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Nicotine Differentially Modulates Antisaccade Eye-Gaze Away from Emotional Stimuli in Nonsmokers Stratified by Pre-Task Baseline Performance

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Abstract

Rationale and objective—Studies indicate that nicotine enhances some aspects of attention and executive functioning and attenuates the attentional salience of emotionally negative distractors. The purpose of this study was to assess whether nicotine can enhance executive control over prepotent responses in emotional contexts in nonsmokers and whether such enhancement is greater in individuals with low baseline performance.

Methods—The antisaccade task (AST) measures the inhibition of the tendency to glance in the direction of the onset of a visual stimulus and thus is an index of control over prepotent responses. Ten male and 14 female nonsmokers wore a nicotine and placebo patch on counterbalanced days that included emotional picture primes and targets.

Results—There were significant beneficial effects of nicotine on antisaccade reaction time (RT). These beneficial effects occurred in individuals with poor- and average-baseline performance, but not in high baseline performers. In slow baseline-RT individuals nicotine reduced RTs associated with negative targets in the left visual field (VF) and reduced RTs associated with positive and neutral targets in the right VF. In contrast, in the average baseline group, nicotine reduced RTs for positive targets in both VFs and neutral targets in the left VF.

Conclusions—The results suggest that nicotine may produce its effects by enhancing executive functions and that the differential effects as a function of VF, target emotion, and group may also reflect lateralized differences in the effects of nicotine on brain reactivity to emotional stimuli.

Keywords

Nicotine; Nonsmokers; Attention; Cognition; Affect; Impulsivity; Executive Control; Inhibitory Control; Hemisphere; Visual Field

Introduction

The effects of nicotine on executive control of prepotent responses are not well characterized in either smokers or in individuals without a history of nicotine exposure. Most nicotine-dependent smokers report that one of the primary reasons that they smoke is to enhance executive functioning and to regulate mood (Gilbert et al. 2000; Spielberger 1986). The antisaccade task (AST) requires executively-directed inhibition of the natural tendency to look at a suddenly appearing novel stimulus in the periphery (Pierrot-Deseilligny et al. 2003). In smokers, nicotine reduces errors during the AST (Dawkins et al. 2007, Larrison et al. 2004; Pettiford et al. 2007) and Larrison et al.(2004) found that nicotine reduced reaction time (RT) during the AST. Powell et al.(2004) demonstrated the potential

clinical relevance of the AST by finding that the degree to which nicotine (lozenge) improved antisaccade performance in overnight deprived smokers was correlated with nicotine dependence and predicted relapse after quitting (Powell et al. 2004).

Two recent studies support the view that nicotine can also facilitate the inhibition of prepotent eye-gaze responses in nonsmokers. Rycroft et al. (2007) found that nicotine reduced reaction time (RT) during the AST but had no effect on AST errors in nonsmokers. In contrast, in the second study, Petrovsky et al. (2012) found in poor-baseline performing nonsmokers that nicotine reduced AST errors, but not RTs. Thus, these two studies support the hypothesis that nicotine can enhance executive control in nonsmokers. However, the differential effects of nicotine across studies (RT only vs. errors) suggest that individual differences in task baseline performance and task differences may moderate the effects of nicotine. These baseline-dependencies and task-related differences need to be replicated and extended using variations in AST task parameters. The assessment of individual difference in AST baseline performance is also supported by previous studies (reviewed by Perkins, 1999) indicating that individuals with poor baseline performance tend to benefit more from nicotine than do those with better baseline performance.

While nicotine can enhance objective measured vigilance task performance in smokers and some nonsmokers (reviewed by Heishman et al. 2010; Newhouse et al. 2004; Perkins et al. 2000), the effects of nicotine on tasks that require impulse control and related executive control are not well characterized in smokers or nonsmokers. If nicotine were shown to enhance the inhibition of impulsive behavior in nonsmokers this could be an important finding because this effect might be experienced as reinforcing, especially in those with low baseline AST performance/executive control problems (Newhouse et al. 2004; Perkins, 1999; Perkins et al. 2000).

Findings suggest that the two hemispheres of the brain are differentially involved in impulse regulation and have differential attentional biases to emotionally negative versus positive stimuli that are modulated by nicotine. The pars opercularis region of the right inferior frontal gyrus appears to play an important and unique role in modulating some kinds of impulsivity (reviewed by Tabibnia et al. 2011) and a substantial body of research suggests greater left hemisphere (LH) attentional biases for positively valenced emotional stimuli but greater right hemisphere (RH) attentional bias for negatively valenced stimuli (Davidson 1992; Dolcos et al. 2004; Pizzagalli et al., 2003; Smith and Bulman-Fleming 2005). There are also hemispheric asymmetries in brain and perceptual responses to the acute administration of nicotine (Carlson et al. 2009; Gilbert, Carlson et al. 2008; Gilbert et al. 1989, 2004, 2005; Rose et al. 2003).

