Psychopharmacology
DOI 10.1007/s00213-009-1571-y

ORIGINAL INVESTIGATION

Effects of nicotine on novelty detection and memory recognition performance: double-blind, placebo-controlled studies of smokers and nonsmokers

Brett Froeliger · David G. Gilbert · F. Joseph McClernon

Received: 15 December 2008 / Accepted: 8 May 2009

Abstract
Rationale Dependent smokers exhibit deficits in attentional and memory processes when smoking abstinent as compared to when satiated. While nicotine replacement therapy improves attention during abstinence, it is unclear whether this is due to the alleviation of withdrawal-related deficits or inherent beneficial effects of nicotine.
Objectives The primary aim of these studies was to test whether nicotine exerts a beneficial effect on novelty detection and whether such effects occur in nonsmokers as well as habitual smokers.
Materials and methods In two parallel, double-blind, placebo-controlled studies, 24 smokers (study 1) and 24 nonsmokers (study 2) were tested in two counterbalanced sessions: once while wearing a nicotine patch (smokers= 14 mg; nonsmokers=7 mg) and once while wearing a placebo patch. On each day, participants performed three content-specific oddball tasks (perceptual, semantic, and emotional) that required them to press a button whenever they saw a novel target (20% of stimuli) embedded in a stream of common nontarget stimuli (80% of stimuli). Recognition memory for targets was subsequently tested. Reports of mood, smoking withdrawal, patch side effects, and blind success were collected in each session.
Results Among smokers, compared to placebo, nicotine decreased target reaction time during all oddball tasks. Among nonsmokers, nicotine increased target detection accuracy and subsequent memory recognition. Nicotine's enhancement on each respective measure was not task-content specific in either sample.
Conclusions These data suggest that acute nicotine administration may exert direct beneficial effects on novelty detection and subsequent memory recognition in both smokers and nonsmokers. Moreover, these effects are not content-specific.

Keywords Nicotine · Smoking · Nonsmoker · Smoker · Novelty · Memory · Cognition · Dopaminergic · Human

B. Froeliger (✉) · F. J. McClernon
Department of Psychiatry and Behavioral Sciences,
Duke University Medical Center,
Box 2701, Durham, NC 27708, USA
e-mail: brett.froeliger@duke.edu

B. Froeliger · D. G. Gilbert
Psychology Department,
Southern Illinois University—Carbondale,
Carbondale, IL, USA

Introduction

Smokers report that one of their primary reasons for continuing to smoke is because smoking improves cognition and abstinence worsens it (Gilbert et al. 2000; Spielberger 1986). While nicotine may produce improvements in cognition in habitual users (Heishman et al. 1994; Levin et al. 2006; Warburton et al. 2001), it remains inconclusive whether these observed benefits are merely due to the attenuation of withdrawal-related deficits or are due to direct, beneficial effects on cognition (Heishman 1998; Waters and Sutton 2000).

Effects of nicotine on attention

Nicotine may improve a variety of cognitive processes among smokers including visual attention (Lawrence et al. 2002), associative processes (Rusted et al. 1998), arousal and vigilance (Gilbert et al. 2004; Knott et al. 1999), memory (Foulds et al. 1996; Warburton et al. 2001), and affective information processing (Gilbert et al. 2000, 2007,

Published online: 02 June 2009

2008). With regard to attention in particular, smokers generally perform better on a variety of attentional tasks following nicotine administration as compared to when deprived (Gilbert et al. 2004; Houlihan et al. 1996; Knott et al. 1999; Thiel and Fink 2008). In nonsmokers, however, the effects of nicotine on attention are less clear. Some studies with nonsmokers have found that nicotine enhances task performance (Ernst et al. 2001; Foulds et al. 1996; Kumari et al. 2003; Wesnes and Warburton 1984), others report no differences (Heishman et al. 1993; Kleykamp et al. 2005), and yet others have reported performance decrements or negative effects of nicotine (Ernst et al. 2001; Foulds et al. 1996, 1997)

The inconsistent findings in nonsmokers are difficult to interpret and require careful consideration of the various ways in which the effects of nicotine have been studied (Waters and Sutton 2000). Two particular issues require consideration when testing for direct effects of nicotine upon attention. First, the dosage amount and delivery method of nicotine to nonsmokers have varied considerably across studies. Studies of the effects of nicotine on nonsmokers have, for instance, used nicotine patch doses ranging from 3.5 to 21 mg. At high doses, acute administration may produce negative side effects in nicotine-naive subjects and attenuate any putative benefits (Gilbert et al. 2003; Srivastava et al. 1991). Second, the general construct of attention is complex and represents multiple different systems and subsystems that carry out different yet interrelated functions (Posner and Petersen 1990). Differential outcomes across studies of attention, therefore, may be related to the particular attentional processes (e.g., automatic vs. strategic) that are being tested across different sensory modalities (e.g., visual, auditory) and in different cognitive processing domains (e.g., perceptual, associative). Therefore, if nicotine directly affects attention, its effects may be both dosage dependent and specific to different types or aspects of attention. The current study sought to address these two issues by delivering nicotine to nonsmokers and smokers in a manner that reduces the potential for negative effects of nicotine and also focuses on a single, specific attentional process—novelty detection for visual verbal stimuli blocked into three distinct content specific domains.

