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THE MODULATORY EFFECTS OF NICOTINE ON PARIETAL CORTEX ACTIVITY IN A CUED TARGET DETECTION TASK DEPEND ON CUE RELIABILITY

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Abstract—This functional magnetic resonance imaging study investigates the effects of nicotine in a cued target detection task when changing cue reliability. Fifteen non-smoking volunteers were studied under placebo and nicotine (Nicorette® polacrilex gum 1 and 2 mg). Validly and invalidly cued trials were arranged in blocks with high, middle and low cue reliability. Two effects of nicotine were investigated: its influence on i) parietal cortex activity underlying the processing of invalid vs. valid trials (i.e. validity effect) and ii) neural activity in the context of low, middle and high informative value of the cue (i.e. cue reliability effect). Nicotine did not affect behavioral performance. However, nicotine reduced the difference in the blood oxygenation level dependent (BOLD) signal between invalid and valid trials in the right intraparietal sulcus. The reduction of parietal activity in invalid trials was smaller in the low cue reliability condition. The same posterior parietal region exhibited a nicotinic modulation of BOLD activity in valid trials which was dependent on cue reliability: Nicotine specifically enhanced the neural activity during valid trials in the context of low cue reliability, i.e. when subjects are already in a state of low certainty. We speculate that the right intraparietal sulcus might be part of two networks working in parallel: one responsible for reorienting attention and the other for the cholinergic modulation of cue reliability. By reducing the use of the cue, nicotine modulates parietal activity related to reorienting attention in conditions with higher cue certainty. On the other hand, nicotine increases parietal activity in states of low certainty. This enhanced activation might influence brain regions, such as the posterior cingulate, directly involved in the processing of cue reliability.

Key words: acetylcholine, attention, Posner paradigm, top-down, uncertainty, validity effect.

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Abbreviations: ACh, acetylcholine; ANOVA, analysis of variance; BOLD, blood oxygenation level dependent; EPI, echoplanar images; fMRI, functional magnetic resonance imaging; HRF, hemodynamic response function; IPS, intraparietal sulcus; RT, reaction time; SEM, standard error of the mean.

Orienting attention in space is facilitated by advance information on the target location. In contrast, misleading advance information in the form of a spatially invalid cue leads to prolonged response times due to reorienting of attention to the unexpected target location. The difference of reaction times (RTs) between validly and invalidly cued targets has been termed the "validity" effect. The increase in response times in invalid trials is dependent upon cue reliability, i.e. the percentage of trials in which the cue accurately predicts the target location. In other words, the certainty of top-down information or the knowledge of how well a cue predicts the upcoming target modulates the validity effect (Eriksen and Yeh, 1985; Riggio and Kirsner, 1997). Therefore, covert reorienting of attention in humans seems to be influenced by learned rules of cue–target relationships derived from prior experience (Bowman et al., 1993). The neural correlates of this effect remain, however, to be elucidated.

It has been proposed that corticopetal cholinergic projections originating in the nucleus basalis of Meynert modulate attention through influences on both a fronto-parietal network thought to mediate "top-down" control and sensory cortices, subserving "bottom-up" stimulus processing (Sarter et al., 2001). Previous behavioral studies observed that increasing cholinergic activity with the cholinergic agonist nicotine and decreasing cholinergic neurotransmission with the muscarinic antagonist scopolamine decrease and increase the validity effect, respectively (Phillips et al., 2000; Witte et al., 1997). Yu and Dayan (2005) postulated that cholinergic modulation using nicotine might reduce the validity effect by influencing subjective cue predictability; they suggested that increased levels of acetylcholine (ACh) may reduce the "certainty" of top-down information. The neurotransmitter ACh would accordingly signal the "expected" uncertainty, arising from the known unreliability of the cue predicting the following target. According to that model, ACh signals the "*expected*" uncertainty while norepinephrine reflects "*unexpected*" uncertainty of cues induced by gross changes in the environment (Yu and Dayan, 2005).

While Yu and Dayan (2005) mainly focused on cholinergic modulation of the cue–target relation other authors interpreted the effects of nicotine in the framework of Posner's theory of attention (Posner et al., 1984). They suggested that nicotine influences the processing *after* target presentation by facilitating the disengagement from the cued location (Murphy and Klein, 1998; Witte et al., 1997) or the reorienting toward unattended targets (Thiel et al., 2005).

Prior neuroimaging work indicates that invalidly cued trials activate a neural network in the posterior parietal

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cortex (see, for example, Giessing et al., 2004; Thiel et al., 2004; Corbetta and Shulman, 2002). This, together with neuropsychological data (Posner et al., 1984) suggests that the posterior parietal cortex is crucial for reorienting of attention. Animal studies demonstrate that there exist cholinergic basal forebrain projections to the posterior parietal cortex (Bucci et al., 1999). Using functional magnetic resonance imaging (fMRI) and a pharmacological challenge, Thiel et al. (2005) provided first evidence in humans that a nicotine-induced modulation of the validity effect is associated with a reduction of the blood oxygenation level dependent (BOLD) signal reflecting reduced neural activity (Logothetis, 2002) in posterior parietal cortex during invalid trials. Consistent with that, animal data suggest that the posterior parietal cortex is an important site for nicotinic modulation of the validity effect (Beane et al., 2002).

There is one neuroimaging study that indicates that the right posterior parietal cortex, among others, may be particularly sensitive to aspects of cue certainty since higher BOLD responses were observed to spatially precise cues (Müller et al., 2003). To date, however, no study investigated whether the parietal areas involved in reorienting of attention are also sensitive to a probabilistic manipulation of cue reliability, i.e. the certainty of top-down information derived from a cue. Nor does any knowledge exist of the nicotinic modulation of cue reliability, its possible neural correlates and interaction with the validity effect. According to Yu and Dayan (2005) an enhanced ACh level should lead to a reduced use of the cue. Therefore, brain regions involved in reorienting might be more strongly affected by nicotine in the context of high cue reliability when the cue has a strong behavioral impact (Bowman et al., 1993). On the other hand one could speculate that nicotine might selectively enforce the effects of unpredicted events biasing further expectations of cue–target relationships in the direction of lower cue reliability. Since unpredicted events occur more often in situations with low cue reliability, nicotine might have stronger effects in the context of low cue reliability.

The present fMRI study examines the cholinergic modulation of reorienting visuospatial attention (validity effect) in the context of manipulating top down information that can be derived from the cue (i.e. cue reliability). We used a cued target detection task where trials were arranged in short blocks with different proportions of valid and invalid trials, thus manipulating cue reliability. Blocks with low cue reliability contained 50% valid and 50% invalid trials, while blocks with high cue reliability consisted of valid trials only. There were additional blocks with medium reliability containing 64% valid trials. This blocked design was evaluated with two event-related analyses. The aim of the first analysis was to replicate our previous findings showing increased posterior parietal cortex activation for invalid as compared with valid trials and a reduction of this differential activity with nicotine (Thiel et al., 2005). More importantly, however, in the second analysis we aimed at investigating the interaction between cue reliability, i.e. the certainty of top down information and cholinergic stimulation. We hypothesized that the influence of nicotine would depend on cue reliability and speculated that a drug by reliability interaction should occur in parietal brain regions.