Given the above evidence of the importance of hemispheric asymmetries in executive control, attentional biases to affective stimuli, and nicotine's effects, the present study incorporated AST-tasks that included emotional targets presented in the left or right visual field (VF) and centrally presented emotional primes. The use of emotional targets and primes was in part based on evidence that in smokers, nicotine, relative to placebo, reduces attention to and distraction by negative stimuli (relative to positive and to neutral stimuli) as assessed by eye-gaze (Gilbert, Rabinovich et al. 2008), brain activation (Engelmann et al. 2011; Gilbert et al. 2007), emotional prime stimuli preceding targets (Asgaard et al. 2010), and RT during task demanding significant executive control and resources (Gilbert et al. 2005). Thus, we hypothesized that nicotine would reduce AST RT and increase accuracy on trials with emotionally negative primes and with emotionally negative peripheral stimuli relative to positive and neutral stimuli. We also hypothesized that there would be a VF by nicotine by emotional valence interaction resulting from negative primes enhancing the attention-grabbing nature of left VF negative targets such that nicotine would provide more

benefit in this condition. Identification of VF by affective valence by nicotine interactions could provide insight into the neurobiological mechanisms associated with the beneficial effects of nicotine on AST performance (Gilbert et al. 2005) and also could provide an index of individual differences in nicotine's benefits.

In summary, the primary goal of the present study was to assess the effects of an acute dose of nicotine on the ability of nonsmokers to inhibit automatic attention to (eye-movement towards) emotionally negative pictures, relative to emotionally neutral and emotionally positive pictures and to test the hypothesis that low baseline-performing nonsmokers would derive greater benefits from nicotine than those with better baseline performance. Another goal was to better understand mechanisms that may reinforce nicotine self-administration in individuals with little or no previous exposure to nicotine. Finding beneficial effects of nicotine on attentional impulsivity in nonsmokers would suggest that these effects may reinforce tobacco use in individuals experimenting with tobacco but with little or no previous nicotine exposure.

More specifically, it was predicted that, relative to placebo, the nicotine patch would reduce antisaccade RTs and would enhance antisaccade accuracy more in poorer relative to better baseline-performing individuals, especially on trials involving emotionally negative prime and/or target pictures. Based on the above-noted evidence that the two hemispheres are different in their sensitivities to emotionally negative versus positive stimuli, it was hypothesized that nicotine would enhance antisaccade RT performance more when negative pictures were presented in the left VF (RH) because of the bias of the RH for negative affect-related stimuli. In contrast, it was expected that nicotine would enhance antisaccade RT performance most with positive targets in the RVF (LH) because of the bias of the LH for positive affect-related stimuli.

Methods

Participants

College students (10 male and 14 female, 6 African Americans and 1 Hispanic) were recruited by local postings and completed the study. Two other individuals did not complete the study. One was sick before the patch application and the other became nauseated after the patch application. Inclusion criteria included participants that reported no smoking in the past year and fewer than 100 lifetime cigarettes. Participant ages ranged from 18 to 30 ($M = 21.3$ yrs). Exclusion criteria included the following: color blindness, irregular sleep patterns, current major psychiatric disorder, history of psychoactive drug use, medications other than moderate alcohol use and occasional marijuana use, and the use of tobacco or nicotine other than fewer than 100 lifetime cigarettes. Only eight of the participants had ever smoked in their lifetime. The three baseline performance groups (defined below) did not differ (all one-way ANOVAs had p 's $> .30$) in terms of age, gender, BMI, or prior nicotine exposure (naïve vs. smoked). The sample size was based on expected moderately large AST effect sizes (e.g., Rycroft et al. 2007) in nonsmokers and significant effects in smokers with in previous studies with as few as 12 subjects (Pettiford et al. 2007). However, the power was limited for the analysis of the hypothesized higher-order interactions. Thus, findings of these higher-order interactions must be viewed as exploratory.

Materials

Eye-tracking system—An Arrington Research Inc eye-tracking system and ViewPoint Software (Scottsdale, AZ) was used to collect eye-gaze direction (toward or away from target) using a 60 Hz sampling rate. A Dell stimulus-presentation computer communicated with the Arrington computer via SuperLab (Cedrus Corporation, San Pedro, CA) serial

output connection that time-marked the onset of visual stimuli with eye-gaze direction in real time. Stimuli were presented by eMagin Z800 3DVisor eye-tracking goggles from Arrington Research Inc.

Patches—Seven mg nicotine patches (Walgreens brand manufactured by Novartis) with slow blood-nicotine rise times were used in order to minimize the likelihood of nausea that has been associated with rapid nicotine rise in the blood (Gilbert, Rabinovich and Rosenberger 2003). The placebo patch consisted of a latex free bandage with the same circular size and shape as the nicotine patch. Both the placebo and the active nicotine patches were covered by a 5cm × 5cm bandage to mask any slight differences in patch appearance to ensure subject and researcher blindness.

