biological pathway associated with affective regulation, were differentially related to positivity offset and negativity bias for males and females. Participants were 109 cigarette smokers who rated a series of affective stimuli to assess reactions to positive and negative pictures. Gender × genotype interactions were found for both SNPs. Males with the 102T allele showed a greater positivity offset than males with the 102C allele. For females, in contrast, the 1019C allele was associated with a greater positivity offset than the 1019G allele, whereas the 102T allele was associated with a greater negativity bias than the 102C allele. Identifying how gender differences may moderate the effect of serotonin receptor genes on affective information processing may provide insight into their role in guiding behavior and regulating affect.

Keywords

Cognitive Processes; Affect regulation; Negativity bias; Positivity bias; Gender; Serotonin receptor gene

1 Introduction

The Evaluative Space Model (ESM) posits that the evaluation of positive and negative stimuli does not necessarily occur on a bipolar continuum (Norris, Gollan, Berntson, & Cacioppo, 2010). That is, feeling “less good” does not imply that one feels “more bad”.

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Within the framework of the ESM, the processing of stimuli occurs through two systems: the appetitive/approach system and the aversive/avoidance system. There is behavioral and biological evidence to support the hypothesis that positive and negative stimuli are not weighted equally when evaluated (Gray, 1982; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). For instance, escaping a predator is more important than finding a mate although both may elicit strong affective responses (Norris et al., 2010).

This asymmetrical activation of affective responses is the basis for the 'negativity bias' and 'positivity offset' postulates of the ESM (Cacioppo, Gardner, & Berntson, 1997; Larsen, Norris, McGraw, Hawkley, & Cacioppo, 2009). The negativity bias represents the tendency for aversive stimuli to evoke stronger affective responses than equally appetitive stimuli, whereas the positivity offset represents the tendency to respond more positively to neutral stimuli (Ito & Cacioppo, 2005). Because the negativity bias assigns greater value to negative stimuli, it triggers an organism to retreat during dangerous situations. In contrast, the positivity offset suggests that neutral stimuli are viewed more positively, which in turn may lead to exploratory behavior (Norris et al., 2010). In general, individual differences in the positivity offset and negativity bias are uncorrelated. For instance, spatial learning for positive and negative stimuli are related to the positivity offset and negativity bias, respectively (Cacioppo, Berntson, Norris, & Gollan, 2011). Thus, the negativity bias and positivity offset predict what individuals learn about their environment and reflect adaptive responses. However, too much or too little of either may lead to maladaptive responses and affective dysregulation (Norris, Larsen, Crawford, & Cacioppo, 2011).

Individual differences in the positivity offset and negativity bias are temporally stable and may have a biological basis (Ito & Cacioppo, 2005; Norris et al., 2011). One plausible biological pathway is the serotonin system. Indeed, altered serotonin transmission in the raphe nucleus, amygdala, and prefrontal cortex is associated with negative affect and behavioral inhibition (Fakra et al., 2009; Lemonde et al., 2003; Weisstaub et al., 2006). Although several genes contribute to serotonin production and transmission, two functional polymorphisms in the *HTR1A* and *HTR2A* receptor genes are widely studied with respect to their association with affective responses. The C/C genotype of 102T>C (rs6313) in the *HTR2A* gene has been shown to be related to reduced post-synaptic serotonin receptor expression (Myers, Airey, Manier, Shelton, & Sanders-Bush, 2007; Turecki et al., 1999), increased levels of impulsivity (Bjork et al., 2002; Jakubczyk et al., 2012) and aggression (Hwu & Chen, 2000), and more frequent suicidal ideation (Du, Bakish, Lapierre, Ravindran, & Hrdina, 2000). In the *HTR1A* gene, the G allele of the functional SNP 1019C>G (rs6295) is associated with higher expression of pre-synaptic receptors, suicide (Lemonde et al., 2003), neuroticism (Strobel et al., 2003), susceptibility to depression (Parsey et al., 2006; Yu, Tsai, Liou, Hong, & Chen, 2006), responses to threatening stimuli (Mekli et al., 2011), and increased levels of impulsivity (Benko et al., 2010). Interestingly, pharmacogenetic associations with response to antidepressant treatment may be specific to females (Viikki et al., 2011; Yu et al., 2006).