Novelty detection

Novelty detection is a fundamental attentional process that underlies both learning and memory (Ranganath and Rainer 2003; Sokolov 1963). Nicotine has been shown to enhance attention as well as facilitate learning and memory in both animals and humans (Levin et al. 2006). However, the investigation into the effects of nicotine on novelty detection has received relatively little attention and no attention at all in the case of nonsmokers.

A stimulus that is new, different, or unfamiliar in some way is considered novel. Orienting to novel stimuli in the environment—or novelty detection—is a process that automatically directs attention and allows an organism to learn new information and facilitates memory (Ranganath and Rainer 2003; Sokolov 1963; Sutton et al. 1965, 1967). The orienting response to novel stimuli includes both an autonomic (Hunt and Campbell 1997) and a motor component (Holland 1977). As such, the orienting response results in changes in physiological (e.g., decreased heart rate, potentiated P300 ERP) and behavioral responses [e.g., faster reaction time (RT), better memory for novel item] (Ranganath and Rainer 2003).

One form of novelty, contextual novelty, arises when a stimulus occurs within an unexpected context. Contextual novelty allows an organism to automatically increase attentional resources to salient stimuli and results in greater encoding of and subsequent memory for biologically relevant stimuli in the environment (Sokolov 1963). The oddball paradigm has been commonly used to investigate contextual novelty detection in the laboratory (Huettel and McCarthy 2004). In general, these tasks involve the random presentation of low frequency of "oddball" targets (e.g. 20% of trials) amidst higher frequency, "common" stimuli (e.g., 80% of trials). Compared to common stimuli, oddball targets are associated with higher amplitude electrocortical responses (Sutton et al. 1965), decreased heart rate, decreased RT (Andreassi 2000), and increased blood oxygen level-dependent signal in dorsolateral prefrontal cortex (PFC; Strange et al. 2000). Furthermore, stimuli encoded as contextually novel as compared to familiar stimuli are better remembered during subsequent recognition memory tasks (Tulving and Kroll 1995), which is consistent with the hypothesis that novelty is believed to be a prerequisite for successful encoding of information (Tulving et al. 1994, 1996).

Effects of nicotine on memory

The hippocampal formation is known to be a critical brain region in learning new information and facilitating storage of that information into long-term memory (Scoville and Milner 1957; Squire 1992; Tulving 1992). Nicotine facilitates synaptic activity in the hippocampus of rats (Gray et al. 1996) as well as increases long-term potentiation in the dentate gyrus of the hippocampal formation. Furthermore, nicotine has been shown to enhance working memory in both humans (McClernon et al. 2003) and in animals (Levin and Christopher 2002; Levin et al. 1997, 2006) and particular long-term memory processes in both healthy smokers and nonsmokers (Foulds et al. 1996; Rusted et al. 1995; Rusted and Trawley 2006). The extant literature has begun to demonstrate nicotine's effects on

long-term memory and the importance of novelty detection in successful long-term recognition memory; however, relatively little is known regarding the effects of nicotine on novelty detection and the resulting influence upon recognition memory.

Goals and hypotheses

The purpose of this study was to evaluate the effects of transdermal nicotine on novelty detection in abstinent smokers (14 mg Nicoderm) and nonsmokers (7 mg Habitrol). Two studies, each utilizing the same experimental design, were conducted concurrently, one with dependent smokers (study 1) and one with nonsmokers (study 2). In a double-blind, counterbalanced order, participants in each study were tested during two sessions, once while wearing a nicotine patch and once while wearing a placebo patch. During each session participants performed three content-specific oddball tasks (perceptual, semantic, and emotional). In addition to novelty detection, the effect of nicotine on subsequent recognition of novel targets was also evaluated as were the effects of nicotine on mood, withdrawal symptoms (smokers only), and patch side effects. Each of the two studies evaluated whether nicotine enhanced novelty detection (i.e., decreased RT, improved accuracy), subsequent recognition memory, and whether these effects were content specific.

Given prior findings that nicotine administration improves attention in abstinent smokers and may potentially improve specific attentional functions in nonsmokers, it was hypothesized that task performance in both smokers and nonsmokers would improve on all oddball tasks while on nicotine as compared to placebo patch. Given that nicotine was hypothesized to enhance attention to novel items and that novel stimuli are bettered remembered than their familiar counterparts, we hypothesized that novel targets would be later recognized at a higher rate during nicotine as compared to placebo patch condition.

Methods

Participants

Participants were 24 smokers and 24 nonsmokers recruited from the surrounding community (see Table 1). Eligibility requirements common to both studies included the following: generally healthy, right handed, having 20/20 vision with corrective lenses, between the ages of 18 and 45, a history free of neurological problems, drug abuse, seizures, or learning disabilities, native English speaker, and—if female—not pregnant. Smokers had to have an expired CO≥10 ppm at screening, report smoking at least ten cigarettes per day continuously for ≥1 year, and without a quit attempt in the last year. Nonsmokers had to have smoked <100 cigarettes in their lifetime and none within the last 12 months. Participants in both studies read and signed an Institutional Review Board approved informed consent form and were paid $75 for completing the study.