Antisaccade Task (AST)—Each AST (Fig 1) consisted of 36 prosaccade and 36 antisaccade targets randomly intermixed. The task format was as follows: a) a fixation cross centered in the middle of the screen for 200 ms, b) a red or green circle followed for 1000 ms (red indicated look away [antisaccade], while green indicated look toward [prosaccade]) the subsequent target face, c) an emotional priming picture (positive, negative, or neutral) presented for 2000 ms, d) a mask presented for 50 ms, e) another fixation cross presented for 1000 ms, f) a blank gap or black screen presented for 200 ms, and g) an emotional target Ekman face (positive, negative, or neutral target) was finally presented for 1000 ms randomly on the right or left part of the screen (all other images were presented in the middle of the screen). Each AST consisted of 72 trials resulting from two repetitions of each trial type in the stimulus matrix: Saccade Type (Pro vs. Anti) × Visual Field (left vs. right) × Prime Valence (positive vs. negative vs. neutral) × Target Valence (positive vs. negative vs. neutral). Thus, a total of 8 repetitions of each trial type were presented across the 4 ASTs on each experimental day. Prime valence was completely crossed with the valence of the emotional targets.

Stimuli—Priming pictures were taken from the International Affective Picture System (Lang et al. 1995). Target pictures were smiling, angry, and neutral faces from the Ekman Picture Series (Ekman and Friesen 1977). The medial edge of target pictures was 4.6° degrees eccentric of the fixation cross and pictures subtended 12.6° vertically and 8.4° horizontally.

Procedure

Recruitment of participants was accomplished through flyers posted around a large university and the surrounding community. Participants were screened through an initial phone screener and through a more comprehensive screening at the beginning of their baseline practice (BP) session to assess study inclusion criteria. After signing the study's SIUC IRB-approved consent, each participant completed one BP session and two afternoon experimental sessions. Neither the participant nor the researcher who administered the AST task had knowledge of which patch type was used (double-blind). The success of the blindness was assessed using the Patch Guess and Attributions Questionnaire (Gilbert et al. 2005). Two individuals who never otherwise interacted with the subject and researcher placed and removed the patches. Consistent with the blindness of the participants to the patch condition, all but one of the participants scored "1" or "0" on an 11-point nausea/sickness scale running from "0" = none to "10" = extremely nauseated/sick. This nausea/sickness scale was administered after each task. The one exception was an individual who scored an average of "6" on this scale but did not report being bothered by this state.

Patches were placed on the arm 6 hours before the 2 afternoon experimental sessions. The experimental sessions were separated by 2 days to 2 weeks. The BP session consisted of

practicing the AST twice. The afternoon experimental sessions consisted of the participant completing the AST four times each session. For all the ASTs the prime and target pictures were the same but picture presentation order was randomized. Saccades were recorded for all trials but RTs were calculated only for correct target gazes. In order to count as a saccade, the participant's eyes had to move more than 3 degrees from the midline in the correct direction and maintain that direction consistently for 150 ms. RTs shorter than 80 ms were excluded from the analysis.

Results

The success of the patch blinding was demonstrated by the finding that when on a nicotine patch participants were 44.1% confident that they were wearing a nicotine patch, but when on the placebo patch they were 47.0% confident that they were wearing a nicotine patch ($p = 0.753$). The error analysis did not include antisaccade versus prosaccade because virtually no errors were expected or occurred with prosaccades. For the error statistical analysis, the 24 individuals were assigned to one of 3 groups based on tertiles on baseline mean errors across the antisaccade conditions during the practice session. Mean baseline errors were 0%, 2.1%, and 21.4%, respectively for the three BP groups. The overall error analysis was a mixed-design MANOVA with one between subjects factor, Baseline Performance (BP) Group (three groups [top, middle, bottom] on practice day) and 4 within subjects factors (Drug [nicotine vs. placebo], Prime Valence [positive, negative, neutral], Target Valence [positive, negative, neutral], and Visual Field [right vs. left]). This MANOVA failed to reveal significant effects or interactions involving Drug on incorrect saccades (5.5% for nicotine versus 7.0% for placebo). Thus, only the statistical analyses of the RT analyses are reported below.

