Nicotine Effects on Brain Function during a Visual Oddball Task: A Comparison between Conventional and EEG-informed fMRI Analysis

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Abstract

■ In a previous oddball task study, it was shown that the inclusion of electrophysiology (EEG), that is, single-trial P3 ERP parameters, in the analysis of fMRI responses can detect activation that is not apparent with conventional fMRI data modeling strategies [Warbrick, T., Mobascher, A., Brinkmeyer, J., Musso, F., Richter, N., Stoecker, T., et al. Single-trial P3 amplitude and latency informed event-related fMRI models yield different BOLD response patterns to a target detection task. *Neuroimage, 47,* 1532–1544, 2009]. Given that P3 is modulated by nicotine, including P3 parameters in the fMRI analysis might provide additional information about nicotine effects on brain function. A 1-mg nasal nicotine spray (0.5 mg each nostril) or placebo (pepper) spray was administered in a double-blind, placebo-controlled, within-subject, randomized, cross-over design. Simultaneous EEG-fMRI and behavioral data were recorded from 19 current smokers in response to an oddball-type visual choice RT task. Conventional general linear model analysis and single-trial P3 amplitude informed general linear model analysis of the fMRI data were performed. Comparing the nicotine with the placebo condition, reduced RTs in the nicotine condition were related to decreased BOLD responses in the conventional analysis encompassing the superior parietal lobule, the precuneus, and the lateral occipital cortex. On the other hand, reduced RTs were related to increased BOLD responses in the precentral and postcentral gyri, and ACC in the EEG-informed fMRI analysis. Our results show how integrated analyses of simultaneous EEG-fMRI data can be used to detect nicotine effects that would not have been revealed through conventional analysis of either measure in isolation. This emphasizes the significance of applying multimodal imaging methods to pharmacoimaging. ■

INTRODUCTION

Measuring the effects of nicotine on cognition can be challenging; the complex interaction between experimental factors, individual factors, and measurement modality means that behavioral, electrophysiological, and fMRI findings are not always easily reconciled with each other (Ettinger et al., 2009; Giessing, Thiel, Rösler, & Fink, 2006; Polich & Criado, 2006; Thiel, Zilles, & Fink, 2005; Jacobsen et al., 2004; Lawrence, Rose, & Stein, 2002; Kumari et al., 2003). Although this may, in part, be dependent on conditions related to task design or even mode of drug administration (Pritchard, Sokhadze, & Houlihan, 2004), interparticipant heterogeneity in behavioral and fMRI responses to nicotine across participants has recently been reported (Warbrick et al., 2011; Ettinger et al., 2009). Furthermore, interpreting the functional significance of these changes, in terms of effects on cognitive function, is also difficult. What does an increase or decrease in the fMRI BOLD response from one condition to another actually mean in physiological terms and how does it relate to better or worse task performance? When conducting drug challenge fMRI studies, a simultaneous fMRI/EEG imaging approach may help to resolve some of these open questions, because it affords the investigation of multiple measures under the same boundary conditions and thus allows an immediate comparison of direct (EEG) and indirect (BOLD) measures of neural activity. In addition, recent developments in simultaneous measurement of EEG and fMRI data allow EEG-informed single-trial analysis of the fMRI data. An advantage of the single-trial approach is that it can utilize variability in brain responses that is lost during standard averaging (Fell, 2007; Debener et al., 2005). This is particularly important in studies where variability in responses may be indicative of stimulus processing modulation or task performance and not simply irrelevant noise (Bagshaw & Warbrick, 2007; Debener et al., 2005; Eichele et al., 2005). In our recent work (Warbrick et al., 2011), we found the magnitude and direction of BOLD response to nicotine to be related to both mean RT and intraparticipant RT variability, suggesting that preserving the variability information, using single-trial measures (i.e., behaviorally relevant variability in single-trial responses is not lost through

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averaging) could be informative when investigating the effects of nicotine on behavior. The single-trial information extracted from the ERP can be included in the fMRI data analysis to predict the BOLD response to each trial (Huster et al., 2011; Mulert et al., 2008; Benar et al., 2007; Debener et al., 2005; Eichele et al., 2005). We recently showed that, by including single-trial P3 parameters in the general linear model (GLM) analysis of the BOLD response, we can detect additional activation in brain regions associated with task performance that would have been concealed with conventional fMRI analysis alone (Warbrick et al., 2009).

The study presented here focuses on responses to a visual two choice RT task with infrequent target stimuli similar to that of an oddball task. The oddball task is used in ERP studies to elicit the P3 that represents target detection/event categorization (Halgren, Marinkovic, & Chauvel, 1998). The amplitude of the P3 component is known to be indicative of the amount of attentional resources allocated to a stimulus (Pritchard et al., 2004; Picton 1992) and is also modulated by nicotine (Polich & Criado, 2006; Pritchard et al., 2004). One of the mechanisms by which nicotine influences performance is thought to be via improvements in attention to the task (Heishman, Kleykamp, & Singleton, 2010), as such modulation of the P3 amplitude by nicotine is expected. In fact, it has been shown that nicotine's effect on processing speed correlates with its effect on P3 amplitude (Pritchard et al., 2004).

The oddball task is also known to elicit a BOLD response in a large distributed network including the supramarginal gyrus, frontal cortex, insula, thalamus, cerebellum, occipital-temporal, superior temporal and cingulate regions (Strobel et al., 2008; Gur et al., 2007; Winterer et al., 2007; Musso et al., 2006; Kiehl et al., 2005; Bledowski et al., 2004). Because the task elicits a robust BOLD and ERP response, it provides a suitable framework for investigating the effects of nicotine on behavioral, electrophysiological, and fMRI measures of the attention and working memory processes involved in it. Comparing the conventional with EEG-informed fMRI analysis, the aim of this study was to investigate whether including single-trial P3 parameters can aid the detection of behaviorally relevant nicotine effects on the BOLD response. We hypothesise that (1) there will be a difference in brain activation between the placebo and nicotine conditions, (2) EEG-informed fMRI analysis will yield nicotine effects in different/additional brain regions compared with the conventional analysis, and (3) nicotine effects on brain activation will be related to nicotine effects on task performance (RT).

METHODS

Participants

Thirty-one healthy smoking participants were recruited from a large population-based database in Germany (Brinkmeyer et al., 2011; Lindenberg et al., 2011; Mobascher et al., 2010) with no history of medical, neurological, or psychiatric illness (DSM-IV Axis 1) or alcohol and drug abuse within the past 6 months as assessed by a full medical interview and examination, routine laboratory tests, a drug screening test, an electrocardiogram, and a standardized psychiatric interview (SCID; First, Spitzer, Giddon, & Williams, 1995). Smoking status was determined according to DSM-IV, and smokers were only included in the study if their Fagerström test for nicotine dependence (FTND) score was ≥4 (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991).