Procedure

Each study comprised one orientation/training session in which participants practiced the experimental tasks and two experimental sessions. At the beginning of each experimental session (8:00–9:00 A.M.), overnight smoking abstinence was biochemically verified (among smokers) by expired breath CO concentrations with a MiniCO7 meter (Catalyst Research Corporation, Owings Mills, MD), using a cutoff of ≤10 ppm. Following abstinence verification, smokers received either a 14-mg transdermal nicotine (Nicoderm®) or identically appearing placebo patch. Nonsmokers received either a 7-mg nicotine (Habitrol®) or a placebo patch. For nonsmokers, in order to avoid nausea and other adverse effects of rapidly rising nicotine, we used a 7-mg Habitrol® patch that has a slower blood nicotine rise profile than the Nicoderm® patch (Gupta et al. 1995). The nonsmoker placebo patch was a 5× 5 cm bandage. In order

Table 1 Subject demographics

	Nonsmoker group (*N*=24)	Smoking group (*N*=24)
Percent female	50%	50%
Mean age (SD)	23.9 (7.1)	21.5 (3.3)
Years of education (SD)	14 (1.4)	13.6 (1.2)
Years smoking (SD)	–	5 (2.7)
Average daily number of cigarettes (SD)	–	16.7 (4.1)
Race		
Asians	–	1
Blacks	6	4
Caucasians	16	18
Hispanics	–	1
Multirace	2	–

to minimize the ability of participants to differentiate active and placebo patches by skin sensations (itching or irritation), we used a cover bandage with capsaicin cream. Both the active and placebo patches were placed in the center of a 6.5× 7.0 cm cover bandage. Then, 0.05 cc of capsaicin, 75% cream (Capzasin-HP7, Chattem, Inc), was applied to the Teflon-coated surface of the cover bandage, covering an area 5-mm wide immediately next to each of the edges of the bandage. The patch was placed on the upper arm of participants. Patch order was counterbalanced in both studies. Participants were allowed to leave the laboratory to conduct their daily activities and were encouraged to consume their typical quantity and type of food and caffeinated beverages. Approximately 8 h post-patch application, participants returned to the laboratory and filled out questionnaires regarding their food and beverage intake and self-report mood questionnaires; smokers were biochemically verified for smoking abstinence, and then they completed three content specific oddball tasks and three subsequent recognition memory tasks. The 8-h delay period between patch application and cognitive testing was used because both patches would have produced their maximal dose at approximately this time (Gupta et al. 1993). A minimum of 1 day and maximum of 10 days separated the two experimental sessions. The experimenters conducting the experimental sessions were not involved in the patch assignment order, patch placement, or patch removal.

Self-report side effects and mood

Self-report side effects and mood were measured using the following scales. A side effects scale measured commonly reported effects of transdermal nicotine exposure including nausea and light-headedness. Each side effect was rated on an 11-point scale from "0" to "10". For reporting purposes, side effects rated as greater than 5 were considered significant. Mood was measured using the 20-item positive and negative affect schedule (Watson et al. 1988). This measure results in two orthogonal scales—positive affect (e.g., attentive, proud) and negative affect (e.g., distressed, angry). Participants were asked at the end of each experimental session to indicate which patch they perceived was administered to them on that given day.

Experimental tasks

The experimental tasks were three oddball tasks that differed only by content (emotional, perceptual, and semantic), each followed by a subsequent memory recognition task. Task order was randomly presented and counterbalanced across subjects, experimental days, patch, and gender. Each task was presented using E-Prime® software, and responses were collected using an E-Prime® serial response box.

Oddball tasks During each of the three oddball tasks, participants saw 200 words presented one at a time in the center of an LCD display (duration = 1,000 ms, ISI = 600 ms). In each oddball task, 160 (80%) of the word stimuli were standards, while 40 (20%) were oddballs. In each of the three oddball tasks, standard stimuli were all emotionally neutral, presented in standard Arial font, and referred to something nonliving. Oddballs were randomly dispersed among standards and were deviant only in their single respective category (e.g., perceptual oddball deviated from standards by being presented in italic font, but were otherwise similar—nonliving referent and emotionally neutral). In the perceptual oddball task, standards were words displayed in standard Arial font (e.g., HOUSE) while oddballs were words displayed in italic Arial font (e.g., *BRICK*). In the semantic oddball task, standards were non-living referents (e.g., PIANO), while oddballs were living referents (e.g., JANITOR). In the emotional oddball task, standards were emotionally neutral (e.g., COMBINE), while the oddballs contained positive or negative emotional valence (e.g., CHARMING, HUMILIATED). At the beginning of each task, participants were informed of the upcoming oddball category and were instructed to provide an accurate and fast key press upon oddball detection.