The current study was aimed at investigating how daily cigarette smokers process health-relevant information, such as anti-smoking PSAs. As an extension of this research topic, we explored select individual difference measures that may aid our understanding of information processing. Based on evidence that individual differences in negativity bias and positivity offset may have a biological basis (Ito & Cacioppo, 2005; Norris et al., 2011) and that individual differences in serotonin receptor expression influence affective responses (Carver, Johnson, & Joormann, 2009; Gonda et al., 2009), we examined the association of two polymorphisms in serotonin receptor genes with negativity bias and positivity offset. Because these are viewed as separable, uncorrelated constructs, we predicted that polymorphisms in these serotonin receptor genes should be differentially related to the

positive offset and negativity bias. Moreover, given the putative importance of gender in the phenotypic expression of these polymorphisms and affective information processing (Yu et al., 2006), we investigated the extent to which the associations differed for males and females in a sample of adult smokers. These data could provide insight into the role of serotonergic function in evaluating affective stimuli, which may be important for understanding dysregulated affect, including anxiety and depression.

2 Material and Methods

2.1 Participants

Participants responding to recruitment flyers and advertisements participated in an initial telephone contact at which eligibility was determined. Eligible participants were those aged 18–65 years who reported smoking at least 10 cigarettes per day for the past 6 months, and were not currently trying to quit smoking, using smoking cessation pharmacotherapies or counseling (Strasser et al., 2009). A total of 199 eligible individuals completed a single 90-min session. Of these 199 participants, 122 self-identified as European American [EA, selected to reduce potential bias because of population stratification (Norton & Owen, 2005)]. Of these, genotype data for 102T>C (rs6313) and 1019C>G (rs6295) were available from 109 participants.

2.2 Materials

Pictures were drawn from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1999). There were a total of 48 positive, neutral, and negative pictures (16 in each category). Positive and negative pictures were matched on the basis of their normative arousal ratings (Ito & Cacioppo, 2005; Norris et al., 2011). Affective stimuli and rating scales were comparable to those used in previous studies of the positivity offset and negativity bias (Cacioppo et al., 1997).

2.3 Procedure

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. Positivity offset and negativity bias were assessed as part of a larger study of physiological responses and opinions while viewing anti-tobacco television ads (for details see, Falcone et al., 2011; Strasser et al., 2009). Participants were all current daily cigarette smokers, who were required to complete demographic assessments, then viewed the series of affective pictures prior to viewing a series of anti-tobacco PSAs and completing self-report measures of beliefs about quitting smoking. The picture series was presented prior to the PSAs so the effect of the PSAs would have no bearing on participants' affective responses. As in prior work (Ito & Cacioppo, 2005; Norris et al., 2011), participants were provided examples and practice trials for how responding to the stimuli would occur[1]. Participants were asked to attend to each stimulus for the entire time it was presented and think about how each stimulus made them feel. Each trial consisted of a 3s fixation point, 6s stimulus presentation, 3s fixation point, and two self-paced ratings. First, participants rated their positive and negative reactions to the stimulus using the evaluative space grid, a 5 × 5 grid that allows for independent assessments of positivity (horizontal axis) and negativity (vertical axis; Larsen et al., 2009). Independent measures of positivity and negativity were scored using two 5-point unipolar scales, ranging from 0 (*not at all positive or not at all negative*) to 4 (*extremely positive or extremely negative*) (Cacioppo et

[1]The IAPS picture numbers were: 2383, 2385, 2514, 2516, 2682, 2749, 3061, 3160, 3230, 3261, 4599, 4606, 4689, 5270, 5455, 5470, 5629, 5700, 6000, 6200, 6571, 7002, 7170, 7180, 7184, 7260, 7289, 7352, 7496, 7500, 8034, 8190, 8200, 8230, 8280, 8420, 8503, 9070, 9080, 9250, 9373, 9582, 9630, 9700, 9800, 9830, 9912, 9920.

al., 1997). Second, participants rated how arousing they found the stimulus on a 9-point scale ranging from 1 (*low arousal*) to 9 (*high arousal*). All procedures were approved by the University of Pennsylvania Institutional Review Board.