EXPERIMENTAL PROCEDURES

Subjects

Nineteen right-handed volunteers (all Caucasians) with no history of neurological or psychiatric disease gave informed consent to participate in the study. We excluded four volunteers from further data analysis on the basis of the following criteria: more than 3 mm or three degrees of head movement during fMRI scanning ($n=3$) or more than 15% incorrect behavioral responses ($n=1$) (no reaction, a RT of less than 125 ms, a reaction with the wrong hand, or a reaction to catch trials) under either placebo or one of the two nicotine conditions (see below). The remaining 15 subjects (nine female, six male; age range: 20–31 years, mean: 24.3 years) 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. Only non-smokers were recruited to avoid confounding effects of nicotine abstinence on cognitive effects, i.e. the possibility of reversing a deprivation-induced attentional deficit, rather than enhancing attentional processes per se. No subject had used nicotine during the last 2 years and most subjects (13 of 15) had never smoked regularly at all. Subjects were asked to abstain from alcohol 12 h before each fMRI session and from caffeine 3 h prior to scanning.

Drug administration

A within-subjects design was used. Each subject was tested on three experimental sessions, separated by at least one week. The order of drug administration was counterbalanced over subjects. Nicotine was delivered in form of a polacrilex gum with mint taste (Nicorette® mint taste, Pharmacia) in 1 and 2 mg doses; and a chewing gum with mint taste served as placebo. Subjects were asked to chew the gum for 30 min at a rate of one chew per 3 s. Scanning started immediately after chewing had finished. Before scanning, the pulse-rate of each subject was measured. In non-smokers, nicotine plasma levels are on average 1.3 ng/ml at this time point chewing 2 mg nicotine gum (Heishman and Henningfield, 2000). The half life of nicotine is about 2 h (Benowitz et al., 1988).

Stimuli and experimental paradigm

The paradigm was a cued target detection task (Posner, 1980) (see Fig. 1). Stimuli were projected onto a screen in front of the

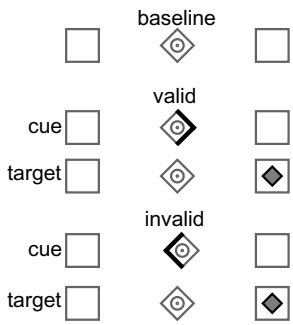

Fig. 1. Experimental paradigm. Illustration of valid and invalid trials, and the baseline condition. The baseline condition consisted of two peripheral boxes and a central diamond. A trial consisted of a cue (100 ms) and target stimulus (100 ms), separated by a 400 or 700 ms cue target interval. Trials were presented every 2000 ms. Subjects were asked to fixate the central diamond during the experiment.

participant in the MRI scanner. Viewing distance was approx. 29 cm. The baseline display consisted 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). For cue stimulus, the same central diamond was used which brightened on one side for 100 ms. The target stimulus was a filled diamond, 1.3° wide and appeared for 100 ms in one of the peripheral boxes. The cue–target interval was either 400 or 700 ms to reduce temporal orienting toward the upcoming target (Coull et al., 2000). Three different trial types occurred: Valid trials, invalid trials and catch trials. In valid trials, the target appeared subsequently on the side indicated by the cue. In invalid trials, the target appeared on the opposite side. In catch trials, a spatial cue but no target appeared. The overall percentage of valid trials was 70.4% (186 trials); 27.3% of trials were invalid trials (72 trials) and 2.3% were catch trials (six trials). Trials were presented every 2 s and were arranged in blocks of 12 trials that alternated with a baseline condition. The duration of the baseline varied between 10 and 14 s with a mean duration of 12 s.

Three different block conditions were used to manipulate cue reliability: i) high cue reliability: blocks with 12 valid trials, i.e. 100% cue reliability, ii) medium cue reliability: blocks with seven valid and four invalid trials, i.e. 64% cue reliability, and one catch trial, and iii) low cue reliability: blocks with six valid and six invalid trials, i.e. 50% cue reliability. Twenty-two blocks were presented (eight blocks with 100 and 50% cue reliability, respectively, and six blocks with 64% cue reliability). Within blocks with medium cue reliability catch trials replaced randomly valid trials. To prevent strategy changes between block conditions and to induce a smooth change in cue reliability, the block order was pseudorandomized so that no more than three blocks with 50% or 100% valid trials occurred in a row. Subjects were instructed to maintain fixation throughout the experiment and to respond to targets as fast as possible. In half of the blocks, responses were made with the index finger of the right hand, in the other half with the left hand since activations found in visuospatial tasks can be influenced by the responding hand (Fink et al., 2000). The response hand was indicated for 4 s before each block of trials (instruction) and was kept constant during the block. The order of block conditions was mirrored over the experiment. The trial sequences within each block changed from block to block over the whole experiment. A break of 10 s was included in the middle of the experiment (with the scanner still running). Prior to scanning, subjects were informed about the different trial types (valid, invalid and catch trials). They were told that the cues were highly informative and encouraged to use these cues to improve performance. Subjects were not informed about changes in the reliability of the cue. A short training session (2 min) preceded scanning. The total length of the experiment was approximately 16 min.

Behavioral analysis: influences of nicotine on the validity effect and cue reliability

Median RTs were calculated for each trial type and drug condition. The means of median RTs were analyzed with two analyses of variance (ANOVAs) for repeated measures. The first 2×3 ANOVA explored the validity effect by drug interaction (first factor: validity, with levels valid trials and invalid trials; second factor: drug, with levels placebo, nicotine 1 mg and nicotine 2 mg). Only low and medium cue reliability conditions were entered into the ANOVA, since in these two conditions only both trial types, i.e. valid and invalid trials, occurred (i.e. valid trials from high cue reliability blocks were not included). In the second 3×3 ANOVA, we investigated the interaction of cue reliability and drug (first factor: cue reliability, with the levels valid trials under low, middle and high cue reliability; second factor: drug, with levels placebo, nicotine 1 mg and nicotine 2 mg) and tested whether the influence of cue reliability follows a linear trend (Gaito, 1977).

Behavioral data: changes of cue reliability within block (learning effects)

Cue reliability might not be established within the first trials in each block but might be developed over trials. To test possible learning effects we used a moving average procedure to compute an index of cue reliability for each trial (see below). Valid trials were dummy-coded as ones and invalid trials as zeros. To implement a memory component, the reliability index of the first trial in a block (b) was defined by the mean of the dummy variables of all trials in the block before (b−1). The reliability index of trial i in block b was defined by the mean of the reliability index of the previous trial (i−1) and the dummy variable of trial i−1. Therefore, the reliability index changed from trial to trial depending on whether the cue predicted the target in the previous trial correctly or not. The reliability index of the first trial of the first block was the overall cue reliability of the whole experiment (the mean over the dummy variables of all trials; start value=70.45). Within each subject we computed a linear regression model using these cue reliability indices as a predictor for RTs.