Of the 31 participants recruited for the study, the data for one participant were discarded because of excessive motion artifact in the fMRI; one participant was excluded because of incorrect response to the task (incorrect response key used). Ten further participants' data were discarded because of poor EEG quality: Data for four participants were discarded because of inadequate ballistocardiogram artifact correction, data for one participant were generally noisy because of the inability to reduce impedance at recording electrodes to <10 kΩ, and the data for five participants were excluded because of not being able to identify a consistent P3 on a single-trial level. Accordingly, data from 19 participants were included in the final analyses; demographic data for the sample are summarized in Table 1.

Study Procedure

The study employed a double-blind, placebo-controlled, within-subject, randomized, cross-over (counterbalanced) design and was conducted in compliance with the declaration of Helsinki in its latest version and according to ICH-GCP (Good Clinical Practice) guidelines following a strict standard operating procedure with regular external monitoring. Written informed consent was obtained from all participants. The study was approved by the ethics committee of the Heinrich-Heine University Düsseldorf and the

Table 1. Demographic and Clinical Information

Participants	19
Age, mean (*SD*) (yr)	34 (12)
Male, *n*	5
Female, *n*	14
FTND score, mean (*SD*)	5 (2)
CO, mean (*SD*) (ppm)	18.42 (10.33)
QSU, mean (*SD*)	107.2 (35.37)
Plasma cotinine, mean (*SD*) (ng/ml)	157 (107)

FTND = Fagerström test for nicotine dependence score was ≥4 (Heatherton et al., 1991); QSU = Questionnaire on Smoking Urges (Tiffany & Drobes, 1991) to assess craving; CO = levels of carbon monoxide in expired air.

federal drug agency in Germany, that is, the Bundesinstitut für Arzneimittel and Medizinprodukte.

All participants completed two 1-hr experimental sessions in the MRI scanner 4 hr apart with the first session being approximately 2 hr after admission. The experimental sessions were conducted after acute challenge with 1 mg nasal nicotine spray (Pfizer, Inc./McNeill AB, Helsingborg, Sweden; 0.5 mg each nostril) or placebo (pepper) spray. A 1-mg dose of nicotine delivered by nasal spray is largely bioequivalent with nicotine consumption by smoking one cigarette Benowitz & Jacob, 1984). A between-challenge interval of 4 hr was chosen for the following reasons. Half-life time of nicotine is 2 hr (Benowitz, Jacob, Jones, & Rosenberg, 1982), that is, approximately 75% of nicotine (administered by nasal spray) is metabolized after 4 hr. At the same time, this relatively short time interval is considered a reasonable compromise to avoid smokers developing serious withdrawal symptoms, which themselves may have an effect on brain function (Polich & Ochoa, 2004). To account for the unavoidable remaining effects of lingering nicotine and beginning withdrawal, the order of the placebo and nicotine challenge was randomized and counterbalanced across participants. Participants were investigated in the context of a multisession pharmacological fMRI study before and after overnight nicotine withdrawal. The interim analyses presented here focus on the experimental sessions from the first day, that is, before overnight nicotine withdrawal. Participants were admitted to the clinical research unit of the Research Centre Juelich for the entire duration of the study. Before admission, smokers were asked to smoke ad libitum with most participants taking the opportunity to have their last cigarette right before admission. After admission, smokers remained abstinent throughout the course of the study. Within 1 hr of arrival at the research center, participants completed the Questionnaire on Smoking Urges (QSU; Tiffany & Drobes, 1991), which is a state-sensitive measure to assess nicotine craving, levels of exhaled carbon monoxide (CO) were measured using a Micro 4 Smokerlyzer (Bedfont Scientific Ltd.), and plasma was collected for cotinine immunoassay measurements (DRI Cotinine Assay, Microgenics, Passau, Germany).

Behavioral Task

Participants performed a visual choice reaction oddball task consisting of 64 infrequent "target" stimuli and 256 frequent stimuli (one additional cognitive task was performed during the same session in a different run but is not reported here). Stimuli were black and white checkerboards, the infrequent target stimuli were identified as a reversal of the pattern of the frequent stimuli. A black screen was presented between stimuli. Stimuli were presented using Presentation Version 11.3 (Neurobehavioral Systems, Albany, CA) via a screen situated behind the scanner. Participants were able to view the screen via a mirror mounted on the head coil. Participants' responses were recorded using Lumitouch keypads (Photon Control Inc., Burnaby, BC, Canada). For infrequent stimuli, participants responded with their right index finger, and for frequent stimuli, they responded with their left index finger; they were asked to respond quickly and accurately to each stimulus, and RT was recorded for each response. Stimuli were presented with a duration of 1000 msec and a pseudorandomized ISI of 4000 (±500) msec.

fMRI Data Acquisition

fMRI were acquired using a 3T scanner (TIM-Trio, Siemens, Erlangen, Germany). Using EPI, 630 volumes were obtained applying the following EPI parameters: 33 slices, slice thickness = 3 mm, interslice gap = 0.3 mm, field of view = 200 × 200 mm, 64 × 64 matrix, repetition time = 2000 msec, echo time = 30 msec, flip angle = 90°. To facilitate localization and coregistration of functional data, structural scans were acquired using T1-weighted MRI sequences (magnetization prepared rapid gradient-echo: repetition time/echo time = 2250/3.03 msec, flip angle = 9°, 176 sagittal slices, field of view = 200 × 200 mm, 64 × 64 matrix, voxel size = 1 × 1 × 1 mm).

EEG Data Acquisition

EEG data were recorded using a 32-channel MR compatible EEG system (Brain Products, Gilching, Germany). The EEG cap (BrainCap MR, EasyCap GmbH, Breitbrunn, Germany) consisted of 30 scalp electrodes distributed according to the 10–20 system and two additional electrodes, one of which was attached to the participants' back for recording the ECG whereas the other was attached on the outer canthus of the left eye for detection of eye movement artifacts. Data were recorded relative to an FCz reference, and a ground electrode was located at Iz (10–5 electrode system; Oostenveld & Praamstra, 2001). Data were sampled at 5000 Hz, with a bandpass of 0.016–250 Hz. Impedance at all recording electrodes was less than 10 kΩ.

fMRI Analysis

fMRI analysis was performed with FSL (FMRIB's software library, www.fmrib.ox.ac.uk/fsl), employing different modules of the FSL software package; motion correction was performed using MCFLIRT (FMRIB's linear registration tool; Jenkinson, Bannister, Brady, & Smith, 2002); nonbrain removal was done using BET (Smith, 2002) and spatial smoothing using a Gaussian kernel of FWHM = 8 mm, mean-based intensity normalization of all volumes by the same factor, and highpass temporal filtering (sigma = 125 sec). GLM time-series statistical analysis of individual data sets was carried out using FILM (FMRIB's improved linear model) with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). Registration of functional images to high-resolution structural images was done with

FLIRT (Jenkinson et al., 2002; Forman et al., 1995). Explanatory variables (EVs) were constructed to represent the onset of each stimulus and were convolved with a gamma hemodynamic response function (HRF). A description of the constructed EVs and the different models used is provided below.

