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Visual and Auditory Alertness: Modality-Specific and Supramodal Neural Mechanisms and Their Modulation by Nicotine

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Thiel CM, Fink GR. Visual and auditory alertness: modality-specific and supramodal neural mechanisms and their modulation by nicotine. *J Neurophysiol* 97: 2758–2768, 2007. First published February 7, 2007; doi:10.1152/jn.00017.2007. Alertness is a nonselective attention component that refers to a state of general readiness that improves stimulus processing and response initiation. We used functional magnetic resonance imaging (fMRI) to identify neural correlates of visual and auditory alertness. A further aim was to investigate the modulatory effects of the cholinergic agonist nicotine. Nonsmoking participants were given either placebo or nicotine (NICORETTE gum, 2 mg) and performed a target-detection task with warned and unwarned trials in the visual and auditory modality. Our results provide evidence for modality-specific correlates of visual and auditory alertness in respective higher-level sensory cortices and in posterior parietal and frontal brain areas. The only region commonly involved in visual and auditory alertness was the right superior temporal gyrus. A connectivity analysis showed that this supramodal region exhibited modality-dependent coupling with respective higher sensory cortices. Nicotine was found to mainly decrease visual and auditory alertness-related activity in several brain regions, which was evident as a significant interaction of nicotine-induced decreases in BOLD signal in warned trials and increases in unwarned trials. The cholinergic drug also affected alerting-dependent activity in the supramodal right superior temporal gyrus; here the effect was the result of a significant increase of neural activity in unwarned trials. We conclude that the role of the right superior temporal gyrus is to induce an "alert" state in response to warning cues and thereby optimize stimulus processing and responding. We speculate that nicotine increases brain mechanisms of alertness specifically in conditions where no extrinsic warning is provided.

INTRODUCTION

Attention encompasses at least two aspects: selectivity and a nonselective alertness component. In contrast to the well-defined and often-studied concept of selective attention (e.g., Corbetta and Shulman 2002; Luck 1995), the nonselective component of attention is often vaguely defined and constitutes the related concepts of arousal, alertness, vigilance, and sustained attention. These concepts refer to a general readiness to process and respond to incoming information *without* any specific prior selection. This paper focuses on the nonselective component of attention.

We refer to the concept of general readiness as *alertness* (Posner and Petersen 1990) and gauge it by comparing target detection in a condition where a warning cue gives approximate temporal but no spatial information with an unwarned condition (Fan et al. 2002). Some authors referred to such a process as *phasic* alertness (Nebes and Brady 1993; Robertson et al. 1998; Sturm and Willmes 2001) because readiness is increased transiently over the range of up to several hundred milliseconds in response to the warning stimulus. There is some debate on whether alertness induced transiently by warning cues is distinct from alertness increased tonically over minutes or hours such as in vigilance tasks. Posner and Boies (1971) pointed out that short- and long-term alerting situations both involve the ability to increase readiness and proposed that transient increases in alertness may be considered as a "miniature vigilance situation." On the other hand, neuroimaging data provide some evidence for an anatomical dissociation (Coull et al. 2001; Paus et al. 1997; Sturm et al. 1999).

Irrespective of whether phasic and tonic alertness are similar or different processes, they are both essential for fast and efficient responding to stimuli in the environment and may influence selective attention. Prior research suggests that both warning-cue–induced alertness and alertness measured with vigilance tasks modulate spatial attention on the behavioral and neural level (Bellgrove et al. 2004; Callejas et al. 2004; Coull et al. 1998; Festa-Martino et al. 2004; however, see Fernandez-Duque and Posner 1997). Furthermore, it was previously proposed that impairments in alertness (as measured with vigilance tasks) may contribute to the lateralized deficits of attention observed in neglect patients (Husain and Rorden 2003; Robertson et al. 1995). Conversely, spatial deficits of neglect patients can be ameliorated by transiently increasing alertness with warning cues (Robertson et al. 1998).

Only few previous studies explored the neural networks that underlie alertness and their results are inconsistent. Some studies found a right-sided fronto-parieto-thalamic network for tonic (Paus et al. 1997; Sturm et al. 1999) and phasic alertness (Sturm and Willmes 2001), whereas other research suggests left lateralized parietal and frontal regions to be involved in warning-cue–induced alertness (Coull et al. 2001). One recent study that investigated warning-cue–induced alertness reports left-sided superior parietal and right-sided ventral prefrontal activity (Konrad et al. 2005), whereas Fan et al. (2005) revealed the most extensive alerting-related activation in the right temporoparietal junction (superior temporal gyrus). In our own studies we mainly found extrastriate regions to exhibit higher blood oxygenation level–dependent (BOLD) activity

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when trials with visual warning cues were compared with uncued trials and we speculated that the results may reflect enhanced sensory processing arising from top-down influences from higher-order frontal and parietal areas (Thiel et al. 2004, 2005). Regarding selective attention, frontal and parietal brain regions are supposed to constitute a supramodal attention system (Eimer and Driver 2001; Macaluso et al. 2002). With respect to alertness, however, supramodal and modality-specific neural systems have not yet been investigated systematically.

On the neurochemical level the thalamus and brain stem noradrenergic neurotransmitter system were linked to arousal and alertness (for review, see Berridge and Waterhouse 2003). It was previously proposed that the neurotransmitter noradrenaline mediates alerting because the noradrenergic α-agonist clonidine slowed reaction times in warned compared with unwarned trials in a cued target-detection task (Coull et al. 2001; Witte and Marrocco 1997). In a functional magnetic resonance imaging (fMRI) study with drug challenge, Coull et al. (2001) found first evidence that the neural signature of such pharmacologic modulation might lie within the left temporoparietal junction (although the effects observed were small). Related to this is a finding showing that increases in phasic arousal counteract the deleterious effects of noradrenergic manipulations on attention, possibly by increasing left thalamic and inferior parietal neural activity (Coull et al. 2004).

There also exists, however, ample evidence for a cholinergic role in arousal and alertness. This is mainly derived from studies showing a correlation between EEG desynchronization, alertness, and cortical acetylcholine (ACh), from neuroimaging studies showing a decrease of cerebral blood flow in the basal forebrain substantia innominata in a vigilance task and from psychopharmacological studies showing an increase in sustained attention and related neural activity after administration of the cholinergic agonist nicotine (Lawrence et al. 2002; Mancuso et al. 1999; Paus et al. 1997; Sarter and Bruno 2000; Wesnes and Warburton 1983, 1984). In contrast, behavioral studies using warning cues to assess alertness often reported that the cholinergic system is involved in orienting rather than alertness (Davidson et al. 1999; Stewart et al. 2001; Witte et al. 1997). In one of our own studies using a cued target-detection task, however, we found profound nicotine-induced neural changes in alerting-related activity in the right posterior parietal and right frontal cortex (Thiel et al. 2005), indicating that cholinergic drugs act on neural systems involved in alertness. The nicotine-induced changes were the result of a significant decrease of neural activity in unwarned trials and a numeric increase in activity in trials with warning cues.

