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ORIGINAL INVESTIGATION

Effects of transdermal nicotine on episodic memory in non-smokers with and without schizophrenia

Lindsay E. Jubelt · Ruth S. Barr · Donald C. Goff · Tanya Logvinenko · Anthony P. Weiss · A. Eden Evins

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Abstract
Rationale Nicotinic agonists may improve attention and memory in humans and may ameliorate some cognitive deficits associated with neuropsychiatric disorders such as schizophrenia.
Materials and methods We investigated the effects of a single dose of nicotine on episodic memory performance in 10 adults with schizophrenia and 12 healthy controls. Participants were nonsmokers in order to avoid confounding effects of nicotine withdrawal and reinstatement on memory. At each of two study visits, participants performed a test of episodic memory before and 4 h after application of a 14-mg transdermal nicotine (or identical placebo) patch in counterbalanced order.
Results Compared with placebo, nicotine treatment was associated with more rapid and accurate recognition of novel items. There was a trend for a treatment by diagnosis interaction, such that the effect of nicotine to reduce false alarms was stronger in the schizophrenia than the control group. There was no effect of nicotine on accuracy or reaction time for identification of previously viewed items.
Conclusions These data suggest that nicotine improves novelty detection in non-smokers, an effect that may be more pronounced in non-smokers with schizophrenia. Because memory deficits are associated with functional impairment in schizophrenia and because impaired novelty detection has been linked to the positive symptoms of schizophrenia, study of the effects of chronic nicotinic agonist treatment on novelty detection may be warranted.

Keywords Nicotine · Memory · Inhibitory control · Novelty detection · False alarm · Impulsivity · Schizophrenia · Acetylcholine

Introduction

Cognitive deficits, including impaired verbal memory, are a significant component of the schizophrenia syndrome and are a strong predictor of functional outcome for those with this disorder (Green 1996). Nicotinic acetylcholine receptor (nAChR) agonists are among several classes of cognitive-enhancing agents under investigation for treatment of cognitive deficits associated with schizophrenia (Levin and Rezvani 2002). Nicotine improves memory in animals (Arendash et al. 1995; Ciamei et al. 2001; Levin and Simon 1998) and improves attention, learning, and memory in healthy adults (Ernst et al. 2001; Lawrence et al. 2002; Levin et al. 1998; Mancuso et al. 1999; McClernon et al. 2003; Rusted et al. 1998; Rusted et al. 2005; Levin et al. 2006). In addition, nicotine has demonstrated benefits in these domains in patients with Alzheimer's disease (Wilson et al. 1995), age-associated memory impairment (White and Levin 2004),

Drs. Evins and Weiss contributed equally to the project.

L. E. Jubelt · R. S. Barr · D. C. Goff · A. P. Weiss · A. E. Evins
Department of Psychiatry, Massachusetts General Hospital,
Boston, MA, USA

T. Logvinenko
Biostatistics Division, Massachusetts General Hospital,
Boston, MA, USA

R. S. Barr · D. C. Goff · T. Logvinenko · A. P. Weiss · A. E. Evins
Harvard Medical School,
Boston, MA, USA

A. E. Evins (✉)
MGH Center for Addiction Medicine,
60 Staniford Street,
Boston, MA 02114, USA
e-mail: a_eden_evins@hms.harvard.edu

attention deficit hyperactivity disorder (Poltavski and Petros 2006), and depression (McClernon et al. 2006).

