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Cognitive effects of nicotine in humans: an fMRI study

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Abstract

To elucidate the neural correlates of cognitive effects of nicotine, we examined behavioral performance and blood oxygenation level-dependent regional brain activity, using functional magnetic resonance imaging, during a parametric "n-back" task in healthy nonsmoking males after the administration of nicotine (12 μg/kg body weight) or saline. Nicotine, compared to placebo, improved accuracy ($P = 0.008$) in all active conditions (2%–11%), and had a load-specific effect on latency ($P = 0.004$; 43.78% decrease at the highest memory load). Within a network of parietal and frontal areas activated by the task ($P < 0.05$, corrected at the voxel level), nicotine produced an increased response ($P < 0.05$; uncorrected within the regions of interest) in the anterior cingulate, superior frontal cortex, and superior parietal cortex. It also produced an increased response in the midbrain tectum in all active conditions and in the parahippocampal gyrus, cerebellum, and medial occipital lobe during rest ($P = 0.05$; uncorrected). The present observations point to altered neuronal activity in a distributed neural network associated with on-line task monitoring and attention and arousal systems as underlying nicotine-related enhancement of attention and working memory in human subjects.

Keywords: Nicotine; Functional magnetic resonance imaging; Cognitive effects; Working memory; Attention; Anterior cingulate; Cerebellum; Parahippocampal gyrus; Neural network; Humans

Introduction

Cholinergic systems are well established as important components of the neural substrates of cognitive functions, and nicotine acts on these systems as an agonist at one of the two principal classes of receptor for the endogenous transmitter, acetylcholine (Clarke, 1995; Levin and Simon, 1998; Rezwani and Levin, 2001). Nicotinic receptors are diverse in their molecular subunit composition and, furthermore, modulate the effects of a wide diversity of transmitter pathways, including the cholinergic system itself, by both post- and presynaptic mechanisms, and by dopamine, serotonin, norepinephrine, glutamate/NMDA, GABA, opioid, and histaminergic systems (Levin and Simon, 1998). Studies in experimental animals as well as in human beings have shown that nicotine/nicotine ligands exert a correspondingly wide range of behavioral effects, including (of central interest to us here) improvements in a variety of cognitive functions, while nicotine antagonists, such as mecamylamine, impair these functions (for review, see Rezwani and Levin, 2001). Animal studies suggest that nicotinic effects upon cognition most often involve the cholinergic projections to neocortex and hippocampus influencing inter alia glutamatergic and GABAergic neurons (Gray et al., 1994; Radcliffe et al., 1999).

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The cognitive effects of nicotine/nicotine ligands in experimental animals have most reliably been demonstrated in terms of improved attention and working memory performance and are seen after both acute and chronic treatments (Levin and Simon, 1998, Rezvani and Levin, 2001). Selective nicotinic agonists, such as dimethylaminoethanol (Levin et al., 1995), epibatidine (Levin et al., 1996a), isonicotone, norisonicotine (Levin et al., 1999), (E)-metanicotine (RJR-2403; Lippiello et al., 1996), or lobeline (Terry et al., 1996) also improve performance.

Nicotine, administered via cigarette smoking, skin patches, or subcutaneous injection, has been shown to improve attention/information processing and working memory measures in smoking-deprived healthy human smoking populations (Foulds et al., 1996; Heishman et al., 1994; Kumari et al., 1996) as well as in nonsmoking populations (Kumari et al., 1997; Le Houezec et al., 1994; but see Ernst et al., 2001a). While it is possible that nicotine-induced cognitive improvements in smoking-deprived subjects reflect restoration of performance deficits caused by nicotine deprivation (Hatsukami et al., 1989), performance enhancement with nicotine in nonsmoking subjects with no preexisting deficits as well as in experimental animals suggests a true beneficial effect of nicotine. Nicotine is known to increase cortical arousal, as measured with electroencephalographic techniques (Knott et al., 1999), which in human beings is thought to be closely associated with the quality of attentional efficiency and thus a potential mediator of enhanced cognitive performance (Eysenck, 1982).

We applied functional magnetic resonance imaging (fMRI) to elucidate the neural correlates of the effects of subcutaneous nicotine administration on behavioral performance and blood oxygenation level-dependent (BOLD) regional brain activity, during a parametric "n-back" working memory task in nonsmoking healthy subjects employing a double-blind placebo-controlled within-subjects design. Previous studies have mainly used fMRI to investigate the neural mechanisms of nicotine effects relevant to nicotine dependence (Stein et al., 1998) or tolerance (Ross et al., 2001). To avoid the potential problems with smoking withdrawal in smoking subjects (Rezvani and Levin, 2001), we chose to examine the effects in subjects who had never smoked (never-smokers). Further, to allow for postulated enhancement to working memory functions in subjects with no preexisting deficits we used a parametric "n-back" task with varying load conditions.

We hypothesized that nicotine would improve working memory performance, as compared to placebo, in general, but specifically with high memory load task conditions, i.e., 2-back and 3-back, and that this would be accompanied by an altered BOLD response in associated network of regions including the prefrontal, premotor, cingulate, and parietal cortices found previously to be activated with this task in normal subjects (Callicott et al., 1999). We made further *specific* predictions as various brain regions within the working memory neural network are thought to subserve more specialized functions. Dorsal prefrontal cortex is specialized for noting task-relevant contents of memory (MacDonald et al., 2000) and anterior cingulate for on-line monitoring, error detection, and response execution (Botvinick et al., 2001; Paus, 2001), whereas the parietal cortex is thought to play a crucial role in short-term storage (Gathercole, 1994; Honey et al., 2000; Paulesu et al., 1993). We thus predicted that specific memory load-related effects of nicotine on response accuracy would be mediated primarily via altered activity in the dorsolateral prefrontal cortex, whereas specific load-related effects on the latency to respond (reaction time, RT) would be mediated via its actions in the parietal cortex. Note, however that the evidence is somewhat mixed for these specialized brain structure–function relationships, with overlapping functions of some brain regions (Cohen et al., 1997). Such overlap, if it exists, would hamper the chances of finding clear changes in activation patterns in different regions within the working memory network with nicotine as hypothesized above. On the basis of previously known effects of nicotine (cited above), we also hypothesized that nicotine-induced generalized improvements (i.e., including improvements at the 0-back condition which has no memory load) would be mediated via its established effects on arousal (Knott et al., 1999), attention (Wesnes and Warburton, 1978), and efficient processing measures (Edwards et al., 1985). We therefore expected corresponding changes in the BOLD response in midbrain and brain stem regions which are implicated in the control of cortical arousal (Paus et al., 1997; Coull, 1998); and in the anterior cingulate within the working memory network, which is known to regulate various aspects of attention (Schall et al., 2002; Luks et al., 2002).