The present study was designed to investigate whether the parietal and frontal modulation of alerting-related activity reflected an action of nicotine on supramodal alertness areas. This would imply a cholinergic modulation of alertness that is independent of stimulus modality. Because there is no prior study investigating systematically supramodal correlates of alertness, we first identified modality-specific and supramodal neural processes of alerting by using visual and auditory alertness conditions and then investigated whether similar effects of nicotine are seen in both conditions. A second aim was to answer the question whether a putative supramodal alertness region would show modality-specific changes in connectivity with respective sensory areas. For this reason the current study used a block design to enable an efficient analysis of connectivity.

METHODS

Subjects

Sixteen right-handed nonsmokers (11 male, five female; age range: 21–39 yr, mean: 27.6 yr) with no history of acute or chronic medical disease gave written informed consent to participate in the study. No subject was on medication (except for contraceptives). All subjects had normal or corrected-to-normal vision. A clinical evaluation was first carried out to ensure that subjects had no conditions contraindicative for nicotine administration. Ethics approval was obtained from the local ethics committee. Nonsmokers were used to avoid confounding effects of nicotine abstinence on cognitive effects, i.e., the possibility of reversing a deprivation-induced attentional deficit, rather than increasing attentional processes per se. No subject had used nicotine during the last 2 yr and most subjects had never smoked regularly at all. Subjects were asked to abstain from alcohol 12 h before each session and from caffeine 3 h before testing. Two volunteers were excluded from further analysis because of excessive head movement (>4 mm over the whole session or 1 mm between successive scans), leaving 14 subjects whose data were analyzed.

Drug administration

We used a within-subjects design. Scanning involved two sessions, separated by at least 1 wk. The order of drug administration was counterbalanced over subjects. Nicotine was delivered in the form of a polacrilex gum (NICORETTE mint taste, 2 mg; Pharmacia). A chewing gum with mint taste served as placebo. To disguise the taste, a drop of Tabasco sauce was added to the gums. Subjects were asked to chew the gum for 30 min at a rate of one chew per 3 s. A dose of 2 mg was chosen because higher doses (4 mg) lead to adverse effects in nonsmokers (Nyberg et al. 1982) and a lower dose did not lead to significantly different behavioral effects in our prior study (Thiel et al. 2005). Scanning started immediately after chewing had finished. In nonsmokers, nicotine plasma levels are on average 1.3 ng/ml at this time point (Heishman and Henningfield 2000) and roughly coincide with peak changes in heart rate (Nyberg et al. 1982). The half-life of nicotine is about 2 h (Benowitz et al. 1988). Pulse-oximetry was performed throughout the experiment.

Stimuli and experimental paradigm

We used a target-detection task with visual and auditory targets and visual, auditory, or no warning cues to capture neural correlates of phasic alertness (see Fig. 1*A*). The advantage of studying phasic alertness induced by warning cues in neuroimaging studies rather than investigating increases or decreases of tonic alertness over the course of the experiment is that unwarned trials can be used as an adequate control condition. Visual stimuli were projected onto a screen in front of the participant in the MRI scanner. Auditory stimuli were presented by electrostatic headphones that passively shielded the subjects from scanner noise. Viewing distance was about 29 cm. Within each drug condition, a 3 × 2 factorial design was used with three different warning cues (no cue, visual cue, auditory cue) and two different target stimuli (visual target, auditory target), leading to six different activation conditions that alternated with a baseline condition. Note that a blocked design, where stimuli of the same type are grouped together rather than presented randomly, was used to enable an efficient analysis of connectivity. Phasic alertness was captured by comparing BOLD activity in blocks of trials with warning cues versus uncued trials (Coull et al. 2001). Both blocks are likely to contain components of sustained attention. In cued blocks, however, there is an additional increase in phasic alertness arising from the warning induced by the cue; the comparison of cued and uncued blocks captures this increase in alertness. Because both the warned and unwarned trials contain targets to which the subject has to react, orienting and target detection should be subtracted out.

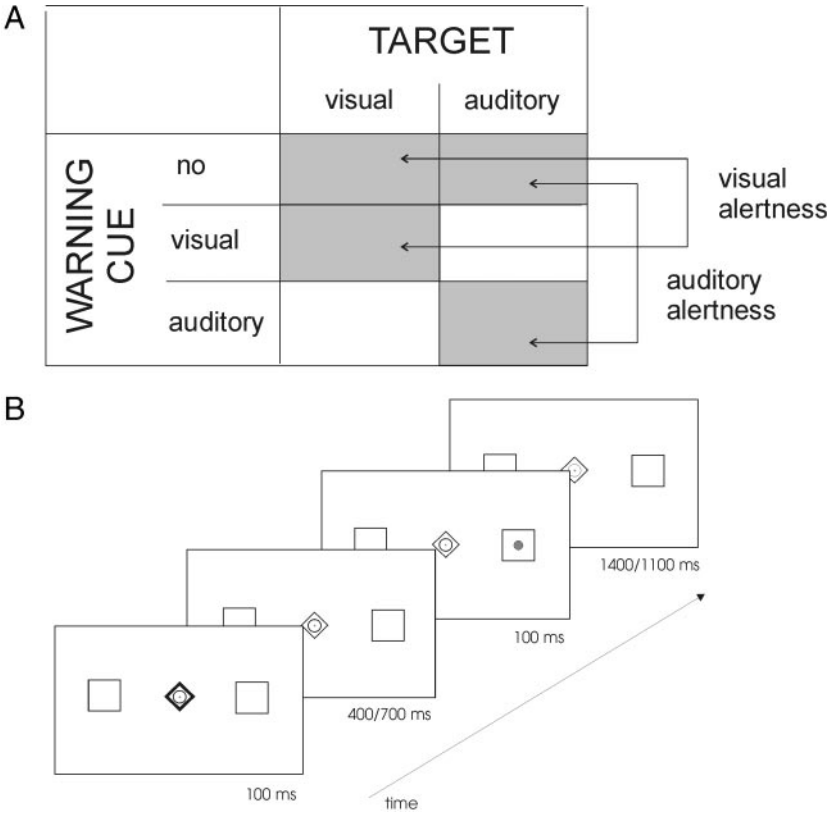

FIG. 1. *A*: schematic overview of the experimental design to measure warning-cue–induced alertness. There were 2 target (visual, auditory) and 3 warning cue conditions (uncued, visual, auditory). Visual alertness was isolated by comparing trials with a visual warning with uncued visual trials; auditory alertness was assessed by comparing trials with an auditory warning with uncued auditory trials. *B*: timing within a trial. The example here illustrates a trial with a visual warning cue. The trial starts with the warning cue (100 ms). After a variable cue-target interval (400–700 ms) a target stimulus (gray circle) appears for 100 ms within one of the 2 peripheral boxes. Subjects are asked to detect with a button press the target appearance. The next trial starts after 1,400 or 1,100 ms (±500-ms jitter).