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, pixel size: 3.12×3.12×4.8 mm^3). Three hundred eighty-five volumes of 24 four mm-thick axial slices were acquired sequentially with a 0.8 mm gap (repetition time for a whole volume=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 head movements, interpolated in time (temporal realignment to the middle slice), and normalized to a standard EPI template volume (sampled to 2×2×2 mm^3 voxels). The data were then smoothed with a Gaussian kernel of 8 mm full-width-half-maximum to accommodate intersubject anatomical variability. A highpass-filter with a cutoff-frequency of 1/128 Hz was used to eliminate noise in the low frequency range.

Statistical analyses of imaging data

Data were analyzed with Statistical Parametric Mapping software SPM2 (Wellcome Department of Imaging Neuroscience, London, UK; Friston et al., 1995). Two different types of data analysis were performed on the same data set employing random effects models investigating i) the neural correlates of the validity effect and the drug by validity interaction comparing invalid with valid trials under placebo and nicotine and ii) the neural correlates of the cue reliability and drug by cue reliability interaction by comparing valid trials in low, middle and high cue reliability conditions under placebo and nicotine.

By comparing invalid and valid trials (i.e. assessing the validity effect) we were able to isolate differences in target-related stimulus processing since the cues were identical in valid and invalid trials and differences arose with target presentation. By comparing valid trials in the context of different cue reliability (i.e. assessing the cue reliability effect) we contrasted physically identical stimuli which differed in terms of top down information provided by the cue. These differences occur at the beginning of the trial but may lead to differences in target processing (i.e. in a context of low cue reliability the predicted target position might be less attended). Therefore, while the validity effect only measures differences in target-related processes, the cue reliability effect measures both cue and target-related cognitive differences.

Neural data: interaction of the validity effect and nicotine

At the first level, data of all sessions (placebo, nicotine 1 mg and nicotine 2 mg) were modeled in one design matrix. We defined 14

regressors for each session. The first five regressors modeled the following event types: valid trials under low cue reliability, invalid trials under low cue reliability, valid trials under medium cue reliability, invalid trials under medium cue reliability, and valid trials under high cue reliability. Further nine regressors of no interest were included, one for catch trials, one for instructions and the break in the middle of the experiment, one for incorrect responses (i.e. incorrect responses with right hand, left hand, no or two responses with different hands) and six regressors for head movement parameters from the realignment procedure. The event types were time-locked to the onset of the target by a canonical synthetic hemodynamic response function (HRF). Time-locking to target was chosen since invalid and valid trials were identical until target presentation.

Due to previous data (Giessing et al., 2004; Thiel et al., 2004, 2005) we expected i) higher parietal cortex activation during invalid in comparison to valid trials (main effect of validity) and ii) a significant reduction of this differential parietal effect resulting from nicotine. Even though we had directed hypotheses we used three two-sided *f*-tests consistent with the analysis of the reliability effect: one to test for the main effect of "validity" under placebo, 1 mg nicotine and 2 mg nicotine [invalid placebo, 1 mg nicotine, 2 mg nicotine vs. valid placebo, 1 mg nicotine, 2 mg nicotine], one for the drug×validity effect interaction under 1 mg nicotine [invalid placebo-valid placebo] vs. [invalid nicotine 1 mg-valid nicotine 1 mg] and one for the drug×validity effect interaction under 2 mg nicotine [invalid placebo-valid placebo] vs. [invalid nicotine 2 mg-valid nicotine 2 mg]. Only trials of the low and medium cue reliability condition were entered into these analyses, since only in these two conditions, both invalid and valid trials were measured (i.e. valid trials from high cue reliability blocks were not included).

Neural data: interaction of the cue reliability effect and nicotine

This parametric analysis tested for brain regions that show a linear relationship between cue reliability and BOLD signal. We modeled valid and invalid trials and two parametric regressors coding the cue reliability (50%, 64% and 100%, according to their block context). Further nine regressors of no interest were included (see above). We tested with three two-tailed *f*-contrasts for an effect of cue reliability in valid trials, and an effect of 1 mg and 2 mg nicotine on cue reliability. Influences of nicotine were tested by comparing the beta estimates of the parametric regressors under placebo and nicotine (1 mg or 2 mg). A significant difference in these beta values would demonstrate that drug effects were inhomogeneous over cue reliability conditions. If the slopes differed, the differences between drug conditions would depend on cue reliability (Jorgensen, 1993). The analysis of cue reliability was restricted to the analysis of valid trials since valid trials were used in each block condition. Events were modeled as delta functions convolved with the HRF even though trials in the 100% cue reliability condition were presented in blocks (Giessing et al., 2004; Mechelli et al., 2003). To be consistent with the analysis of the validity effect trials were modeled on the target.

Region of interest analyses and dose-related effects of nicotine

In a previous study we used a similar paradigm to investigate the validity effect (Giessing et al., 2004). We found stronger activations during invalid in comparison to valid trials within the intraparietal sulcus (IPS). Two region of interest analyses were performed to show i) whether brain areas involved in reorienting of attention are significantly influenced by nicotine and ii) whether the effect of nicotine depends on cue reliability. To investigate dose-related effects of nicotine we tested whether the drug effects are best predicted by a linear trend that is not further improved by additional polynomial expansions.

Data were scan-wise globally scaled to reduce globally distributed confounding effects (Kiebel and Holmes, 2004). Due to the low correlation between the global mean and the contrast-weighted design matrices for both the validity effect and the cue reliability effect we can rule out that global scaling might have produced artificial deactivations (Aguirre et al., 1998; validity effect: averaged absolute values of correlations in the placebo session $r=0.04$, 1 mg nicotine session $r=0.04$ and 2 mg nicotine session $r=0.04$; cue reliability effect: averaged absolute values of correlations in the placebo session $r=0.05$, 1 mg nicotine session $r=0.07$ and 2 mg nicotine session $r=0.05$). Results are reported on a two-sided significance level of $P<0.001$ (uncorrected) and a cluster extent threshold >10 voxels. Post hoc tests of behavioral and neural data are reported on a two-tailed significance level.

Due to our a priori hypotheses we restrict our discussion to significant activations within the parietal cortex but for matters of completeness we report also non-parietal activations. This is for the following reasons: First, parietal cortex has been hypothesized to be involved in the detection of invalidly cued targets (Corbetta et al., 2000; Petersen et al., 1989) and prior fMRI data indicate that nicotine influences parietal cortex activity in attentional paradigms including cued target-detection tasks (Lawrence et al., 2002; Thiel et al., 2005). Second, animal evidence suggests that it is the parietal cortex where nicotine exerts its behavioral effects on covert orienting (Beane et al., 2002). Since we assumed that the influence of nicotine on the validity effect and the cue reliability effect might result from changes in the same neural mechanisms, we expected to find a validity effect and cue reliability effect×drug interaction in parietal brain areas.