Stimuli Stimuli consisted of 1,400 words—100 emotionally positive, 100 emotionally negative, and 1,200 emotionally neutral. Emotional word stimuli were selected from the affective norms for English words (ANEW) (Bradley and Lang 1999). Words were matched for concreteness (350–700), familiarity (350–700), and frequency (>1) (Kucera and Francis 1967) in the English language as reported in the MRC Psycholinguistic Database. All words were controlled for the numbers of letters (three to nine) and syllables (one to three). Word types were confined to adjectives, nouns, and verbs. Each word was presented to a participant only once during oddball tasks over the entire study in order to avoid confounding habituation effects from repeated exposure.

Each oddball task resulted in measures of accuracy (proportion of oddballs detected), standard error of accuracy (estimated SD of the error), and median RT. Only RTs to targets were included in the analyses, and those <200 ms were excluded. Participant median RT was used in order to reduce the influence of outlying RTs on the measure of central tendency that may be produced by patch, smoking group, or an interaction between patch and smoking group. The distribution of median RTs was positively skewed and was therefore log10 transformed prior to statistical analyses on the group mean of the individual median scores.

Recognition memory task Directly following each oddball task, participants were administered a recognition memory task in which the 40 previously viewed oddballs and 40 matched foils were presented in random order on an LCD display (duration=1,000 ms, ISI=600 ms). The presentation of the stimuli (targets and foils) was in the same format that was presented to the participant during the respective oddball task (e.g., perceptual task, target-*ROCK* and foil-*HOUSE*). Participants were instructed to press a designated key if they recognized seeing the word during the previous task and to not respond to new or uncertain items. Recognition memory performance was computed as the proportion correct derived from corrected recognition (hits–false alarms).

Statistical procedures

Parallel data sets were acquired from a smoker (study 1) and a nonsmoker (study 2) sample. Given the fundamental group differences in nicotine exposure and the use of different patches, the results from each group were analyzed separately and are reported as two independent studies. In each study, mood and side effect data were analyzed in a one-way (patch, nicotine and placebo) within-subjects repeated measures analysis of variance (ANOVA). Cognitive performance variables were analyzed in a 2 (patch—nicotine and placebo)×3 (task—perceptual, semantic, and emotional) within-subjects repeated measures ANOVA. The performance variables analyzed in the oddball tasks included RT to correct detections and target accuracy as measured by proportion correctly detected. The performance variable analyzed in the recognition memory tasks was a proportion of corrected recognition (e.g., correct target recognition–false alarms). A statistical threshold of $p < 0.05$ was used for all analyses.

Results

Study 1: Smoker sample

Blind Smokers were not able to identify at a rate better than chance which patch they were administered at visit one [χ^2 (1, N=24)=1.87, p=0.17] but were able to correctly identify the patch at visit two, [χ^2 (1, N=24)=4.37, p=0.04].

Biochemical verification Morning and pre-testing CO levels are presented in Table 2. Smokers were compliant with instructions to not smoke overnight as evidenced by CO levels ≤10 ppm.

Table 2 Results of statistical analyses for outcome measures for smokers

Measure	Placebo (0mg)		Nicotine (7mg)		Statistical analyses				
	Mean	SD	Mean	SD	Measure	Effects	F	Sig.	Partial η^2
Cognitive									
Accuracy[a]									
Perceptual	0.92	0.13	0.94	0.11	Accuracy	Patch	$F(1,23)=3.3$	$p=0.08$	0.126
Semantic	0.87	0.1	0.875	0.07		Task	$F(2,22)=19$	$p<$ 0.000	0.634
Emotional	0.72	0.15	0.782	0.12		Patch×task	$F(2,22)=2.3$	$p=0.12$	0.17
RT	676.63	13.01	651.01	11.4					
Perceptual	579.53	13.47	552.53	12.34	RT	Patch	$F(1,23)=9.7$	$p=0.005$	0.297
Semantic	686.39	15.15	670	14.11		Task	$F(2,22)=83.47$	$p<$ 0.000	0.884
Emotional	763.99	17.8	730.48	15.87		Patch×task	$F(2,22)=1.2$	$p=$ 0.334	0.095
Recognition[a]	0.45	0.028	0.46	0.026					
Perceptual	0.27	0.13	0.28	0.13	Recognition	Patch	$F(1,23)=0.52$	$p=0.478$	0.022
Semantic	0.63	0.18	0.63	0.18		Task	$F(2,22)=75.99$	$p<$ 0.000	0.874
Emotional	0.46	0.17	0.49	0.14		Patch×task	$F(2,22)=0.24$	$p=0.79$	0.021
Subjective									
Positive effect	16.71	2.14	19.17	2.63					
Negative effect	8.35	1.36	4.75	0.99					
Light-headed	0.42	0.31	0.46	0.3					
Nauseated	0.38	0.3	0.21	0.13					
Morning CO	8.08	0.78	7.04	0.87					
Pre-test CO	4.37	2.19	3.63	2.36					

[a] Proportion correct

Side effects, mood, and withdrawal symptoms Smokers reported greater negative affect on the placebo day, $F(1,23)=7.45$, $p=0.012$, partial $\eta^2=0.245$. No other statistical differences on these measures were observed (Table 2).