The baseline condition lasted 14 s and was a display consisting of a central diamond (1.3° eccentric in each visual field) and two peripheral boxes (3° wide and 9.6° eccentric in each visual field). The activation conditions lasted 24 s and consisted of 12 cue-target trials. The visual warning cue consisted of the central diamond brightening for 100 ms. The visual target was a filled circle (1.3° wide) and appeared for 100 ms in one of the peripheral boxes. The auditory warning cue was a 500-Hz sine tone, presented to both ears. The auditory target, a 100-ms complex harmonic tone with a fundamental frequency of 100 Hz, was presented to either the left or right ear. In unwarned trials, the cue stimulus was omitted, giving no indication that a target would subsequently appear. Unilateral peripheral targets were used for reasons of comparability with our prior neuroimaging studies {Thiel 2004, 2442/id; Thiel 2005, 2648/id}. Two different intervals were used to reduce temporal orienting toward the target; i.e., volunteers had only approximate information on when the target was going to appear. The length of the cue-target intervals chosen was comparable to prior studies on warning-cue–induced alertness (Coull et al. 2001; Fan et al. 2002; Robertson et al. 1998; Witte et al. 1997). Trial onset asynchrony within activation conditions was 2,000 ± 500 ms (randomly jittered). The order of left and right targets and cue-target intervals was randomized within blocks. Subjects were instructed to maintain fixation throughout the experiment and to covertly detect any peripheral target as fast as possible. Volunteers made responses with the right index finger on a button of a keypad placed on the right side of the body. Before scanning, subjects were informed about the different conditions. A short training was performed before each scanning session.

Data acquisition

A SONATA MRI system (Siemens, Erlangen, Germany) operating at 1.5 T was used to obtain T2*-weighted echoplanar (EPI) images with BOLD contrast (matrix size: 64 × 64; voxel size: 3.12 × 3.12 mm^2). In all, 555 volumes of 24 4-mm-thick axial slices were acquired sequentially with an 0.8-mm gap (repetition time = 2.5 s, echo time = 66 ms). The first five volumes were discarded to allow for T1 equilibration effects. Images were spatially realigned to the first volume to correct for interscan movement and normalized to a standard EPI template (resampled to 3 × 3 × 3-mm^3 voxels). The data were then smoothed with a Gaussian kernel of 8-mm full-width at half-maximum to accommodate intersubject anatomical variability. A high-pass filter (using a cutoff of 512 s) and a correction for temporal autocorrelation in the data (AR 1 + white noise) were applied to accommodate serial correlations.

Statistical analyses of imaging data

Data were analyzed with Statistical Parametric Mapping software SPM2 [Wellcome Department of Imaging Neuroscience, London (http://www.fil.ion.ucl.ac.uk/spm2.html); Friston et al. (1995)] using random-effects models. At the first level, the two sessions (i.e., placebo, nicotine) were incorporated into one design matrix. For each session, the six conditions were modeled as a boxcar function convolved with the canonical hemodynamic response function (HRF). The six head-movement parameters (three rigid body translations and rotations) were included as confounds. The analysis herein focuses mainly on visual and auditory unimodal phasic alerting and its modulation by nicotine. For this purpose the following condition-specific effects for each subject were estimated according to the general linear model and the parameter estimates were passed into a second-level ANOVA with nonsphericity correction: visual warning (visual cue/visual target), auditory warning (auditory cue/auditory target), uncued visual (no cue/visual target), uncued auditory (no cue/auditory target), each under placebo and nicotine. Modality-specific alerting-related activity was isolated by comparing blocks with warning-cue trials with blocks with uncued trials in the visual and auditory modality, respectively, using *t*-contrasts. Alerting-related activity is therefore defined as differential neural activity to warned versus unwarned conditions. Differences between modalities were

compared with two further *t*-contrasts; i.e., [(cued visual − uncued visual) − (cued auditory − uncued auditory)] and vice versa.

To investigate brain areas commonly involved in visual and auditory alertness under placebo, a conjunction analysis testing for a logical AND was used (Nichols et al. 2005). The BOLD signal time course of the resulting activation (right lateral posterior superior temporal gyrus) was then entered into a psychophysiological interaction (PPI) analysis to further investigate this common activation in terms of functional interactions (Friston et al. 1997). Briefly, a PPI analysis aims to explain neural responses in one brain area in terms of the interaction between influences of another brain region and a cognitive/sensory process. Thus a psychophysiological interaction can be seen as a condition-specific change of coupling between brain areas. The PPI analysis consists of a design matrix with three regressors: *1*) the "psychological variable" representing the cognitive/sensory process of interest (here visual vs. auditory alertness), *2*) the "physiological variable" representing the neural response in a given brain region (here the right superior temporal gyrus), and *3*) the interaction term of *1*) and *2*). The psychological variable used was a vector coding for the modality of alerting (1 for visual warning, −1 for auditory warning) convolved with the HRF. To obtain data for the physiological variable we extracted the individual time series (radius: 6 mm) centered on the coordinates of subject-specific activations in the right superior temporal gyrus. Three subjects did not show any activation within the right superior temporal gyrus and did not enter into the analysis. Of the remaining 11 subjects the physiological factor was then multiplied with the psychological factor, i.e., the vector coding for the modality of alerting: this constitutes the interaction term. PPI analyses were then carried out for each subject involving the creation of a design matrix with the interaction term, the psychological factor, and the physiological factor as regressors. Subject-specific contrast images using the contrast [1 0 0], where the first column represents the interaction term, were then entered into a random-effects group analysis.

The modulatory effects of nicotine were investigated with the drug by alerting interactions using two *f*-contrasts for undirected hypothesis testing. These *f*-contrasts are equivalent to a two-tailed version of *t*-contrasts testing for increased and decreased alerting-related activity under nicotine. To capture drug modulation only in those regions significantly involved in alertness under placebo, the activations were masked with alerting-related activity under placebo (thresholded at $P < 0.001$). Activations of all analyses are reported at a level of significance of $P < 0.001$ (uncorrected) and a cluster threshold of more than five contiguous voxels as in our prior studies (Thiel et al. 2004, 2005). Additionally, parameter estimates (reflecting response amplitude) for the effect maxima in some of the second-level analyses were plotted to further illustrate the results. The reported coordinates correspond to the standard Montreal Neurological Institute (MNI) brain. Activations are displayed at the above threshold on a coregistered and normalized average structural group T1 image.