EEG Data Analysis

Raw EEG data were processed off-line using BrainVision Analyzer 2 (Brain Products, Gilching, Germany). Gradient artifact correction was performed using modified versions of the algorithms proposed by Allen, Josephs, and Turner (2000), wherein a gradient artifact template is subtracted from the EEG using a baseline-corrected sliding average of 20 MR volumes. Data were then down-sampled to 250 Hz. Following gradient artifact correction, the data were corrected for cardioballistic artifacts. An average artifact subtraction method (Allen, Polizz, Krakow, Fish, & Lemieux, 1998) was implemented in Brain Vision Analyzer 2. This method involves subtracting the artifact on a second-by-second basis using heartbeat events (R peaks) detected in the previous 10 sec. As such it requires accurate detection of R peaks, which is aided by the employment of a moving average low pass filter and a finite impulse response high pass filter (for details, see Allen et al., 1998). In this study, the R peaks were detected semiautomatically, with manual adjustment for peaks misidentified by the software. To average the artifact in the EEG channels, the R peaks are transferred from the ECG to the EEG over a selectable time delay. The average artifact was then subtracted from the EEG. Once corrected for gradient and cardioballistic artifacts, the data were rereferenced to a common average reference, baseline-corrected, filtered 0.5–20 Hz, and segmented into 1000-msec epochs (−200 to 800 msec) for the purposes of ERP analysis. Data were then inspected for artifacts resulting from eye blink or other muscular sources, and any epoch containing such artifacts or a voltage change of more than 150 μV was rejected. To maximize the signal-to-noise ratio for single-trial analysis data from four electrodes (Cz, Pz, CP1, CP2) were pooled. Single-trial P3 parameters were extracted from responses to target stimuli for each participant by identifying the peak positive amplitude in a window from 280 to 550 msec poststimulus. The window for single-trial P3 amplitude extraction was determined by the P3 peak in the grand-averaged ERP. The single-trial amplitudes were then screened for outliers using Z scores; any trials with a value of more than 3 standard deviations away from the mean were discarded; a mean of 92% (SD = 7%) and 90% (SD = 7%) of trials were kept for further analysis in the placebo and nicotine conditions, respectively.

Combined fMRI/ERP Analysis

First, we performed a conventional GLM analysis of the data to assess group level BOLD responses for the task by using one EV with a constant impulse function (same height and duration) positioned at stimulus onset (Figure 1A). It is worth noting that in all models the input functions (onset time, event duration, and event intensity) are convolved with the gamma HRF, which blurs and delays the waveform to match the difference between the input function and the measured hemodynamic response. To test the effects of using P3 amplitude to modify the basis function, we used a model based on our previous work (Warbrick et al., 2009): We included demeaned P3 amplitude as a regressor to provide a basis function with variable height, that is, a variable impulse model (Figure 1B; P3 amplitude informed model). Both analyses used the same time course for target stimuli onsets and were performed in the same way, that is, one EV of interest convolved with a gamma HRF. The only difference was the EEG information included in the EV, thus changing the prediction about the shape of the hemodynamic response on a single-trial basis in the P3 amplitude informed model. Additional EVs of no interest were created for nontarget stimuli and trials wherein EEG information was missing due to artifact, leaving a baseline of only the blank screen. Only target

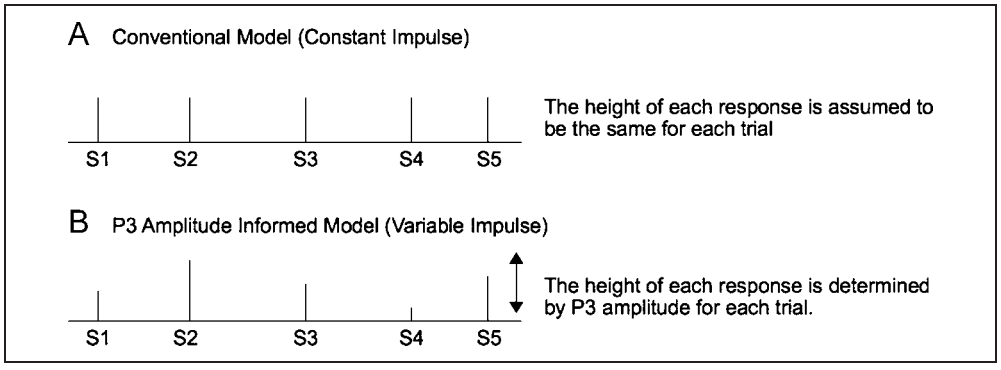

Figure 1. Summary of how the basis function is modified by including single-trial parameters in the GLM. (A) The conventional analysis where a constant impulse (same height and duration) is positioned at stimulus onset. (B) A variable impulse model where the height of the basis function is modified by single-trial P3 amplitude. When P3 amplitude was included in the model, this resulted in the height of the basis function being higher when P3 amplitude was larger. This reflects differences in the intensity of responses, as reflected in P3 amplitude. For both models, the input functions (onset time, event duration, and event intensity) were convolved with the gamma HRF, which blurs and delays the waveform to match the difference between the input function and the measured hemodynamic response.

stimuli were considered because some of the relevant stimulus identification and decision-making processes that might be influenced by nicotine are involved in the response to both types of stimuli; some of this information may be lost if they are directly contrasted. We have demonstrated that considering target stimuli only is appropriate for this paradigm (Warbrick et al., 2009, 2011). So, all first-level analyses represent target stimuli > baseline activation. Group level mixed-effect analyses were conducted using FLAME (FMRIB's local analysis of mixed effects) with spatial normalization to Montreal Neurological Institute (MNI) space and applying a cluster significance threshold of $Z > 2.3$ (Forman et al., 1995; Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994; Worsley, Evans, Marrett, & Neelin, 1992). For a complete description of task-induced BOLD changes, group level deactivation (target < baseline) was also calculated for illustrative purposes only; the target > baseline contrast remains the primary interest.

Differences between the placebo and nicotine conditions in both analysis approaches were investigated using paired samples *t* tests (contrasts: placebo > nicotine, nicotine > placebo) to test our hypotheses that (1) there would be a difference in BOLD activation between the placebo and nicotine conditions (i.e., a nicotine effect) and (2) that this nicotine effect would be observed in different brain regions in the P3 informed analysis.