The 24 subjects were assigned to one of 3 groups based on tertiles on their baseline RTs during the practice session. The grouping for the error analyses was based on both 3 groups of 8 and on 2 groups of 12. However, as noted below there were no effects of nicotine on errors. For the RT grouping, mean RTs across the prosaccade and antisaccade conditions were used. While square-root transforms were used for all RT analyses for better normalization of data, the figures used and descriptions are in raw units to maximize generalizability to other published findings. Raw mean baseline RTs across saccade types were 251 ms (SD = 19), 286 ms (SD = 9), and 346 ms (SD = 34), respectively for the three BP groups. The observed patterns reported below remained even after controlling for age and gender as covariates in MANCOVAs. The only significant interaction in the MANCOVAs was a significant Age $\times$ Drug $\times$ Prime Valence interaction, $F(2,18) = 3.64$; $p = .047$. On average per subject 136 "correct" trials were available for RT analysis on the nicotine day and 134 correct trials on the placebo day. An exploratory analysis using the order of the nicotine patch (first vs. second session) showed that nicotine order interacted with Drug effect but not with other interactions involving Drug. Thus, subsequent analyses did not include nicotine order as a factor.

The initial MANOVA revealed a number of predicted main effects and interactions. As expected, antisaccade RTs were much slower than prosaccade RTs, $F(1, 20) = 83.357$, $p < .001$, (Fig 2). In addition, there was a main effect of prime valence, $F(2, 19) = 6.457$, $p = .007$, such that, relative to neutral primes, negative primes were associated with longer RTs, $p = .001$. Negative primes also tended to be associated with longer RTs relative to positive primes ($p = .057$). However, prime valence did not interact significantly with Drug. As expected, shorter RTs occurred with nicotine compared to placebo in the antisaccade ($p = .018$), but not the prosaccade condition ($p = .548$) (Fig 2), Drug $\times$ Saccade Type interaction, $F(1,20) = 5.235$, $p = .033$. Relative to placebo, nicotine significantly reduced RTs in different valence $\times$ VF conditions (Fig 3) in both the slow BP and the middle BP groups, but

had only one effect (noted below) in the fast BP group, Drug $\times$ Saccade Type $\times$ BP Group $\times$ Visual Field $\times$ Target Valence interaction, $F(4,36) = 3.106$, $p = .027$.

To further explore the above-described interactions, Drug $\times$ Saccade Type $\times$ Visual Field $\times$ Target Valence MANOVAs were performed separately for each group. The MANOVA for the fast group revealed only one significant effect involving drug, a drug by VF interaction such that nicotine relative to placebo had slower RTs in the left VF, $F(1,6) = 13.173$, $p = .011$. The parallel MANOVA for the middle group revealed a Drug $\times$ Saccade Type interaction, $F(1,6) = 7.034$, $p = .033$, such that nicotine relative to placebo reduced RT only in the antisaccade condition. The MANOVA for the slow BP group revealed a Drug $\times$ Saccade Type $\times$ Target Valence $\times$ VF interaction, $F(2,6) = 5.785$, $p = .040$, such that in the antisaccade condition, nicotine relative to placebo, was associated with shorter RTs in right VF for positive and neutral targets, $p = .131$ and $p = .022$ respectively, but shorter RTs in the left VF for negative targets, $p = .040$.

Further comparisons were limited to the antisaccade and were based on nicotine benefits (placebo RT – nicotine RT) using a BP Group $\times$ Visual Field $\times$ Target Valence MANOVA with follow-ups of significant interactions. There was a significant BP Group $\times$ Visual Field $\times$ Target Valence quadratic interaction, $F(3,36) = 4.751$, $p = .021$, that is depicted in Figure 3. Follow-up analyses and subsequent group comparisons (Fig 3) revealed that: 1) for negative targets nicotine produced maximal and most significant RT benefits for negative targets in the slow BP group when targets were presented in the left VF, while other conditions involving negative targets were not significant; 2) for positive targets nicotine produced its maximal and most significant RT benefits in the medium BP group, and although significant, less pronounced benefits were demonstrated when positive targets were presented in the right VF in both the slow and medium BP groups; and 3) for neutral targets nicotine produced the maximal and most significant RT benefits in the slow (RH) and medium (LH) BP groups. Comparisons of differences in nicotine benefits between three baseline performance groups are also presented in Figure 3, where differences between groups on for VF by target valence conditions are depicted by similar letters. The largest and most significant difference was the predicted greater nicotine benefit for the slow group relative to the fast group for left VF negative targets ($p = .005$). There was a greater nicotine benefit for both left VF positive and neutral targets for the medium group, relative to the fast group (both $p < .05$). Finally, for neutral targets in the right VF, the slow baseline group benefitted more than the fast group ($p < .05$). Overall, there were significant differences across the three BP groups in terms of how nicotine benefits varied as a function of VF and target valence. However, the dominant effect of nicotine was to reduce antisaccade RTs in slow and medium BP groups but to have no effect in the fast BP group and to produce a decrement in RT for targets (pro- and antisaccade combined) presented to the left VF.