Several lines of research suggest that nicotine may be therapeutic in patients with schizophrenia. First, the smoking rate among those with schizophrenia is several-fold higher than in the general population (de Leon et al. 1995; de Leon and Diaz 2005; Hughes 1986), with estimated rates as high as 72–90%, and smokers with schizophrenia smoke each cigarette more intensively and extract more nicotine per cigarette than smokers without psychiatric illness (Olincy et al. 1997; Strand and Nyback 2005; Tidey et al. 2005; Williams et al. 2005). There is evidence for disordered nicotinic neurotransmission in schizophrenia relative to controls, including reduced expression of α4β2 and α7 nAChRs in post-mortem brain tissue (Durany et al. 2000; Freedman et al. 1995) and reduced upregulation of high affinity neuronal nAChR expression in response to smoking (Breese et al. 2000). Third, exogenous nicotine ameliorates some aspects of cognitive and neurophysiologic dysfunction in schizophrenia, including deficits in auditory sensory gating (Adler et al. 1993; Adler et al. 1992), eye tracking (Sherr et al. 2002), working memory (Jacobsen et al. 2004), and attention (Barr et al. 2007; Depatie et al. 2002; Smith et al. 2006). In addition, nicotine deprivation and nAChR blockade impair visuospatial working memory in smokers with schizophrenia but not controls (George et al. 2002; Sacco et al. 2005), although this finding has not been consistently demonstrated (Evins et al. 2005).

These findings support the hypothesis that nAChR agonists may enhance abnormally low nicotinic cholinergic activity in schizophrenia. Perhaps critically, stimulation of presynaptic α4β2 and α7 nAChRs on glutamatergic and dopaminergic neurons increases activity of these neurons in relevant brain regions, including the hippocampus and prefrontal cortex (Janhunen and Ahtee 2007; Kiba and Jayaraman 1994; Lambe et al. 2003; Mansvelder and McGehee 2000; Nomikos et al. 2000; Sziraki et al. 1998), which may have relevance for improving cognitive performance in patients (Laruelle et al. 2003; Newcomer et al. 1999; Olney and Farber 1995). Evidence for a modulatory effect of nicotine on *N*-methyl-D-aspartate (NMDA) glutamate function at the molecular level has been illustrated via differences in gene expression related to NMDA post-synaptic density and other gene groups in the postmortem hippocampi of smokers and nonsmokers. Most notably, the significant interaction between smoking status and the diagnosis of schizophrenia suggests that nicotine results in differential expression of genes related to hippocampal NMDA glutamate receptor complex function in patients with schizophrenia (Mexal et al. 2005).

There have been few investigations of the effect of nicotine on memory performance in schizophrenia despite strong evidence for impaired verbal memory in this disorder (Cirillo and Seidman 2003) and the important role of the cholinergic system in memory processes (Hasselmo and Giocomo 2006). We therefore conducted a study of the effects of a single dose of transdermal nicotine on recognition memory performance in non-smoking adults with schizophrenia and matched non-psychiatrically ill controls using a double-blind, placebo-controlled, crossover design. This was an ancillary study conducted in a subset of participants in a larger study of the effect of nicotine on cognitive performance in non-smokers (Barr et al. 2007). Non-smokers were studied to avoid the potentially confounding effects of nicotine withdrawal and reinstatement on memory function. Our hypothesis was that nicotine would improve memory accuracy as assessed by increased hit rate, improved source memory accuracy, reduced false alarm rate, and reduced hit reaction time in both groups, with greater improvement expected with nicotine treatment in those with schizophrenia. Secondary analyses were planned for the commonly used signal detection variables of discriminability and response bias.

Materials and methods

The Institutional Review Boards of the Massachusetts General Hospital and the Commonwealth of Massachusetts Department of Mental Health approved the study. All participants provided written informed consent prior to participation.

Participants

Non-smoking adults with a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association 1994) diagnosis of schizophrenia or schizoaffective disorder, depressed type, were recruited from an urban community mental health clinic. Psychiatric diagnosis was made by a research psychiatrist (AEE, RSB) based on clinical interview and chart review. All patients were on a stable antipsychotic treatment regimen for ≥4 weeks prior to enrollment and remained on these medications during the study. Non-smoking adults without psychiatric illness were recruited from the local community and completed a screening interview using the Structured Clinical Interview for DSM-IV non-patient edition to rule out lifetime history of any Axis I psychiatric disorders and a supplemental questionnaire to rule out schizophrenia spectrum disorders in first-degree relatives.