Cognitive performance Mean proportion and standard error of accuracy, mean of median RT, corrected recognition accuracy, and statistic summaries for the smoking sample are presented in Table 2. Main effects of task were observed for all performance measures. With respect to patch effects, smokers were faster in the nicotine as compared to the placebo condition. Likewise, there was a trend for greater oddball target detection accuracy in the nicotine condition. No significant effect of nicotine condition on memory recognition was observed. No patch×task interactions were observed for any measures.

Study 2: Non-smoker sample

Blind Nonsmokers were not able to identify at a rate better than chance which patch they were administered at the first [χ^2 (1, N = 24)=0.229, $p=0.63$] or second visit [χ^2 (1, $N=24$)=0.02, $p=0.88$].

Side effects and mood No effects of patch were observed (Table 3).

Cognitive performance Mean and standard error of accuracy, mean of median RT, corrected recognition accuracy, and statistic summaries for the non-smoker sample are presented in Table 3. Main effects of task were observed for all measures. With respect to patch effects, nicotine significantly increased oddball target detection accuracy. Nonsmokers demonstrated a trend for faster RTs in the nicotine as compared to the placebo condition. Nicotine also significantly increased subsequent memory recognition. No patch× task interactions were observed.

Discussion

In the present study, we evaluated the effects of transdermal nicotine on novelty detection and recognition memory in separate studies of smokers and nonsmokers. The results from each study are discussed separately below, followed by a discussion on the potential mechanisms underlying the effects observed in both.

Study 1: Smoker sample

Abstinent smokers had significantly shorter RTs (faster responses) to novel oddball targets during the nicotine as compared to placebo patch condition—an effect consistent with prior findings of nicotine's effect on motor response

Table 3 Results of statistical analyses for outcome measures for nonsmokers

	Placebo (0mg)		Nicotine (7mg)		Statistical Analyses				
Measure	Mean	SD	Mean	SD	Measure	Effects	F	Sig	partial η^2
Cognitive									
Accuracy[a]									
Perceptual	0.91	0.15	0.94	0.12	Accuracy	Patch	$F(1,23)=18.8$,	$p<0.000$	0.45
Semantic	0.87	0.09	0.91	0.08		Task	$F(2,22)=9.2$	$p=0.001$	0.455
Emotional	0.76	0.14	0.83	0.12		Patch×task	$F(2,22)=.8$	$p>0.1$	
RT	669.22	12.61	651.94	12.94					
Perceptual	575.73	15.18	568.28	15.07	RT	Patch	$F(1,23)=4$	$p=0.056$	0.149
Semantic	679.10	14.74	659.46	14.83		Task	$F(2,22)=79.7$	$p<0.000$	0.879
Emotional	752.83	14.57	728.06	15.78		Patch×task	$F(2,22)=.4$	$p>0.5$	
Recognition[a]									
Perceptual	0.28	0.17	0.35	0.19	Recognition	Patch	$F(1,23)=7.26$	$p=0.013$	0.24
Semantic	0.60	0.16	0.67	0.14		Task	$F(2,22)=37.3$	$p<0.000$	0.772
Emotional	0.54	0.14	0.59	0.12		Patch×task	$F(2,22)=.09$	$p>0.9$	
Subjective									
Positive effect	23.41	1.84	24.44	2					
Negative effect	1.5	0.47	1.83	0.5					
Light-headed	0.04	0.04	0.35	0.23					
Nauseated	0	0	0.35	0.21					

[a] Proportion correct

(Ernst et al. 2001; Houlihan et al. 1996). These findings expand on previous studies by providing evidence that among smokers, nicotine (1) enhances the speed for detecting novel stimuli and (2) enhancement in RT is independent of the content of the novel stimuli. Given that smoking abstinence, relative to satiety, results in worse attention, increased drowsiness, and slowed cortical activity (Gilbert et al. 2004; Knott et al. 1999), the observed effect of nicotine on RT may potentially reflect a reversal of withdrawal-related decrements in attention and alertness.

Study 2: Nonsmoker sample

In study 2, nonsmokers detected significantly more novel oddball targets across task content categories during nicotine as compared to placebo patch condition. A trend toward significance was observed for shorter (faster) RTs during nicotine as compared to placebo patch condition. These findings are consistent with previous studies, which have observed improvements in cognitive performance by nicotine among nonsmokers (Ernst et al. 2001; Foulds et al. 1996; Kumari et al. 2003) but also builds upon the extant literature by demonstrating that these effects extend to novelty detection.

In addition to improvements in novelty detection, nonsmokers also correctly recognized more previously seen targets during a delayed recognition task during nicotine as compared to placebo patch condition. Novel stimuli garner more attention and are better remembered than their familiar counterparts (Ranganath and Rainer 2003; Sokolov 1963; Tulving and Kroll 1995). Thus, the present findings potentially suggest that nicotine improved attention to novel stimuli (as evidenced by improved accuracy), which subsequently also improved recognition memory.