Discussion

The present placebo-controlled double-blind study investigated the influence of nicotine on prosaccade and antisaccade eye movements in healthy, male and female nonsmokers stratified for slow, medium, and fast-antisaccade performance during a task-practice session that occurred prior to the nicotine and placebo patch sessions. While there was a significant beneficial effect of nicotine relative to placebo on RT in the antisaccade condition, this effect was limited to the slow and medium baseline-performing subjects. In contrast, nicotine slowed RTs of the fast BP group across pro- and antisaccade targets presented to the left VF. As predicted, antisaccade RTs to negative targets in the left visual field (VF) were shortened more by nicotine than in any other VF by valence condition, but this effect was limited to the slow BP group. Support for the hypothesis that RT to right VF positive targets would be enhanced by nicotine more than left VF positive targets was supported only

in the slow BP group. Nicotine's effects on AST RTs were not moderated by the emotional valence of the prime pictures despite the fact that negative primes slowed RTs relative to neutral primes and tended to do so in the case of positive primes.

Importantly, our results replicate and extend the findings of Rycroft et al. (2007) who found that nicotine reduced RTs but not the number of errors in nonsmokers. In contrast, Petrovsky et al. (2012) found the nicotine reduced AST errors in low BP nonsmokers, but had no effect on RTs. The following discussion first addresses potential reasons for differences between our findings of Petrovsky et al.; it then addresses the baseline-dependent effects of nicotine on our affective valence manipulations in the AST.

Besides the use of emotional prime and target stimuli, the current study was different from previous ones in that it used nicotine patches that produce gradual rises in blood nicotine concentration and are very difficult or impossible for most subjects to identify as nicotine patches (Gilbert et al. 2003; Gilbert, Rabinovich et al. 2008). The nicotine patches used by Petrovsky et al. (2012) and most others in the field that are easily identified as containing nicotine by a great majority of subjects (Petrovsky et al. 2012). Equally important and unlike previous studies, the current investigation classified individuals into low, medium, and high-performance groups on a day prior to the two experimental sessions so that biases inherent in having randomly poor performance on the placebo day would not bias the findings via a regression towards to the individual subject's personal mean on the nicotine day relative to the placebo day. The full practice session prior to the two patch sessions was also used to minimize practice effects across the two patch days. This practice session likely led to a reduction in the number of antisaccade errors, something that may have led to a ceiling effect that minimized any ability of nicotine to reduce errors in our study. Rycroft et al. (2007) and others have found practice to lead to a reduction in errors in the AST.

Our finding that nicotine shortened RTs on antisaccade but not prosaccade trials is consistent with previous findings (Larrison et al. 2004; Petrovsky et al. 2012; Rycroft et al. 2007) and may reflect difficulty in the ability to inhibit the automatic (impulsive) prosaccade impulses (Pettiford et al. 2007). That is, the antisaccade condition required the use of executive control of prepotent eye-gaze responses while the prosaccade condition did not. This executive control hypothesis of nicotine's effects on performance is also supported by previous studies using tasks that require high levels of executive functioning. Specifically, nicotine enhances cognitive performance on many tasks in individuals with less than optimal (higher-level) performance to a greater extent than in those with optimal performance (Heishman et al. 1994, Heishman et al. 2010; Newhouse et al. 2004; Perkins 1999). The current and previous (Petrovsky et al. 2012) work suggests that baseline performance level is an important individual difference moderator of the effects of nicotine on AST RT and possibly on executive functioning during this task.

The slow BP group findings support the hypothesis that nicotine's greatest benefits would be for the right VF positive targets and for the left VF negative targets. This VF by target valence interaction of nicotine is consistent with previous findings, including research indicating that nicotine has lateralized effects on brain functioning (Gilbert 1995; Gilbert et al. 2005). It may be that the nicotine by valence interaction observed in low-baseline individuals reflects executive demands that differ as a function of hemisphere and emotional valence of target stimuli. It can be argued that the conditions that are most demanding of executive functioning are those that combine antisaccade emotional stimuli that are most attention-grabbing for the specific VF. This interpretation is based on evidence supporting the valence model of emotional processing (Dolcos et al. 2004; Gainotti 1972; Pizzagalli et al. 2003) that indicates that the left hemisphere is involved to a greater extent in the processing of positively valenced emotions and stimuli whereas the right hemisphere is

more associated with negatively valenced emotions and stimuli. Assuming that greater executive functioning is required to overcome more distracting stimuli, the greater benefits of nicotine in the case of more distracting conditions would be predicted, especially in those with poor executive functioning as assessed by poor baseline performance. However, it is important to note that some of the observed beneficial effects of nicotine, including the target-valence by VF interactions, may in part reflect bottom-up brain mechanisms previously observed to account for nicotine's modulation of some automatic attentional processes (Thiel and Fink 2008). Also, the medium BP-group pattern of nicotine benefits did not support our hypothesis that greater left VF effects would be observed for positive targets. Thus, replication of these findings in larger samples is critical before assuming the reliability of the presently observed pattern of baseline performance group-specific valence by visual field effects of nicotine. Finally, it should be noted that while we have interpreted our findings on the assumption that individual differences in baseline scores reflected differences in executive functioning capacity, factors other than executive competence may have contributed to or even fully accounted for the observed differences in baseline performance and the nicotine by baseline performance interaction.