2.4 Genotyping

Genotyping for SNPs rs6313 and rs6295 was completed using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). PCR was performed with 2.25 ng of DNA, 2.5 μl of ABI Taqman Universal Mastermix, 0.125 μl of water, and 0.125 μl of 40X Assay on Demand SNP Assay for the *HTR2A* and *HTR1A* variants (ABI, Foster City, CA). The 5-μl reactions were performed in a 384-well plate (ABI). The plates were thermal cycled using the same conditions described previously (Lerman et al., 2006). The plates were scanned utilizing the Allelic Discrimination End-Point Analysis on the ABI Prism 7900HT Sequence Detection System. The allelic discrimination data were analyzed by the AutoCall algorithm of the SDS v2.1 Software (ABI). Hardy-Weinberg equilibrium (HWE) was tested for each SNP (Rodriguez, Gaunt, & Day, 2009).

2.5 Dependent measures

The positivity offset score was calculated as the difference in positive ratings and negative ratings of neutral stimuli (i.e., P–N). The negativity bias score was measured as the difference in negative ratings of very unpleasant stimuli and positive ratings of very pleasant stimuli (i.e., N–P) (Norris et al., 2010).

2.6 Statistical analysis

Two-way ANOVAs tested main effects of sex and genotype and their interaction in age, education, cigarettes per day, and nicotine dependence. Separate multivariate ANCOVAs were analyzed to assess differences in positivity offset and negativity bias between genotype groups for 102T>C (C/C, C/T, and T/T) and 1019C>G (C/C, C/G, and G/G) and the sex by genotype interaction was tested. Age and education were covariates in all models. For significant interactions, *t*-tests were conducted to probe differences across genotypes within sex. Effect sizes are presented as partial η^2 for ANCOVA models and as Cohen's *d* for follow-up *t*-tests. To assess the robustness of significant sex by genotype interactions, model selection was validated by bootstrap resampling using a forward selection regression model.

3 Results

3.1 Participant characteristics and genotype

Demographic, smoking characteristics, and genotype frequencies are presented in Table 1. There were no significant differences in sex, age, cigarettes per day, nicotine dependence, or education for either SNP, all *p*s>0.23. Males were more likely to have a high school degree, $\chi^2(1)=4.4$, $p=0.04$, but there were no other significant sex by genotype interactions, *p*s>0.18. Neither SNP deviated from HWE *p*s>0.08.

3.2 Negativity bias

For 102T>C, there was a significant sex × genotype interaction for negativity bias, $F(2,101)=3.5$, $p=0.04$, $\eta^2=0.057$. Females in the C/C group had a higher negativity bias (mean=0.83, *SE*=0.22) compared to females in the T/T group (mean=-0.13, *SE*=0.23), $t(28)=2.83$, $p=0.007$, $d=1.1$ (Figure 1). The C/C group tended to have a higher negativity bias compared to the C/T group (mean=0.25, *SE*=0.20) suggesting a dose effect of genotype, $t(31)=1.94$, $p=0.06$, $d=0.68$. However, the C/T group was not different from the T/T group, $p=0.2$, $d=0.45$. There was no genotype association among males, *p*s>0.58. For 1019C>G,

there were no significant associations with sex, genotype, or the sex × genotype interaction on negativity bias, all *p*s>0.17.