Material and methods

Subjects

Twelve right-handed 20–40-year-old males (mean weight = 65 kg, SD = 4.5) served as subjects. All potential subjects underwent a semistructured medical screening procedure for thyroid dysfunction, glaucoma, heart disease, hypo- or hypertension, history of severe mental illness, anorexia, rapid mood changes, regular medical prescription and over the counter medications or herbal supplements, and alcohol dependency and drug abuse (ascertained by urine analysis), before being accepted as study participants. The study sample was restricted to males only in order to control for the effects of gender and hormonal variation on drug metabolism. One subject was discarded because of data acquisition problems. The final sample thus consisted of 11 subjects (nine white Caucasian and two Asian) only. All subjects who participated in the study signed a consent form approved by the Ethical Committee at the Institute of Psychiatry. Subjects received £75 each for their participation.

Experimental design

All subjects were tested (double-blind) identically on two occasions (once under saline, once under nicotine), 2 weeks apart. They were randomly assigned in equal numbers (six/drug order) using one of two drug orders. Drug order I consisted of placebo (saline) on occasion 1 and 12 μg/kg nicotine on occasion 2; drug order II, of nicotine on occasion 1 and placebo on occasion 2. The time of day at which testing was conducted was kept constant (± 30 min) for each subject for the two occasions of testing, but varied across subjects (between 1 and 5 PM).

Drug dose and administration

Active drug (nicotine) as well as placebo (saline) were given subcutaneously in the triceps region of the left upper arm, using a fine needle. The dose of nicotine was prepared as 1 mg nicotine base in 1 ml of 0.9% saline with added sodium bicarbonate (2.13 g/250 ml of prepared solution). The choice of the drug dose and delivery method was dictated by both scientific and ethical reasons. We had observed positive effects of nicotine at this dose given subcutaneuously on information processing measures in never-smokers with little adverse side effects (Kumari et al., 1997). As our study was carried out in never-smokers we did not opt for a higher dose, likely to cause side effects and thus interfere with the performance. The drug latency period of 9–11 min and task duration of 12.5 min were chosen to cover the period of maximum effects of nicotine given subcutaneously (Russell et al., 1990).

Experimental paradigm

A modified version of the parametric n-back working memory task of Callicott et al. (1999) was used in order to allow for nicotine-induced enhancement in performance. It involved both spatial and verbal working memory, monitoring visually presented Arabic numerals (2,4,6, or 8; presentation time: 400 ms; interstimulus-interval: 1350 ms; a particular number always appeared in the same location) within a diamond-shaped box on the screen at a given delay from the original occurrence (0-back, 1-back, 2-back, and 3-back). There were five 30-s conditions in total (rest, 0-back, 1-back, 2-back, 3-back), each presented to subjects five times in pseudorandom order, controlling for any order effect. In total, 15 stimuli were presented in each 30-s active block. Subjects viewed the paradigm projected onto a screen at the end of the scanner couch via a prismatic mirror as they lay in the scanner. On-line accuracy and latency data were determined via button presses on every trial using the right thumb from all subjects while they underwent fMRI. Subjects were required to press the button corresponding to the correct numeral/location after they viewed the 0, 1, 2, or 3 forward stimulus (chance performance equals 25%).

Image acquisition

Echoplanar MR brain images were acquired using a 1.5 T GE Signa system (General Electric, Milwaukee WI, USA) at the Maudsley Hospital, London. Daily quality assurance was carried out to ensure high signal-to-ghost ratio, consistent high signal-to-noise ratio, and excellent temporal stability using an automated quality control procedure (Simmons et al., 1999). A quadrature birdcage head coil was used for RF transmission and reception. In each of 16 near-axial noncontiguous planes parallel to the intercommissural (AC-PC) plane, 250 T_2*-weighted MR images depicting BOLD contrast (Ogawa et al., 1980) were acquired over the 12.5-min experiment with echo time (TE) = 40 ms, repetition time (TR) = 3 s, in-plane resolution = 3.1 mm, slice thickness = 7.0 mm, and interslice gap = 0.7 mm. Head movement was limited by foam padding within the head coil and a restraining band across the forehead. At the same session, a high resolution 3-D inversion recovery prepared spoiled GRASS volume dataset was acquired in the AC-PC plane with TE = 5.3 ms, TI = 300 ms, TR = 12.2 s, in-plane resolution = 0.94 mm, slice thickness = 1.5 mm.

General procedure

Subjects were told that the purpose of the study was to investigate the brain correlates of the effects of nicotine on cognitive performance. They were requested to abstain from alcohol and any medication for at least 24 h prior to their appointment, and also to abstain from any drink containing caffeine for at least 4 h prior to their scheduled scans. Caffeine has a physiological half life of 3 1/2 h and is known to interact with nicotine administration in humans (Parsons and Neims, 1978). After the measurement of blood pressure, heart rate, and body weight, subjects were injected with drug/placebo and taken to the imaging laboratory (adjacent to the injection room). After the scanning was over, all subjects were debriefed and asked, on each occasion after the scanning, whether they thought they had been given nicotine or placebo. All subjects performed the task (once) a week in advance of their scheduled scan to minimize any practice effects and had been in the scanner at least once before participating in the current study.

Behavioral measures

Behavioral performance was assessed as percentage of response correct (accuracy) and the time (in ms) taken to respond (RT) for correct responses (latency). The effects of nicotine on response accuracy and latencies over 0-back, 1-back, 2-back, and 3-back load conditions were analyzed (separate analyses for response accuracy and latency) by drug condition (nicotine/placebo) × drug order (I, II) × load (0-back, 1-back, 2-back, and 3-back trials) analyses of variance (ANOVA) with drug condition, and load as within-

subjects factors and drug order as a between subjects factor, followed by paired *t* tests wherever appropriate. All analyses were performed by SPSS windows (version 10).