Finally, an additional post hoc analysis was conducted in the placebo group to clarify whether the observed increase in neural activity in sensory cortices depends on the modality of the cue or the target. Four conjunction analyses (Nichols et al. 2005) including the unimodal and cross-modal conditions were performed. These analyses investigated common activations under conditions with *1*) a visual target (visual warning/visual target ∩ auditory warning/visual target), *2*) a visual warning cue (visual warning/visual target ∩ visual warning/auditory target), *3*) an auditory target (auditory warning/auditory target ∩ visual warning/auditory target), and *4*) an auditory warning cue (auditory warning/auditory target ∩ auditory warning/visual target). If the increased activity in sensory areas depends on the modality of the warning cue and not on the modality of the target, then increases in sensory areas should be evident in alertness tasks with identical warning-cue conditions [i.e., *2*) and *4*)]. If, on the other hand, the increases in sensory areas are driven by the modality of the target, the conjunction analyses *1*) and *3*) should yield significant activations in the respective sensory areas.

Statistical analyses of behavioral data

Median reaction times (RTs) were calculated for each trial type and drug condition in each subject. The means of median RTs were analyzed with a repeated-measures ANOVA with the factors drug (placebo/nicotine), alertness (warning cue/no cue), and modality (visual/auditory).

Subjective and physiological measures

In every session, subjective drug effects were assessed with visual analogue scales (Bond and Lader 1974). Rating scores were grouped into the three factors "alertness," "contentedness," and "calmness" according to Bond and Lader (1974). Note that these are subjective ratings and are different from the RTs obtained in the preceding experimental paradigm. Subjective ratings were analyzed for drug effects with paired *t*-test. The pulse was checked before the start of the scanning session and analyzed for drug effects with a paired *t*-test. Pulse data of two volunteers were lost.

RESULTS

Subjective and physiological data

Nicotine significantly increased the pulse rate [placebo: 68.3 ± 2.9 (mean ± SE), nicotine 73.0 ± 3.3; $t(1,11) = 2.3$ $P = 0.039$]. There were no significant effects of nicotine on subjective ratings of alertness, contentedness, or calmness before or after scanning (all $P > 0.14$).

Behavioral data

Reaction time data are presented in Fig. 2. Behavioral benefits of alerting were seen in both the visual and auditory modality: the warning cue accelerated RTs in both modalities [$F(1,13) = 65.56$, $P < 0.001$]. RTs to visual targets were significantly faster than RTs to auditory targets [$F(1,13) = 13.02$, $P = 0.003$]. There was an alertness by modality interaction that is reflected in an increased reaction time in the unwarned condition in the auditory modality [$F(1,13) = 8.54$, $P = 0.012$]. The three-way interaction between alertness, modality, and drug just missed significance [$F(1,13) = 4.67$, $P = 0.05$] and reflected a numerically stronger influence of

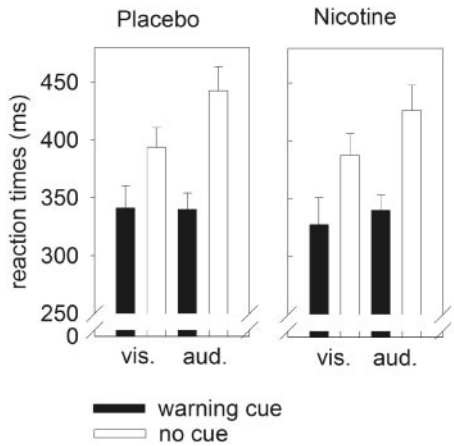

FIG. 2. Behavioral data. Mean (±SE) reactions times (RTs) for each condition and drug treatment.

nicotine on trials with warning cues in the visual condition compared with the auditory condition and a stronger influence on unwarned trials in the auditory compared with the visual condition.

Brain regions involved in visual and auditory alerting

Brain areas involved in visual alerting were identified by comparing BOLD activity for conditions with visual warning cues versus uncued visual conditions under placebo (Fig. 3, warm colors). The contrast yielded activity in left and right extrastriate areas, with peak activations in the inferior occipital gyrus ($x = 30$, $y = -90$, $z = 0$, $Z = 5.73$; and $x = -42$, $y = -90$, $z = -6$, $Z = 4.88$). Additional significant activations were found in bilateral posterior parietal cortex including the supramarginal gyrus ($x = -30$, $y = -45$, $z = 45$, $Z = 4.25$; and $x = 36$, $y = -45$, $z = 36$, $Z = 4.03$) and the intraparietal sulcus ($x = -24$, $y = -69$, $z = 39$, $Z = 3.90$; and $x = 36$, $y = -57$, $z = 51$, $Z = 3.90$), the left mid-cingulate cortex ($x = -12$, $y = -30$, $z = 45$, $Z = 3.97$), the right lateral posterior superior temporal gyrus ($x = 69$, $y = -30$, $z = 18$, $Z = 3.88$), and several frontal brain regions (left middle frontal gyrus: $x = -39$, $y = 51$, $z = 24$, $Z = 3.99$; right precentral gyrus: $x = 60$, $y = 12$, $z = 33$, $Z = 3.65$; bilateral superior frontal sulcus: $x = 24$, $y = -3$, $z = 63$, $Z = 3.65$; and $x = -24$, $y = 0$, $z = 54$, $Z = 3.53$).

Neural correlates of auditory alerting were isolated by comparing BOLD activity for conditions with auditory warning cues versus uncued auditory conditions under placebo (Fig. 3, cold colors). This contrast revealed significant neural activation along the extent of the superior temporal gyri bilaterally ($x = 54$, $y = -6$, $z = -9$, $Z = 4.74$; and $x = -48$, $y = -36$, $z = 15$, $Z = 4.67$). Additionally we found increased activity in several frontal brain regions including the left inferior frontal gyrus ($x = -36$, $y = 6$, $z = 36$, $Z = 4.68$), the middle frontal gyri bilaterally ($x = 39$, $y = 27$, $z = 51$, $Z = 4.11$; and $x = -24$, $y = 3$, $z = 57$, $Z = 3.82$), and the right precentral gyrus ($x = 66$, $y = 3$, $z = 24$, $Z = 3.80$). Further activations were found in the left precuneus ($x = -9$, $y = -66$, $z = 51$, $Z = 4.20$), the left mid-cingulate cortex ($x = -9$, $y = -9$, $z = 45$, $Z = 4.52$), the left inferior colliculus ($x = -6$, $y = -36$, $z = -9$, $Z = 3.44$), and the cerebellum ($x = 42$, $y = -60$, $z = -36$, $Z = 3.39$). Note the different pattern of alerting-related activity in the visual and auditory modalities.