To test our hypothesis that any nicotine effects on BOLD activation would be related to nicotine effects on performance (RT), additional analyses were conducted with the inclusion of change in RT between the two conditions as a covariate. A difference value for nicotine-placebo was calculated to assess whether each participant showed a decrease or an increase in RT from placebo to nicotine. A second-level fixed-effects analysis (placebo vs. nicotine) was performed for each participant to give a statistic representing the difference between the placebo and nicotine conditions. These data were then taken through to group level mixed-effects analyses wherein the RT difference values were included as covariates. Functional data were imported to MRIcron (Rorden, Karnath, & Bonilha, 2007) for visual display purposes.

Statistical Analyses

Pearsons correlation coefficient *r* was used to test relationships between measures. Differences in measures between the placebo and nicotine conditions were tested using paired samples *t* tests. All statistical analyses were performed using the SPSS (SPSS Inc., Chicago, IL) statistical analysis program.

RESULTS

Behavioral Data

Participants performed the task with an average of 99.1% ($SD = 0.5\%$) and 97.8% ($SD = 0.9\%$) correct responses to target stimuli for the placebo and nicotine conditions, respectively. No false responses were recorded, but an average of 0.9% and 2.2% of stimuli were missed in the placebo and nicotine conditions, respectively. Mean RT to target stimuli was 578 msec ($SD = 54$ msec) in the placebo condition and 547 msec ($SD = 55$ msec) in the nicotine condition [$t(18) = 0.81$, $p = .43$].

EEG Data

The grand-averaged ERP and single-trial EEG responses to target stimuli (Figure 2) showed the typical morphology in response to visual stimuli during a decision-making task at centro-parietal electrodes with N1 (100 and 96 msec poststimulus for the placebo and nicotine conditions, respectively), P2 (190 and 216 msec poststimulus for the placebo and nicotine conditions, respectively), and P3 (364 and 380 msec poststimulus) being identified.

Comparing the nicotine and placebo condition (Figure 2) revealed no significant difference in mean P3 amplitude [$t(18) = 0.32$, $p = .70$; placebo: mean = 3.1, $SD = 2.9$; nicotine: mean = 3.32, $SD = 3.33$]. No significant difference was also observed for the standard deviation of the ST P3 amplitudes [$t(18) = 0.63$, $p = .54$; placebo: mean = 3.60, $SD = 2.1$; nicotine: mean = 3.9, $SD = 1.4$].

fMRI Data

Conventional Analysis

For both placebo and nicotine conditions, the conventional BOLD analysis revealed task-related activation (target > baseline) in response to infrequent target stimuli in the precentral gyrus, cerebellum, supramarginal gyrus, insula, and lateral occipital cortex (Figure 3; Table 2). Also, task-related deactivation (baseline > target) was found in the middle frontal gyrus and frontal pole for both the placebo and nicotine conditions and the superior frontal gyrus and middle temporal gyrus for the placebo condition only (Figure 3; Table 2).

The placebo > nicotine contrast revealed no significant differences in BOLD activation between conditions. However, the nicotine > placebo contrast revealed increased BOLD activation in the nicotine condition compared with the placebo condition in the middle frontal gyrus, superior frontal gyrus, and precentral gyrus (Figure 4; Table 3).

EEG-informed fMRI Analysis

Compared with the conventional fMRI analysis, the P3 amplitude informed model (nicotine > placebo contrast) revealed considerably stronger and more extended nicotine effects with increased BOLD activation in the nicotine condition compared with the placebo condition in the paracingulate gyrus, superior frontal gyrus, frontal pole, ACC, and middle frontal gyrus (Figure 4; Table 3).

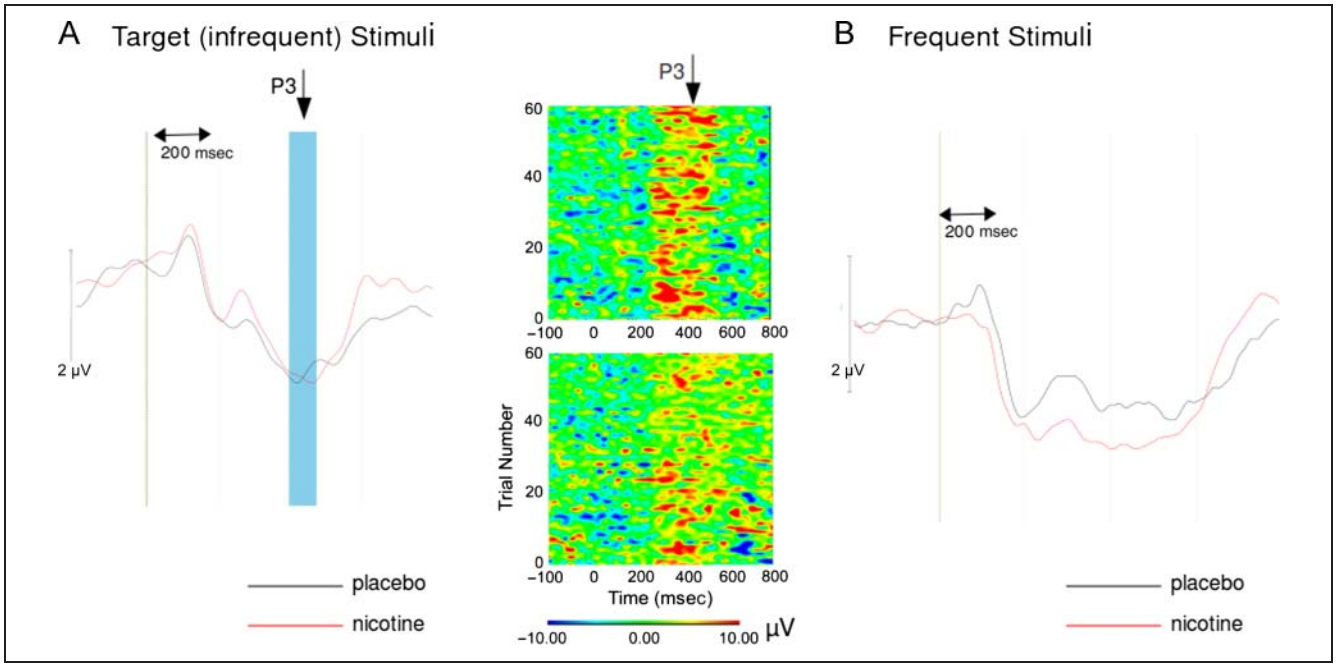

Figure 2. Grand-averaged ERPs for the electrode pool (Cz, Pz, CP1, CP2) in the placebo (black line) and nicotine (red line) conditions for the target (left side) and infrequent stimuli (right side). The central part of the figure shows stacked plots of single-trial responses to target stimuli for two representative participants, illustrating a consistent positivity around 350–400 msec poststimulus.