Functional MRI

Image preprocessing

For each subject, the 250 volume functional time series was motion corrected (Friston et al., 1996), transformed into stereotactic space, spatially smoothed with a 10-mm FWHM Gaussian filter, and band pass filtered using statistical parametric mapping software (SPM99; http://www.fil.ion.ucl.ac.uk/spm). Data for individual subjects were first examined for excessive motion (rotations no larger than 1 degree or translations no greater than 1 mm) and then examined for any differences between the drug and placebo conditions using a drug condition × movement dimension (*x, y, z,* pitch, roll, yaw) × drug order ANOVA. The high resolution structural image from each subject was transformed into stereotactic space and averaged to form a mean structural image for the superposition of activation maxima.

Models

Data were analyzed using a two-stage random effect procedure in order to make inferences about the population as a whole (Friston et al., 1999). The first stage identified subject-specific activations in a parametric model consisting of one covariate with four levels (0-back, 1-back, 2-back, 3-back) and rest as an implicit baseline. The boxcar for each 30-s epoch was convolved with the hemodynamic response function. The zero order model parameter related to activations from rest irrespective of working memory load, while the first order parameter related to activations from rest with a linear relationship to load. Separate subject-specific analyses were performed for drug and placebo conditions. The second stage of the random effect model tested for generic activations across subject-specific images using a one-sample *t* test. Separate tests were performed for zero order and first order effects in both drug and placebo conditions. Drug and placebo subject-specific images were pooled to test for activations common to both conditions. Drug effects at each working memory load were investigated using a two-sample *t* test on the subject-specific activation maps for 0-back vs rest, 1-back vs rest, 2-back vs rest, and 3-back vs rest.

Statistical inferences

Generic drug or placebo activations were considered significant at $P < 0.05$, corrected for multiple comparisons at the voxel level. Differences in drug and placebo activations at each working memory load were considered significant at $P < 0.05$ uncorrected within regions of interest defined by the generic drug and placebo activation map as shown in Fig. 2. Differences were also tested using a threshold of $P < 0.05$ corrected at the voxel level within 5 mm spherical regions of interest. Finally, we repeated the above analyses with the data from only the last 15 s of each block, so reducing the chances of type II error due to the possibility that the BOLD signal at the beginning of a given block might be influenced by the level of BOLD signal in the preceding block.

Baseline comparison

Differences in baseline (rest) activity under nicotine and placebo were also examined. For each subject, functional images related to rest were averaged after correcting for global signal intensity variations and the mean image under drug and placebo compared with a paired *t* test. The method used is insensitive to global differences which are removed in the analysis. However, the method is sensitive to local differences. Differences in baseline were considered significant at $P < 0.05$ uncorrected at the voxel level.

Brain activity and behavioral performance

Subject-specific parameter estimates were extracted from regions of interest defined by task related activations (the zero order effect) and drug modulation. The relationship of activity in these regions to behavioral performance, working memory load, and drug condition was examined in repeated measures ANCOVAs, with brain activity as a within-subject variable and change in performance as a covariate. The effects of nicotine administration on accuracy and RT measures were also reevaluated with ANCOVAs, with repeated measures on memory load and drug condition and changes in brain activity during the rest condition (as a function of nicotine administration) in relevant regions as a covariate.

Results

Behavioral measures

Mean response accuracy and latency under all experimental conditions, collapsed across drug orders, for both the drug and placebo conditions are presented in Fig. 1a and 1b. There was a decrease in response accuracy with increasing working memory load in both the drug and placebo conditions, as indicated by a main significant effect of load (F [3,27] = 66.90, $P < 0.001$; see Fig. 1a). Subjects showed faster RTs over memory load conditions than without any memory load (F [3,27] = 5.36, $P < 0.005$; Fig. 1b). They also showed better performance in terms of response accuracy over all trials after the administration of nicotine than after placebo (F [1,27] = 11.68, $P = 0.008$). The drug condition × load interaction was not significant for response accuracy ($F > 1$) but was significant for response latency (F [3,27] = 5.60, $P < 0.004$). Subjects had faster RTs (t [10] = 2.3, $P = 0.04$) after nicotine than placebo administration for the 3-back condition, but no significant differences were seen for other conditions, although there was a trend (t [10] = 2.11, $P = 0.06$) for increased RT under nicotine in the 0-back condition. No main or interactive effects of drug order were found on either response

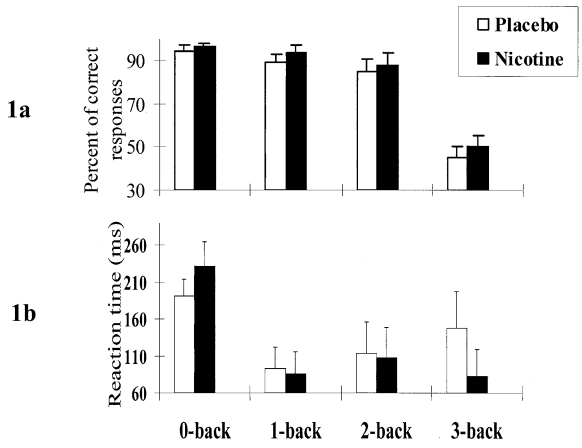

Fig. 1. Response accuracy (% correct; error bars demonstrate standard error of the mean; (a) and response latency (in ms; error bars demonstrate standard error of the mean; (b) for 0-back, 1-back, 2-back, and 3-back trials (chance performance for accuracy equals 25%) for the placebo and nicotine conditions.

accuracy or latency measures. The fast reaction times found implied that subjects had prepared their motor response by placing their thumb on the correct button in advance of the cue to press (the presentation of the 1, 2, or 3 forward stimulus).

Functional MRI

There was no difference between the placebo and drug condition for motion on any dimension ($F > 1$). As expected (Callicott et al., 1999), a network of frontal and parietal areas was activated by the task. The network included bilateral activations in the superior frontal gyrus, the superior parietal lobule, the anterior cingulate gyrus, the right dorsolateral prefrontal cortex, and unilateral activations in right cerebellum and left sensorimotor cortex, corresponding to the right-hand button press. Table 1 displays the zero order activations for drug and placebo conditions. The same regions showed a linear load dependency (first order effects). Based on the t values, some regions appear to be activated equally in the two conditions (e.g., left superior parietal lobe) while others show a difference in activation (e.g., anterior cingulate). Furthermore, midbrain tectum was activated under nicotine but not under the placebo condition.