3.3 Positivity offset

For 102T>C, there was a significant sex × genotype interaction for positivity offset, $F(2,101)=4.2$, $p=0.02$, $\eta^2=0.071$. Males in the C/C group had a higher positivity offset (mean=0.57, *SE*=0.11) compared to males in the T/T group (mean=0.01, *SE*=0.14), $t(32)=3.15$, $p=0.003$, $d=0.99$ (Figure 2). The C/T group (mean=0.32, *SE*=0.10) was marginally different from the T/T and the C/C group, *p*s=0.08 and 0.09, *d*s=0.53 and 0.51, respectively, suggesting a dose effect for genotype. The pattern of means was opposite for females. The positivity offset was lower among the C/C genotype (mean=0.12, *SE*=0.19) compared to the T/T group (mean=0.51, *SE*=0.19), but this difference was not significant, $t(28)=1.36$, $p=0.18$, $d=0.53$.

For 1019C>G, there was a significant sex × genotype interaction for positivity offset, $F(2,101)=3.5$, $p=0.04$, $\eta^2=0.059$. In contrast to 102T>C, there was a significant genotype association among females on positivity offset. Specifically, females in the G/G group had a significantly lower positivity offset (mean=−0.13, *SE*=0.20) compared to females in the C/C group (mean=0.37, *SE*=0.17) and the C/G group (mean=0.44, *SE*=0.12), $t(33)=2.05$, $p=0.04$, $d=0.80$ and $t(21)=2.59$, $p=0.01$, $d=0.93$, respectively. There was no genotype association among males, all *p*s>0.44.

3.4 Bootstrap analyses

To assess the robustness of the sex × genotype interactions, we conducted forward selection of the interaction term for a regression model on 1000 bootstrapped data sets (method of Austin & Tu, 2004), using a criterion of $p<0.1$ to enter. Models were adjusted for genotype, sex, age, and education. For negativity bias, the sex × genotype interaction for 102T>C was included 923 times out of 1,000 replications. For positivity offset, the sex × genotype interactions for both 102T>C and 1019C>G were included in more than 80% of the replications (815 times for 1019C>G and 905 times for 102T>C). Model selection provides evidence that the sex × genotype interactions were robust predictors of positivity offset and negativity bias.

4 Discussion

The ESM posits that negativity bias and positivity offset are characterized by differences in the evaluation of positive and negative stimuli, which may have implications for cognition, cognitive biases, and affective regulation (Cacioppo et al., 1997; Norris et al., 2011). This is the first study that we know of to examine the association between polymorphisms in two serotonin receptor genes and sex on the negativity bias and positivity offset. The findings that sex interacted with 102T>C on negativity bias and with both 102T>C and 1019C>G on positivity offset, provide support for the notion that affective evaluation may be influenced by the serotonin system and suggest that this association may differ between males and females. The implications for understanding individual differences in negativity bias and positivity offset and the possible relationship to underlying biological mechanisms are discussed.

The current data suggest that two SNPs that modulate serotonin receptor function were differentially related to positivity offset for males and females. Specifically, for 102T>C there was a genotype association among males, whereas for 1019C>G, there was a genotype association among females. This is particularly interesting because much of the previous research on positivity offset and negativity bias was conducted in female-only samples

(Norris et al., 2011). However, this is the first study to examine moderating factors, such as genetic differences, on phenotypic variation. The positivity offset reflects the tendency to evaluate neutral stimuli more positively, which may lead to exploratory behavior (Cacioppo et al., 1997; Norris et al., 2010) and at the extreme, impulsive behavior (Evenden, 1999). In the current study, males with the C/C genotype of 102T>C, which is associated with higher levels of impulsivity (Bjork et al., 2002; Jakubczyk et al., 2012), had a higher positivity offset than those with the T/T genotype. At the other extreme, without the positivity offset, an individual is unlikely to approach novel stimuli, which may be related to anxiety or depression (McNaughton & Corr, 2004) and at least one study has demonstrated an association between the T allele of 102T>C and social anxiety disorder (Lochner et al., 2007). We also found a linear dose effect of the C allele among males, such that there was a large difference in positivity offset between C/C and T/T homozygotes, whereas there was a medium sized effect between heterozygotes and both homozygote groups. With regard to 1019C>G, we found that females with the G/G genotype, which is associated with decreased serotonin transmission (Lemonde et al., 2003), had a lower positivity offset compared to those carrying a C allele. Consistent with this finding, individuals homozygous for the G allele had higher depression scores and showed less symptom reduction (Villafuerte et al., 2009).