Clinical relevance

These greater benefits of nicotine in individuals who were average or poor-performing (long-RT) during the practice day condition are consistent with the self-medication hypothesis of nicotine use (Eysenck 1973; Eysenck 1997; Perkins 1999). High baseline performers may rarely if ever benefit from nicotine and this could be one reason they never started smoking. High baseline performing individuals may have optimal psychobiological functioning during normal circumstance so that nicotine is incapable of enhancing their performance because of a ceiling effect. Consistent with this ceiling hypothesis, when stimuli were presented in the left VF of the high-performing group their RTs were lengthened by nicotine, relative to placebo. In contrast, individuals with average and low baseline performance benefitted from nicotine. That is, nicotine enhanced the executive functioning of those with suboptimal RTs during the AST, a task requiring the inhibition of prepotent responses. This outcome could provide empirical support for clinical interventions to prevent progression to nicotine dependence in individuals with low or average baseline executive functioning and/or ability to inhibit prepotent responses. It will be important to demonstrate that AST performance benefits of nicotine reliably predict control over other forms prepotent behavior, something suggested by the findings of Powell et al. (2004) in their study of relapse after quitting.

Study limitations

Study limitations include the modest sample size, the use of only young individuals with no known psychiatric disorders, and no tobacco or substance abusers. Future studies with larger numbers of participants as well as emotional prime and target stimuli ranging in degree of potency and arousal characteristics are needed to fully test the reliability and generalizability of the current findings. Because of the exploratory nature of this study and the modest sample size, controls for multiple comparisons of interactions involving nicotine were not used. However, it should be noted that a number of the effects involving group, visual field, and valence were highly significant and survive controls for multiple comparisons. The study also did not include self-reported measures of impulsivity or other behavioral measures of impulsivity. Other measures of cognitive control and other types of prepotent responses were not included. The addition of such tasks in future studies could help better characterize whether the benefits of nicotine in the AST in nonsmokers extend to other tasks and behaviors (Dawkins et al. 2007).

Conclusions

The current findings provide strong support for the baseline-dependency model of nicotine's effects on behavior (Perkins 1999) and less compelling evidence in support of the lateralized affective network model hypothesis of the broader Situation by Trait Adaptive Response (STAR) model (Gilbert 1997). The STAR model proposes that situational demands, hemispheric asymmetries in affective stimulus processing, and individual differences in executive capacity determine when and in whom nicotine will have beneficial effects. The finding that nicotine reduced RTs for negative stimuli presented to the RH in low baseline nonsmokers is also consistent with recent findings that nicotine can reduce attentional bias toward negative stimuli in nicotine-dependent smokers (Gilbert, Rabinovich et al. 2008). However, it is not clear why the medium BP group did not show this pattern of left VF (RH) sensitivity to negative targets. The most important and robust finding is that nicotine enhanced AST RT performance in slow and in average-baseline performance nonsmokers, but not in those with high baseline performance. It would be interesting to test the hypothesis that individual differences in lateralized emotional-AST performance benefits of nicotine predict smoking relapse and situations and affective states associated with relapse. Finally, it is important to note that the current findings demonstrating a lack of nicotine benefits (and actual left-VF decrements) in fast BP responders may not generalize to states of fatigue and other conditions that may temporarily reduce performance to suboptimal levels.

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References

- Asgaard GL, Gilbert DG, Malpass D, Sugai C, Dillon A. Nicotine primes attention to competing affective stimuli in the context of salient alternatives. *Exp Clin Psychopharmacol.* 2010; 18:51–60.10.1037/a0018516 [PubMed: 20158294]
- Carlson JM, Gilbert DG, Riise H, Rabinovich NE, Froeliger B, Sugai C. Serotonin transporter genotype and depressive symptoms moderate effects of nicotine on spatial working memory. *Exp Clin Psychopharmacol.* 2009; 17:173–180.10.1037/a0016384 [PubMed: 19586232]
- Davidson RJ. Anterior cerebral asymmetry and the nature of emotion. *Brain and Cognition.* 1992; 20:125–151.10.1016/0278-2626(92)90065-T [PubMed: 1389117]
- Dawkins L, Powell JH, West R, Powell J, Pickering A. A double-blind placebo-controlled experimental study of nicotine: II—Effects on response inhibition and executive functioning. *Psychopharmacology.* 2007; 190:457–467.10.1007/s00213-006-0634-6 [PubMed: 17205318]
- Dolcos F, LaBar KS, Cabeza R. Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: An event-related fMRI study. *Neuroimage.* 2004; 23:64–74.10.1016/j.neuroimage.2004.05.015 [PubMed: 15325353]
- Engelmann JM, Gewirtz JC, Cuthbert BN. Emotional reactivity to emotional and smoking cues during smoking abstinence: Potentiated startle and P300 suppression. *Psychophysiology.* 2011; 48:1656–1668.
- Eysenck, HJ. Personality and the maintenance of the smoking habit. In: Dunn, WL., editor. *Smoking behavior: Motives and incentives.* Washington DC: V. H. Winston; 1973. p. 113-146.
- Eysenck HJ. Addiction, personality and motivation. *Human Psychopharmacol.* 1997; 12:S79–S97.10.1002/(SICI)1099-1077(199706)12:2+3.0.CO;2-T
- Ekman, P.; Friesen, WV. *Manual for the Facial Action Coding System.* Palo Alto: Consulting Psychologists Press; 1977.