To test whether these differences were significant and whether they varied with working memory load, drug and placebo activations were compared using a paired t test for 0-back, 1-back, 2-back, and 3-back levels (each compared to rest). Because the random effect method is less sensitive when subject numbers or effect size is small (Friston et al., 1999), we used a region of interest approach, lowering our threshold of significance but restricting our search to the network of areas described above. As shown in Fig. 2, nicotine was associated with a relative increase in response in the right anterior cingulate (0-back [centered at the coordinates, $x = 6$, $y = -5$, $z = 40$], 1-back [centered at $x = 5$, $y = 0$, $z = 40$], and 2-back [centered at $x = 6$, $y = 0$, $z = 43$] contrasted with rest), superior frontal cortex (bilateral for 1-back [centered at $x = 51$, $y = 2$, $z = 41$ and $x = -51$, $y = 4$, $z = 36$] and 2-back conditions [centered at $x = 51$, $y = 2$, $z = 41$ and $x = -51$, $y = 2$, $z = 37$], right side only

Table 1
Brain regions showing significant increases in activity ($P < 0.05$ corrected at voxel level) irrespective of working memory load (zero-order effect) under nicotine and placebo conditions

	Talaraich[a] coordinates (in mm)							
	Left				Right			
	x	*y*	*z*	*t* value	*x*	*y*	*z*	*t* value
Nicotine								
Anterior cingulate	−6	8	48	18.32	—	—	—	
Dorsolateral prefrontal cortex	—	—	—		40	42	24	9.43
Superior frontal gyrus	−32	−8	50	13.85	36	−6	46	14.32
Sensorimotor cortex	−48	−24	46	8.95	—	—	—	
Superior parietal lobe	−34	−54	42	13.64	38	−46	44	9.79
Cerebellum	—	—	—		30	−52	−34	9.50
Midbrain tectum	−6	−22	−2	10.15	—	—	—	
Placebo								
Anterior cingulate	−6	8	52	14.61	—	—	—	
Dorsolateral prefrontal cortex	—	—	—		36	40	24	5.82[b]
Superior frontal gyrus	−30	−4	52	9.33	36	−6	−46	14.32
Sensorimotor cortex	−38	−30	46	14.65	—	—	—	
Superior parietal lobe	−32	−54	48	13.00	36	−44	40	12.65
Cerebellum	—	—	—		22	−58	−28	8.82

[a] Talairach and Tournoux (1988).
[b] $P < 0.0001$ uncorrected.

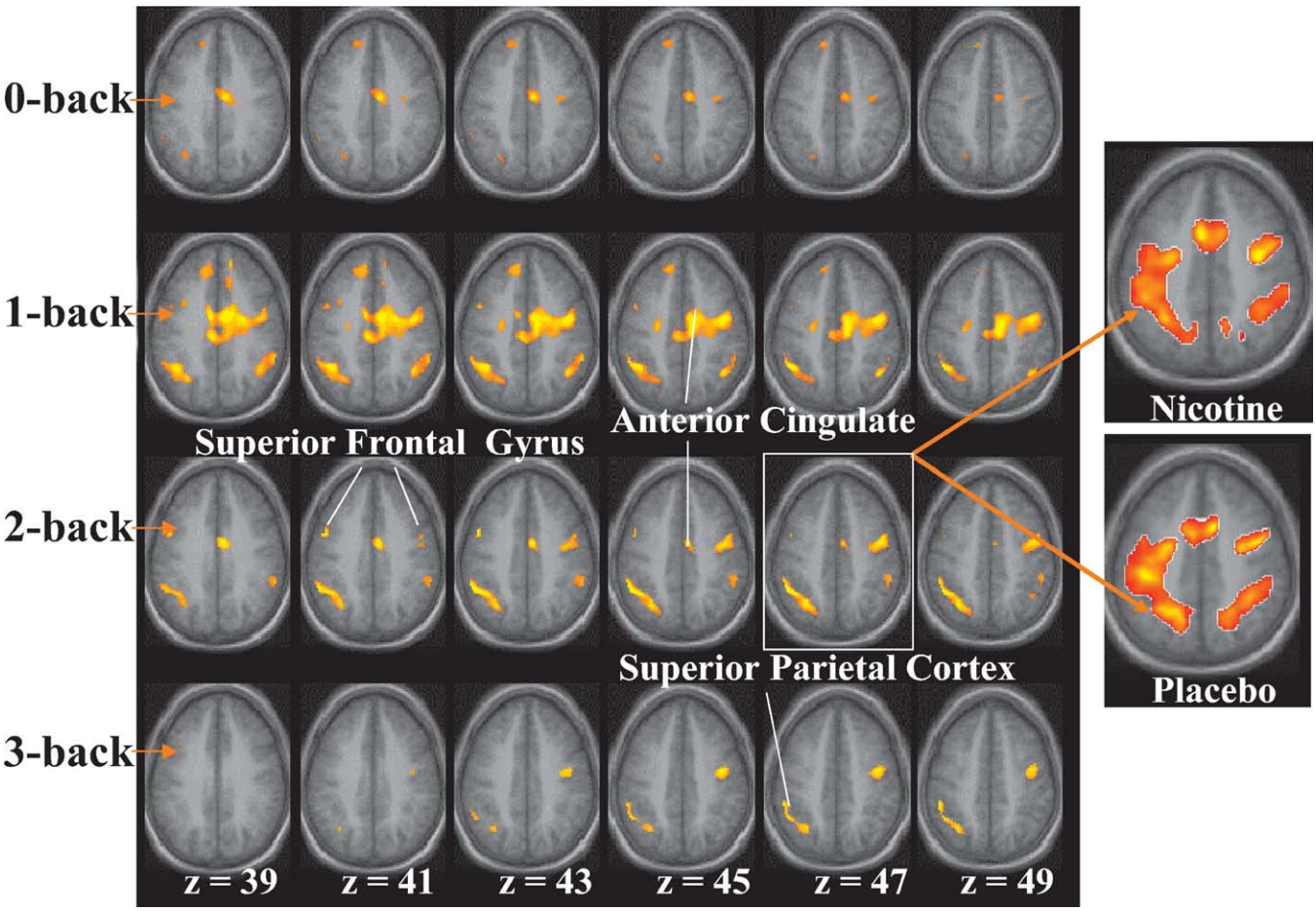

Fig. 2. Nicotine-related modulations at each working memory load. The significant differences between nicotine and placebo activations (paired *t* test) for 0-back, 1-back, 2-back, and 3-back vs rest contrasts are shown superimposed on the average structural image. Six transverse slices are shown from each condition with their associated Talairach *z* coordinates. The images have been thresholded at $P < 0.05$ uncorrected although most regions are significant at $P < 0.05$ corrected within a 5-mm sphere located within the regions of interest. The left hemisphere is shown on the left of each slice. Increased activation is demonstrated in the anterior cingulate (0-back *minus* rest; 1-back *minus* rest, and 2-back *minus* rest), superior frontal cortex (bilateral for 1-back *minus* rest and 2-back *minus* rest; right side only for 3-back *minus* rest), and superior parietal cortex (bilateral for 1-back *minus* rest and 2-back *minus* rest; left side only for 3-back *minus* rest third row). The inset panel shows the generic maps (one sample *t* test) under nicotine and placebo for the 2-back *minus* rest comparison from which the difference map is constructed.