RESULTS

Behavioral data: influences of nicotine on the validity effect and cue reliability

Subjects showed 4% incorrect behavioral responses (placebo: 5%, 1 mg nicotine: 3%, 2 mg nicotine: 4%). The mean number of responses to the six catch trials (i.e. false alarm) was less than 1 (placebo: 0.8, 1 mg nicotine: 0.2, 2 mg nicotine: 1). Subsequent analyses were confined to correct responses only.

The 2×3 ANOVA for repeated measurements with the factors validity effect and drug revealed a significant validity effect which was manifest in longer RTs for invalid than for valid trials (means and standard error of the means [SEMs]: valid: 265±6 ms, invalid: 297±8 ms; $F(1,14)=78.82$, $P<0.001$). We found neither a significant main effect of drug nor a drug×validity effect interaction. To ensure that the cue was used for orienting attention even in the low reliability condition, we tested post hoc whether subjects showed significantly shorter RTs for valid than for invalid trials in the 50% blocks under placebo. Valid trials yielded significantly shorter RTs than invalid trials (valid trials: 269±9 ms, invalid: 301±10 ms; $t(14)=8.07$, $P<0.001$).

The 3×3 ANOVA for repeated measurements with the factors cue reliability and drug revealed a significant cue reliability effect ($F(2,28)=5.41$, $P<0.05$). We found no significant main effect of drug or drug×cue reliability interaction. Effects of cue reliability on RTs can be best described by a linear trend ($t(14)=-2.86$, $P<0.05$). The quadratic trend revealed no significant result ($t(14)=-1.93$, $P=0.07$; means over drug conditions and SEMs: valid trials in low cue reliability blocks: 264±6 ms, in middle cue reliability blocks: 267±7 ms, in high cue reliability blocks: 261±6

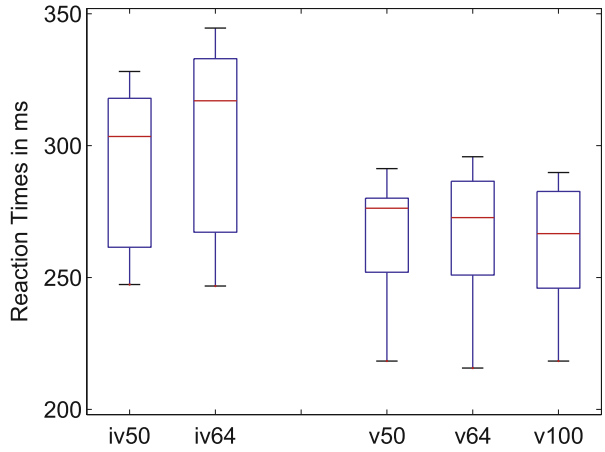

Fig. 2. RTs averaged across drug conditions (box and whisker plot). RTs during invalid trials have longer durations than during valid trials. RTs during valid trials in the 50, 64 and 100% cue reliability conditions are best described by a linear trend. Abbreviations: iv50/iv64, invalid trials in 50 or 64% cue reliability condition; v50/v64/v100, valid trials in 50, 64 or 100% cue reliability condition. The box has lines at the lower quartile, median (red), and upper quartile values. The whiskers are lines extending from each end of the box to show the extent of the rest of the data. Outliers are data with values beyond the ends of the whiskers. If there are no data outside the whisker, a dot is placed at the bottom whisker. Outlier values are symboled by crosses.

ms). Note, that the observed mean in the middle cue reliability condition was higher than in the low cue reliability condition but this difference was not significant ($t(14)=1.16$, $P=0.26$) and medians followed the predicted order (low cue reliability: 276 ms, middle cue reliability blocks: 273 ms, high cue reliability: 267 ms; see Fig. 2).

Behavioral and neural data: changes of cue reliability within a block (learning effects)

Cue reliability might be derived over trials within a block. Therefore we used a moving average procedure (see section Experimental Procedures) to compute a reliability index of each trial. This index was used in a linear regression model to predict RTs during invalid and valid trials. Using a summary statistic approach we computed *t*-tests on the regression coefficients of all subjects. We found a consistent positive linear relationship between the reliability index and RTs during invalid trials ($\bar{r}=0.16$, *t*-test on regression coefficients: $t(14)=6.51$, $P<0.001$; Barker, 1990). This indicates that RTs during invalid trials tended to be slower in trials with high cue reliability (correlations and regression coefficients were averaged over drug conditions). Furthermore, the data revealed a small (almost zero) consistent negative linear relationship between the reliability index and RTs during valid trials ($\bar{r}=-0.06$, *t*-test on betas: $t(14)=-3.42$, $P<0.005$). An explorative analysis of neural activity during invalid trials over all drug conditions revealed a significant linear relationship between the cue reliability index and the BOLD signal within the right inferior frontal sulcus ($x=40$, $y=24$, $z=26$, $F(1,14)=36.13$, $Z=4.00$, 39 voxel) and right middle frontal gyrus ($x=32$, $y=38$, $z=42$, $F(1,14)=30.55$, $Z=3.79$, 14 voxel). No further activations were observed. During valid trials the strongest activation was found in the superior frontal sulcus ($x=-24$, $y=44$, $z=42$, $F(1,14)=49.14$, $Z=4.37$, 95 voxel).

Neural data: the validity effect and interactions with nicotine

Increased neural activity to invalid as compared with valid trials averaged over all drug conditions (main effect) was observed in the right superior parietal gyrus, left posterior cingulate gyrus, the left and right IPS and bilateral temporoparietal junction. Activations in the IPS and temporoparietal junction are shown in Fig. 3A. The strongest activation was found in the left superior frontal gyrus. A complete list of all activations is provided in Table 1. The only parietal region showing a significant drug by validity effect was the right IPS (under 2 mg of nicotine; see Fig. 3B). This interaction was due to a significant reduction of parietal cortex activity in invalidly cued trials under 2 mg of nicotine (post hoc *t*-test, $t(14)=-2.78$, $P<0.05$) and a tendency toward a significant enhancement of neural activity during valid trials ($t(14)=1.95$, $P=0.07$). By further exploring the beta estimates in this voxel in an ANOVA the data revealed a significant cue reliability by drug interaction ($F(1,14)=11.80$, $P<0.01$) and a tendency toward a significant result for a drug by validity by cue reliability interaction ($F(1,14)=4.26$; $P=0.06$). This three-way interaction was mainly due to a strong activation during invalid trials in the 64% cue reliability condition under placebo which was significantly reduced under 2 mg nicotine ($t(14)=-3.66$, $P<0.005$; see Fig. 4). While we observed under placebo a significant validity effect ($F(1,14)=15.66$, $P<0.001$), cue reliability effect ($F(1,14)=7.42$, $P<0.05$), and cue reliability by validity interaction ($F(1,14)=5.89$, $P<0.05$) these effects were not significant under 2 mg nicotine. Therefore, nicotine seems to reduce differences between invalid and valid trials that depend on cue reliability under placebo.