Relationship between behavioral and brain responses to nicotine. P3 amplitude and RT were unrelated [$r(31) = -0.1$, $p = .39$ and $r(31) = 0.01$, $p = .9$, for the placebo and nicotine conditions, respectively]. To test the relationship between the nicotine effect on brain function and the nicotine effect on RT based on the differences between the placebo and nicotine condition; the change in RT from placebo to nicotine was

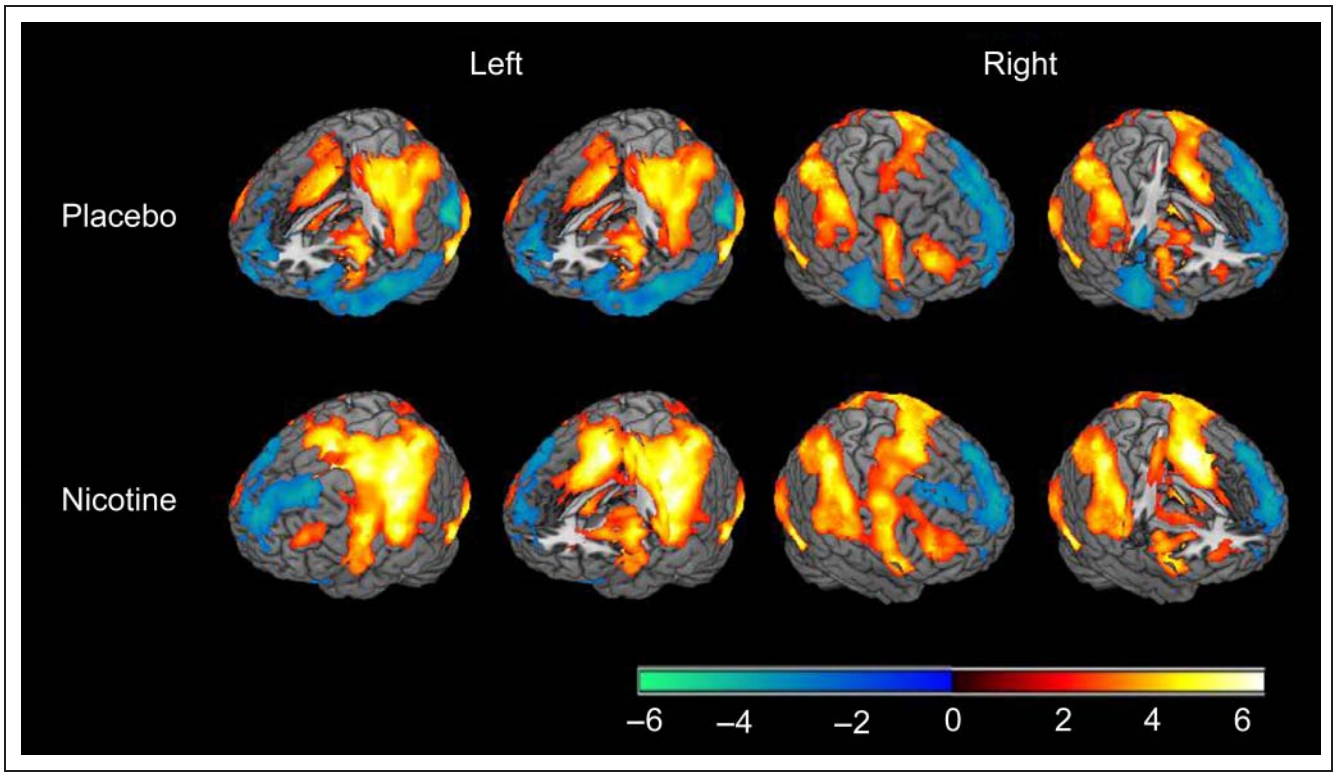

Figure 3. BOLD activation (target > baseline, red) and deactivation (target < baseline, blue) for the conventional analysis (second-level mixed-effects FLAME, $n = 19$, cluster-corrected threshold $Z = 2.3$, $p = .05$) for the placebo and nicotine conditions.

Table 2. Brain Regions and Local Maxima of Responses to Target Stimuli

Region (Harvard–Oxford, Maximum Probability)	MNI Coordinates of Local Maxima			Maximum Z Value Placebo	Maximum Z Value Nicotine
	x	*y*	*z*		
Target > Baseline (Task-Related Activation)					
Postcentral gyrus	−34	−30	62	5.7	6.1
Anterior cingulate cortex	0	10	42	4.3	5.5
Supplementary motor cortex	−4	2	48	5.8	6.3
Lateral occipital cortex	−44	−74	−16	5.9	5.3
Supramarginal gyrus	−56	−28	44	6	
Insula	−36	−2	4	4.6	4.7
Cerebellum[a]	32	−56	−24	6.1	4.7
Target < Baseline (Task-Related Deactivation)					
Middle frontal gyrus	−26	34	44	4.3	3.1
Frontal pole	0	58	18	3	3.1
Superior frontal gyrus	−2	42	52	5.2	–
Middle temporal gyrus	−58	−14	−16	4.3	–

Target-related activation (target > baseline) and deactivation (target < baseline). Cluster-corrected at $Z = 2.3$, $p = .05$. $n = 19$.

included as a regressor, as described in the Methods section.

In the conventional fMRI analysis, the mean RT change was positively related to the BOLD response in the nicotine > placebo contrast (Figure 5; Table 4), in line with our previous article on an overlapping sample (Warbrick et al., 2011). A decrease in BOLD activation from placebo to nicotine was related to a decrease in RT from placebo to nicotine and vice versa. So improved task performance (i.e., faster RT) was related to a decrease in BOLD activation. The regions in which BOLD activation correlated with mean RT were as follows: precuneus, superior parietal lobule, lateral occipital cortex and supramarginal gyrus.