When testing statistically for differences between visual and auditory alertness, higher activations to visual compared with auditory alertness were found in the inferior occipital gyri

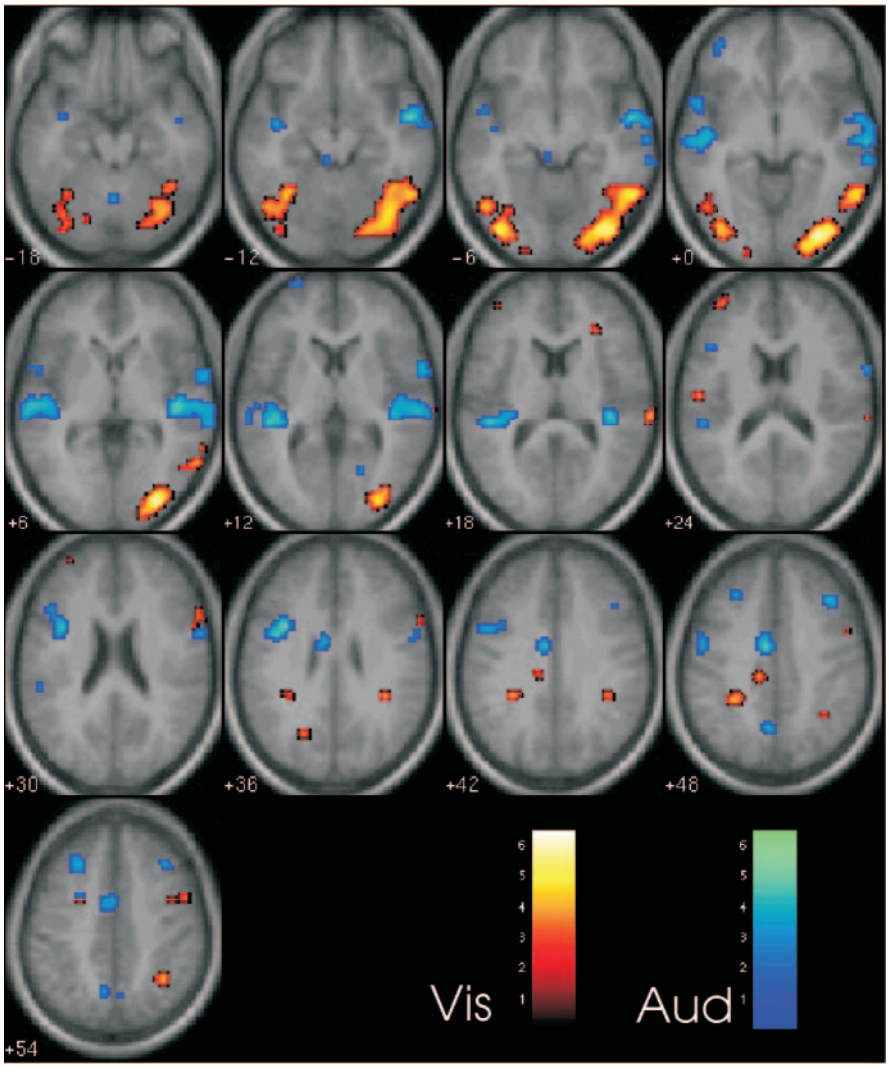

FIG. 3. Visual and auditory alertness. Brain regions significantly more activated during conditions with warning cues compared with uncued conditions in the visual (warm colors) and auditory (cold colors) modality under placebo. Visual alerting activated bilateral extrastriate, posterior parietal, and frontal brain areas. Auditory alerting activated the superior temporal gyri and frontal brain regions bilaterally. All activations shown are thresholded at $P < 0.001$ and rendered onto the averaged structural magnetic resonance (MR) of all subjects.

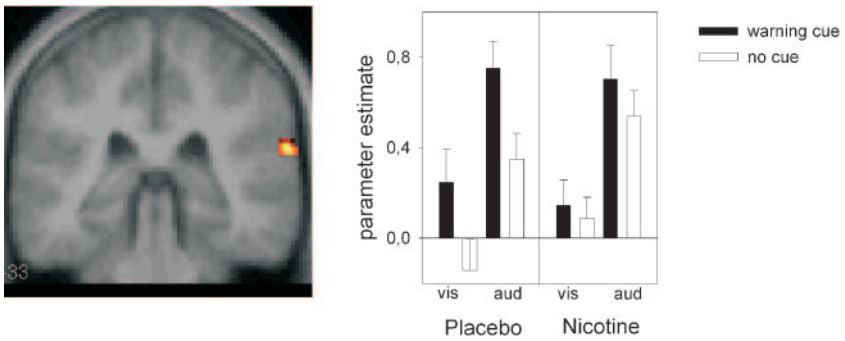

FIG. 4. Conjunction analysis. *Left*: activation common to visual and auditory alertness in right superior temporal gyrus. *Right*: plot of parameter estimates of maximum activity in superior temporal gyrus as a function of warning cue, modality, and drug.

bilaterally. Note that differences in posterior parietal cortex were significant only at $P = 0.005$. The reverse contrast (auditory alertness minus visual alertness) revealed differential activity in bilateral superior temporal gyri, the right middle frontal gyrus, and the left inferior and superior frontal gyri.

To identify areas that were commonly involved in alertness in the visual and auditory modality, a conjunction analysis including the visual and auditory alertness conditions was performed that yielded activation in the right lateral posterior superior temporal gyrus (x = 66, y = −33, z = 15, Z = 3.99) only. This brain region showed higher activity when a warning cue was presented, independent of its modality (Fig. 4). To further investigate this common activation in terms of functional interactions we tested whether any regions in the brain showed modality-specific changes in coupling with this right superior temporal region and hypothesized that this supramodal region should increase its influence on higher-level visual areas during visual alertness and on higher-level auditory areas during auditory alertness, respectively. Results of the psychophysiological interaction analysis are shown in Fig. 5. The right superior temporal gyrus increased its influence during visual alertness on right extrastriate (inferior temporal gyrus: x = 48, y = −54, z = −6, Z = 3.71), right parietal (intraparietal sulcus: x = 33, y = −45, z = 51, Z = 4.27; x = 36, y = −30, z = 51, Z = 4.03; x = 24, y = −66, z = 60, Z = 3.70; postcentral gyrus: x = 21, y = −48, z = 69, Z = 3.66), left frontal areas (superior frontal sulcus: x = −27, y = −9, z = 69, Z = 3.83; inferior frontal gyrus: x = −45, y = 3, z = 30, Z = 3.49), and the left mid-cingulate cortex (x = −15, y = −18, z = 42, Z = 3.75). During auditory alertness on the other hand, the right superior temporal gyrus was coupled more strongly with the right superior temporal sulcus (x = 48, y = −33, z = 6, Z = 3.37) and with the left parahippocampal gyrus (x = −15, y = −30, z = −9, Z = 4.83). In other words, the right lateral posterior superior temporal gyrus exhibited a modality-specific coupling with higher sensory areas under alertness.