The findings among nonsmokers suggest that nicotine produces a direct enhancing effect on novelty detection accuracy and subsequent memory recognition of previously novel encoded stimuli in these individuals. These main effects of nicotine were not specific to the content (e.g., perceptual, semantic, and emotional) of the novel stimuli.

Potential mechanism The effects of nicotine observed in each study suggest that nicotine may modulate novelty detection via a deviance detection system subserved at the cortical level in the PFC. A recent brain imaging study utilizing a similar task design and a healthy control sample (Strange et al. 2000) reported right PFC to be commonly activated across oddball categories. Consistent with this, frontal lobe damage patients display attenuated electrocortical responses and behavioral deficits when detecting novel targets (Daffner et al. 2000). Moreover, PFC has direct and indirect connectivity with midbrain dopamine (DA) neurons, which also play an important role in novelty detection and learning. Both animal (Lee et al. 2006) and human (Bunzeck and Duzel 2006) studies have shown that midbrain DA neurons become activated while processing novel stimuli in the absence of any reinforcement. Furthermore, anticipating novelty activates midbrain DA and enhances subsequent memory for the novel stimuli (Wittmann et al. 2007).

Based on the current findings, we hypothesize the effects of nicotine on novelty detection may be due to modulation of the relationship between midbrain and PFC DA neurons. Nicotine stimulates the release of midbrain DA (Corrigall et al. 1992) but, with continual exposure, leads to desensitization of these neurons (Pidoplichko et al. 1997). Nicotine's modulation of midbrain DA transmission may potentially tune the DA neurons that code for novelty. The desensitization of DA neurons with repeated nicotine exposure may explain the differential behavioral effects between smokers and nonsmokers. A smoker's history with repeated tobacco use may explain why motor preparedness was possibly reinstated, but higher order cognitive effects (i.e. accuracy and recognition) were not observed. Further research that is better equipped to address this hypothesis is required.

Subjective effects of nicotine

Study 1: Smoker sample

In smokers, a significant increase in negative affect was observed while wearing the placebo as compared to the nicotine patch. This is an expected effect since irritability and negative affect are commonly reported smoking withdrawal symptoms. Smokers were unable to detect at a rate better than chance which patch they were on during their first visit. However, they were able to significantly correctly identify which patch they had received on their second visit. By the time that smokers indicated on the second visit which patch they thought they had received on that day, they likely compared how they were feeling with how they had felt while wearing the other patch on the first day.

Study 2: Nonsmoker sample

In nonsmokers, no significant differences in subjective ratings of positive or negative effect or patch-related side effects were observed due to patch condition. Furthermore, nonsmokers were unable to detect at a rate better than chance which patch they had received during either experimental day.

Limitations and future directions While nicotine patch produced significant RT changes in the smoker group, the

current study was not designed to investigate the mechanisms underlying this effect. For example, it is unclear whether improvement in task performance while on nicotine patch resulted from alleviation of withdrawal related cognitive impairments or if nicotine patch provided an improvement to baseline cognitive functions in smokers. Future studies will address this question more directly by comparing smoking as usual with different mechanisms of nicotine delivery (e.g., transdermal, gum, nasal) and abstinence. Furthermore, future studies manipulating nicotine dosage may provide valuable insight on the amount of nicotine that produces maximal effects on novelty detection.

The subsequent memory recognition paradigm implemented in the current study leaves many questions unanswered. In particular, it is not clear whether nicotine directly enhanced memory retrieval processes or if nicotine's enhancement of attentional processes resulted in a deeper level of encoding of the novel stimuli. Future studies may better address this issue by blocking the task phase (encoding vs. retrieval) with nicotine administration. More specifically, nicotine may be administered prior to encoding or retrieval. This latter condition isolates nicotine's putative effects on memory retrieval processes and is independent of any modulatory influence during encoding. Furthermore, future studies should also consider evaluating nicotine's effects on different forms of long term memory (e.g., semantic, episodic) under different retrieval strategies (e.g., recall, recognition).

Future studies investing putative direct effects of nicotine on cognition may benefit from including physiological measure of arousal (e.g., heart rate, skin conductance) during cognitive testing. Moreover, brain imaging techniques (e.g., functional magnetic resonance imaging) can provide further insight into nicotine's effects on specific brain structures and networks that subserve specific cognitive functions. Additional research examining the relationship between nicotine and DA in the midbrain and PFC are needed.

Summary The results of these studies suggest that acute nicotine may enhance novelty detection independent of the content being encoded. Acute nicotine improved RT performance in smokers and is consistent with the extant literature reporting that deprived smokers experience a variety of cognitive deficits that are restored upon smoking satiety or nicotine administration. These findings suggest that transdermal nicotine may alleviate abstinent-induced deficits in novelty detection, which may have direct implications for the efficacy of transdermal nicotine to reduce the rates of relapse given that smokers report that one of the primary reasons for relapse is to restore cognitive functioning (Gilbert et al. 2000).