- Gainotti G. Emotional behavior and hemispheric side of the lesion. *Cortex*. 1972; 8:41–55. [PubMed: 5031258]
- Gilbert, DG. Smoking: Individual differences, psychopathology and emotion. Washington, DC: Taylor and Francis; 1995.
- Gilbert DG. The situation x trait adaptive response (STAR) model of substance use and craving. *Human Psychopharmacol*. 1997; 12:S89–S102.10.1002/(SICI)1099-1077(199706)12:2+3.0.CO;2-P
- Gilbert DG, Carlson JM, Riise H, Rabinovich NE, Sugai C, Froeliger B. Effects of nicotine and depressive traits on affective priming of lateralized emotional word identification. *Exp Clin Psychopharmacol*. 2008; 16:293–300.10.1037/a0012871 [PubMed: 18729683]
- Gilbert DG, Izetelny A, Radtke R, Hammersley J, Rabinovich NE, Jameson TR, Huggenvik JI. Dopamine receptor (DRD2) genotype-dependent effects of nicotine on attention and distraction during rapid visual information processing. *Nicotine Tob Res*. 2005; 7:361–379.10.1080/14622200500125245 [PubMed: 16085504]
- Gilbert DG, McClernon FJ, Rabinovich NE, Sugai C, Plath LC, Asgaard G, Zuo Y, Huggenvik J, Botros N. Effects of quitting smoking on EEG activation and attention last for more than 31 days and are more severe with stress, dependence, DRD2 A1 allele, and depressive traits. *Nicotine Tob Res*. 2004; 6:249–267.10.1080/14622200410001676305 [PubMed: 15203798]
- Gilbert, DG.; Rabinovich, NE.; Rosenberger, S. Effects of Fast and Slow Blood-Rise Nicotine Patches on Nausea and Feeling States in Nonsmokers. Poster presented at the Ninth Annual Scientific Sessions of the Society for Research on Nicotine; New Orleans, LA. 2003.
- Gilbert DG, Robinson JH, Chamberlin CL, Spielberger CD. Effects of smoking/nicotine on anxiety, heart rate, and lateralization of EEG during a stressful movie. *Psychophysiology*. 1989; 26:311–320.10.1111/j.1469-8986.1989.tb01924.x [PubMed: 2756080]
- Gilbert DG, Sharpe JP, Ramanaiah NV, Detwiler FRJ, Anderson AE. Development of a Situation x Trait Adaptive Response (STAR) model-based smoking motivation questionnaire. *Personality and Individual Differences*. 2000; 29:65–84.10.1016/S0191-8869(99)00178-6
- Gilbert DG, Sugai C, Zuo Y, Rabinovich NE, McClernon FJ, Froeliger B. Brain indices of nicotine's effects on attentional bias to smoking and emotional pictures and to task-relevant targets. *Nicotine Tob Res*. 2007; 9:351–363.10.1080/14622200701188810 [PubMed: 17365767]
- Gilbert DG, Rabinovich NE, Malpass D, Mrnak J, Riise H, Adams L, Sugai C, DevlescHoward M. Effects of nicotine on affect are moderated by stressor proximity and frequency, positive alternatives, and smoker status. *Nicotine Tob Res*. 2008; 10:1171–1183.10.1080/14622200802163092 [PubMed: 18629727]
- Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology*. 2010; 210:453–469.10.1007/s00213-010-1848-1 [PubMed: 20414766]
- Heishman SJ, Taylor RC, Henningfield JE. Nicotine and smoking: A review of the effects on human performance. *Exp Clin Psychopharmacol*. 1994; 2:345–395.10.1037/1064-1297.2.4.345
- Lang, PJ.; Bradly, MM.; Cuthbert, BN. International Affective Picture System (IAPS): Technical Manual and Affective Ratings. NIMH Center for the Study of Emotion and Attention; 1995.
- Larrison AL, Briand KA, Sereno AB. Nicotine improves antisaccade task performance without affecting prosaccades. *Human Psychopharmacol*. 2004; 19:409–419.10.1002/hup.604
- Newhouse PA, Potter A, Singh A. Effects of nicotinic stimulation on cognitive performance. *Current Opinion in Pharmacology*. 2004; 4:36–46.10.1016/j.physletb.2003.10.071 [PubMed: 15018837]
- Perkins KA. Baseline-dependency of nicotine effects: A review. *Behav Pharmacol*. 1999; 10:597–615. [PubMed: 10780501]
- Perkins KA, Gerlach D, Broge M, Grobe JE, Wilson A. Greater sensitivity to subjective effects of nicotine in nonsmokers high in sensation seeking. *Exp Clin Psychopharmacol*. 2000; 8:462–471.10.1037/1064-1297.8.4.462 [PubMed: 11127418]
- Pettiford J, Kozink RV, Lutz AM, Kollins SH, Rose JE, McClernon FJ. Increases in impulsivity following smoking abstinence are related to baseline nicotine intake and boredom susceptibility. *Addict Behav*. 2007; 32:2351–2357.10.1016/j.addbeh.2007.02.004 [PubMed: 17399907]