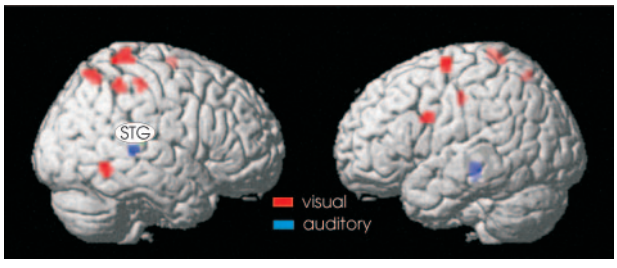

FIG. 5. Psychophysiological interaction (PPI) of the right superior temporal gyrus showing modality-specific coupling. Areas that are stronger coupled to right superior temporal gyrus during visual alertness are in red; areas that are stronger influenced by right superior temporal gyrus during auditory alertness are in blue.

The conjunction analyses that included the unimodal and cross-modal conditions were performed to investigate whether neural activity in higher sensory areas reflected cue- or target-induced processes. These analyses revealed extensive bilateral extrastriate activity (x = 36, y = −87, z = −6, Z = 4.49; x = −39, y = −87, z = −6, Z = 4.13) when both conditions entering the conjunction had a visual cue but not when they both had a visual target. Large areas of the bilateral auditory cortex (x = −48, y = −33, z = 15, Z = 4.29; x = 57, y = −24, z = 6, Z = 4.05) were active, on the other hand, when both conditions entering the conjunction had an auditory cue but not when both conditions had an auditory target. In other words, increased activity in sensory areas in cued-target detection tasks depends on the modality of the warning cue and not on the modality of the target.

Nicotinic modulation

The drug by alerting interaction for each modality is shown in Fig. 6. The *f*-contrast used identifies brain regions in which neural activity in trials with an alertness-inducing warning cue and those without a cue is differentially affected by placebo and nicotine. Note that only those regions are displayed that show a significant alerting effect under placebo. In the visual modality, the effects of nicotine were evident in the right lateral posterior superior temporal gyrus (x = 69, y = −27, z = 15, Z = 3.53) and as the result of a significant interaction of nicotine-induced decreases in BOLD signal in the condition with the warning-cue and nicotine-induced increases in the uncued condition (thus reducing differential activity for the warned vs. unwarned condition, i.e., alertness-related activity; see Fig. 6*B*). In the auditory condition, effects of nicotine were found in several frontal areas (e.g., right middle frontal gyrus: x = 36, y = 27, z = 51, Z = 4.01; bilateral inferior frontal gyri: x = −30, y = 51, z = 3, Z = 3.69; and x = 60, y = 3, z = 9, Z = 3.49; mid-cingulate cortex: x = −9, y = −6, z = 45; Z = 3.46) and in a parietooccipital region (x = 18, y = −69, z = 15, Z = 4.16). As before, the effect of the cholinergic agonist nicotine arose from a significant interaction of decreased BOLD signal in the condition with the warning cue and an increased neural signal in the uncued condition. No significant differences between placebo and nicotine were found in higher-level visual or auditory cortices.

Our previous study on visual alertness yielded alerting-related activity in the right angular gyrus/intraparietal sulcus and middle and superior frontal gyri under nicotine that was reversed under placebo (Thiel et al. 2005). Because we did not

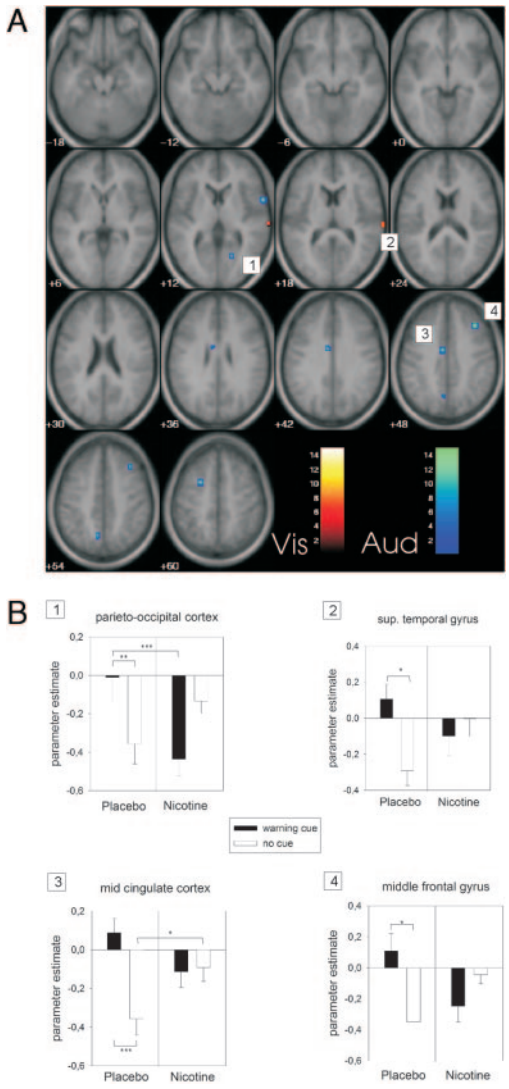

FIG. 6. Cholinergic modulation of visual and auditory alertness. *A*: activations in warm colors are areas that are modulated by nicotine during visual alertness. Areas shown in cold colors are modulated by nicotine during auditory alertness. *B*: plot of parameter estimates for some of the most extensive activations as a function of the respective cueing and drug to illustrate the interactions obtained. Note that for the superior temporal gyrus, the plots relate to the visual alertness conditions; for all other figures, the plots relate to the auditory alertness conditions. In all areas shown, the nicotinic modulation is seen as an interaction of reduced neural activity in the warned condition and increased activations in the unwarned condition. $***P < 0.001$, $**P < 0.01$, $*P < 0.05$ post hoc Tukey tests comparing activations in conditions with warning cues and without warning cues between placebo and nicotine.

find a nicotinic modulation of right parietal and frontal activity in the visual alertness condition with the present design (and statistical threshold) we performed an explorative region of interest (ROI) analysis using the right parietal, middle frontal, and superior frontal voxels of our previous study as search volumes (sphere of 15 mm). This revealed alerting-related activity in the right angular gyrus (x = 48, y = −54, z = 39, Z = 3.52; $P = 0.048$ SVC corrected; Fig. 7) under nicotine that was reversed under placebo. That is, with this hypothesis-driven ROI analysis we were able to replicate the modulation of alerting-related right parietal cortex activity previously found in an event-related design under nicotine. An inspection of the BOLD signal in this brain region in the auditory condition suggests that the nicotinic modulation of alerting-related activity found previously was specific to the visual condition [see Fig. 7, *right*; drug × cuing × modality interaction; $F(1,13) = 5.86$, $P = 0.03$]. Right frontal neural activity was not affected by nicotine in the present study.