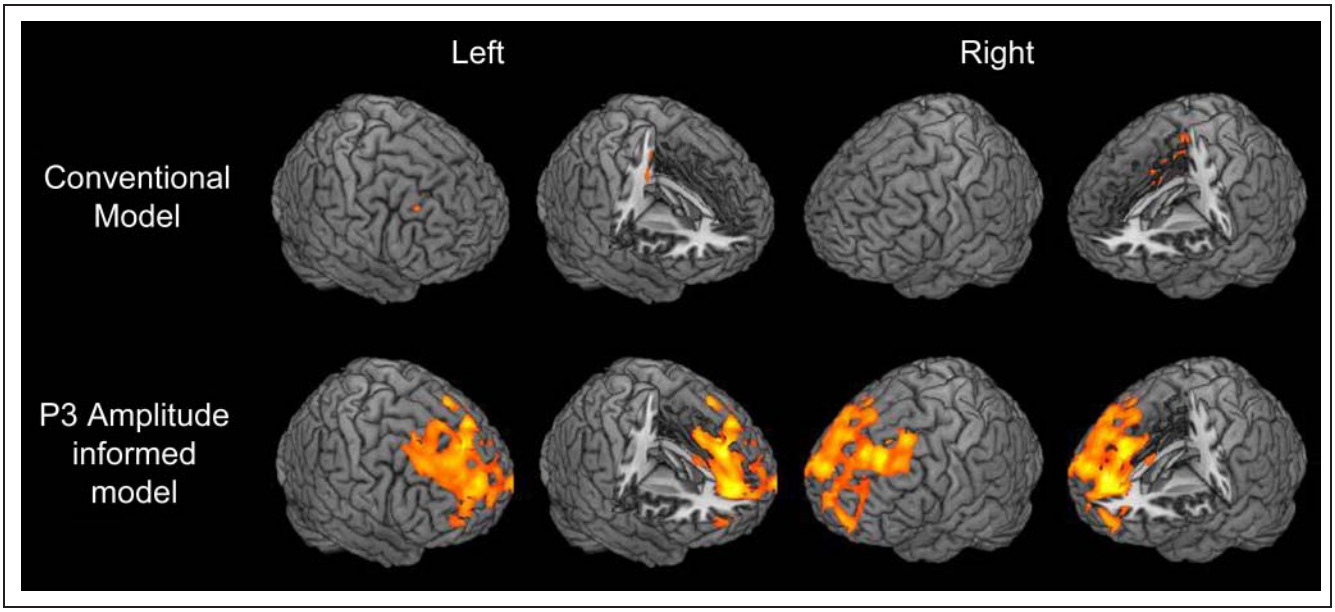

Figure 4. Nicotine effects (nicotine > placebo) on the BOLD response to target stimuli (target > baseline) for both the conventional and P3 amplitude informed models (second-level mixed-effects FLAME, $n = 19$, cluster-corrected threshold $Z = 2.3$, $p = .05$).

Table 3. Nicotine Effects on Brain Function: Conventional and EEG-informed fMRI Analysis

	MNI Coordinates of Local Maxima			
Region (Harvard–Oxford, Maximum Probability)	*x*	*y*	*z*	*Maximum Z Value*
Conventional Analysis				
Precentral gyrus	10	−20	24	3.3
Superior frontal gyrus	24	16	42	2.8
Middle frontal gyrus	24	28	32	2.5
EEG-informed fMRI Analysis				
Paracingulate gyrus	8	46	14	4.3
Anterior cingulate cortex	2	26	32	3.9
Superior frontal gyrus	−24	32	44	3.8
Frontal pole	44	52	16	2.5
Middle frontal gyrus	44	20	44	3.7

Contrast nicotine > placebo. Top: conventional fMRI analysis. Bottom: EEG-informed analysis (variable impulse [P3 amplitude] model). Cluster corrected at $Z = 2.3$, $p = .05$. $n = 19$.

The P3 amplitude informed model provided additional information: a decrease in RT from placebo to nicotine was related to an increase in BOLD activation in postcentral gyrus, precentral gyrus, precuneus, ACC, middle temporal gyrus, and temporal pole (Figure 5; Table 4). Interestingly, an opposite relationship compared with the conventional analysis was seen, that is, an increased BOLD response in the nicotine condition was related to faster RT.

Relationship of behavior and brain function to smoking variables. We also sought to establish whether smoking-status-related quantitative variables were related to the

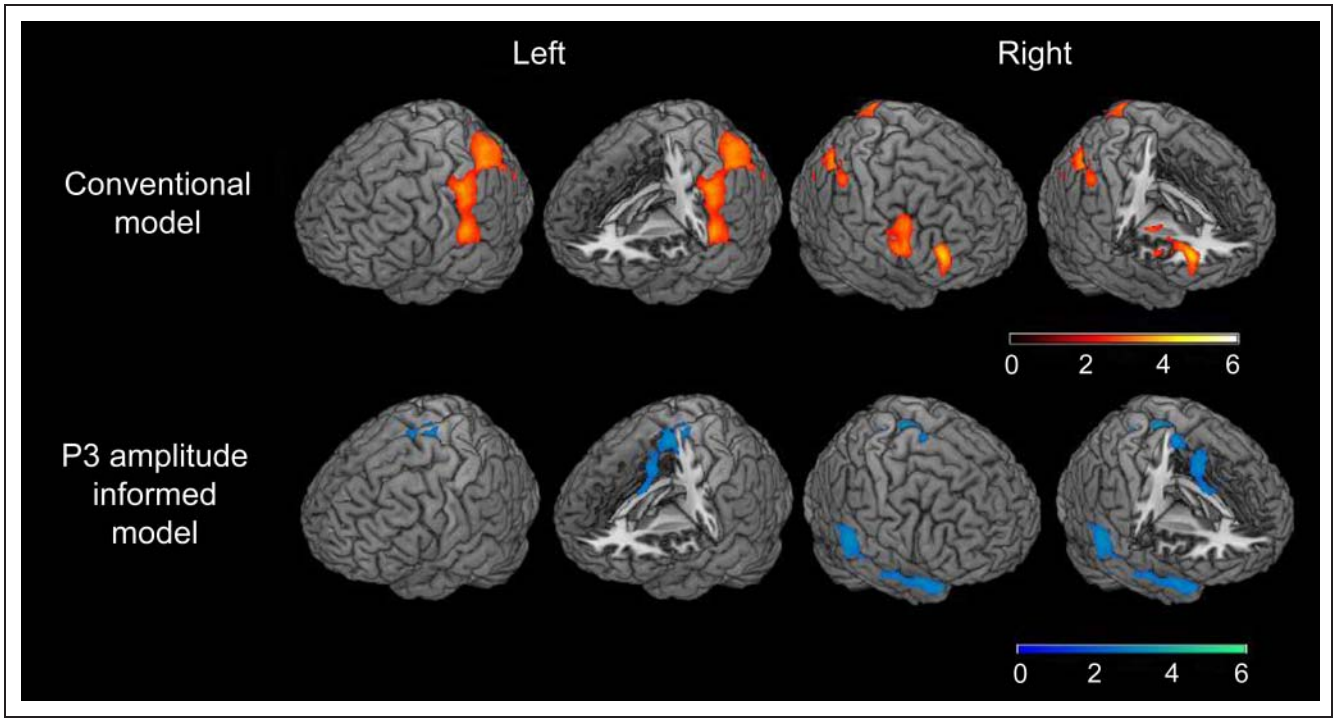

Figure 5. Nicotine effects on BOLD activation that covary with the nicotine effect on RT for the conventional and P3 informed models (second-level mixed-effects FLAME, $n = 19$, cluster-corrected threshold $Z = 2.3$, $p = .05$). There is a positive relationship between the change in RT and change in BOLD activation from the placebo condition to the nicotine condition in the conventional model (red scale), whereas there is a negative relationship (blue scale) for the P3 amplitude informed model.