Neural data: the cue reliability effect and interactions with nicotine

The effect of cue reliability was captured by a parametric analysis of valid trials testing for brain regions that show a linear relationship with cue reliability (50, 64 and 100%). The strongest correlations averaged over all drug conditions were found in the right and left cingulate gyrus including anterior and posterior regions. The posterior cingulate gyrus showed stronger activations with enhanced cue reliability (see Fig. 5A). A complete list of all activations is displayed in Table 2.

The only parietal regions showing a significant effect of nicotine on cue reliability were the right superior parietal sulcus under 1 mg and the right IPS under 2 mg nicotine (see Table 2). Fig. 5B shows the activation in the right IPS. These regions revealed a “more positive” linear relationship with cue reliability under placebo than under nicotine which means that drug effects were not homogenous over cue reliability conditions. The nicotine effect was significantly larger on valid trials in the low cue reliability condi-

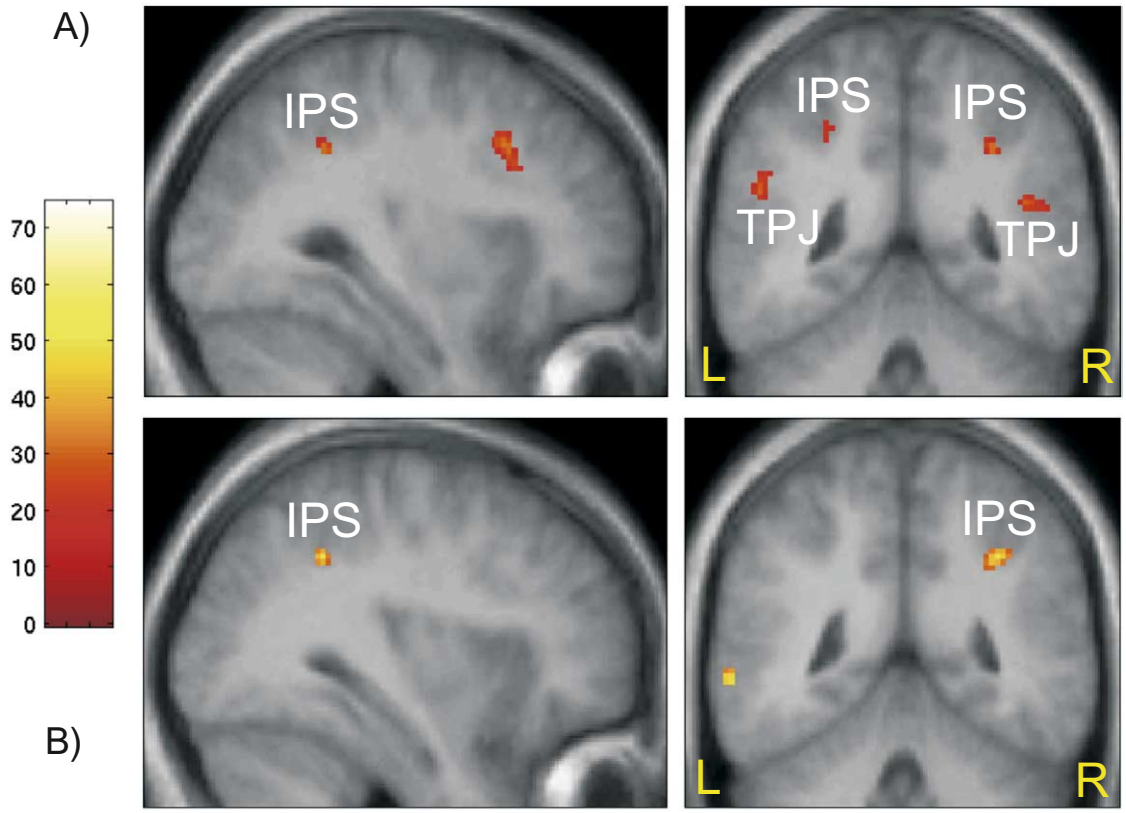

Fig. 3. Neural correlates of the validity effect (A) and its interaction with nicotine (B). (A) Upper panels: Activation in the IPS and temporoparietal junction which was significantly different in invalid as compared with valid trials (main effect of validity). All activations ($P<0.001$, uncorrected, cluster threshold >10 voxels) are shown on the normalized mean structural MR image of the volunteers. (B) Lower panels: Parietal regions exhibiting a drug by validity effect interaction in the 2 mg nicotine condition (placebo [invalid trials−valid trials] vs. nicotine 2 mg [invalid trials−valid trials]). L/R, left and right hemisphere; TPJ, temporoparietal junction.

tion in comparison to the high cue reliability condition ($t(14)=4.67$, $P<0.001$). This cue reliability effect by drug interaction was mainly due to a tendency of significant enhancement during valid trials in the low cue reliability condition ($t(14)=1.89$, $P=0.08$).

Neural data: region of interest analyses

The right IPS ($x=33$, $y=-51$, $z=51$) revealed significantly stronger activations during invalid than valid trials (Giessing et al., 2004). We conducted a region of interest analysis with the activation maximum in the right IPS as midpoint of a 15 mm sphere (due to the different voxel size the mni coordinates changed slightly to $x=32$, $y=-50$, $z=52$). These analyses revealed a significant drug by validity effect interaction under 2 mg nicotine (22 voxel, $x=34$, $y=-48$, $z=38$; $Z=3.89$; $P<0.05$, FWE-corrected for multiple comparisons) and a significant influence of nicotine on cue reliability in the 2 mg condition (13 voxel, $x=34$, $y=-48$, $z=38$; $Z=3.92$; $P<0.05$, FWE-corrected for multiple comparisons). Therefore, nicotine significantly reduced the activations during invalid and valid trials in brain areas which are involved in the processing of unattended targets and drug effects during valid trials depend on the context of cue reliability.

Neural data: dose-related effects of nicotine

Dose-related activations were found within the right IPS for both, the validity and cue reliability effect (parameter estimates for cue reliability effect placebo: −0.28, cue reliability effect 1 mg nicotine: 0.05, cue reliability effect 2 mg nicotine: 0.24; validity effect placebo: 0.64, validity effect nicotine 1 mg: 0.60, validity effect nicotine 2 mg: −0.19). Within the accuracy of measurements, both nicotinic parietal modulations can be reasonably described by a linear trend (validity effect: $F(1,14)=28.86$, $P<0.001$; cue reliability effect: $F(1,14)=21.80$, $P<0.001$). With larger doses of nicotine the invalidity effect decreased while the cue reliability effect increased. Note, that in both cases an additional quadratic term does not significantly improve the prediction. Even though we tested only three drug levels our data revealed evidence that the influences of nicotine on the cue reliability and validity effect can be best described by a linear regression model.