Results of the preceding analyses suggest that the areas modulated by nicotine depend on the modality, which might, however, be explained by the fact that the networks involved in visual and auditory alertness also depend on the modality used and overlapped in only one brain region, i.e., the right superior temporal gyrus. To investigate whether there is a common effect of nicotine in this supramodal region, we performed a post hoc analysis on the signal in this right posterior superior temporal region (i.e., on the effect maximum plotted in Fig. 4). A 2 × 2 × 2 ANOVA with the factors drug, modality, and cuing was performed and yielded a drug × cuing interaction [$F(1,13) = 13.16$, $P = 0.003$] driven mainly by significantly increased activity in the uncued condition under nicotine for both modalities (post hoc Tukey HSD test, $P = 0.01$). This means that there was a modality-independent action of nicotine in this supramodal alertness region that involved an increase in BOLD signal in the condition where no warning cues were provided.

DISCUSSION

We provide evidence for modality-specific correlates of visual and auditory alertness in respective higher-level sensory cortices as well as posterior parietal and frontal brain regions. We further identified a supramodal brain region in the posterior aspect of the right superior temporal gyrus involved commonly in visually and auditorily induced alertness. This supramodal region showed modality-specific coupling with the respective higher sensory cortices. The cholinergic agonist nicotine was found to modulate alerting-dependent activity in this su-

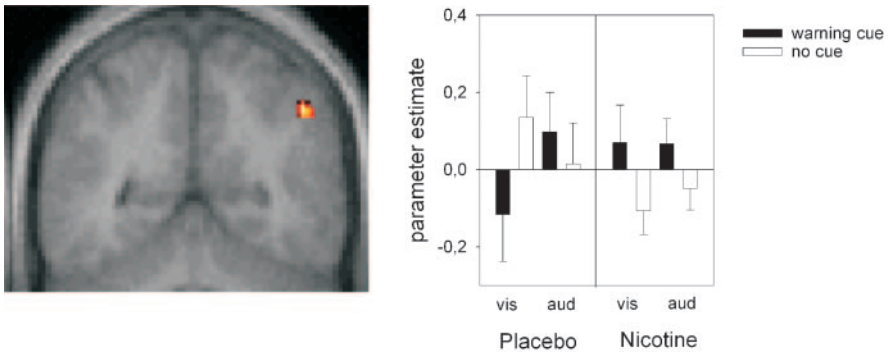

FIG. 7. Drug modulation in the right angular gyrus. *Left*: region of interest (ROI) analysis of the effects of nicotine on visual alertness. Alerting-related activity is increased in the right angular gyrus under nicotine (activations shown at $P < 0.001$, one-sided). *Right*: plot of parameter estimates of maximum activity in angular gyrus as a function of warning cue, modality, and drug.

pramodal alertness region but also affected other brain areas in a modality-specific way.

Modality-specific correlates of alertness

Neural correlates of visual alertness were found in bilateral extrastriate areas as in previous studies (Thiel et al. 2004, 2005). In analogy, an alerting-related increase of neural activity in higher-level auditory cortices was found when using an auditory alertness task. That such increases in sensory cortices are related to transient increases in attention and not purely to sensory summation of cue and target activity was recently demonstrated by Liu et al. (2005). The authors were able to demonstrate that uninformative peripheral cues increase the BOLD signal in visual areas only when presented before—but not when presented after—the target. BOLD increases in sensory areas of the corresponding stimulus modality were also reported in studies where subjects focused attention on a stimulus in the respective modality (Johnson and Zatorre 2005; Loose et al. 2003; O'Leary et al. 1997). Results of the conjunction analyses involving the unimodal and cross-modal alertness conditions further suggest that increased activity in sensory areas in cued target-detection tasks depends on the modality of the warning cue and not on the modality of the target. The novel finding in our data, discussed in the following text, is that these higher-level sensory cortices also change their coupling with a supramodal alertness area (i.e., the superior temporal gyrus).

Alerting-related activations were further found in bilateral inferior parietal and frontal brain areas in the visual modality and in bilateral frontal brain regions in the auditory modality. This is in contrast to our prior event-related studies, where we did not observe parietal or frontal neural activity with warning-cue–induced alertness. The data thus suggest that parietal and frontal activations may preferentially be observed when using block designs to assess alertness. One explanation for such design-related differences is that blocked and event-related approaches differ, among others, in their sensitivity to capture transient and sustained activations (for further discussion, see Giessing et al. 2004). Thus alerting-related parietal and frontal activations reported here and by others (Coull et al. 2001; Sturm et al. 1999) may have resulted from frontal and parietal cortices showing a sustained rather than transient increase in neural activity after a warning cue is provided.

Further, the current data suggest that alerting in the auditory modality relies more on frontal cortical areas than alerting in the visual modality and one might speculate that the common behavioral outcome of warning cues (i.e., the benefits in reaction time) could arise from differing cognitive operations/strategies reflected consequently in different activation patterns. Because there are currently no other neural data on modality-specific responses regarding the nonselective attention component of alertness this hypothesis needs further investigation. Studies on *spatial* aspects of multisensory integration suggest that parietal and frontal brain regions constitute a supramodal network for selective spatial attention (Eimer and Driver 2001; Macaluso et al. 2002). Our data on spatially nonselective attention indicate that a supramodal alertness network is within the superior temporal gyrus and that frontal brain regions are rather differentially engaged by auditory and visual alertness conditions. At least with respect to the parietal cortex (which however just failed to show significantly different involvement in visual vs. auditory alertness), there is recent transcranial magnetic stimulation (TMS) evidence that suggests that the inferior parietal cortex may be crucial for spatial attention in the visual rather than auditory modality (Chambers et al. 2004). Electrophysiological recordings in monkeys performing a cued target-detection task support this suggestion by showing that firing rates in the lateral intraparietal area are stronger for visual cues, even though visual and auditory cues were used in a similar fashion (Cohen et al. 2004). Alternatively, the different activation patterns under visual and auditory alerting may be explained by a different time course of visual and auditory alertness. If this was the case, reaction times for the two cue-target intervals (400 and 700 ms) should differ for visual and auditory cues. A post hoc analysis of reaction times confirmed, however, that benefits of visual and auditory warning cues were similar for both cue-target intervals.

