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Effects of nicotine on emotional distraction of attentional orienting: evidence of possible moderation by dopamine type 2 receptor genotype

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ABSTRACT

Introduction: Growing evidence suggests that attentional bias to, and distraction by, emotional stimuli may moderate affective states and motivation for nicotine and other drug use.
Methods: The present study assessed the effects of nicotine and dopamine receptor genotype on distraction by emotional pictures, during a modified spatial attention task, in 46 overnight-deprived smokers.
Results: Relative to placebo, 14 mg nicotine patch produced shorter overall reaction times (RTs) and individuals with two dopamine type 2 receptor (DRD2) A2 alleles exhibited the greatest RT benefit from nicotine following emotionally negative pictures after the longest cue-target delay (800 ms), but benefitted least from nicotine following positive pictures after the shortest delay (400 ms). In contrast, at the shortest delay, A1 carriers did not benefit from nicotine following emotionally negative pictures but did following positive ones.
Conclusions: These genetic differences in the effects of nicotine on attention immediately following emotionally positive versus negative stimuli may reflect differential excitatory and inhibitory transmitter processes related to approach (reward) and avoidance (punishment) sensitivities of dopamine-related neural networks that support positive and negative affect.

1. Introduction

Abstinent smokers frequently report negative mood states and increased distractibility by emotion-related stimuli (Kalman, 2002; Kassel et al., 2003; Spielberger, 1986). Recent studies suggest that attentional and affective responses to nicotine abstinence and nicotine replacement therapy (NRT) are moderated by dopamine-related genetic polymorphisms (Gilbert et al., 2005, 2009) and affect-related attentional and situational factors (Gilbert et al., 2008a,b). Relatively little is known about when, how, and in whom nicotine withdrawal symptoms are most likely to occur (Gilbert et al., 2009; Kassel et al., 2003), though it is widely recognized that both nicotinic cholinergic and dopaminergic receptors are critical modulators of attentional processes and reinforcing effects of nicotine (Corrigall et al., 1992; Robinson and Berridge, 1993). Thus, characterizing genetically based individual differences in the effects of NRT on attentional orienting, in contexts that include emotional stimuli, could be useful in better understanding stress-related relapse in individuals attempting to remain smoking abstinent.

Placebo-controlled studies support the view that NRT in nicotine-deprived habitual smokers promotes attentional bias toward positive stimuli, but possibly not toward negative stimuli (Dawkins et al., 2006; Powell et al., 2004). These findings may largely reflect nicotine withdrawal in dependent individuals, though they could also in part reflect inherent effects of nicotine. Complementing these findings, others have found NRT in abstinent smokers to reduce distraction by emotionally negative stimuli (Gilbert et al., 2004a,b, 2005, 2007; Rzetelny et al., 2008). However, none of these studies has assessed the effects of nicotine on emotional distraction during a spatial attention task using lateralized (left and right visual field) targets. Characterizing such effects of nicotine also allows testing of the hypothesis that the effects of nicotine, NRT, and nicotine withdrawal-related affective changes are based in part on changes in attentional bias to emotional stimuli. Such processes may reflect neural networks that include left-right brain differences in densities of receptors for dopamine, acetylcholine and other neurotransmitters (Gilbert et al., 2005) according to the the lateralized affective networks hypothesis of the Situation by Trait Adaptive Response (STAR) model (Gilbert, 1995).

Consistent with this lateralized neural networks hypothesis, a number of studies support the view that nicotine and other cholinergic and dopaminergic receptor agonists and antagonists can alter responses to left versus right visual field stimuli (McClernon et al., 2003; reviewed by Gilbert et al., 2005 and by Tucker and Williamson, 1984). Thus, spatial attention tasks using lateralized targets could broaden understanding of brain mechanisms for nicotine replacement in nicotine-abstinent

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smokers. Examining how NRT alters attention to emotional stimuli could provide insight into the stressful effects of nicotine abstinence and into beneficial effects of NRT.

Dopamine is the neurotransmitter most frequently hypothesized to play an important role in the effects of nicotine and other drugs on attention, affect, and self-administration (Corrigall et al., 1992; Robinson and Berridge, 1993). The A1 genetic polymorphism of the dopamine type 2 receptor (DRD2) genotype has been found to be associated with a reduced number of DRD2 receptors (Thompson et al., 1998), with the attenuating effects of nicotine on distraction (Gilbert et al., 2005), and with brain stress reactivity during smoking abstinence (Gilbert et al., 2004a,b). Therefore, there is reason to believe that the DRD2 A1 allele may be associated with psychological benefits of NRT. The most widely analyzed DRD2-related genetic polymorphism, Taq1A, resides 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 et al., 2004). This close proximity allows linkage of the Taq1A polymorphism to DRD2 expression.

Given genetic influences on broad factors including the disposition to smoke, smoking-related personality traits, the effects of nicotine, attention, and attentional bias and distraction (Gilbert et al., 2005; Gilbert and Gilbert, 1995; Heath et al., 1995), we chose to explore the possible moderating influences of dopamine receptor genotype on the ability of NRT to modulate attentional orienting in the context of emotional distractors. Though other genotypes may moderate the effects of NRT, only DRD2 polymorphisms were evaluated at present because of the modest sample size.