Nicotine's improvement of target accuracy and subsequent recognition in nonsmokers suggests a direct beneficial effect on novelty detection. These main effects occurred under a successful blind, in the absence of negative side effect, and without changes in negative or positive affect across patch type. These data suggest that acute nicotine results in direct enhancement of the neurobiological systems involved in the orienting response and subsequent recognition memory.

References

Andreassi JL (2000) Psychophysiology human behavior and physiological response, 4th edn. Erlbaum, Mahwah, NJ

Bradley MM, Lang PJ (1999) Affective norms for English words (ANEW): instruction manual and affective ratings. In: F. U. o. F. Gainesville, The Center for Research in Psychophysiology (ed.)

Bunzeck N, Duzel E (2006) Absolute coding of stimulus novelty in the human substantia nigra/VTA. Neuron 51(3):369–379

Corrigall WA, Franklin KB, Coen KM, Clarke PB (1992) The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology (Berl) 107(2–3):285–289

Daffner KR, Mesulam MM, Scinto LF, Acar D, Calvo V, Faust R et al (2000) The central role of the prefrontal cortex in directing attention to novel events. Brain 123(Pt 5):927–939

Ernst M, Matochik JA, Heishman SJ, Van Horn JD, Jons PH, Henningfield JE et al (2001) Effect of nicotine on brain activation during performance of a working memory task. Proc Natl Acad Sci U S A 98(8):4728–4733

Foulds J, Stapleton J, Swettenham J, Bell N, McSorley K, Russell MA (1996) Cognitive performance effects of subcutaneous nicotine in smokers and never-smokers. Psychopharmacology (Berl) 127 (1):31–38

Foulds J, Stapleton JA, Bell N, Swettenham J, Jarvis MJ, Russell MA (1997) Mood and physiological effects of subcutaneous nicotine in smokers and never-smokers. Drug Alcohol Depend 44(2–3):105–115

Gilbert DG, Sharpe JP, Ramanaiah NV, Detwiler FRJ, Anderson AE (2000) Development of a Situation x Trait Adaptive Response (STAR) model-based smoking motivation questionnaire. Pers Individ Differ 29:65–84

Gilbert DG, Rabinovich N, Rosenberger SR (2003) Effects of fast and slow blood-rise nicotine patches on nausea and feeling states in never-smokers. Paper presented at the Society for Research on Nicotine and Tobacco, New Orleans

Gilbert DG, McClernon J, Rabinovich N, Sugai C, Plath L, Asgaard G et al (2004) 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 6(2):249–267

Gilbert DG, Sugai C, Zuo Y, Rabinovich NE, McClernon FJ, Froeliger B (2007) Brain indices of nicotine's effects on attentional bias to smoking and emotional pictures and to task-relevant targets. Nicotine Tob Res 9(3):351–363

Gilbert DG, Carlson JM, Riise H, Rabinovich NE, Sugai C, Froeliger B (2008) Effects of nicotine and depressive traits on affective priming of lateralized emotional word identification. Exp Clin Psychopharmacol 16(4):293–300

Gray R, Rajan AS, Radcliffe KA, Yakehiro M, Dani JA (1996) Hippocampal synaptic transmission enhanced by low concentrations of nicotine. Nature 383(6602):713–716

Gupta SK, Benowitz NL, Jacob P 3rd, Rolf CN, Gorsline J (1993) Bioavailability and absorption kinetics of nicotine following application of a transdermal system. Br J Clin Pharmacol 36 (3):221–227

Gupta SK, Okerholm RA, Eller M, Wei G, Rolf CN, Gorsline J (1995) Comparison of the pharmacokinetics of two nicotine transdermal systems: nicoderm and habitrol. J Clin Pharmacol 35(5):493–498

Heishman SJ (1998) What aspects of human performance are truly enhanced by nicotine? Addiction 93(3):317–320

Heishman SJ, Snyder FR, Henningfield JE (1993) Performance, subjective, and physiological effects of nicotine in non-smokers. Drug Alcohol Depend 34(1):11–18

Heishman SJ, Taylor RC, Henningfield JE (1994) Nicotine and smoking: a review of effects on human performance. Exp Clin Psychopharmacol 2(4):345–395

Holland PC (1977) Conditioned stimulus as a determinant of the form of the Pavlovian conditioned response. J Exp Psychol Anim Behav Processes 3(1):77–104

Houlihan ME, Pritchard WS, Robinson JH (1996) Faster P300 latency after smoking in visual but not auditory oddball tasks. Psychopharmacology (Berl) 123(3):231–238

Huettel SA, McCarthy G (2004) What is odd in the oddball task? Prefrontal cortex is activated by dynamic changes in response strategy. Neuropsychologia 42(3):379–386

Hunt PS, Campbell BA (1997) Autonomic and behavioral correlates of appetitive conditioning in rats. Behav Neurosci 111(3):494–502

Kleykamp BA, Jennings JM, Blank MD, Eissenberg T (2005) The effects of nicotine on attention and working memory in never-smokers. Psychol Addict Behav 19(4):433–438

Knott V, Bosman M, Mahoney C, Ilivitsky V, Quirt K (1999) Transdermal nicotine: single dose effects on mood, EEG, performance, and event-related potentials. Pharmacol Biochem Behav 63(2):253–261