We also found that for 102T>C, the association with negativity bias was moderated by sex. Among females, there was a linear dose effect of 102T>C, suggesting that C/C females had a higher negativity bias compared to females carrying a T allele, with the largest difference between C/C and T/T homozygotes. The C/C genotype has been associated with affect regulation, including the development of depression (Jokela et al., 2007), schizophrenia (Abdolmaleky, Faraone, Glatt, & Tsuang, 2004), suicide attempts (Vaquero-Lorenzo et al., 2008), and anxietyrelated traits (Golimbet, Alfimova, & Mityushina, 2004). Interestingly, rs6311, a functional variant in almost perfect LD with 102T>C, is associated with obsessive compulsive disorder and eating disorders, but only in females (for a review, see Norton & Owen, 2005). The negativity bias may be adaptive, but a heightened sensitivity to negative stimuli can lead to difficulty regulating affect, which may in turn increase symptoms of anxiety and depression (Norris et al., 2010). Females homozygous for the C allele for 102T>C had a higher negativity bias and lower positivity offset than their male counterparts providing further evidence for an association between serotonin receptor function and affective dysregulation.

Several limitations of the present study warrant consideration. First, this was a relatively small sample size comprised of adult daily cigarette smokers, which may limit the generalizability of our findings. However, smokers represent approximately 20% of the U.S. population and including smoking rate as a covariate in our analyses did not substantially change our findings. In addition, the three significant interactions yielded medium effect sizes (η^2=0.057 - 0.071) and were validated as independent predictors in post-hoc bootstrap models. Likewise, the effect sizes for the follow-up *t*-tests were all in the medium to large range (*d*=0.51–1.1). Previous work suggests that the effect size for gender on positivity offset is in the medium to large range, and the effect size for gender on negativity bias is in the small to medium range (Ito & Cacioppo, 2005). Nevertheless, these effects require replication in a larger, more representative sample. Second, although we restricted our analyses to self-identified European Americans, ethnic admixture may have biased our results. Third, the association between polymorphisms in the serotonin receptor gene and positivity offset and negativity bias depended on sex. Despite findings that estrogen may modulate the effects of serotonin (Fink & Sumner, 1996), previous evidence of sexual dimorphisms in the *HTR2A* and *HTR1A* genes is inconsistent (Norton & Owen, 2005) and we should be cautious in our interpretation of the current findings. Fourth, it is possible that other genes involved in the serotonin system as well as other neurotransmitter systems (i.e.,

dopamine) may modulate positivity offset and negativity bias. We targeted the functional 102T>C and 1019C>G SNPs based on substantial evidence of their association with affect across multiple populations (Du et al., 2000; Lemonde et al., 2003; Yu et al., 2006). Future work is necessary to test this hypothesis and whether these genes interact with one another.

In conclusion, we report the interactive associations between sex and two functional serotonin receptor SNPs on positivity offset and negativity bias. The ESM posits that responses to positive and negative stimuli occur through the appetitive/approach and aversive/avoidance systems that guide behavior. Although these data require replication, our findings support the notion that sex differences in serotonin receptor expression may be important for understanding the biological basis of the positivity offset and negativity bias. Evaluation of affective stimuli plays an important role in guiding behavior and the ability to regulate affect. Indeed, genetic associations with the processing of health-behavior messages predict intentions for behavior change (Falcone et al., 2011). Identifying individual differences in serotonin receptor genes that may modulate the positivity offset and negativity bias may enhance our understanding of regulation of affect, processing of information, and response to treatment.

