

Nicotine Effects on Brain Function and Functional Connectivity in Schizophrenia

Leslie K. Jacobsen, D. Cyril D'Souza, W. Einar Mencl, Kenneth R. Pugh, Pawel Skudlarski, and John H. Krystal

Background: Nicotine in tobacco smoke can improve functioning in multiple cognitive domains. High rates of smoking among schizophrenic patients may reflect an effort to remediate cognitive dysfunction. Our primary aim was to determine whether nicotine improves cognitive function by facilitating activation of brain regions mediating task performance or by facilitating functional connectivity.

Methods: Thirteen smokers with schizophrenia and 13 smokers with no mental illness were withdrawn from tobacco and underwent functional magnetic resonance imaging (fMRI) scanning twice, once after placement of a placebo patch and once after placement of a nicotine patch. During scanning, subjects performed an n-back task with two levels of working memory load and of selective attention load.

Results: During the most difficult (dichotic 2-back) task condition, nicotine improved performance of schizophrenic subjects and worsened performance of control subjects. Nicotine also enhanced activation of a network of regions, including anterior cingulate cortex and bilateral thalamus, and modulated thalamocortical functional connectivity to a greater degree in schizophrenic than in control subjects during dichotic 2-back task performance.

Conclusions: In tasks that tax working memory and selective attention, nicotine may improve performance in schizophrenia patients by enhancing activation of and functional connectivity between brain regions that mediate task performance.

Key Words: Brain function, connectivity, attention, memory, nicotine, schizophrenia

Patients with schizophrenia have higher rates of smoking, smoke more heavily, extract more nicotine during smoking, and have more severe symptoms of nicotine dependence than do persons in the general population (Dalack et al 1998; de Leon et al 2002; Hughes et al 1986; Leonard et al 2001; Olincy et al 1997). This elevated prevalence persists after controlling for known demographic confounders and may reflect altered function of nicotinic acetylcholine receptors (nAChRs) in schizophrenia (Hughes et al 1986; Lohr and Flynn 1992).

In patients with schizophrenia, nicotine transiently reverses eye-tracking abnormalities (Olincy et al 2003; Sherr et al 2002), improves antipsychotic associated deficits in spatial working memory and complex reaction time (Levin et al 1996), improves sustained attention (Levin et al 1996), normalizes the auditory sensory gating (P50) deficit (Adler et al 1993), and reverses abstinence related deficits in spatial working memory (George et al 2002). The P50 deficit in schizophrenia has been genetically linked to a locus at 15q14 (Freedman et al 1997) that contains the low affinity $\alpha 7$ nAChR gene. Postmortem studies have reported reduced $\alpha 7$ nAChR binding in hippocampus, thalamus, and in frontal cortex of patients with schizophrenia (Court et al 1999; Freedman et al 1995; Guan et al 1999); however, at brain concentrations of nicotine typically achieved during smoking (Benowitz et al 1990; Henningfield et al 1993), binding of

nicotine to mammalian brain is primarily associated with the high affinity $\alpha 4\beta 2$ subunit containing nAChR (Alkondon et al 2000). Tobacco smoking increases high-affinity nAChR binding sites in healthy smokers in a dose-dependent manner that is reversible with smoking cessation (Breese et al 2000; Perry et al 1999); however, patients with schizophrenia fail to upregulate high-affinity nAChRs in hippocampus, thalamus, cortex, and caudate in response to smoking (Breese et al 2000).

Multiple domains of cognitive function are disrupted in schizophrenia, including attention, verbal and visuospatial working memory, and learning and memory (Sharma and Antonova 2003). Work in schizophrenic and healthy smokers, in nonsmokers, and in animals has provided evidence that nicotine can improve cognitive function in many of these domains (Levin and Resvani 2002). Recently, the mechanisms underlying nicotine effects on cognition in healthy smokers and nonsmokers have been examined using functional brain imaging methods. Nicotine administered by patch to 2.3-hour abstinent smokers performing the rapid visual information processing task, which requires both sustained attention and working memory, improved performance and increased task-related activity in a network of regions that included bilateral parietal and occipital cortex, posterior cingulate, thalamus, and caudate (Lawrence et al 2002). Similarly, nicotine administered subcutaneously to nonsmokers performing an n-back working memory task improved performance and increased activation of anterior cingulate, superior frontal cortex, superior parietal cortex, and mid-brain tectum (Kumari et al 2003). Nicotine administered intravenously to smokers and nonsmokers performing a maze task did not modify performance but did increase task related activity in parietooccipital cortex and decrease activity in anterior cingulate cortex and cerebellum (Ghatan et al 1998). Nicotine administered via gum to subjects performing an n-back task did not modify performance but reduced activation in cingulate, parietal, and inferior frontal cortex in smokers and increased activation in prefrontal cortex in ex-smokers (Ernst et al 2001). Thus, most previous work has found that nicotine administration increases task-related brain activation, with this effect being most consistent when concomitant nicotine-related improvement in

From the Departments of Psychiatry (LKJ, DCD'S, JHK), Pediatrics (LKJ, KRP), and Diagnostic Radiology (PS), Yale University School of Medicine, and Haskins Laboratories (WEM, KRP), New Haven, and Department of Psychiatry (LKJ, DCD'S, JHK) Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut.

Address correspondence to Leslie K. Jacobsen, M.D., Departments of Psychiatry and Pediatrics, Yale University School of Medicine, 100 York Street 2B, New Haven, CT 06511.

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task performance is observed (Kumari et al 2003; Lawrence et al 2002).