Current findings are from a larger study that found that the effects of NRT on distraction during a rapid visual information processing (RVIP) task were moderated by DRD2 genotype (Gilbert et al., 2005). Specifically, in the earlier report NRT was found to increase target detection accuracy and shorten RTs more in the presence of left-visual-field (LVF) than right-visual-field (RVF) emotional distractors, but shortened RTs more with RVF than LVF numeric distractors. Additionally, nicotine replacement therapy facilitated performance more in individuals with at least one A1 allele than in homozygous A2A2 individuals, especially with numeric distractors presented to the left hemisphere. NRT also tended to shorten RT to targets following negative stimuli more than other types of stimuli. The task described in the present report complements the earlier study by assessing the effects of NRT on spatial attention to lateralized target stimuli following centrally presented emotional distractors.

The present study used a modified version of Posner's (1980) cued target detection task (CTDT). The CTDT has been used in several studies to characterize nicotine's effects on cued attentional orienting (e.g., Thiel et al., 2005), though none of these studies assessed the influence of emotional stimuli as moderators. The CTDT requires the participant to fixate centrally while covertly directing attention to the side of a computer screen, cued by a central arrow. The individual then responds as quickly as possible to the appearance of the peripheral target, an asterisk. On different trials, the central arrow either directs attention to the side in which the target subsequently appears (valid cue) or to the side opposite of where the target appears (invalid cue). Reaction times (RTs) to targets are more rapid when the target is preceded by a valid central arrow cue, as attention has already been allocated to this location. The CTDT has advantages over other spatial and selective attention tasks, which include the ability to manipulate both the visual field of the targets and the time intervals between cues and the targets.

The present study used central pictures differing in affective valence, rather than presenting central arrow cues, in order to better characterize the effects of emotion-related distraction by positive and negative valence pictures on subsequent lateralized targets.

Based on the above-reviewed evidence, it was hypothesized that DRD2 genotype, length of delay between the distractor and target stimulus, and the emotional valence (positive or negative) of the distractor would moderate the effects of nicotine replacement therapy on emotional distraction in overnight-abstinent smokers. The hypothesis that delay between the emotional distractor and target stimulus would be moderated by nicotine replacement therapy and genotype was based on the Situation by Trait Adaptive Response (STAR) model hypothesis (Gilbert, 1995, p. 213) that genotype moderates the effects of nicotine on the dissipation rate of attentional biasing to affective stimuli.

2. Methods

2.1. Participants

Forty-six smokers (24 females, 22 males) averaging 18.4 cigarettes per day (5.4 SD, 10–40 range) were used in the statistical analyses of nicotine's effects on attention. Mean age was 23.5 years (7.5 SD, 18–47 range). Because of the focus on genetics, only northern European Caucasians were used. Nicotine dependence was assessed with the Fagerström Test of Nicotine Dependence (FTND; Heatherton et al., 1991). The mean FTND score was 4.5 (1.6 SD, 1–8 range), indicating a moderate degree of dependence.

Participants were recruited by ads and community postings. Exclusion criteria included smoking fewer than 10 cigarettes/day on average for the past year, habitually using cigarettes with estimated nicotine deliveries of less than 0.6 mg, reported use of psychoactive drugs or medications other than caffeine, marijuana, and alcohol, excessive alcohol use (>28 drinks/wk), non-English speaking, atypical sleep cycles, pregnancy, and visual problems.

Participants were instructed not to smoke for the 12 h preceding each of the experimental sessions and only those who adhered to this 12-hour abstinence were included in the data analysis. Adherence was verified prior to each session with expired breath carbon monoxide (CO) concentration and self-report. Adherence was confirmed after sessions through nicotine and plasma cotinine levels. Sessions were rescheduled for those exceeding the maximum allowable CO ($N = 7$) and for those reporting 3 or more alcoholic drinks the night before session, fewer than 5 h of sleep, illness, or drug use ($N = 8$). Marijuana use was prohibited for 72 h prior to experimental sessions. Genotype was not significantly associated with age, FTND score, pre-session plasma cotinine level or patch-related plasma nicotine boost.

2.2. Design

During each of 4 experimental sessions, participants completed the emotional distractor target-detection (EDTD) task once, 4 h after patch application. The study was double blind for the nicotine vs. placebo status of the patches. The active vs. placebo patch orders were counterbalanced across sessions in a within-participants design. Each participant received a nicotine patch on one of the first two experimental sessions and a second nicotine patch during one of the last 2 experimental sessions, while being on placebo patches during the other 2 sessions.

2.3. Procedures

Participants who completed 2 orientation sessions and 4 experimental sessions earned $200. The study and consent form were approved by Southern Illinois University Human Subjects Committee. During the orientation, after an eligibility assessment, participants signed the IRB-approved consent form, and then completed questionnaires and practiced experimental tasks. Handedness was tested with the Edinburgh Handedness Inventory (Oldfield, 1971), and there were 43 right handed and 3 left handed individuals in the reported analyses. Participants were also screened for any visual deficits that would interfere with task performance. Participants were instructed to not consume alcohol or tobacco within 12 h of the experimental session onset. Participants were provided no direct or suggestive information about the effects of nicotine.