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Individual differences in response to positive and negative stimuli guide behavior.

Genes that regulate serotonergic transmission may influence affective evaluation.

There were sex-specific associations between serotonin genes and affective responses.

Identifying individual differences may increase knowledge of affective regulation.

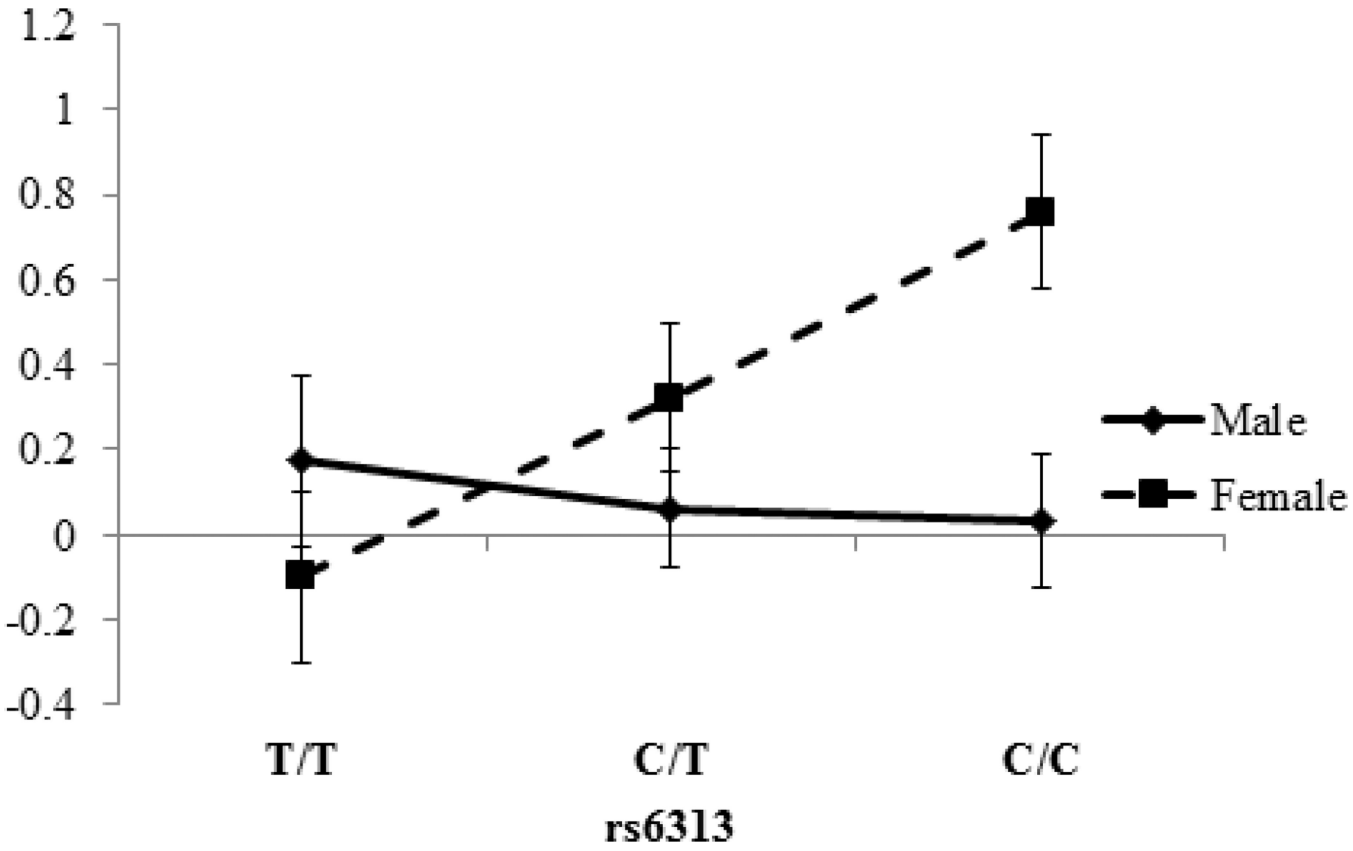

Figure 1.
Negativity bias for each sex by genotype group for 102T>C.