for the 3-back [centered at $x = 46$, $y = -1$, $z = 49$]) and superior parietal cortex (bilateral for 1-back [centered at $x = 56$, $y = -43$, $z = 39$ and $x = -53$, $y = -45$, $z = 39$] and 2-back conditions [centered at $x = 56$, $y = -43$, $z = 39$ and $x = -53$, $y = -45$, $z = 39$], left side only for 3-back [centered at $x = -44$, $y = -52$, $z = 51$]). In addition, nicotine was also associated with a relative decrease in response in the right superior parietal cortex for the 3-back contrasted with rest comparison. Fig. 2 also shows that the differences in activation between nicotine and placebo were located at the margins of the activation clusters, suggesting that nicotine influenced the spatial extent of the cluster but not the percentage change in BOLD signal within it. The figure also shows that nicotine has its largest influence in the 1-back condition. Activations in the sensorimotor cortex and dorsolateral prefrontal cortex regions of interest were not significantly different ($P > 0.05$) in the drug and placebo conditions at any working memory load. Activation in the cerebellum (centered at $x = 24$, $y = -60$, $z = -28$) was significantly different between the drug and placebo conditions only for the 1-back working memory load. Nicotine related activation in the midbrain tectum was present across all active conditions, with additional activation seen in the caudate nucleus, thalamus, orbitofrontal cortex, and temporal region in some, but not all, active conditions, as shown in Fig. 3. These variable activations were not identified in our zero-order model and thus fall outside our specified regions of interest.

Essentially the same results were found when the analyses were repeated, using the data from only the last 15 s of each block rather than entire 30-s blocks. The consistency between these two sets of results presumably reflects the success with which block order was counter-balanced for each run (i.e, each block of a given load was preceded by a block of each of the remaining loads).

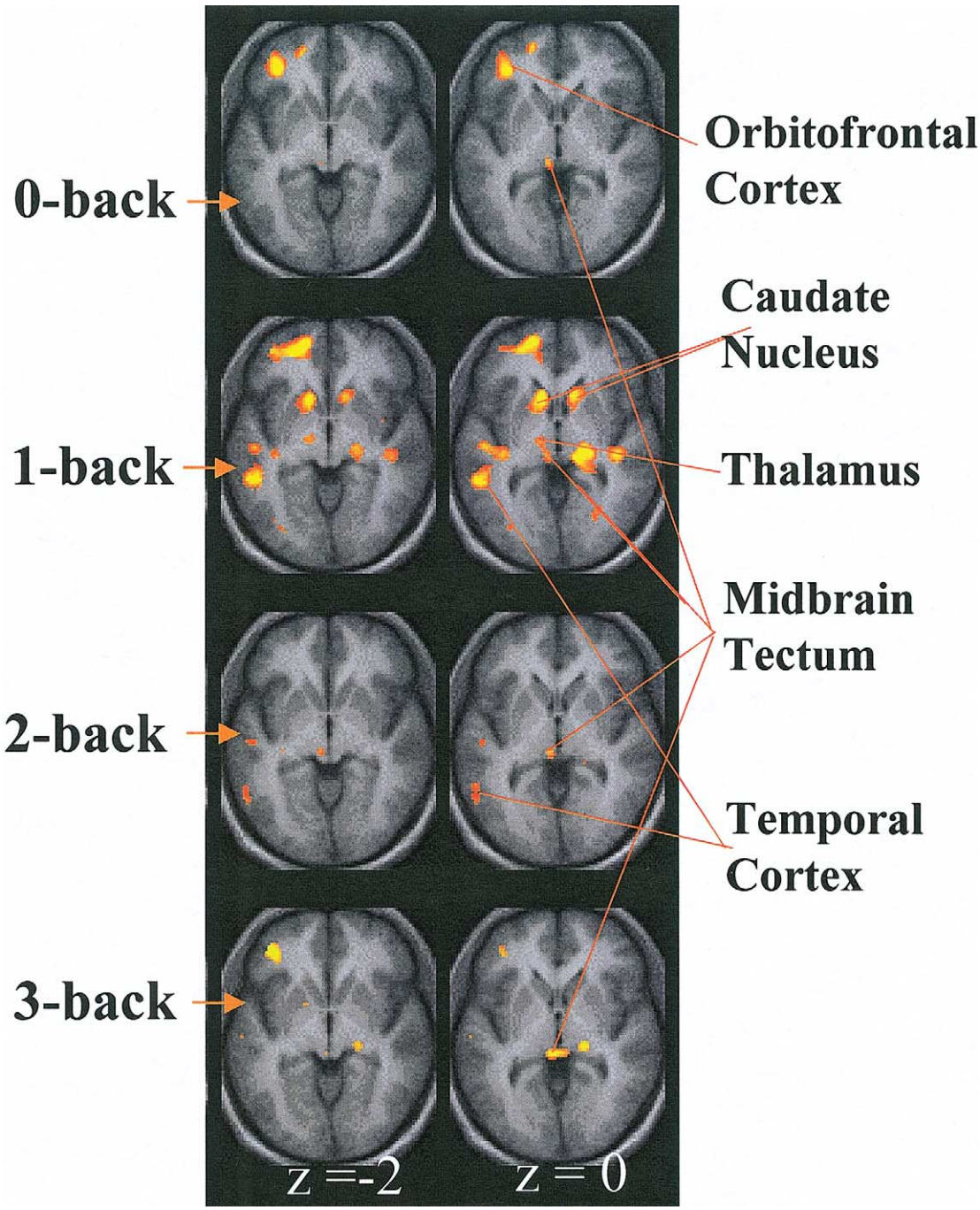

Fig. 3. Transverse slices of the average structural image with associated Talairach *z* coordinates demonstrating nicotine specific activity in the midbrain tectum for all active conditions contrasted with rest. The images (showing differences between nicotine and placebo activations) have been thresholded at $P < 0.05$ uncorrected.