English was the first-learned language for all participants. Exclusion criteria for both groups included a lifetime diagnosis of cognitive impairment secondary to head injury, dementia, or general medical illness, current

diagnosis of substance abuse or dependence (except for caffeine), use of investigational medications in the past month, current diagnosis of major depressive disorder, current unstable medical illness, known allergy to any constituents of the nicotine patch, tobacco smoking within the last 3 months, or a Wide Range Achievement Test-3 (WRAT-3 Blue Reading Subset, Jastak Associates, Wilmington, DE, USA) raw score of <35 (range=0–57). During the preliminary visit, substance use was assessed with a semi-quantitative salivary assay (Accutest Saliva Test™, JANT Pharmacal, Encino, CA, USA; ALCO Screen, CHEMATICS, North Webster, IN, USA), and non-smoking status was confirmed by self-report, by a salivary cotinine <10 ng/ml (Nicalert™, JANT Pharmacal), and by an expired air carbon monoxide (CO) <9 ppm (Micro Smokerlyzer III, Bedfont Scientific, Kent, UK).

Study design

Each participant completed two study visits in which they received either nicotine or placebo by patch in counterbalanced order. Each visit contained two experimental sessions, one in the morning (pre-dose) and one in the afternoon (post-dose). At the beginning of each visit day, participants were evaluated to reconfirm non-smoking status by self-report, expired air CO (<9 ppm), and salivary cotinine (<30 ng/ml). Saliva was analyzed for ethanol, tetrahydrocannabinol (THC), cocaine, phencyclidine, opiates, amphetamine, and methamphetamine. Participants then performed the episodic memory task as part of a neurocognitive battery assessing attention [Continuous Performance Test Identical Pairs (CPT-IP), three-card Stroop, and letter number sequencing], processing speed and cognitive interference (three-card Stroop), working memory (letter number sequencing), and lateralized psychomotor speed (Grooved Pegboard; Barr et al. 2007). After participants performed baseline cognitive testing, the randomly assigned treatment patch was administered—either two 7-mg transdermal nicotine patches (Nicoderm CQ Alza, Mountain View, CA, USA) or two identical placebo patches (1-800-Patches, Salt Lake City, UT, USA). Participants repeated the episodic memory task 4 h after patch application, at the time of expected peak serum nicotine levels (Benowitz 1995; Gupta et al. 1993). Patches were removed upon completion of the episodic memory task (approximately 4.5 h after patch placement), and blood was drawn for serum nicotine levels. For male and postmenopausal female participants (nine controls, ten patients), the mean time between visits was 9.3 days (range=6–15 days). Due to known effects of estrogen on cognitive performance in women with schizophrenia (Hoff et al. 2001), cycling female participants (none with schizophrenia, three controls) returned for the second visit at the same phase in their cycle as they had been on the first visit (mean inter-visit period=42.3 days; range=28–66 days).

Procedure

The episodic memory paradigm consisted of a previously described source monitoring task (Weiss et al. 2007), modified here to consist of three interleaved encoding and testing sessions. During each encoding session, participants simultaneously saw and heard 26 English words (13 spoken by a man, 13 spoken by a woman) and were asked to identify the gender of the voice using a keypad button. Words were presented visually on a screen approximately 18 in. from each participant and aurally via Dell Inspiron 8600 laptop speakers at a clearly audible sound level using Presentation version 0.80 (Neurobehavioral Systems, Albany, CA, USA). Immediately following each encoding block, a test containing the 26 previously studied items and 26 new items was presented visually, and participants were asked to indicate whether the word had been spoken by the man, the woman, or was new by pressing one of three labeled keys. Thus the paradigm tests both simple recognition memory (distinguishing previously presented from novel items) as well as source memory (remembering the gender of the voice that spoke the previously presented items).

Statistical analysis

Simple recognition memory was assessed by hit rate (rate of correct identification of old items as old) and false alarm rate (rate of incorrect identification of new words as old). Source memory accuracy was calculated as the percentage of correctly identified old items attributed to their correct source.