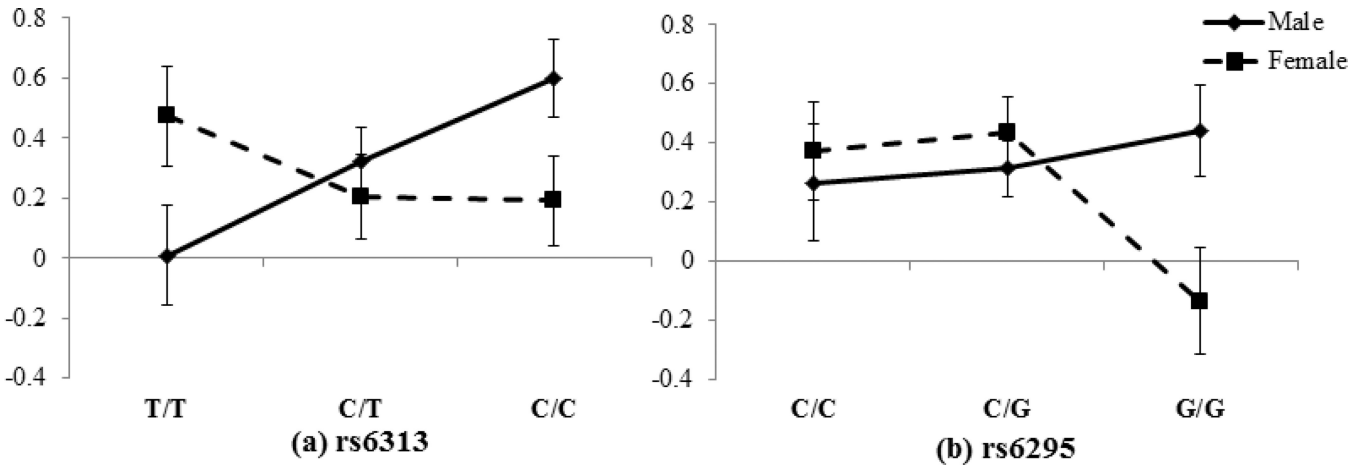

Figure 2.
Positivity offset for each sex by genotype group for 102T>C (panel a; left) and 1019C>G (panel b; right).

Table 1

Demographic and smoking characteristics by genotype group and sex for 102T>C and 1019C>G (Total *N*=109)

	102T>C						1019C>G					
	T/T		C/T		C/C		C/C		C/G		G/G	
	Males n=13	Females n=14	Males n=28	Females n=17	Males n=21	Females n=16	Males n=8	Females n=12	Males n=39	Females n=24	Males n=15	Females n=11
Age (years)	42(12)	46(8)	44(13)	39(12)	42(13)	35(12)	37(12)	40(10)	44(14)	39(12)	44(11)	40(12)
Education (% HS graduate)	77%	36%	75%	53%	67%	69%	88%	58%	72%	50%	67%	55%
Cigarettes per day	21(10)	19(7)	22(11)	20(8)	21(7)	19(7)	21(13)	21(7)	23(9)	19(7)	20(8)	18(9)
Nicotine dependence	5.1(3)	5.3(2)	5.2(2.5)	5.3(2.5)	5.1(2.3)	5.1(2.5)	4.1(2.8)	5.8(2.4)	5.6(2.4)	5.1(2.2)	4.5(2.4)	4.8(2.9)

Note. All values are mean(SD) unless otherwise noted.