During the rest condition, nicotine was associated with greater baseline activity in the posterior cingulate, medial occipital lobe, parahippocampal gyrus, and cerebellum, and decreased baseline activity in the medial prefrontal cortex (see Fig. 4). While the effects are small ($P < 0.05$, uncorrected), the regions identified were consistent across subjects and relate to previous studies of nicotine effects (see Discussion).

Brain activity, performance, and drug effects

Activity in the anterior cingulate and superior parietal cortex covaried with behavioral measures across all levels of working memory, suggesting a relationship between the fMRI and behavioral effects of nicotine (seven out of nine fMRI effects became nonsignificant after covarying for both accuracy and latency; see Table 2). In contrast, activity in

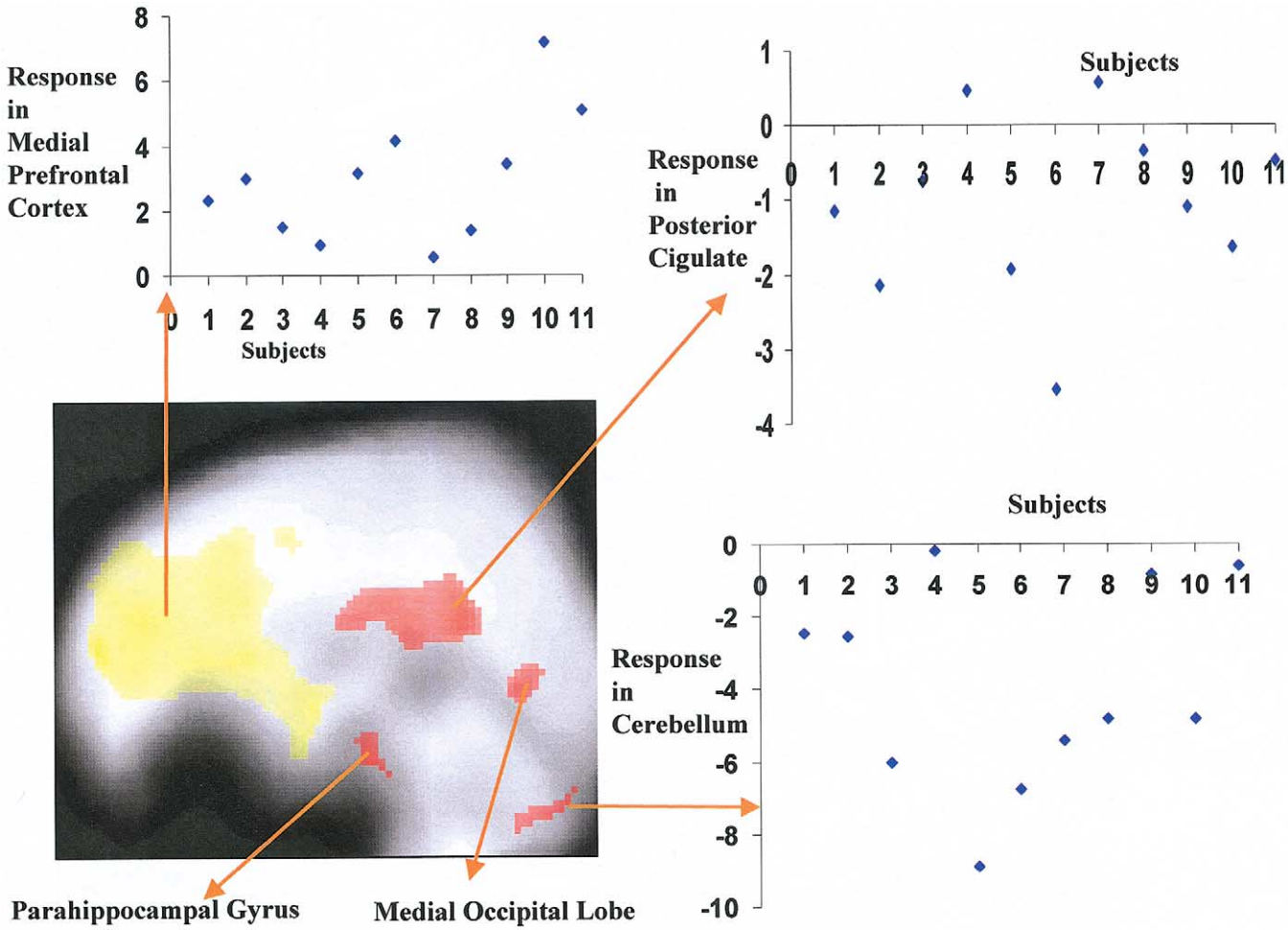

Fig. 4. A sagittal slice of the average functional image during the rest condition demonstrating altered baseline activity with nicotine. Increases under nicotine are shown in red and decreases in yellow ($P < 0.05$ uncorrected). The graphs for each region show the difference between placebo and drug conditions (placebo *minus* drug) for each of the 11 subjects. A negative number indicates that activity under nicotine was greater than under placebo; a positive number indicates the reverse.

the superior frontal cortex showed only a weak association with behavioral measures (only one out of four fMRI effects of nicotine became nonsignificant after covarying for both accuracy and latency; see Table 2). Activity in the midbrain tectum (superior colliculus) showed an association with behavioral measures only at the lowest cognitive load, i.e., the drug effect became nonsignificant [F value reduced from 6.75 to 3.82] after covarying for both accuracy and speed measures for the 0-back condition, but remained more or less unchanged for all active conditions with varying working memory load.

We also examined the relationship between behavioral performance and nicotine-related modulations in baseline cerebral activity in the cerebellar, medial occipital, parahippocampal, posterior cingulate, and medial frontal regions identified above. The effect of nicotine on accuracy over all working memory loads was abolished when the analyses controlled for baseline changes in cerebellar activity [F (1,24) = 1.03, ns], but remained significant (though attenuated in some cases) when controlling for baseline changes in the medial occipital lobe [F (1,24) = 6.83, P = 0.03], parahippocampal gyrus [F (1,24) = 11.28, P = 0.01], posterior cingulate [F (1,24) = 5.64, P = 0.04], and medial prefrontal cortex [F (1,24) = 11.48, P = 0.01]. For the RT data, the drug condition × load interaction became nonsignificant after controlling for increased activity in the cerebellum ($F < 1$) or medial occipital lobe [F (1,24) = 2.41, ns] but was unaffected by other regions.