Mean hit reaction time was calculated for correct identification of old items (regardless of source accuracy) and new items. Accuracy and response time values were collapsed across the three test runs at each of the four memory assessments (Wilding 1999). Additional composite signal-detection parameters for discriminability (d') and response bias (C) were calculated in standard fashion based on the hit rate and false alarm rate values (Macmillan and Creelman 1991; Snodgrass and Corwin 1988).

Baseline (visit 1 pre-dose) between-group differences in accuracy and reaction time were compared using an unpaired Student's t test. To assess the effect of treatment (nicotine vs. placebo), difference scores for outcome measures were calculated for each visit as (post-dose−pre-dose score). These difference scores were then entered into separate repeated-measures linear mixed models with treatment (nicotine vs. placebo), diagnosis (schizophrenia

vs. control), and a group-by-treatment interaction term as fixed effects and participant as a random effect. Age and gender were included as covariates in all models and removed if not significant. As there were four primary outcomes of interest, the statistical significance was set at a two-sided alpha of 0.0125. Analyses were conducted on SPSS version 11 for Mac OSX or SAS version 9.1 for Windows.

Results

Of the 38 participants who were screened, 29 met eligibility requirements and were enrolled. One participant with schizophrenia and three controls were withdrawn from the study prior to randomization due to either change in interest in participating in the study or being lost to follow-up. The remaining 25 subjects were randomized for order of receiving nicotine and placebo patches. One participant in each group was unable to complete the memory task due to nausea, and one additional participant with schizophrenia had unusable data due to technical error. Analyses therefore included the 10 participants with schizophrenia and 12 controls who completed the post-dose episodic memory task. Demographic characteristics of these participants are presented in Table 1. The groups differed in age, intelligence quotient (IQ; WRAT-3 raw scores converted into age-adjusted standard scores), and prior smoking history. Eight participants with schizophrenia were on a second-generation antipsychotic medication, and two participants were taking a combination of first- and second-generation antipsychotic medications. Half of the participants with schizophrenia were taking clozapine. A list of the patients' medications is presented in Table 2. Ten participants (four subjects with schizophrenia, six control subjects) agreed to have blood drawn for serum nicotine at the end of each testing sessions. Mean (±SD) serum nicotine levels were 0.43 (±0.87) ng/ml after the placebo patch condition and 6.14 (±2.44) ng/ml after the nicotine patch condition (t=−7.10, p<0.0001). Serum nicotine levels did not differ between the schizophrenia group and control group in either the placebo patch condition (t=0.98, p=0.36) or the nicotine patch condition (t=0.74, p=0.48).

Table 1 Baseline characteristics

Variable	Schizophrenia (N=10) Mean±SD	Control (N=12) Mean± SD
Demographic characteristics		
Age at entry (years)	46±10	35±2*
Gender (F/M)	5/5	8/4
Race (% white, non-Hispanic)	90%	100%
IQ score	97±14.2	111.8±6.8*
Education (years)	14.0±3.9	16.8±2.9
Mother's education (years)	14.0±2.7	14.4±3.4
Father's education (years)	15.8±4.4	15.3±4.3
Disease characteristics		
Taking Clozapine (%)	50	
PANSS positive	12.8±4.4	
PANSS negative	12.5±3.9	
PANSS global	27.5±6.1	
PANSS total	52.8±9.9	
Previous tobacco use		
Prior regular consumption of tobacco (%)	8/10	4/12*
Tobacco consumption duration (years)	14.9±12.9	5.8±5.1
Cigarettes per day	30.7±25.6	8.3±8.8
Years since end of tobacco consumption	10.9±12.1	16.3± 17.6

*The groups differed by age, IQ, and past smoking

Baseline memory performance

At baseline, participants with schizophrenia demonstrated poorer recognition memory performance compared with controls, controlling for age, with a lower hit rate (67.2± 14.8% vs. 83.2±10.8%, t=2.93, p<0.01), a higher false alarm rate (15.1±16.6 vs. 2.5±4.0, t=−2.4, p<0.05), and lower source memory accuracy (68.6±14.9% vs. 86.0± 10.4%, t=3.21, p<0.01). Patients with schizophrenia were slower when making correct responses compared with controls [hit reaction time for old items (1,798±294 m vs. 1,308±299 ms, t=3.86, p<0.01), new items (1,562± 342 ms vs. 946±80 ms, t=5.57, p<0.001)]. Those with schizophrenia also had poorer discriminability than controls at baseline (1.7±0.7 vs. 3.1±0.7, t=5.15, p<0.001), but there was no between-group difference in response bias (0.37±0.47 vs. 0.51±0.36, t=0.77, p=0.45).