In this study, we used fMRI to test the hypothesis that nicotine-induced improvements in verbal working memory and selective attention in smokers with schizophrenia would be associated with enhanced task-related brain activation. Recent work has suggested that cognitive dysfunction in schizophrenia may involve not only impaired function of specific brain regions but also impaired functional connectivity (i.e., impaired ability to coactivate functional networks subserving task performance) (Andreasen 1999; Friston and Frith 1995; Meyer-Lindenberg et al 2001). We therefore also tested for evidence that nicotine modulates functional connectivity in schizophrenia. Because recent preclinical work has shown that nicotine induces glutamate release from thalamocortical terminals in prefrontal cortex (Lambe et al 2003), we hypothesized that nicotine enhances thalamocortical functional connectivity in patients with schizophrenia.

Methods and Materials

Participants

We studied 13 smokers who met DSM-IV criteria for schizophrenia (10 paranoid subtype, 1 disorganized subtype, 2 undifferentiated subtype) and 13 control smokers who were free of current and past psychiatric illness as determined by structured clinical interview (First et al 1997). All patients were stable outpatients; one was taking typical antipsychotic medication (haloperidol), 11 were taking atypical antipsychotic medication (olanzapine [5], risperidone [3], aripiprazole [2], clozapine [1]), and one was taking both types of medication (haloperidol and olanzapine). Subjects with a history of head trauma, medical illnesses compromising the central nervous system, or substance or alcohol abuse within 12 months of study participation were excluded. Diabetes was exclusionary. Two subjects with stable, medication-controlled hypertension were included.

Schizophrenia patients and control subjects did not significantly differ in age (mean age \pm SD of patients = 42.9 ± 7.2 years, control subjects = 41.8 ± 6.5 years, $t(24) = .4$, $p > .6$), years of education (patients = 13.3 ± 2.9 years, control subjects = 13.5 ± 1.8 years, $t(24) = .1$, $p > .9$), gender (patients included 2 women, control subjects included 4 women, $\chi^2 = .9$, Fischer's Exact Test $p > .6$), handedness (3 patients and 1 one control subject were left-handed, $\chi^2 = 1.2$, Fischer's Exact Test $p > .5$), estimated full-scale IQ (Wechsler 1981; patients = 99.2 ± 16.8 , control subjects = 99.8 ± 20.0 , $t(20) = .1$, $p > .9$; data not available from three patients and one control), or reading achievement (Woodcock–Johnson Psychoeducational Battery letter–word identification subscale standard score: patients = 99.2 ± 18.2 , control subjects = 99.8 ± 20.0 , $t(24) = .08$, $p = > .9$). Although patients and control subjects did not significantly differ in number of cigarettes smoked per day (patients = 26.3 ± 10.5 , control subjects = 27.6 ± 11.3 , $t(24) = .3$, $p > .7$) or pack-years ($=$ [total number of cigarettes smoked/(20 \times 365)]: patients = 27.4 ± 15.0 , control subjects = 34.7 ± 26.4 , $t(24) = .9$, $p > .3$); plasma nicotine and cotinine concentrations of the patients were higher than those of the control subjects at screening (nicotine: patients = 27.7 ± 18.2 ng/mL, control subjects = 10.3 ± 9.6 ng/mL; $t(24) = 3.04$, $p = .006$; cotinine: patients = 452.7 ± 244.6 , control subjects = 245.1 ± 156.0 ; $t(24) = 2.58$, $p = .02$) and patients reported more symptoms of nicotine dependence (mean Fagerstrom Test for Nicotine Dependence (FTND) score: patients = 7.5 ± 1.5 , control subjects = 5.8

± 1.9 ; $t(24) = 2.55$, $p = .02$). Plasma nicotine and cotinine were measured at screening during the afternoon of a day of ad libitum smoking. The time between last cigarette and screening blood draw was not controlled.

Procedure

All subjects provided written informed consent before enrollment in the study, which was approved by the Yale Human Investigations Committee and the VA Connecticut Human Studies Subcommittee. Subjects were scanned twice, once after placement of a placebo patch and once after placement of a nicotine patch (Nicotine Transdermal System USP, Schein Pharmaceuticals, Melville, New York). Order of patch placement was randomized and double blind. Dose of nicotine was 28 mg for subjects with body mass index (BMI) less than 26 kg/m^2 and 35 mg for subjects with BMI greater than 26 kg/m^2 . Nicotine was delivered by patch to avoid potential confounds arising from group differences in nicotine extraction during self-administration (by smoking or chewing gum). To ensure abstinence from tobacco for at least 15 hours before scanning, all subjects were admitted to the Yale University General Clinical Research Center. Six hours before scanning, nicotine or placebo patches were placed on the upper thigh and were not removed until scanning was completed. Blood was drawn to measure plasma nicotine immediately before scanning. Plasma concentrations of nicotine and cotinine were determined by gas chromatography (Jacob et al 1981). With this method, limits of quantification are 1 ng/mL for nicotine and 10 ng/mL for cotinine.

Before scanning, subjective and objective symptoms of nicotine withdrawal were assessed, respectively, using the Minnesota Nicotine Withdrawal Scale (Hughes and Hatsukami 1998) and the Clinical Institute for Narcotic Withdrawal Scale (CINA). Tobacco craving was assessed with the Tiffany Scale for Smoking Urges (Tiffany and Drobes 1991). Depressive symptoms were evaluated using the Hamilton Depression Scale (Hamilton 1961) and the Beck Depression Inventory (Beck et al 1961). Subjects with schizophrenia were further evaluated using the Scale for Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1983, 1984).