Table 4. Brain Regions and Local Maxima for Regions in the Nicotine > Placebo Contrast Related[a] to the Change in RT from Placebo to Nicotine for the Conventional Analysis and the P3 Amplitude Informed Model

	MNI Coordinates of Local Maxima			
Region (Harvard–Oxford, Maximum Probability)	*x*	*y*	*z*	*Maximum Z Value*
Conventional Analysis				
Lateral occipital cortex	28	−62	42	5.1
Postcentral gyrus	−48	−30	48	3.7
Supramarginal gyrus	−60	−24	22	3.7
Superior parietal lobule	−32	−56	50	3.6
Precuneus	4	−62	66	3.1
Variable Impulse Model				
Middle temporal gyrus	68	−40	−4	3.4
Temporal pole	48	14	−24	3.3
Precentral gyrus	0	−30	70	3.24
Anterior cingulate cortex	−2	2	44	3.24
Precuneus	10	−46	54	2.6
Postcentral gyrus	2	−38	60	2.9

[a]Change in RT was included as a covariate in GLM analysis of the BOLD response.

Cluster corrected at $Z = 2.3$, $p = .05$. $n = 19$.

nicotine effects observed in the imaging and behavioral data. We looked at the relationships between our EEG, fMRI, and RT measures and nicotine dependence (FTND), carbon monoxide in expired air (CO), smoking urges (QSU), and plasma cotinine. We found these smoking-related variables to be unrelated to the behavioral, electrophysiological, and fMRI measures ($p > .05$).

DISCUSSION

The aim of this study was to investigate whether including single-trial P3 parameters can aid the detection of behaviorally relevant nicotine effects on the BOLD response. Comparing placebo with nicotine challenge, we found no significant effect of nicotine on P3 amplitude but only a trend (P3 amplitude increase). This was not entirely unexpected, given the relatively small and in part equivocal effects of acute nicotine on P300 amplitude reported in literature (Polich & Criado, 2006). We found no difference in RT between the placebo and nicotine conditions. The conventional fMRI group level analysis revealed increased BOLD activation in the nicotine compared with the placebo condition in task-related brain regions. Furthermore, the EEG informed GLM analysis detected additional nicotine effects on BOLD activation that were not apparent in the conventional GLM analysis. We also found nicotine effects on RT to be related to nicotine effects on measures of brain activation.

Nicotine Effects: Conventional Analysis

The conventional analysis (constant impulse model) revealed increased BOLD activation in the nicotine condition compared with the placebo condition in the middle frontal gyrus, superior frontal gyrus, and precentral gyrus. These regions are known to be involved in cognitive functions such as executive function and short-term and working memory and are also involved in the performance of the oddball task (Strobel et al., 2008; Gur et al., 2007; Winterer et al., 2007; Halgren, Baudena, Clarke, Heit, Liégeois, et al., 1995; Halgren, Baudena, Clarke, Heit, Marinkovic, et al., 1995).

Despite finding an overall increase in BOLD activation in response to nicotine compared with placebo, our previous work (with an overlapping sample) showed that some participants showed an increase in BOLD activation whereas some participants showed a decrease in BOLD activation in response to nicotine (Warbrick et al., 2011). We therefore performed analyses based on the nicotine > placebo contrast to investigate the change in BOLD activation between the two conditions. This change in BOLD activation from the placebo to nicotine condition was also related to behavioral performance on the task, with faster RT in the nicotine condition being related to a decreased BOLD activation in the superior parietal lobule, lateral occipital cortex, precuneus, and supramarginal gyrus. The relationship between the decrease in BOLD response from the placebo to nicotine and faster

RT in the nicotine condition is plausible for the regions involved. The lateral occipital cortex is not only indicative of processing visual stimuli but has also been implicated in attention allocation (Goldman et al., 2009; Weissman, Roberts, Visscher, & Woldorff, 2006). Furthermore, there is evidence to suggest that the parietal regions are involved in the nicotine effects on attention (Thiel et al., 2005). Accordingly, the reduced activation seen here could be indicative of more efficient processing in the nicotine condition. The role of these regions (parietal) in cognitive control and the fact that they are influenced by cholinergic neurotransmission suggests that this result reflects nicotine-enhanced decision-making.

Nicotine Effects: P3 Amplitude Informed Model

We found a different pattern of nicotine-related BOLD activation using the P3 amplitude informed model. The inclusion of single-trial P3 amplitude in the model resulted in the height of the basis function being increased when the P3 amplitude was larger. In addition, it appears likely that this reflects differences in the intensity of responses. Given that P3 amplitude is influenced by attention and arousal (Pritchard et al., 2004; Picton, 1992), it was expected that brain regions associated with these functions would be preferentially emphasized using this model. This was indeed the case with the P3 amplitude informed model revealing increased BOLD activation in the nicotine condition compared with the placebo condition in the paracingulate gyrus, superior frontal gyrus, frontal pole, ACC, and middle frontal gyrus. Activation in these regions is known to be modulated by attention. For example, ACC and prefrontal regions are known to be involved in attention and executive function (Kaping, Vinck, Hutchison, Everling, & Womelsdorf, 2011). Furthermore, ACC is influenced by cholinergic neurotransmission (Sarter, Gehring, & Kozak, 2006) and is connected to the pFC, both of which have been shown to be activated by nicotine (Stein et al., 1998). Our findings are also supported by those of Karch et al. (2010), who found P3 amplitude to be correlated with BOLD activation in frontal and parietal cortex during a voluntary selection condition in a go/no-go paradigm, emphasizing the importance of the regions in attentional processing. P3 amplitude reflects target detection and is modulated by attention allocated to the task (Picton, 1992). It is therefore likely that the activation in these areas is related to the attentional modulation reflected in the P3 and thus indicating brain regions involved in the effects of nicotine on attention. The fact that a nicotine effect was not apparent in the same regions in the conventional analysis shows that a truly integrated approach to EEG-fMRI analysis can detect the effects of nicotine that are remain undetected using a unimodal approach.

The change in EEG-informed BOLD activation from the placebo to nicotine condition was also related to behavioral performance; however, faster RT in the nicotine condition compared with the placebo condition was related to an increase in BOLD activation, showing the opposite relationship compared with the conventional fMRI analysis. One important point here is that the correlation with RT can be considered as a strong indication that the obtained results are not spurious findings. Improved RT performance in the nicotine condition compared with the placebo condition was related to an increase in BOLD activation in the postcentral gyrus, precentral gyrus, ACC, precuneus, middle temporal gyrus, and temporal pole. The precuneus is involved in visuospatial processing and is also involved in motor planning. This fits with a recent report (Rose, Rose, & Kurup, 2010) that nicotine also influences information processing output or the preparing of motor responses as well as influencing attentional processes. In addition, the precuneus has shown increased activation when participants are engaged in target detection (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000). It is plausible that the areas associated with visuospatial attention (precuneus) show increased activation during better performance because they are related to allocating more attentional resources to correctly identifying the target stimuli (as indicated by the P3 findings discussed above), whereas the regions identified by the conventional analysis as showing decreased activation when performance is high reflect executive function where improved performance is related to speed of processing and therefore less activation could reflect more "efficient" processing.