Physiological measures and questionnaire

Nicotine increased the pulse rate dose dependently (placebo: 68±2.80 mean and SEM, nicotine 1 mg: 71±1.67, nicotine 2 mg: 73±2.50; specific contrast testing a linear trend: $F(1,12)=7.53$, $P<0.05$). The quadratic trend was

Table 1. Neural activations underlying the validity effect and validity×nicotine interactions

Brain region	Side	MNI coordinates			*Z*-value	Cluster size
		x	*y*	*z*		
A. Main effect validity: invalid vs. valid						
Superior frontal gyrus	L	−18	10	58	4.87	163
Middle frontal gyrus	R	34	20	32	3.90	70
	L	−44	2	44	3.85	75
Inferior frontal gyrus	L	−48	12	26	3.86	20
	L	−28	26	−2	2.39	12
Precentral gyrus	R	50	14	30	3.69	11
Transverse orbital sulcus	L	−30	40	−6	3.58	11
Posterior cingulate gyrus	L	−8	−24	32	3.87	21
IPS	L	−28	−52	42	3.96	164
	R	32	−48	36	3.78	14
Superior parietal gyrus	R	20	−66	62	3.63	60
Temporoparietal junction	L	−42	−56	20	3.91	53
	R	44	−48	18	3.71	56
	L	−52	−46	22	3.76	42
Lingual gyrus	R	20	−80	−10	3.46	21
Middle occipital sulcus	L	−38	−68	−2	4.03	51
Thalamus	R	20	−24	0	4.20	22
	R	12	−26	6	4.03	16
	L	−16	−32	10	3.47	14
B. Validity effect placebo vs. validity effect nicotine 1 mg						
Parahippocampal gyrus	R	16	−12	−26	4.38	54
Thalamus	L	−8	−6	−4	3.95	22
C. Validity effect placebo vs. validity effect nicotine 2 mg						
Superior frontal gyrus	L	−10	50	−14	3.49	14
Middle frontal gyrus	R	38	4	44	3.85	11
Middle temporal gyrus	L	−64	−46	−4	4.25	27
IPS	R	34	−48	38	3.72	29
Lateral occipital sulcus	L	−44	−72	−4	3.65	25
Lingual gyrus	L	−18	−88	−12	3.44	13

Results are presented at a two-tailed significance level of $P<0.001$, uncorrected and a cluster size threshold >10 voxels.

not significant ($F(1,12)=0.13$, $P=0.73$). All subjects correctly indicated the nicotine sessions.

DISCUSSION

We investigated the influence of nicotine on task-related neural activations involved in the detection of validly and invalidly cued targets in the context of changing cue reliability. At 1 and 2 mg nicotine, we found no significant influence of nicotine at the behavioral level. The fMRI data revealed, however, a nicotinic modulation of neural activity in the right posterior parietal cortex with regard to i) the validity effect and ii) the certainty in the top-down information derived from the cue (i.e. cue reliability).

Behavioral and physiological data

In general, subjects showed shorter RTs for valid than for invalid trials. The behavioral validity effect was even present in blocks with low cue reliability (i.e. 50% invalid trials). This demonstrates that subjects used the information provided by the cue to direct their attention even in a context in which the cue was objectively of no informational value. We did not find any significant influence of nicotine on the validity effect nor the cue reliability effect at the behavioral level. In general, nicotinic effects on behavioral measures in non-smoking subjects are known to be small or may be even absent (see Newhouse et al., 2004 for a review). While several studies in animals and smoking subjects reported a reduction of the validity effect with nicotine (Witte et al., 1997; Shirtcliff and Marrocco, 2003; Stewart et al., 2001), studies in nonsmokers either reported only a tendency for a reduction of the validity effect (Thiel et al., 2005) or were unable to find an influence of nicotine (Griesar et al., 2002). We nevertheless decided to use non-smoking subjects for the following reasons: First, only in these subjects nicotine effects can be clearly ascribed to a modulation of the cognitive process of interest rather than the reduction of a deprivation induced deficit. Second, Thiel et al. (2005) documented effects on *neural* activity even though nonsmokers revealed only weak (i.e. insignificant) behavioral effects. Finally, it is well known that significant changes in the pattern of brain activations

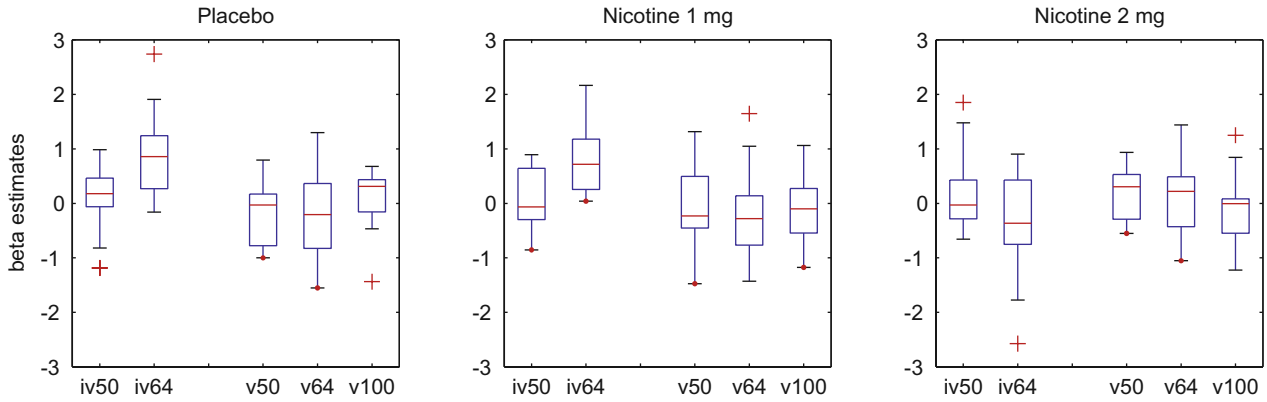

Fig. 4. Signal change in the right IPS (box and whisker plot). Signal changes of invalid and valid trials in the 50, 64 and 100% cue reliability condition are plotted. Data are presented for each drug condition (left plot: placebo, central plot: 1 mg nicotine, right plot: 2 mg nicotine). For abbr. and information regarding box and whisker plot see Fig. 2

can occur even without a corresponding change in overt behavior (Fink et al., 2002) and that these changes can inform cognitive theory (Wilkinson and Halligan, 2004). For example, changes in cognitive processes or effort are not necessarily reflected by behavioral measures such as RT data but may nevertheless show changes in neural activity. Thus, drug actions may often be better reflected in neural than behavioral data and there are several pharmacological fMRI studies which show drug-related changes in neural activity in the absence of behavioral effects (e.g. Bullmore et al., 2003; Ghatan et al., 1998; Hershey et al., 2004). Importantly, pulse rate was modulated by nicotine and increased linearly over placebo, 1 and 2 mg nicotine conditions indicating a dose-related drug effect. This documents that nicotine can show differential effects on the behavioral, physiological and neural level (see below) and that each level can provide information in its own right.