Supramodal correlates of alertness

We expected to find a supramodal region subserving visual and auditory alertness within the parietal lobe because there is strong evidence that the parietal cortex is implicated in the supramodal control of *selective* attention (Eimer and Driver 2001; Macaluso et al. 2002). The alerting-related activations in the intraparietal sulcus and supramarginal gyrus seen here, however, were specific to the visual modality. Instead, common visual and auditory alerting-related neural activity was found in the posterior aspect of the right superior temporal gyrus. With respect to selective attention, there is some debate on whether the superior temporal gyrus is part of a stimulus-driven bottom-up attentional system that reacts to behaviorally relevant target stimuli (Corbetta et al. 2000) or implicated in top-down control of selective attention because it was found to be active to spatial cues rather than to targets (Hopfinger et al. 2000). It was previously shown that the superior temporal gyrus receives multisensory inputs. Neurons in this superior temporal area process somatosensory, auditory, and visual stimuli (Downar et al. 2000; Jones and Powell 1970; Matsuhashi et al. 2004). Studies on audiovisual speech perception further showed that the posterior part of the superior temporal gyrus is activated in common by visual and auditory inputs and is important for cross-modal integration (Calvert et al. 1997). Recent evidence indicates that the superior temporal gyrus might also be implicated in nonselective attention. In an event-related fMRI study by Fan et al. (2005) on visual alertness, this region showed the most prominent alerting-related activation. Activity in the right temporoparietal junction was also observed in a subgroup of five subjects when auditory and visual–auditory alertness conditions were compared with a sensory-motor control task (Sturm and Willmes 2001). Our data therefore add to the evidence that the right lateral posterior superior temporal gyrus is involved in warning-cue–induced alertness and that this involvement is modality independent. Our data further demonstrate that the right superior temporal gyrus constitutes a supramodal region for alertness and increases its coupling with respective higher sensory areas in response to warning cues in the respective modality. Within the visual condition, a modality-specific coupling was found with the right inferior temporal gyrus, a

higher visual brain region crucial for visual processing, perception, and object recognition (Peyrin et al. 2005; Tanaka 1993) as well as with frontal and parietal brain areas. In contrast, within the auditory condition, a modality-specific connectivity was evident with the right superior temporal sulcus, a higher auditory region that previously was shown to be active in fMRI studies when volunteers process pitch sequences (Patterson et al. 2002).

What is the role of the right superior temporal gyrus in alertness? In keeping with the view that the temporoparietal junction is part of a bottom-up attentional network (Corbetta et al. 2000), one might speculate that the behavioral relevance of warning cues (and possibly the automatic alerting to such cues) activates the right superior temporal gyrus. This is reflected in a change of coupling of this area with the respective higher-level sensory cortices. Warning-cue–induced activation of the superior temporal gyrus would reflect an "alert" state, capable of breaking ongoing activity and optimizing responses to following targets.

Nicotinic modulation of alertness

A key issue in fMRI studies with drug challenges is the effect of a drug on global and local cerebral blood flow or cerebrovascular coupling, which may confound the BOLD signal. Gollub et al. (1998) demonstrated that an infusion of cocaine increased heart rate, mean blood pressure, and global cerebral blood flow without affecting the BOLD signal. This suggests that the BOLD signal can be measured reliably despite significant changes in blood flow. Regarding nicotine, Ghatan et al. (1998) found no changes in global blood flow and cerebral oxygen uptake after nicotine versus saline infusions. Furthermore, Jacobsen et al. (2002), who measured the BOLD signal in the visual cortex to photic stimulation, showed that neither the height nor the extent of signal changed under nicotine infusion, arguing against nicotine-induced alterations in cerebrovascular coupling. Similar results were found by Salmeron and Stein (2002) in the motor cortex. Finally, it should be noted that pharmacological effects mediated through neurovascular coupling are unlikely to affect responses to cued relative to uncued trials differentially.

Another issue in pharmacological fMRI studies is how to interpret changes in BOLD signal in the absence of a behavioral drug effect. The lack of a behavioral drug effect—while at the same time changes in brain activity are observed—were reported in several neuroimaging studies (Bullmore et al. 2003; Ghatan et al. 1998; Hariri et al. 2002; Kirsch et al. 2005). Thus it has been argued that neuroimaging data might be more informative than behavioral data because changes in cognitive strategies or effort are not necessarily reflected in behavioral measures such as reaction times but would be evident as changes in brain activity (Fink et al. 2002; Wilkinson and Halligan 2004). fMRI is thus a valuable tool to assess subtle drug effects that do not manifest in reaction times and was used here to investigate the cholinergic modulation of alertness.

As shown previously, nicotine did not significantly influence reaction time measures of warning-cue–induced alertness (Mancuso et al. 2001; Stewart et al. 2001; Witte et al. 1997). There was, however, a trend for a differential behavioral effect of the drug in the visual and auditory modality: although nicotine did not further increase the benefits of an auditory warning stimulus, it did so, at least numerically, in the visual modality. A dissociation of the behavioral effects of nicotine regarding visual and auditory stimuli was reported previously but was never investigated systematically in further detail (Friedman and Meares 1980).

Even though reaction time measures alone would speak against a cholinergic modulation of alerting, the nicotinic effects on alerting-related neural activity speak in favor of a cholinergic role in alertness. Several imaging studies found an effect of nicotine on parietal and frontal neural activity in different cognitive paradigms, some with a concurrent behavioral effect (Ernst et al. 2001; Lawrence et al. 2002) and some without (Ghatan et al. 1998). The present data show several brain regions to be modulated by nicotine under visual and auditory alertness. As in our previous study, nicotine induced alerting-related neural activity in the right angular gyrus, which was not present under placebo (although the effects were smaller than before; Thiel et al. 2005). Here we show that this effect is specific to the visual condition. In contrast to our previous study, we further found a nicotinic reduction of alerting-related activity in the right lateral posterior superior temporal gyrus in the visual condition. These areas of drug modulation differed from those found in the auditory condition, which were located primarily in occipitoparietal and frontal regions, and also showed a reduction of alerting-related activity induced by an interaction of reduced neural activity in the warned condition and increased activations in the unwarned condition. Taken together, the results suggest that the location of cholinergic modulation of alertness is mostly modality specific and involves increases of activity in unwarned and decreases of activity in warned trials. In this respect, it is of interest to note that nicotine did not significantly influence alerting-related activity in sensory cortices, even though nicotine was shown to enhance physiological measures of sensory responsiveness both in humans and in animals (Metherate 2004) and the highest concentration of cholinergic nicotinic receptors within the cortex is found in sensory cortices (Zilles et al. 2002).

In contrast to our prior event-related study, where both decreases and increases of alerting-related activity were found under nicotine, the present study used a block design and yielded mainly decreased alerting-related activity. As discussed earlier, alerting-related activity already differed under placebo in both studies with only the block design, showing alerting-related neural activity in frontal and parietal cortices. We suggested that this may be explained by the different sensitivity of blocked and event-related approaches to capture transient and sustained activations. Similarly, the effects of nicotine observed here and in our prior study might reflect a modulation of transient versus sustained alertness-related signals.

Even though the effects of nicotine were mostly modality specific, a post hoc analysis of neural activity in the posterior aspect of the right lateral superior temporal gyrus, which was identified as a supramodal alertness region, showed that in this brain region nicotine influenced neural activity in a similar fashion for visual and auditory stimuli by significantly increasing neural activity in the uncued visual and auditory condition. Given the finding that the right lateral superior temporal gyrus is activated in response to warning cues and that its activation might reflect an "alert" state that optimizes responding to

following targets, one could speculate that the nicotine-induced increase of neural activity in this brain region to uncued targets indicates that nicotine induces an "alert" state specifically in conditions where no extrinsic warning is provided. That is, nicotine increases neural correlates of alertness specifically in situations with lower levels of alertness.

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