Postexperiment briefing

Four subjects correctly stated when they received nicotine, five subjects were unsure, and the remaining two stated incorrectly which treatment they received on each occasion of testing. These numbers are sufficiently close to chance expectation that even the four subjects whose statements corresponded to the treatments received may have been guessing.

Table 2
ANOVAs and ANCOVAs of nicotine-related changes in cerebral activity for each working memory load with change in response accuracy (% correct) and latency (RT) as co-variates

	ANOVA (df = 1,10)	With change in % correct (df = 1,9)	With change in RT (df = 1,9)	With change in RT and % (df = 1,8)
Right anterior cingulate				
0-back minus rest	$F = 4.57$, $P = 0.05$	$F = 3.87$, ns	$F = 1.32$, ns	$F = 0.05$, ns
1-back minus rest	$F = 5.80$, $P = 0.04$	$F = 2.88$, ns	$F = 5.61$, $P = 0.04$	$F = 2.78$, ns
2-back minus rest	$F = 6.63$, $P = 0.03$	$F = 9.74$, $P = 0.01$	$F = 5.89$, $P = 0.04$	$F = 8.14$, $P = 0.02$
Right superior frontal gyrus				
1-back minus rest	$F = 6.69$, $P = 0.03$	$F = 8.76$, $P = 0.02$	$F = 5.99$, $P = 0.04$	$F = 8.27$, $P = 0.02$
2-back minus rest	$F = 5.38$, $P = 0.04$	$F = 6.98$, $P = 0.02$	$F = 5.12$, $P = 0.05$	$F = 7.395$, $P = 0.03$
Left superior frontal gyrus				
1-back minus rest	$F = 5.16$, $P = 0.05$	$F = 4.62$, ns	$F = 5.16$, $P = 0.05$	$F = 0.05$, ns
2-back minus rest	$F = 5.55$, $P = 0.04$	$F = 8.02$, $P = 0.02$	$F = 7.78$, $P = 0.02$	$F = 8.79$, $P = 0.02$
Right superior parietal lobe				
1-back minus rest	$F = 5.27$, $P = 0.04$	$F = 2.28$, ns	$F = 5.06$, $P = 0.05$	$F = 1.17$, ns
2-back minus rest	$F = 5.06$, $P = 0.05$	$F = 3.61$, ns	$F = 5.34$, $P = 0.05$	$F = 4.04$, ns
3-back minus rest	$F = 6.21$, $P = 0.03$	$F = 7.28$, $P = 0.02$	$F = 8.32$, $P = 0.02$	$F = 7.96$, $P = 0.02$
Left superior parietal lobe				
1-back minus rest	$F = 7.06$, $P = 0.02$	$F = 4.56$, ns	$F = 6.17$, $P = 0.04$	$F = 3.43$, ns
2-back minus rest	$F = 6.10$, $P = 0.03$	$F = 6.07$, $P = 0.04$	$F = 5.60$, $P = 0.04$	$F = 4.89$, ns
3-back minus rest	$F = 6.84$, $P = 0.03$	$F = 4.35$, ns	$F = 1.88$, ns	$F = 0.25$, ns

Note. ns, nonsignificant ($P > 0.05$).

Discussion

The present study was designed to investigate nicotine-induced enhancement in working memory functions and the neural mechanisms underlying this effect in normal healthy nonsmoking subjects. At the behavioral level, we found that nicotine improved performance in all active conditions in terms of response accuracy but, contrary to our expectations, did not show load-specific effects on this measure. However, in line with our predictions, nicotine did have load-specific effects on response latency. These followed a biphasic pattern: significantly faster RTs at the highest load (3-back) and a strong trend ($P = 0.06$) toward slower RTs at the lowest load (0-back). A possible interpretation of these results is that subjects were more relaxed under nicotine, perhaps due to anxiolytic effects mediated through GABA receptors and the endorphins (Sullivan and Covey, 2002), and therefore showed slowed reaction time for the 0-back condition (in which a fast reaction was not required to enhance accuracy). At higher load, however, nicotine-induced enhancement of cognitive arousal led to faster responding, given that a speeded response now helped maximize performance (by unloading from memory as quickly as possible to permit reloading). This apparently paradoxical combination of increased relaxation and increased arousal has frequently been noted in smokers' self-reports and in studies of the behavioral effects of nicotine (Wesnes and Warburton, 1978). The combined increase in speed and accuracy in the 3-back condition rules out speed-accuracy trade-off.

At the neural level, a network comprising frontal and parietal regions was activated with increasing memory load in both the drug and placebo conditions. These observations are congruent with previous studies of working memory, reporting involvement of the frontal and parietal regions using both positron emission tomography (PET) and fMRI (Callicott et al., 1999; Cohen et al., 1997; Ernst et al., 2001b; Honey et al., 2000; Smith and Jonides, 1997). Within the working memory neural network, nicotine increased the extent of activation in the anterior cingulate (0-back, 1-back, and 2-back), superior frontal (1-back and 2-back) and left superior parietal cortex (1-back, 2-back, and 3-back) (see Fig. 2). It also decreased activation in the right superior parietal cortex during the 3-back condition. In a previous study (Ernst et al., 2001b) using PET, the administration of 4-mg nicotine gum enhanced activation (which correlated with the percentage of correct responses) during a working memory task (2-back v look for X) in ex-smokers but reduced activation in smokers; the latter effect was thought to reflect tolerance. In general, our findings, showing mostly enhanced activation under nicotine in nonsmokers, are in line with these previous data.

Overall, the observed effects of nicotine on cognitive function, in terms of improved accuracy over all active conditions including the 0-back condition (with no working memory load), are congruent with those reported previously for attention and working memory in human and animal subjects (see Introduction for references). They can be interpreted in terms of enhanced attentional resources, motor representation, and arousal with nicotine, while the influence of load on response speed may reflect a load-dependent shift in processing strategy toward faster responding and therefore a reduced need for short-term memory storage. Relating these effects to our fMRI results, it can be suggested that, during low load conditions (including the 0-back), subjects utilized strategies involving frontal re-

gions, which focused on error monitoring, a cognitive function subserved by the anterior cingulate, and nicotine enhanced activity in this region. In contrast, during high load conditions, subjects may have utilized strategies involving parietal regions, which focused on speed (unloading from memory as quickly as possible in order to load new information), and nicotine also enhanced this strategy.