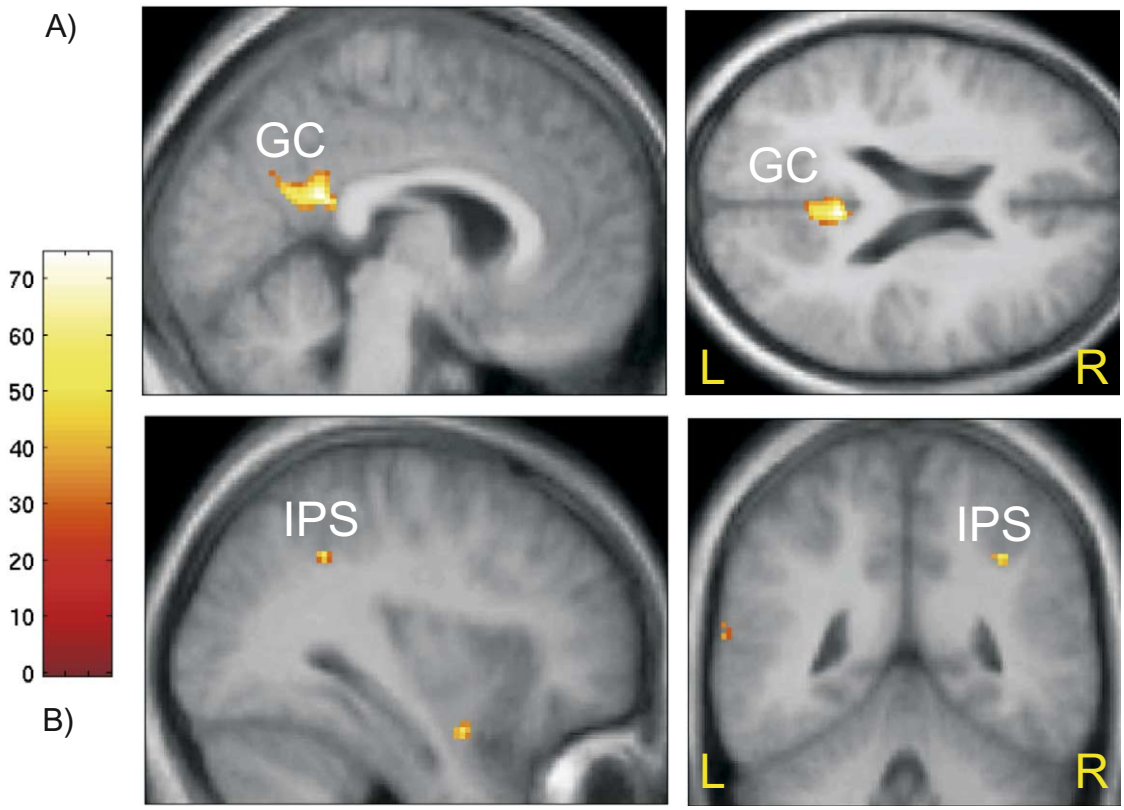

Fig. 5. Neural correlates of the cue reliability effect (A) and its interaction with nicotine (B). (A) Upper panels: Activations in the posterior cingulate gyrus are significantly influenced by cue reliability. (B) Lower panels: Parietal regions exhibiting a drug by cue reliability effect interaction in the 2 mg nicotine condition. GC, cingulate gyrus.

Table 2. Neural activations underlying the cue reliability effect and cue reliability×nicotine interactions

Brain region	Side	MNI coordinates			*Z*-value	Cluster size
		x	*y*	*z*		
A. Main effect cue reliability effect						
Superior frontal sulcus	L	−24	36	44	3.48	14
Middle frontal gyrus	R	44	−2	58	3.31	13
Cingulate gyrus	R/L	4	−48	20	4.20	327
	L	−10	12	38	4.21	18
	L	−8	−8	32	3.64	11
Superior temporal sulcus	R	58	−16	−10	3.84	19
Postcentral gyrus	R	58	−30	54	4.08	36
Superior parietal gyrus	R	24	−90	26	3.66	37
Fourth occipital gyrus	L	−22	−86	−14	3.61	22
B. Cue reliability effect placebo vs. cue reliability effect nicotine 1 mg						
Superior temporal sulcus	L	−58	−18	−12	3.55	34
	L	−64	−42	0	3.54	11
	L	−48	−34	−4	3.40	16
Inferior temporal gyrus	L	−46	−26	−24	4.98	43
Pons/parahippocampal gyrus	R	12	−16	−20	4.37	44
Superior parietal sulcus	R	24	−58	60	3.78	16
Supramarginal gyrus	L	−48	−34	36	3.68	13
Superior occipital gyrus	L	−12	−100	12	4.29	34
C. Cue reliability effect placebo vs. cue reliability effect nicotine 2 mg						
Superior frontal sulcus	L	−20	26	40	3.67	10
Superior temporal sulcus	L	−68	−38	4	3.77	26
IPS	R	34	−48	38	3.92	13
Lateral fissure	R	34	2	−24	3.88	14
Superior occipital gyrus	L	−20	−106	−2	4.27	19
	L	−8	−104	10	3.87	34
Fourth occipital gyrus	L	−42	−58	−24	3.68	36

Results are presented at a two-tailed significance level of $P<0.001$, uncorrected and a cluster size threshold >10 voxels.

Changes in context vs. changes in cue reliability

Yu and Dayan (2005) distinguished expected and unexpected cue uncertainty. Expected uncertainty should arise from known unreliability of predictive events (like a cue in a Posner task) while unexpected cue uncertainty should be induced by gross changes in cue–target relationships. These large changes in context should lead to uncertainty which of several cues should be believed to be relevant (note that Yu and Dayan (2005) used a paradigm with more than one cue). As mentioned by Yu and Dayan (2005) the border between both concepts is not easily defined. However, we think that our paradigm only measured changes in expected uncertainty or reliability. Since we used only one cue type, there was no need for subjects to decide about cue identity. The simplest assumption is to assume only one cognitive process: Subject tried to estimate (consciously or subconsciously) on each trial the cue reliability of the current block (using the previous trials in each block).

The validity effect, parietal cortex and its modulation by nicotine

Animal evidence confirms that systemic nicotine increases frontal cortical ACh release (Tani et al., 1998). It has been suggested that such ACh release is critically involved in attentional processing since frontoparietal ACh release is increased in rats performing sustained attention tasks (Arnold et al., 2002). Conversely, lesions of the cholinergic forebrain projection impair attentional functions, including the validity effect (Chiba et al., 1999). Several imaging studies have found an effect of nicotine on parietal and frontal neural activity in different cognitive paradigms (Ernst et al., 2001; Ghatan et al., 1998; Kumari et al., 2003; Lawrence et al., 2002). The first study investigating the effects of nicotine on neural correlates of attention in the human brain was performed by Lawrence et al. (2002). They used a sustained attention task in smokers and found, among others, increased activity in the left and right parietal cortex under nicotine. Using a cued target detection task, Thiel et al. (2005) previously found the left and right posterior parietal cortex to be implicated in the validity effect and showed that nicotine reduces neural activity in this area. The present study used again a cued target detection task but additionally varied cue reliability. As expected, neural correlates of the validity effect were found in bilateral parietal cortex around the IPS and the temporoparietal junction (e.g. Corbetta et al., 2000; Thiel et al.,

2004; Small et al., 2003). More importantly, we were able to reproduce the specific nicotine induced reduction of parietal cortex activity in invalid trials (Thiel et al., 2005).