- Pevtrosky N, Ettinger U, Quednow BB, Walter H, Schnell K, Kessler H, Mössner R, Maier W, Wagner M. Nicotine differentially modulates antisaccade performance in healthy male non-smoking volunteers stratified for low and high accuracy. *Psychopharmacology*. 2012; 221:27–38.10.1007/s00213-011-2540-9 [PubMed: 22038536]
- Pierrot-Deseilligny C, Müri RM, Ploner CJ, Gaymard B, Demeret S, Rivaud-Pechoux S. Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. *Brain*. 2003; 126:1460–1473.10.1093/brain/awg148 [PubMed: 12764065]
- Pizzagalli, D.; Shackman, AJ.; Davidson, RJ. The functional neuroimaging of human emotion: Asymmetric contributions of cortical and subcortical circuitry. In: Hugdahl, K.; Davidson, RJ., editors. *The asymmetrical brain*. MIT Press; Cambridge MA: 2003. p. 511-532.
- Powell JH, Pickering AD, Dawkins L, West R, Powell JF. Cognitive and psychological correlates of smoking abstinence, and predictors of successful cessation. *Addictive Behaviors*. 2004; 29:1407–1426. [PubMed: 15345273]
- Rose JE, Behm FM, Westman EC, Mathew RJ, London ED, Hawk TC, Turkington TG, Coleman RE. PET studies of the influences of nicotine on neural systems in cigarette smokers. *Am J Psychiatry*. 2003; 160:323–333. [PubMed: 12562580]
- Rycroft N, Hutton SB, Clowry O, Groomsbridge C, Sierakowski A, Rusted JM. Non-cholinergic modulation of antisaccade performance: a modafinil-nicotine comparison. *Psychopharmacology*. 2007; 195:245–253.10.1007/s00213-007-0885-x [PubMed: 17676402]
- Smith SD, Bulman-Fleming MB. An examination of the right-hemisphere hypothesis of the lateralization of emotion. *Brain Cog*. 2005; 57:210–213.10.1016/j.bandc.2004.08.046
- Spielberger, CD. Psychological determinants of smoking behavior. In: Tollison, RD., editor. *Smoking and society: Toward a more balanced assessment*. DC Heath; Lexington MA: 1986. p. 89-134.
- Tabibnia G, Monterosso JR, Baicy K, Aron AR, Poldrack RA, Chakrapani S, Lee B, London ED. Different forms of self-control share a neurocognitive substrate. *J Neurosci*. 2011; 31:4805–4810.10.1523/JNEUROSCI.2859-10.201 [PubMed: 21451018]
- Thiel CM, Fink GR. Effects of the cholinergic agonist nicotine on reorienting of visual spatial attention and top-down attentional control. *Cog Neurosci*. 2008; 152:381–390.10.1016/j.neuroscience.2007.10.061

Fig. 1.
Stimulus sequence during the antisaccade and prosaccade conditions.

Fig. 2.

Effects of nicotine on RT as a function of saccade type (anti vs. pro). Nicotine reduced RT in the antisaccade, but not prosaccade trials. $*p < .001$.

Fig. 3.

Effects of baseline target valence, VF and performance group on nicotine benefits (placebo RT – nicotine RT). Asterisks refer to within-subjects analyses of placebo RT – nicotine RT for each condition ($*p < .05$; $**p < .01$; $***p < .005$). Significant differences in nicotine benefits between three baseline performance groups are depicted by similar letters (upper case letters = $p < .005$, lower case $p < .05$).