Task

During image acquisition, subjects performed an auditory n-back task with two levels of verbal working memory (1-back and 2-back) and two levels of selective attention load (binaural and dichotic stimulus presentation). Stimuli for the activation task were consonant–vowel–consonant nonwords. Before each run, subjects were instructed as to whether the task was 1-back (listening for a back to back repeat, such as “bip bip”) or 2-back (listening for a repeat separated by a different word, such as “bip gex bip”) and whether the stimuli would be the same in both ears (binaural) or different in each ear (dichotic). Subjects indicated a response (yes or no) for each stimulus presentation with a button press. Forty-eight nonwords were presented during each run, and each task condition was presented twice for a total of 8 runs. Order of task presentation was randomized. For dichotic runs, subjects were told to which ear targets would be presented, and stimuli were delivered 30% louder to the attended ear. Within each 3-minute, 20-sec run, three 40-sec n-back blocks were interleaved with four 20-sec control blocks during which tones rising or falling in pitch were presented binaurally. Subjects indicated whether the tones were rising or falling with a button press. This task involved perceiving sound and pressing a button

but did not involve selective attention or working memory. The interstimulus interval for both nonwords and tone sweeps was 2.5 sec. To reduce variance related to learning, subjects were trained, using different stimuli lists than those presented during scanning, until they correctly identified a minimum of 85% of targets across all four conditions (binaural 1-back, binaural 2-back, dichotic 1-back, dichotic 2-back).

fMRI Acquisition and Processing

Subjects were scanned using a 1.5-Tesla Signa LX MRI system (General Electric, Milwaukee, Wisconsin). Before image acquisition, anterior (AC) and posterior commissures (PC) were localized for slice orientation. Axial oblique T1-weighted anatomic images were acquired parallel to the AC–PC line using a spin echo pulse sequence (18, 7-mm contiguous slices; echo time (TE) = 11 msec; repetition time (TR) = 500 msec; matrix = 256×192 pixels; field of view (FOV) 20×20 cm; number of excitations (NEX) = 2). Echoplanar functional images were acquired in the same relative slice locations using a single shot, gradient echo pulse sequence (flip angle = 60° ; TE = 60 msec; TR = 2 sec; matrix = 64×64 pixels; in-plane resolution = 3.125 mm; FOV = 20×20 cm; 1 NEX). A total of 120 functional images were collected per slice per activation condition.

Image analysis was performed using software written in Matlab (MathWorks, Natick, Massachusetts). Before statistical analysis, images from each scanning session were motion corrected for three translational directions and for the three possible rotations using SPM 99 (Friston et al 1995). One volume was discarded at the end and at the beginning of each block to avoid variance stemming from hemodynamic changes that occur during task transitions. The remaining images were spatially smoothed with a 6.25-mm full width at half maximum Gaussian kernel. In the temporal domain, a high pass filter was applied to remove drift at frequencies lower than twice the period of the activation paradigm.

Statistical Analysis

Single subject activation data were obtained by subtracting pixel intensity during the control task from pixel intensity during the experimental task and dividing this difference by the average signal intensity during the entire run to obtain normalized percent signal change for each task condition. Surface and subcortical landmarks were identified on the anatomic images, which were then transformed into standard stereotaxic space (Talairach and Tournoux 1988), using piecewise, linear in-plane transformation and slice interpolation. The transformation parameters were then applied to the activation maps. Effects of patch condition (placebo or nicotine), diagnosis, and task were assessed at each voxel using mixed model repeated measures analysis of variance (ANOVA; Holmes and Friston, unpublished data; Kirk 1982; Woods 1996) with level of working memory load (1-back or 2-back), level of selective attention load (binaural or dichotic), and patch condition as within-subjects factors and diagnosis as a between-subjects factor. Because of the exploratory nature of this study, the significance level was set at $\alpha = .01$ (not corrected for multiple comparisons), with a cluster-size threshold of eight contiguous voxels.

Effects of diagnosis and plasma nicotine concentration on mood, nicotine withdrawal, tobacco craving, task performance, and positive and negative symptoms of schizophrenia were evaluated using linear mixed effects regression analysis implemented in S-Plus (Insightful Corporation, Seattle, Washington), with subject modeled as a random effect, diagnosis as a fixed

categorical effect, and plasma nicotine concentration as a fixed continuous effect. Accuracy of working memory performance was assessed by computing D' (Repp and Frost 1988) as follows: $D' = [\text{LN}((\text{pHit} * (1 - \text{pFA})) / ((1 - \text{pFA}) * \text{pHit}))] / 2$ (Repp and Frost 1988), where LN is the natural logarithm, pHit is the number of targets correctly identified divided by the total number of targets, and pFA is the number of nontargets incorrectly identified as targets divided by the total number of nontargets. D' provides a measure of signal detection that takes into account the probability of correct and incorrect identifications.

Connectivity Methods

Effects of diagnosis and patch condition on functional connectivity were examined using a method based on the seed-voxel correlation approach (Friston 1994; Horwitz et al 1998) and interregional partial least squares (PLS) analysis (McIntosh et al 1996). This multivariate analysis tests for interregional correlations in functional activity that show the greatest changes in strength or direction across diagnostic groups, nicotine patch conditions, or both (McIntosh et al 1997). Maps of correlations are computed for each diagnostic group and patch condition between the source region and every other voxel in the brain and thus reflect the degree to which the source region coactivates with every other region in each condition. Strongly positive or negative correlations between regions imply that these regions are functionally connected. Because these correlations reflect the activity of a distributed system, PLS is then used to extract the primary components of the correlational pattern. This is achieved by singular value decomposition of the correlation matrices, producing a small set of multivariate components. Within each component, loadings to brain regions are overlaid on anatomic images and indicate the set of areas that correlate with the source region. Each component also includes loadings to diagnostic category and patch conditions (i.e., how strongly each diagnostic group reflects a given correlation pattern when receiving nicotine or when receiving placebo). In this way, PLS can be used to identify functional connectivity patterns that are common across diagnostic groups and patch condition and those that differ across group and patch condition.