Table 2 Concomitant psychotropic medications

Subject	Medication
1	Clozapine, bupropion
2	Clozapine, citalopram, divalproex sodium, lorazepam
3	Ziprasidone
4	Clozapine, quetiapine, clonazepam, divalproex sodium
5	Clozapine, clonazepam
6	Aripiprazole, fluoxetine, clonazepam
7	Risperidone
8	Ziprasidone, perphenazine, citalopram, oxcarbazepine, gabapentin, lorazepam
9	Clozapine
10	Olanzapine

Nicotine effect on identification of old and new items

As shown in Table 3, there was no effect of treatment on hit rate. There was an effect of treatment on false alarms such that there was a reduction in false alarms in the nicotine treatment condition relative to placebo [$F(1,17)=8.47$, $p<0.01$, Cohen's d effect size=0.71). There was a trend level treatment by diagnosis interaction that reflects a greater effect of nicotine on reduction in false alarms in the schizophrenia group as compared with the control group [medication by diagnosis interaction: $F(1,17)=3.13$; $p=0.095$, Cohen's d effect size=0.43; Fig. 1a].

Source memory accuracy

There was no effect of nicotine on source memory accuracy: $F(1,18)=0.42$, $p=0.53$.

Reaction time

As shown in Fig. 1b, hit reaction time was faster during correct identification of new items in the nicotine condition [main effect of study medication, $F(1,18)=9.11$; $p=0.007$, Cohen's d effect size=0.71]. There was no treatment effect on the reaction time for correct identification of old items [$F(1,18)=2.06$; $p=0.17$].

Discriminability and response bias

When the responses to new and old items were considered together, there was no effect of treatment on discriminability. There was a main effect of treatment on response bias, such that participants on nicotine showed a decreased tendency to respond "old" to a test item, regardless of the stimulus type [main effect for nicotine, $F(1,18)=10.06$; $p=0.005$], an effect that did not differ by diagnosis.

Control analyses

Inclusion of age and gender as a covariate did not change the outcome of any of the above analyses. There was no effect of order of treatment administration for any of the four primary outcome measures, indicating no significant carry-over effect of nicotine administration on any of the four primary outcome measures examined.

Discussion

The main finding of this study was that nicotine significantly and selectively improved accuracy and speeded reaction times for identification of novel items on an episodic memory task. Improvement in false alarms on this

Table 3 Effect of nicotine on source memory performance in non-smokers with and without Schizophrenia