Kucera H, Francis WN (1967) Computational analysis of present-day American English. Brown University Press, Providence

Kumari V, Gray JA, ffytche DH, Mitterschiffthaler MT, Das M, Zachariah E et al (2003) Cognitive effects of nicotine in humans: an fMRI study. Neuroimage 19(3):1002–1013

Lawrence NS, Ross TJ, Stein EA (2002) Cognitive mechanisms of nicotine on visual attention. Neuron 36(3):539–548

Lee HJ, Youn JM, O MJ, Gallagher M, Holland PC (2006) Role of substantia nigra-amygdala connections in surprise-induced enhancement of attention. J Neurosci 26(22):6077–6081

Levin ED, Christopher NC (2002) Persistence of nicotinic agonist RJR 2403-induced working memory improvement in rats. Drug Dev Res 55(2):97–103

Levin ED, Kaplan S, Boardman A (1997) Acute nicotine interactions with nicotinic and muscarinic antagonists: working and reference memory effects in the 16-arm radial maze. Behav Pharmacol 8 (2–3):236–242

Levin ED, McClernon FJ, Rezvani AH (2006) Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. Psychopharmacology (Berl) 184(3–4):523–539

McClernon FJ, Gilbert DG, Radtke R (2003) Effects of transdermal nicotine on lateralized identification and memory interference. Hum Psychopharmacol 18(5):339–343

Pidoplichko VI, DeBiasi M, Williams JT, Dani JA (1997) Nicotine activates and desensitizes midbrain dopamine neurons. Nature 390(6658):401–404

Posner MI, Petersen SE (1990) The attention system of the human brain. Annu Rev Neurosci 13(1):25–42

Ranganath C, Rainer G (2003) Neural mechanisms for detecting and remembering novel events. Nat Rev Neurosci 4(3):193–202

Rusted JM, Trawley S (2006) Comparable effects of nicotine in smokers and nonsmokers on a prospective memory task. Neuropsychopharmacology 31(7):1545–1549

Rusted J, Graupner L, Warburton D (1995) Effects of post-trial administration of nicotine on human memory: evaluating the conditions for improving memory. Psychopharmacology V119 (4):405–413 10.1007/BF02245856

Rusted JM, Graupner L, Tennant A, Warburton DM (1998) Effortful processing is a requirement for nicotine-induced improvements in memory. Psychopharmacology 138(3–4):362–368

Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neurochem 20(1):11–21

Sokolov EN (1963) Perception and the conditioned reflex. Macmillan, New York

Spielberger CD (1986) Psychological determinants of smoking behavior. In: Tollinson RD (ed) Smoking and society: toward a more balanced assessment. Heath, Lexington, MA

Squire LR (1992) Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 99 (2):195–231

Srivastava E, Russell M, Feyerabend C, Masterson J, Rhodes J (1991) Sensitivity and tolerance to nicotine in smokers and nonsmokers. Psychopharmacology 105(1):63–68

Strange BA, Henson RN, Friston KJ, Dolan RJ (2000) Brain mechanisms for detecting perceptual, semantic, and emotional deviance. Neuroimage 12(4):425–433

Sutton S, Braren M, Zubin J, John ER (1965) Evoked-potential correlates of stimulus uncertainty. Science 150(700):1187–1188

Sutton S, Tueting P, Zubin J, John ER (1967) Information delivery and the sensory evoked potential. Science 155(768):1436–1439

Thiel CM, Fink GR (2008) Effects of the cholinergic agonist nicotine on reorienting of visual spatial attention and top-down attentional control. Neuroscience 152(2):381–390

Tulving E (1992) Memory systems and the brain. Clin Neuropharmacol 15(Suppl 1 Pt A):327A–328A

Tulving E, Kroll N (1995) Novelty assessment in the brain and long-term-memory encoding. Annu Rev Neurosci 2(3):387–390

Tulving E, Markowitsch HJ, Kapur S, Habib R, Houle S (1994) Novelty encoding networks in the human brain: positron emission tomography data. Neuroreport 5(18):2525–2528

Tulving E, Markowitsch HJ, Craik FE, Habib R, Houle S (1996) Novelty and familiarity activations in PET studies of memory encoding and retrieval. Cereb Cortex 6(1):71–79

Warburton DM, Skinner A, Martin CD (2001) Improved incidental memory with nicotine after semantic processing, but not after phonological processing. Psychopharmacology (Berl) 153 (2):258–263

Waters AJ, Sutton SR (2000) Direct and indirect effects of nicotine/smoking on cognition in humans. Addict Behav 25(1):29–43

Watson D, Clark LA, Tellegen A (1988) Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 54(6):1063–1070

Wesnes K, Warburton DM (1984) The effects of cigarettes of varying yield on rapid information processing performance. Psychopharmacology (Berl) 82(4):338–342

Wittmann BC, Bunzeck N, Dolan RJ, Duzel E (2007) Anticipation of novelty recruits reward system and hippocampus while promoting recollection. Neuroimage 38(1):194–202