Results

Nicotine Plasma Levels and Effects of Nicotine and Diagnosis on Behavior

The average duration between study days was 14.6 ± 8.5 days and did not differ between groups. Plasma nicotine levels were significantly higher during the active patch condition across groups (plasma nicotine concentration before scanning on active patch = 11.0 ± 6.5 ng/mL, on placebo patch = $.97 \pm 1.2$ ng/mL; effect of patch condition $\beta = 8.2$, SE = 1.52, $t = 5.4$, $df = 24$, $p < .0001$) and did not differ between groups during the active or the placebo patch conditions. Mixed linear regression analysis revealed no significant effects of diagnosis or plasma nicotine concentration on measures of mood ($p > .1$) or on CINA scores ($p > .3$). Similarly, effects of nicotine plasma concentration on SANS and SAPS scores were not significant (p values $> .5$). There was a trend for higher plasma nicotine concentrations to be associated with fewer symptoms of nicotine withdrawal ($\beta = -.39$, SE = .21, $t = -1.88$, $p = .07$). Results of mixed linear regression analysis of the ratings of tobacco craving and of task performance during scanning are presented in Table 1. Higher plasma nicotine concentrations were significantly associated with decreased tobacco craving across groups. Reaction times

Table 1. Results from Linear Mixed Effects Regression Analysis of Diagnosis and Plasma Nicotine Concentration Effects on Tobacco Craving and Performance Accuracy and Reaction Time during Scanning

Independent Variable	Tiffany	Binaural 1-Back		Binaural 2-Back		Dichotic 1-Back		Dichotic 2-Back	
		D'	RT	D'	RT	D'	RT	D'	RT
Diagnosis									
β	-6.23	-.64	150.58	-.66	127.36	-.65	203.58	-.68	95.11
Standard error	12.73	.27	55.73	.26	66.24	.30	62.27	-.29	76.45
<i>t</i>	-.49	-2.38	2.70	-2.52	1.92	-2.12	3.27	-2.36	1.24
<i>p</i>	.63	.02	.01	.02	.07	.04	.003	.03	.22
Plasma Nicotine Concentration									
β	-2.12	.02	-2.68	-.01	-2.52	.01	.70	-.04	-2.80
Standard error	.70	.02	3.43	.02	4.78	.02	3.44	.02	6.24
<i>t</i>	-3.03	.78	-.78	-.74	-.53	-.66	.20	-2.09	-.45
<i>p</i>	.006	.44	.44	.47	.60	.52	.84	.05	.66
Diagnosis by Plasma Nicotine Concentration Interaction									
β	1.69	-.01	-1.77	.04	-.94	-.01	-6.99	.06	.68
Standard error	.85	.02	4.17	.02	5.83	.02	4.19	.02	7.62
<i>t</i>	1.98	-.40	-.42	1.56	-.16	-.48	-1.67	2.30	.09
<i>p</i>	.06	.69	.67	.13	.87	.64	.11	.03	.93
Comment	^a	S < C	S > C	S < C	S > C	S < C	S > C	^b	

Bold denotes significant *p* values.

Tiffany, Tiffany Scale for Smoking Urges; D', a measure of accuracy of task performance (Repp and Frost 1988); RT, reaction time; S, schizophrenia patient; C, control subject.

^aHigher plasma nicotine concentrations were associated with lower tobacco craving across groups.

^bSee Figure 1.

during the tone sweep control task were significantly more rapid than reaction times during the n-back tasks (all $p < .0001$), consistent with the minimal attention and working memory requirements of the tone sweep task. Accuracy of performance during the tone sweep task did not differ from that during the n-back tasks except for the dichotic 2-back task, in which tone sweep performance was significantly more accurate ($p < .02$). There were no effects of diagnosis or patch condition on tone sweep performance accuracy or reaction time.

Across n-back task conditions, patients with schizophrenia had longer reaction times and performed less accurately than did control subjects. Plasma nicotine concentration did not have a significant effect on speed or accuracy of task performance except during the dichotic 2-back condition, the most challenging task. Here higher plasma nicotine concentrations were associated with an improvement in performance accuracy among patients with schizophrenia and with deterioration in performance accuracy among control subjects (Figure 1). Reanalysis of the behavioral data adding FTND as a fixed effect to control for group differences in FTND scores did not change the direction or significance of any of the findings. Order of patch condition did not exert a significant effect on any of the behavioral measures in either control subjects or patients.

Effects of Diagnosis and Nicotine on Brain Activation

Across patch conditions, increasing working memory load was associated with increased activation of bilateral middle frontal gyrus (Brodmann's area [BA] 9/46) in both groups, whereas increasing selective attention load was associated with increased activation of bilateral superior temporal gyrus (BA 22) and bilateral inferior parietal lobule (BA 39/40) in both groups. Voxelwise mixed model repeated-measures ANOVA was conducted to identify brain regions demonstrating task related activity that changed differently in response to nicotine across groups (group by nicotine condition by task condition interactions).

Table 2 presents Talairach coordinates of regions showing significant diagnosis by nicotine by task condition interactions. On the left two panels in Figure 2 are presented results of the memory load by nicotine condition contrasts for each group. Functional data have been projected onto a standardized T1-weighted image of a brain sliced axially, parallel to the AC-PC line. Images are displayed per radiologic convention, with the right side of the brain on the left side of the figure. Loadings in these contrasts were set to identify regions that show increases in activity on nicotine under high working memory load (2-back) and decreases or no change in activity from the control condition off of nicotine. Regions demonstrating this pattern are shown in red and yellow. Regions demonstrating the opposite pattern

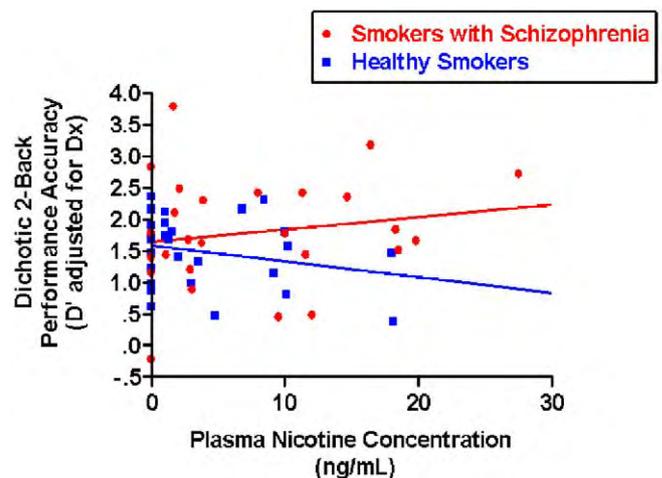


Figure 1. The relationship between plasma nicotine concentration and dichotic 2-back performance accuracy; performance scores have been adjusted by removing the mean effect of diagnosis independent of nicotine; diagnosis by plasma nicotine $\beta = .06$, $t = 2.3$, $p = .03$.