	Schizophrenia				Control				Treatment effect		Treatment × diagnosis interaction	
	Nicotine		Placebo		Nicotine		Placebo					
	Pre-drug Mean (SD)	Post-drug Mean (SD)	Pre-drug Mean (SD)	Post-drug Mean (SD)	Pre-drug Mean (SD)	Post-drug Mean (SD)	Pre-drug Mean (SD)	Post-drug Mean (SD)	F (df)	p	F (df)	p
Performance measure												
Hit rate (%)	72.4 (11.1)	72.8 (7.3)	66.7 (14.7)	72.2 (6.6)	86.6 (10.6)	88.6 (10.1)	84.7 (12.2)	87.8 (13.1)	1.11 (1,19)	0.31		
False alarm rate (%)	19.0 (17.5)	15.9 (21.6)	13.3 (18.3)	19.0 (20.9)	3.4 (3.8)	2.0 (3.1)	1.7 (2.5)	2.5 (3.1)	8.47 (1,17)	<0.01	3.13 (1,17)	0.095[a]
Source memory accuracy (%)	66.9 (13.2)	70.0 (11.9)	70.4 (13.8)	73.0 (11.7)	84.6 (13.0)	88.6 (10.6)	86.3 (12.6)	87.6 (12.8)	0.42 (1,18)	0.53		
Discriminability (d')	1.7	1.9	1.8	1.7	3.1	3.5	3.3	3.3	0.49 (1,19)	0.49		
Response bias (C)	0.2 (0.4)	0.3 (0.5)	0.4 (0.4)	0.3 (0.5)	0.3 (0.3)	0.4 (0.2)	0.5 (0.3)	0.3 (0.3)	10.06 (1,18)	<0.01	0.20 (1,18)	0.66
Reaction times (ms)												
Correct old items	1,750 (274)	1,693 (266)	1,745 (294)	1,647 (295)	1,237 (230)	1,207 (211)	1,320 (286)	1,205 (221)	2.06 (1,18)	0.17		
Correct new items	1,564 (338)	1,447 (292)	1,453 (287)	1,502 (322)	1,012 (201)	887 (89)	953 (78)	943 (131)	9.11 (1,18)	<0.01	0.51 (1,18)	0.49