However, at the highest load, nicotine increased activation only in the left superior parietal cortex; in the *right* superior parietal cortex *reduced* activation was observed. The latter effect can perhaps be explained in terms of increased bias for verbal over spatial cues (Algan et al., 1997). Verbal working memory systems are thought to be located predominantly in the left hemisphere and spatial working memory systems, in the right (Smith and Jonides, 1997). The task used in this study could be performed efficiently with either spatial or verbal cues. In the post-experimental debriefing, subjects reported encoding information using spatial cues. However, given that a particular numeral always appeared in the same location, it is possible that they used verbal (coding the numerals) as well as spatial cues to maximize performance. The left lateralization of the observed nicotine-induced increase in parietal activation perhaps therefore reflects a shift toward increased use of verbally mediated working memory.

It is also worth noting that changes with nicotine in working memory load-related brain activations appear to be strongest for the 1-back condition (Fig. 2). This might be the result of ceiling or floor effects in task-related activations. When regions were maximally activated by the task due to a high cognitive load under placebo, nicotine was unable to enhance the response further. An example of this saturation effect would be the anterior cingulate in the 3-back condition. Conversely, regions that were minimally activated by the task in low load conditions would also not be enhanced by nicotine (e.g., superior parietal cortex during 0-back condition). Nicotine seems to exert its maximal effect in the middle of the dynamic range of the brain's response in the relevant regions.

We did not see any effect of nicotine in the dorsolateral prefrontal cortex. Interestingly, a previous study (Park et al., 2000) found that nicotine impairs spatial working memory, as measured in a delayed response task, in smokers (but not in nonsmokers), but leaves spatial attention intact in both nonsmokers and smokers. They (Park et al., 2000) thus proposed that nicotine disrupts functions of dorsolateral prefrontal cortex. We did not see any effects of nicotine in this study in the dorsolateral prefrontal cortex, although this region is known to have a crucial role in working memory (Callicott et al., 1999) and is functionally connected with anterior cingulate (Paus, 2001). As mentioned earlier, it has been suggested (MacDonald et al., 2000) that the dorsolateral prefrontal cortex has a role in noting task-relevant contents of memory, and the anterior cingulate one in monitoring on-line performance. If this suggestion is correct, our data indicate that the latter function, and not the former, was affected by nicotine.

Increased midbrain (superior colliculus) activity with nicotine (Fig. 3) is consistent with findings from animal studies (Gray et al., 1994) and may reflect an increase in behavioral arousal or alertness which, as mentioned in the Introduction, is likely to be associated with better performance across all active conditions via improved attentional efficiency (Eysenck, 1982). This effect, however, covaried with improvements in behavioral measures only for the 0-back condition. This could be due to two reasons. First, following the theoretical expectations of the Yerkes-Dodson Law of arousal and performance (Yerkes and Dodson, 1908), an increase in arousal level would facilitate performance at tasks of low cognitive load (i.e., low potential for task-induced arousal) but not when the task itself is difficult and arousing. This law posits a curvilinear relationship between arousal and performance, such that, for given difficulty there exists an optimal arousal with under- and over-arousal producing weaker performance. Second, there may be a specific role of this region in visual orientation and spatial analyses (Lomber et al., 2001) but not in working memory. As we have suggested above, it is possible that with increasing memory load there was a shift from reliance upon such analyses toward increasing use of verbally mediated memorial strategies.

Other nicotine related effects during the active task conditions were present in the caudate nucleus, thalamus, orbitofrontal cortex, and temporal regions, although not reported in detail as they were not identified in the zero-order model which we used to identify our regions of interest. In general, these region specific effects of nicotine are in line with those seen in another recent fMRI study of the effects of nicotine (Lawrence et al., 2002) and most likely reflect direct effects of nicotine administration given that nicotinic ACh receptors are present with the highest density in the caudate, thalamus, and substantia nigra, and in moderate-to-low densities in the frontal, parietal, temporal and occipital cortex, hippocampus, and cerebellum of the human brain (Paterson and Nordberg, 2000).

Nicotine-related changes in activity in the posterior cingulate, medial frontal lobe, and medial occipital lobe during rest were mostly independent of changes in behavioral measures or only weakly associated with them. However, activity in the cerebellum appeared to be strongly associated with nicotine-induced changes in performance. The cerebellum is known to show enhanced activation with increasing memory load (Smith and Jonides, 1997) and its role in spatial event processing and learning is also well supported by numerous observations in animals (Petrosini et al., 1998). It would appear that higher baseline activation (during rest) in this region was beneficial to performance on this task, which involved processing of verbal cues and spatial representation of keys on the button box in order to respond accurately. Nicotine is also found to increase blood flow in the cerebellum and cortical and subcortical regions of the

visual system in rats (McNamara et al., 1990); the latter effect has been postulated to reflect improved visual processing and attention in human subjects (Warburton and Arnall, 1994)

Finally, we noted that nicotine tended to increase the spatial extent of activation more than the amplitude of the BOLD response. We do not have a clear explanation for this finding. One possibility is that nicotine influenced hemodynamic coupling so that a larger cortical area received an inflow of oxygenated blood. A second is that nicotine enhanced neural activity in neighboring subregions of those areas activated by the task. A third is that the change in spatial extent represents a statistical anomaly in which a larger amplitude BOLD response has, through smoothing, increased its spatial extent into regions not otherwise activated by placebo (the statistical difference between the two conditions may thus be more apparent in the margins of an activation focus than the center of the focus).

Overall, the present observations are consistent with previous studies of the effects of nicotine on cognitive functions and suggest that the nicotine-induced enhancement in this study is primarily mediated via its effects on attention and arousal systems. We had controlled for the gender but did not control for ethnic origins. As described earlier, two of 11 subjects included in the final sample were of Asian origin. Asians are known to have slower nicotine metabolism and lower intake than whites (Benowitz et al., 1999, 2002) and so this may have caused some variability in nicotine-related changes in performance and brain activations leading to some loss of power in detecting drug-related modulations. Future studies should examine the mechanisms of nicotine-induced enhancement of working memory using tasks that allow disentanglement of different components of this function in normal smokers and nonsmokers and also in clinical populations where nicotine has been shown to improve cognitive performance such as in patients with attention deficit hyperactivity disorder (Conners et al., 1996; Levin et al., 1996b), Alzheimer's disease (Jones et al., 1992; Nordberg, 2001) and schizophrenia (Kumari et al., 2001; Newhouse and Kelton, 2000), while taking into account factors such as gender and ethnic origin that are known to produce variability in the response to nicotine.

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