Table 2. Regions Demonstrating Significant Diagnosis by Nicotine by Task Condition Interactions

Region	X ^a	Y ^a	Z ^a	Volume (mm ³)
Diagnosis by Nicotine by Memory Load				
Left insula	-27.7	-1.1	13.7	1190
Right putamen	18.5	3.1	13.7	238
Right thalamus	19.0	-11.7	13.7	268
Right occipitotemporal gyrus (BA19/37)	48.3	-53.1	-5.4	714
Right globus pallidus	17.1	-.6	-5.4	268
Diagnosis by Nicotine by Attention Load				
Anterior cingulate gyrus (BA 32)	3.7	46.4	4.6	1041
Left thalamus	-14.5	-26.3	4.6	1517
Right thalamus	17.0	-17.6	4.6	476
Right hippocampus	20.5	-31.3	4.6	773
Right middle occipital gyrus (BA 18)	24.6	-80.3	4.6	238
Right middle/inferior frontal gyrus (BA 47)	47.0	36.9	-5.4	357
Right globus pallidus	22.5	-9.4	-5.4	1071
Right lingual gyrus (BA 19)	30.0	-47.5	-5.4	446
Left lingual gyrus (BA 19)	-37.8	-52.5	-5.4	476
Right cerebellum	6.7	-51.2	-5.4	416

BA, Brodmann's area.

^aX, Y, and Z are Talairach coordinates of the centroid of activation.

(decreasing in activity under high working memory load on nicotine and increasing or showing no change from the control condition off of nicotine) are shown in blue. In the right panel of Figure 2 are presented results from the diagnosis by memory load by nicotine condition contrast, in which the two groups are directly compared. Examination of the three sets of contrasts indicates that the significant diagnosis by memory load by nicotine condition effects at left insula and right putamen result from increases in activity under high working memory load on nicotine relative to the off nicotine condition among schizophrenic patients. The significant three-way interaction at right occipitotemporal gyrus (BA 19/37) results primarily from increased activity of this region under high working memory load on nicotine relative to the off nicotine condition in control subjects, and the significant three-way interaction at right globus

pallidus results from decreased activity of this region under high working memory load on nicotine relative to the off nicotine condition in control subjects. Activity of right thalamus also showed a greater relative increase in activity on nicotine under high working memory load in patients than in control subjects.

On the left two panels in Figure 3 are presented results of the attention load by nicotine condition contrasts for each group. Loadings in these contrasts were set to identify regions that show increases in activity on nicotine under high selective attention load (dichotic stimulus presentation) and decreases or no change in activity from the control condition off of nicotine. Regions demonstrating this pattern are shown in red and yellow. Regions demonstrating the opposite pattern (decreasing in activity under high selective attention load on nicotine and increasing or showing no change from the control condition off of nicotine)

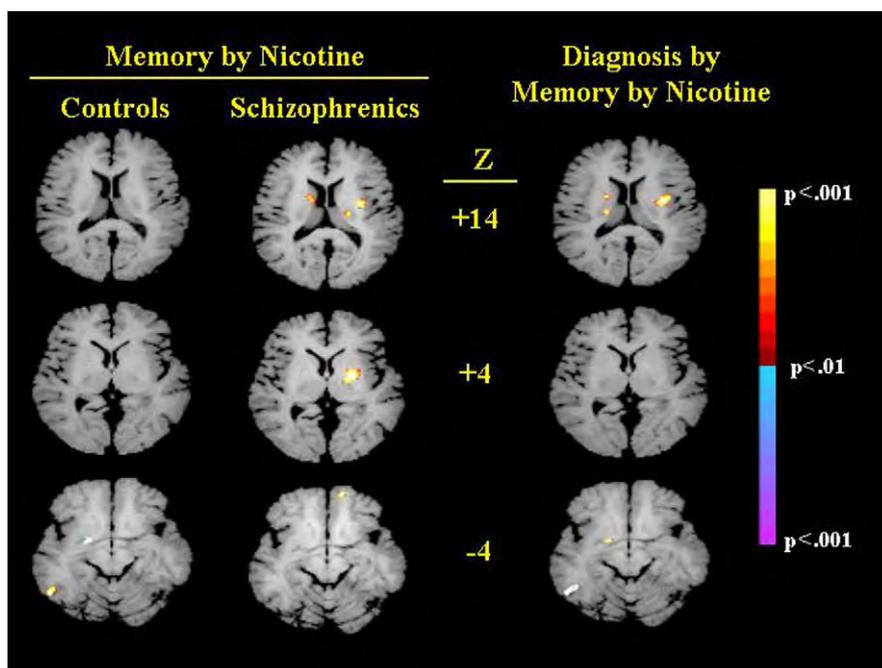


Figure 2. Voxelwise analysis of variance: The two left panels present results of the memory load by nicotine condition contrasts for each group. The right side of the brain is on the left side of the figure. Loadings in these contrasts were set to identify regions that show increases in activity on nicotine under high working memory load (2-back) and decreases or no change in activity from the control condition off of nicotine. Regions demonstrating this pattern are shown in red and yellow. Regions demonstrating the opposite pattern (decreasing in activity under high working memory load on nicotine and increasing or showing no change from the control condition off of nicotine) are shown in blue. The right panel of the figure presents results from the diagnosis by memory load by nicotine condition contrast, in which the two groups are directly compared. Here regions showing a greater increase in activity during high working memory load on nicotine in schizophrenic patients relative to control subjects are shown in red and yellow. Voxel threshold: $p < .01$; cluster threshold: eight contiguous voxels.