[a] Age was included as a covariate in the analyses of false alarm rates

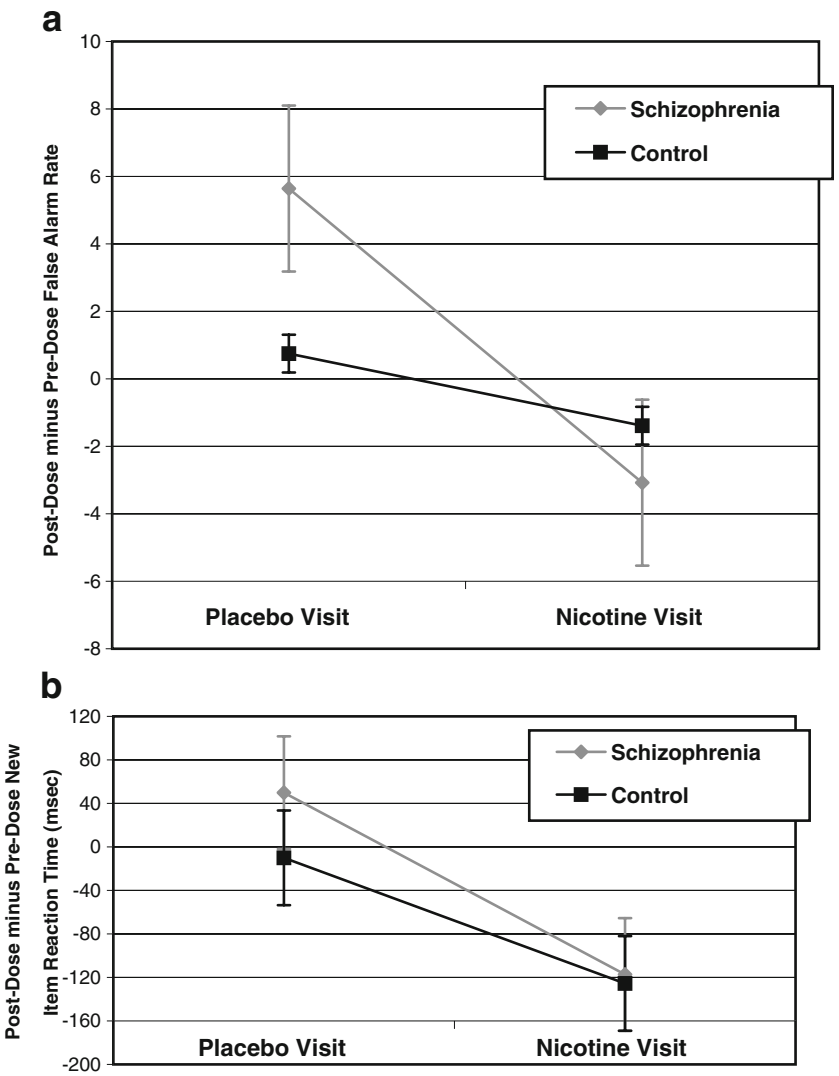

Fig. 1 **a** Nicotine effect on false alarm rate in an episodic memory task. Main effect for nicotine, $F(1,17)=8.47$, $p<0.01$. Treatment × group interaction, $F(1,17)=3.13$; $p=0.095$. **b** Nicotine effect on hit reaction time for novel items. Main effect of nicotine, $F(1,18)=9.11$; $p=0.007$

task indicates improvement in recognition of novel items as novel, as measured by reduction in incidence of reporting having previously viewed items that were in fact novel. There was some indication that this improvement in novelty detection with nicotine may be greater in those with schizophrenia than in normal control participants. Improvements in novelty detection may be of clinical significance, as irregularities in novel item recognition have been associated with positive symptoms in schizophrenia (Brebion et al. 1998; Ishigaki and Tanno 1999).

As in our study, prior studies have not found effects of nicotine on overall verbal memory performance in schizophrenia (Harris et al. 2004; Smith et al. 2006). These studies did not specifically assess treatment effect on recognition of new vs. previously viewed words, and as with the present study, measures of recognition memory that assess overall memory performance (e.g., discriminability) may not detect an effect of nicotine if these effects are specific to novelty detection. In one prior study that investigated the effect of nicotine on novelty detection during a delayed recognition memory task, nicotine (1 mg via nasal spray) reduced false alarm rates in 2-h-withdrawn smokers with schizophrenia, an effect not observed in non-smokers with schizophrenia or healthy controls (Myers et al. 2004). As in the present study, nicotine did not improve hit rate. These results differ from those of the current study in which nicotine was associated with improved novelty detection in those with and without schizophrenia. This dissimilarity may be due to differences in the recognition memory paradigms utilized in the experiments. Myers et al. (2004) employed a self-paced test of visuospatial design recognition, as opposed to a paced test that utilized written and spoken words employed in the present study.

The type of novelty effect demonstrated in the present paradigm is known as stimulus novelty, a phenomenon that has been well studied in humans, non-human primates, and rodents (Kumaran and Maguire 2007; Ranganath and Rainer 2003). The neural basis of stimulus novelty involves

a suppression of neural firing with stimulus repetition, an effect observed within 90 ms of stimulus presentation (Brown and Bashir 2002). Although these repetition-suppression effects are seen across many regions of the cortex, they appear to be most robust within the cortical aspects of the medial temporal lobe, especially within the perirhinal cortex. This region receives a high degree of cholinergic projections and contains a uniquely high density of nicotinic receptors (Perry et al. 1993); thus cholinergic mechanisms are thought to be at the core of these novelty-detection capabilities (Hasselmo and Giocomo 2006).

The repetition-suppression mechanism underlying stimulus novelty detection is similar to two other electrophysiological sensory gating effects: prepulse inhibition (PPI) of the acoustic startle response and P50 auditory-evoked potential suppression. The potential link between stimulus novelty detection, PPI, and P50 suppression is of particular interest as these latter two effects are abnormal in patients with schizophrenia and their first-degree relatives, are considered leading candidates for endophenotypes of the illness (Turetsky et al. 2007), and are ameliorated by nicotine (Adler et al. 1993; Adler et al. 1992; Duncan et al. 2001; Kumari et al. 2001; Postma et al. 2006). While novelty detection in the episodic memory test differs in processing time from that of sensory gating studies, nicotine improves differentiation of target from on-target stimuli in all of these tasks. The effects of nicotine on stimulus novelty detection may therefore be related to these well-described sensory gating findings. Further research is necessary to determine the relationship between stimulus novelty detection and these sensory gating findings.