A validity effect by drug interaction was found in the 2 mg nicotine condition in the right IPS, which was due to significantly lower neural activity during invalid trials and a trend for significant enhancement of neural signal during valid trials under nicotine. Even though the influences of nicotine on the validity effect can best be described by a linear trend, the pattern of right posterior parietal cortex activity under 1 mg of nicotine was similar to the placebo condition. This is in contrast to our previous study (Thiel et al., 2005) where both doses of nicotine exerted similar effects on posterior parietal brain areas. Another difference between our previous study and the current one was that in the latter, the effects of nicotine were predominantly observed in the right IPS while effects in our previous study were stronger on the left side. One possible explanation for this difference is that subjects in the study of Thiel et al. (2005) responded only with the right hand while in the current study subjects used both hands for responses (see also Fink et al., 2000). Taken together, previous studies (Lawrence et al., 2002; Thiel et al., 2005) and our results indicate that in different attentional paradigms nicotine influences parietal cortex activation.

Under placebo, the validity effect in the right IPS was context dependent and stronger in the condition with middle cue reliability as compared with the low cue reliability condition. This is in line with previous behavioral studies which have shown that the validity effect is a function of cue reliability (Eriksen and Yeh, 1985; Giessing et al., 2004; Riggio and Kirsner, 1997). The context dependent differences in parietal activity between invalid and valid trials were reduced by nicotine so that under 2 mg nicotine the IPS did not show any differential activation between invalid and valid trials. This result is in agreement with the theory of Yu and Dayan (2005) who suggest that enhanced ACh levels suppress the use of the cue and might therefore reduce differences between valid and invalid trials and the effects of cue reliability.

Previous functional imaging and neuropsychological studies revealed evidence that parietal areas are part of a network that is responsible for changes from local to global attention (Fink et al., 1996; Halligan and Marshall, 1993). Likewise, patient studies and models of attention suggest that the parietal cortex is involved in the narrowing and widening of the attentional spotlight (Mesulam, 1981, 1983; Townsend and Courchesne, 1994). One could thus speculate that the influence of nicotine on cue reliability enlarges the spotlight of attention in the sense of a wide-angle zoom (Eriksen and St. James, 1986; Fernandez-Duque and Johnson, 1999). This, in turn, would explain why nicotine reduces the neural activity during invalid trials. Under nicotine, even targets at an uncued position would be within the "widened" spotlight of attention and therefore would not induce a re-direction of the attentional focus.

The cue reliability effect and the posterior cingulate

Even though we found an interaction of cue reliability and nicotine in parietal cortex the main effect of cue reliability is evident in an extensive activation of the right and left posterior cingulate cortex. This brain region showed stronger activations with enhanced cue reliability. It has been suggested, that the posterior cingulate cortex might be involved in the emergence of cue induced expectancies (Mesulam et al., 2001; Hopfinger et al., 2000). Small et al. (2003) compared valid trials in which the cue elicited a benefit in RTs (in comparison to a neutral cue condition) with those that showed no benefit. When contrasting valid trials that elicited benefits with those that did not, the posterior cingulate cortex revealed a significant activation. A region of interest analysis within a 15 mm sphere and the activation maximum of this posterior cingulate activity as midpoint revealed that our cue reliability effect was within the same brain region (126 voxel, $x=4$, $y=-48$, $z=20$; $Z=4.20$; $P<0.05$, FWE-corrected for multiple comparisons). Furthermore, Small et al. (2003) found an inverse relationship between cue benefit and neural activity in the IPS and visual cortex. Neuroanatomical evidence shows extensive connections between posterior cingulate and parietal cortex (Vogt et al., 1979) and both regions might interact in the processing of cue reliability or "expectancy."

Cholinergic modulation of the cue reliability effect in parietal cortex

To our knowledge, this is the first study to investigate whether cholinergic modulation of parietal activity in a visual spatial attention task depends on cue reliability, i.e. the top down information that can be derived from a cue dependent upon its context. The effect of nicotine (2 mg dose) in the right IPS during valid trials depended significantly on the level of cue reliability. This interaction was due to enhanced BOLD responses to valid trials under nicotine in the context of low cue reliability. Thus, when the "confidence" in the top-down information derived from the cue was low, neural activity during valid trials in right posterior parietal cortex increased by cholinergic stimulation with nicotine. This is in contrast to the effects of nicotine during invalid trials, where stronger influences were seen in a context of higher cue reliability. A possible explanation for a drug showing opposing context-dependent effects within one brain region, is that activity in this brain region might reflect different underlying cognitive processes which recruit different neural networks and are differentially modulated by the drug. According to Corbetta and Shulman (2002), the IPS is part of both a bottom-up ventral frontoparietal network and a top-down dorsal frontoparietal system. While the first network might modulate IPS activity in relation to reorienting of attention, the second is involved in top-down information provided, for example, by cue reliability. Some evidence for the involvement of the IPS in cue reliability processing is given by Small et al. (2003) who contrasted valid trials with different cue benefit (see above). Our data revealed evidence that the effects of nicotine depend on cue reliability in the IPS. Thus, our results suggest that the parietal cortex is part of a neural network where nicotine exerts its influence on cue evaluation. Whether the observed action of nicotine in parietal cortex is due to direct binding of the drug in this

area or due to a modulation of parietal activity through binding elsewhere (e.g. thalamus) cannot be answered with fMRI. Postmortem human data show the highest binding site densities for nicotinic receptors subcortically, within the thalamus. The levels of cortical binding are comparably low with highest binding in primary sensory cortices (Zilles et al., 2002).

Neural data: dose related effects of nicotine

The influence of nicotine on the validity and cue reliability effect in the right intraparietal cortex can be reasonably described by a linear trend. Furthermore, the observed means of the cue reliability and validity effect under each drug condition are ordered according to the drug dose. Note, that the model fit was not improved by an additional quadratic term, arguing for a true linear trend. Even though three drug levels provide limited evidence to characterize dose response curves this result gives further support that our results are indeed significant.

CONCLUSION

In summary, we found that one neural correlate of the validity effect is increased posterior parietal activity that is reduced with nicotine. The modulation of top-down information by changing cue reliability most strongly activated the posterior cingulate cortex. Even though this brain region was not significantly modulated by nicotine it is connected to posterior parietal cortex which showed a nicotinic modulation of neural activity depending on cue reliability.

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