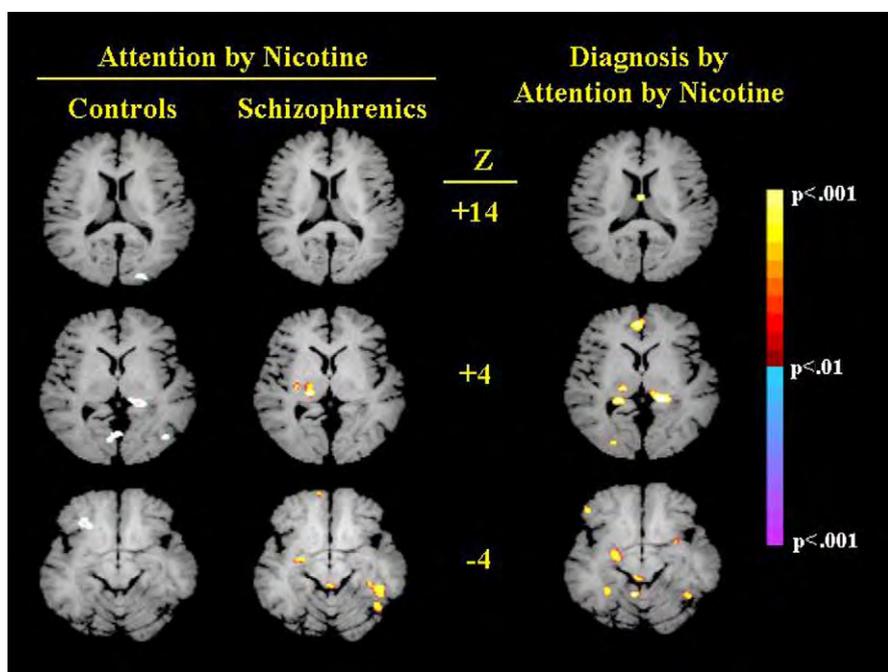


Figure 3. Voxelwise analysis of variance: the two left panels present results of the attention load by nicotine condition contrasts for each group. Loadings in these contrasts were set to identify regions that show increases in activity on nicotine under high selective attention load (dichotic stimulus presentation) and decreases or no change in activity from the control condition off of nicotine. Regions demonstrating this pattern are shown in red and yellow. Regions demonstrating the opposite pattern (decreasing in activity under high selective attention load on nicotine and increasing or showing no change from the control condition off of nicotine) are shown in blue. On the right are presented results from the diagnosis by attention load by nicotine condition contrast. Here regions showing a greater increase in activity during high selective attention load on nicotine in schizophrenic patients relative to control subjects are shown in red and yellow. Voxel threshold: $p < .01$; cluster threshold: eight contiguous voxels.

are shown in blue. On the right in Figure 3 are presented results from the diagnosis by attention load by nicotine condition contrast. Examination of these contrasts indicates that significant three-way interactions at right thalamus, right globus pallidus, and left lingual gyrus stem from increases in activity under high selective attention load on nicotine relative to the off nicotine condition among patients. The significant three-way interaction at left thalamus results from decreased activity of this region under high selective attention load on nicotine relative to the off nicotine condition in control subjects. Activity of anterior cingulate gyrus, right hippocampus, right middle occipital gyrus, right middle/inferior frontal gyrus, right lingual gyrus, and right cerebellum also showed a greater relative increase in activity on nicotine under high selective attention load in patients than in control subjects.

Because a significant diagnosis by nicotine interaction effect was observed on accuracy of performance of the dichotic 2-back task, diagnosis by nicotine condition effects were also examined using data acquired while subjects performed this task specifically (Figure 4). This analysis was designed to identify regions that significantly increased in activity in patients on nicotine relative to the placebo condition and decreased or showed no change in activity on nicotine relative to the placebo condition in control subjects (identified in Figure 4 by red and yellow). A broad network of regions that increased in activity on nicotine relative to the placebo condition in patients, but in control subjects showed no change or decreases in activity on nicotine relative to placebo were identified. These included left precentral gyrus (BA 4/6; Talairach coordinates: $X = -40, Y = -12, Z = 39$), right precuneus (BA 19; $X = 13, Y = -64, Z = 35$), right medial frontal gyrus (BA 9; $X = 7, Y = 40, Z = 32$), posterior cingulate gyrus (BA 23; $X = -8, Y = -47, Z = 25$), right inferior parietal lobule (BA 39/40; $X = 52, Y = -47, Z = 25$), left occipital gyrus (BA 19; $X = -25, Y = -82, Z = 20$), anterior cingulate gyrus (BA 32; $X = 0, Y = 47, Z = 2$), left putamen ($X = -24, Y = 2, Z = 4$), left thalamus ($X = -20, Y = -30, Z = 5$), right thalamus ($X = 18, Y = -28, Z = 5$), left occipitotemporal

gyrus (BA 37; $X = -38, Y = -67, Z = 5$), and lingual gyrus (BA 18; $X = 14, Y = -75, Z = 5$).