The specific mechanism by which nicotine may improve performance on these tasks is incompletely understood. Most work has focused on nicotine's stimulation of α-7 nAChRs on γ-aminobutyric acid (GABA) interneurons of the hippocampus (Albuquerque et al. 1998). Such stimulation increases GABA activity, which is thought to inhibit a hyperactive hippocampal response to repeated stimuli in schizophrenia, thereby enhancing response inhibition to irrelevant stimuli (Hajos et al. 2005; Ji and Dani 2000).

Alterations in early electrophysiological responses, e.g., improved repetition suppression, may lead to improved downstream decision-making, including greater capacity for inhibitory control of inappropriate responses. In the larger study, of which this study was a part, Barr et al. (2007) found that nicotine reduced errors of commission on the CPT-IP test of attention and improved performance on the Stroop Task in non-smokers with schizophrenia and non-psychiatric controls, effects that were more pronounced in those with schizophrenia than controls. The authors postulate that these effects are the result of a nicotine-mediated improvement in inhibitory control. Our finding that nicotine shifted participants' response bias in the conservative direction may be an indication that inhibitory mechanisms are involved.

While we are proposing that enhanced pre-attentional mechanisms are responsible for the effects of nicotine seen in this study, it remains possible that nicotine's effects on attention and working memory also play a role. Nicotine is thought to improve attention and working memory by increasing release of dopamine in the frontal lobe. Memory encoding has been shown to be dependent on attention and working memory, and it is impaired when carried out under conditions of divided attention (Craik et al. 1996; Naveh-Benjamin et al. 2000). By improving attention and working memory, and thereby memory encoding, nicotine may enhance a participant's ability to differentiate words that have not been previously viewed from those that have been.

Individuals with schizophrenia have difficulty filtering relevant from irrelevant material as well as determining internally generated from externally generated information (Brebion et al. 1997; Keefe et al. 1999). These deficits have been associated with positive symptomatology in schizophrenia (Brebion et al. 2000; Brebion et al. 1998; Franck et al. 2000), such that hallucinations were associated with an increased false alarm rate on a recognition memory task. If nicotine has an effect of reducing false alarm rates and/or improving filtering of irrelevant from relevant events, it is conceivable that it could play some role in improving positive symptoms. A recent study demonstrating reduced positive symptoms in smokers relative to non-smokers with schizophrenia provides some preliminary evidence for this reasoning (Zhang et al. 2007).

The results of the present study are limited by several factors. The small sample size may have limited our power to detect an effect of nicotine on memory, potentially leading to type II errors, although the crossover design increased the power to detect a treatment effect. That said, the effect size of treatment on false alarm rate and on reaction time to novel items was moderate to large, while the effect size of the diagnosis by treatment interaction on false alarm rate was moderate. Second, the non-smoking status of our participants may limit the generalizability of the findings to non-smokers with schizophrenia, as the pathophysiology of schizophrenia has been postulated to differ between smokers and non-smokers (Kelly and McCreadie 1999), although the present study did include former smokers. Third, the effects of clozapine and other antipsychotic medications may modulate the effects of nicotine. Clozapine has been shown to attenuate the effects of nicotine on attention and memory in an animal model of schizophrenia (Rezvani et al. 2007), suggesting that clozapine treatment could reduce the effects of nicotine in the patient group. We were unable to detect a nicotine treatment by clozapine treatment interaction on false alarm rate scores or reaction times to new items, but we were

severely limited in our power to detect such effect. This issue should be prospectively explored in a larger sample. Finally, it is possible that the cognitive tests administered before the episodic memory test may have impacted subjects' performance on the episodic memory test. While this is a potential confounding variable in all neurocognitive batteries, such effect was minimized by the placebo-controlled, crossover design of the study and because other neurocognitive tests administered were not verbally intensive, and there was no delay or intervening task between encoding and retrieval in the episodic memory test.

Overall, our findings support the general hypothesis that nicotine improves recognition of novel events in non-smokers, particularly in those with schizophrenia, with little or no modulation of overall episodic memory ability. Further study utilizing neuroimaging or electrophysiological approaches may be warranted to investigate the neural correlates of this effect.

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