Functional Connectivity

We focused our connectivity analysis on functional data generated during the dichotic 2-back condition, in which significant diagnosis by nicotine effects on performance accuracy were observed. A seed voxel in the right thalamus was used in this analysis because this region showed a significant diagnosis by nicotine interaction during the dichotic 2-back task, the thalamus has among the highest concentrations of high-affinity nicotinic acetylcholine receptors (nAChRs) in the brain (Rubboli et al 1994;

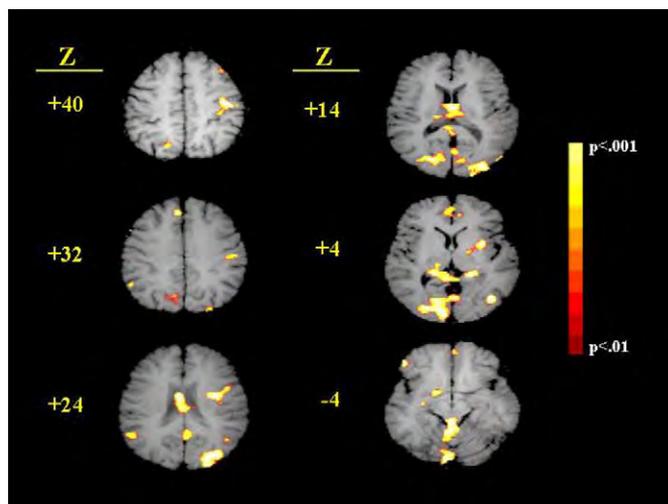


Figure 4. Voxelwise analysis of variance: dichotic 2-back task. Regions showing significant increases in activity during this task in schizophrenic patients on nicotine relative to the placebo condition and decreases or no change in activity on nicotine relative to the placebo condition in control subjects are shown in red/yellow. Voxel threshold: $p < .01$, cluster threshold: 8 contiguous voxels.

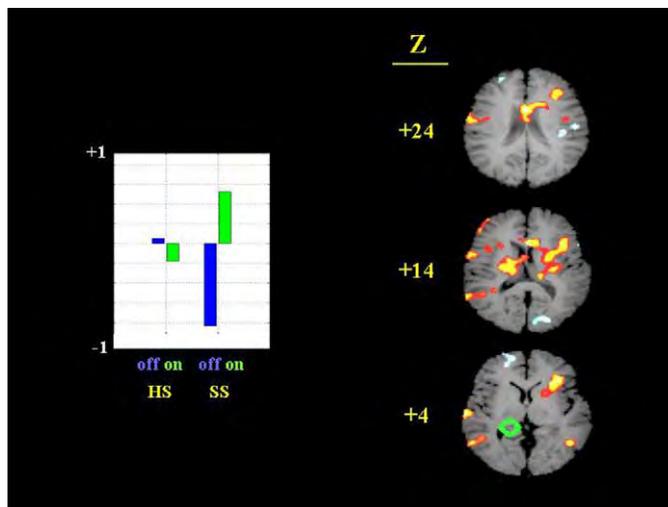


Figure 5. Partial least squares (PLS) analysis: At left are shown factor loadings for the third component of the PLS analysis, which accounted for 11% of the variance and strongly differentiated the groups in terms of loadings to nicotine patch conditions (factor loadings: control subjects, placebo patch = .05; control subjects, active patch = -.18; schizophrenic patients, placebo patch = -.83; schizophrenic patients, active patch = .52). At right are shown maps for the third component; red and yellow indicates regions demonstrating functional connectivity with the seed region (encircled in green, Talairach coordinates: $X = 18, Y = -30, Z = 5$) that is consistent with the factor loadings; blue indicates regions demonstrating functional connectivity with the seed region that is the reverse of the factor loadings. Off, placebo patch condition; On, active patch condition; HS, healthy smokers; SS, smokers with schizophrenia.

Spurden et al 1997), and postmortem work has demonstrated that regulation of thalamic high-affinity nAChRs is abnormal in patients with schizophrenia (Breese et al 2000).

This analysis produced three components that accounted for the majority of the variance in the imaging data. The first component, accounting for 68% of the variance, primarily reflected positive functional connectivity between the right and left thalamus, with similar loadings across groups and nicotine patch conditions. The second component, accounting for 13% of the variance, chiefly reflected an effect of diagnosis on connectivity (factor loadings: control subjects, placebo patch = -.44 and active patch = -.61; patients, placebo patch = .42, patients and active patch = .50), with positive loadings to right precuneus, bilateral inferior parietal lobule, and right middle temporal gyrus. The third component, accounting for 11% of the variance, strongly differentiated the groups in terms of loadings to nicotine patch conditions (factor loadings: control subjects, placebo patch = .05; control subjects, active patch = -.18; patients, placebo patch = -.83; patients, active patch = .52; left panel; Figure 5). Connectivity maps for this component are shown on the right side of Figure 5, where red and yellow indicates regions demonstrating functional connectivity with the seed region (encircled in green, Talairach coordinates: $X = 18, Y = -30, Z = 5$) that is consistent with the factor loadings, whereas blue indicates regions demonstrating functional connectivity with the seed region that is the reverse of the factor loadings. Positive loadings were observed at right putamen and thalamus ($X = 23, Y = -8, Z = 14$), left putamen ($X = -23, Y = 4, Z = 14$), bilateral middle temporal gyrus (BA 21; $X = 54, Y = -52, Z = 5$ and $X = -43, Y = -52, Z = 5$), right precentral gyrus (BA 6; $X = 59, Y = -2, Z = 23$), and left inferior frontal gyrus (BA 45/46; $X = -37, Y = 20, Z = 14$). Thus, in patients with schizophrenia, activity of these

regions was negatively correlated with activity of the right thalamic seed voxel during the placebo patch condition and positively correlated with activity of the right thalamic seed voxel during the active patch condition, when accuracy of performance improved. In contrast, the relationship between activity of these regions with that of the right thalamic seed voxel was weak during both the placebo and the active patch conditions in control smokers.

Discussion

Nicotine reduced tobacco craving and tended to reduce symptoms of nicotine withdrawal in all subjects. Patients with schizophrenia performed more slowly and less accurately than control subjects irrespective of plasma nicotine concentration across task conditions except during the dichotic 2-back task, in which nicotine improved performance accuracy in patients and worsened performance accuracy in control subjects. This finding replicates previous work by George et al (2002), who observed that tobacco smoking improved withdrawal associated impairments in spatial working memory in patients but worsened performance in control smokers (George et al 2002). Findings in our study remained significant after controlling for FTND scores, suggesting that the observed effects of diagnosis and plasma nicotine concentration on cognitive function did not stem from group differences in severity of nicotine dependence.

Nicotinic receptors desensitize following exposure to nicotine, with desensitization occurring over seconds and resensitization occurring over minutes (Grady et al 1994). Because healthy smokers upregulate high-affinity nAChRs in response to smoking, these subjects will have an increased number of sensitized nAChR receptors available to the endogenous ligand acetylcholine during nicotine withdrawal (Leonard and Giordano 2002). Enhancement of cholinergic neurotransmission has been shown to improve working memory performance by improving the selectivity of perceptual processing during encoding (Furey et al 2000). Observations in our study and in that of George et al (2002) suggest that patients with schizophrenia, perhaps because of reduced density of both high- and low-affinity nAChRs (Breese et al 2000; Court et al 1999; Freedman et al 1995; Guan et al 1999; Perry et al 1999), do not experience increased cholinergic neurotransmission when performing challenging cognitive tasks during nicotine withdrawal and instead require exogenous nicotine to sustain task performance (Leonard and Giordano 2002).

Under high working memory load, nicotine increased activity of left insula, right putamen, and right thalamus in patients to a greater degree than in control subjects, and increased activity of right occipitotemporal cortex and decreased activity of right globus pallidus in control subjects to a greater degree than in patients. Left insula has been shown to be active during the delay period of working memory tasks and has been proposed to be a component of the subvocal rehearsal system operant during verbal working memory (Cohen et al 1997; Paulesu et al 1993). This suggests that increased activity of this region in patients in the presence of nicotine and high working memory load may have facilitated phonologic rehearsal during task performance. Although previous work has demonstrated modulation of frontal cortical activity by nicotine in healthy nonsmokers and smokers performing the n-back task (Ernst et al 2001; Kumari et al 2003), we did not observe evidence that nicotine modulation of frontal cortical activity during high working memory load is different in schizophrenic versus control smokers.

Under high selective attention load, nicotine increased activity

of anterior cingulate cortex, right thalamus, right hippocampus, right occipital gyrus, right middle and inferior frontal gyrus, right globus pallidus, and bilateral lingual gyrus in patients to a greater degree than in control subjects and decreased activity of left thalamus in control subjects to a greater degree than in patients. Previous work has shown that anterior cingulate cortex, thalamus, and frontal cortex are substrates of selective attention (Braus et al 2002; Carter et al 1997; Coull 1998; Coull et al 1998; Frith and Friston 1996; Kiehl and Liddle 2001) and that these regions fail to activate normally in schizophrenic patients performing selective attention tasks (Braus et al 2002; Carter et al 1997). During the dichotic 2-back task, in which nicotine improved performance in patients and worsened performance in control subjects, all of these regions showed greater increases in activation in response to nicotine in patients than in control subjects. This observation is consistent with the notion that function of these brain regions in patients is improved in the presence of nicotine relative to nicotine withdrawal. These observations are also consistent with previous studies demonstrating that nicotine-related improvements in task performance are associated with increases in task-related brain activation (Kumari et al 2003; Lawrence et al 2002).

Results of the connectivity analysis showed that a modest proportion of the variance in interregional correlations in activity across groups and patch conditions during the dichotic 2-back task stemmed from a pattern that clearly distinguished the groups in terms of nicotine response. Positive loading of this pattern to left inferior frontal gyrus, right precentral gyrus, bilateral middle temporal gyrus, bilateral putamen, and right thalamus reflected a positive relationship between activity of these regions and activity of right thalamus in patients during the active patch condition and a negative relationship between activity of these regions and activity of the right thalamus in patients during the placebo patch condition. Control smokers showed only weak relationships between activity of these regions and activity of the right thalamus that was not strongly modulated by patch condition.

Our observations suggest that nicotine may facilitate the performance of patients on tasks involving high cognitive load by facilitating activation of cortical regions mediating task performance or by modulating thalamocortical connectivity. If impaired functional connectivity contributes to cognitive dysfunction in schizophrenia (Andreasen 1999; Friston and Frith 1995; Meyer-Lindenberg et al 2001), then modulation of functional connectivity by nicotine may permit more effective recruitment and coordination of brain regions needed for task performance in these patients. Previous work has shown that nicotine induces glutamate release from thalamocortical terminals in frontal cortex and facilitates thalamocortical neurotransmission (Gioanni et al 1999; Lambe et al 2003). This effect is mediated by high-affinity nAChRs (Lambe et al 2003). As noted earlier, patients with schizophrenia do not upregulate high-affinity nAChRs normally in response to smoking (Breese et al 2000). The observation of divergent modulation of thalamocortical connectivity by nicotine in schizophrenic and healthy smokers further suggests that the response of high affinity nAChRs to nicotine or nAChR stimulated modulation of neurotransmitter release may be altered in schizophrenia.

Because the majority of the patients in this study were taking atypical antipsychotics, which have been shown to modulate cholinergic neurotransmission (Imperato et al 1993; Parada et al 1998), the possibility that group differences in nicotine response

reflect an effect of medication rather than diagnosis cannot be excluded. Medication type and dose in these stable patients did not change across the two scanning sessions. This design would control for some aspects of potentially confounding medication effects, but not for a specific effect of medication on nAChR receptor function or response to nicotine. In addition, because all participants in this study were chronic smokers, these observations may not extend to patients with schizophrenia who do not smoke. Thus, these findings must be viewed as preliminary until replicated in medication-free or medication naïve smokers and nonsmokers with schizophrenia.

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