The differential relationship between the nicotine effect on the BOLD response and the nicotine effect on RT for the two analysis approaches (conventional and P3 informed) is perhaps the most interesting finding. We offer a potential explanation for this finding in that the reduction in BOLD response related to faster RT in the conventional analysis might reflect more "efficient" process whereas the increase in BOLD-response related to faster RT in the P3 informed analysis might reflect allocation of more resources. Given that the regions implicated in the P3 informed analysis are involved in target detection and motor response planning, it is plausible that the P3 informed analyses preferentially emphasizes activation related to the response and the conventional analysis emphasizes regions involved in the perceptual aspects of stimulus processing. This interpretation is further supported by the fact that the variable impulse model employed in the P3 informed analysis results in both the height and width of the HRF being increased (Grinband, Wager, Lindquist, Ferrera, & Hirsch, 2008), meaning that more response-related activation could be captured by the longer time window. This is a speculative explanation, and further investigation of what multimodal imaging can add to pharmacoimaging is necessary. These findings also highlight the necessity to fully understand what an increase and/or decrease in BOLD activation in relation to a task means; this is particularly salient when investigating pharmacological effects where the mechanisms of the drug are under investigation.

Taken together, these findings provide evidence for two mechanisms by which nicotine improves cognitive performance: (1) by allowing allocation of additional resources in attention related areas thus improving encoding of visual stimuli and (2) by allowing faster/more efficient processing in regions involved in executive function and working memory.

Limitations and Considerations

One obvious limitation of our study is the amount of data lost due to EEG quality (the reasons for this are given in the Methods section). This emphasizes that simultaneous EEG-fMRI is a demanding technique; however, the potential benefits of multimodal imaging make the investment worthwhile. Furthermore, developments in hardware and analysis techniques make this approach feasible.

A second concern to note is that our behavioral results did not reach significance; we found no difference in RT between the placebo and nicotine conditions. This could be for a number of reasons. Our task was very simple: because of testing a sample of schizophrenic patients within the same study framework (data not reported here), a possible reason for the lack of significant results therefore is a ceiling effect on the behavioral level. Furthermore, on calculating the difference score between the placebo and nicotine conditions, it is evident that some participants show an improvement in RT from placebo to nicotine whereas other show a deterioration in performance. It is possible that this effect leads to a null result when making a statistical comparison. This interparticipant heterogeneity in responses to nicotine is discussed in our previous article (Warbrick et al., 2011). A further possible explanation for the absence of behavioral effects despite seeing convincing effects in the neuroimaging data is that brain responses subserving specific cognitive and emotional processes may be more objectively measurable than the subjective experience or behavioral representation of these same processes (Hariri & Weinberger, 2003). Therefore, it is not unexpected that we observe significant effects in the imaging data while observing no effects on overt behavior.

One particular advantage of our study is that we investigated nicotine effects on brain function in a sample drawn from the general population (Brinkmeyer et al., 2011; Lindenberg et al., 2011; Mobascher et al., 2010), in awareness of the growing concern regarding the overrepresentation of students in study samples in cognitive neuroscience (*Nature Neuroscience* Editorial, 2010).

In conclusion, we provide evidence for mechanisms by which nicotine enhances attention and working memory processing in a visual choice reaction oddball task. We have also shown how integrated analyses of simultaneous EEG-fMRI and behavioral data can be used to detect nicotine effects that would not have been revealed through conventional analysis of either measure in isolation. This emphasizes the importance of applying multimodal imaging methods to cognitive neuroscience and pharmacoimaging.

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REFERENCES

Allen, P., Josephs, O., & Turner, R. (2000). A method for removing imaging artifact from continuous EEG recorded during functional MRI. *Neuroimage, 1,* 230–239.

Allen, P., Polizz, G., Krakow, K., Fish, D. R., & Lemieux, L. (1998). Identification of EEG events in the MR scanner: The problem of pulse artifact and a method for its subtraction. *Neuroimage, 8,* 229–239.

Bagshaw, A. P., & Warbrick, T. (2007). Single-trial variability of EEG and fMRI responses to visual stimuli. *Neuroimage, 38,* 280–292.

Benar, C., Schoen, D., Grimault, S., Nazarian, B., Burle, B., Roth, M., et al. (2007). Single-trail analysis of oddball event-related potentials in simultaneous EEG-fMRI. *Human Brain Mapping, 28,* 602–613.

Benowitz, N. L., & Jacob, P., III (1984). Daily intake of nicotine during cigarette smoking. *Clinical Pharmacology and Therapeutics, 35,* 499–504.

Benowitz, N. L., Jacob, P., III, Jones, R. T., & Rosenberg, J. (1982). Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. *Journal of Pharmacology and Experimental Therapeutics, 221,* 368–372.

Bledowski, C., Prvulovic, D., Hoechstetter, K., Scherg, M., Wibral, M., Goebel, R., et al. (2004). Localizing P300 generators in visual target and distractor processing: A combined event-related potential and functional magnetic resonance imaging study. *Journal of Neuroscience, 24,* 9353–9360.

Brinkmeyer, J., Mobascher, A., Musso, F., Schmitz, M., Wagner, M., Frommann, I., et al. (2011). P50 sensory gating and smoking in the general population. *Addiction Biology, 16,* 485–498.

Corbetta, M., Kincade, J. M., Ollinger, J. M., McAvoy, M. P., & Shulman, G. L. (2000). Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nature Neuroscience, 3,* 292–297.

Debener, S., Ullsperger, M., Siegel, M., Fiehler, K., von Cramon, D. Y., & Engels, A. K. (2005). Trial-by-trial coupling of concurrent electroencephalogram and functional magnetic resonance imaging identifies the dynamics of performance monitoring. *Journal of Neuroscience, 25,* 11730–11737.

Eichele, T., Specht, K., Moosman, M., Jongsma, M. L., Quiroga, R. Q., Nordby, H., et al. (2005). Assessing the spatiotemporal evolution of neuronal activation with single-trial event-related potentials and functional MRI. *Proceedings of the National Academy of Sciences, U.S.A., 102,* 17798–17803.

Ettinger, U., Williams, S. C. R., Patel, D., Michel, T. M., Nwaigwe, A., Caceres, A., et al. (2009). Effects of acute nicotine on brain function in healthy smokers and non-smokers: Estimation of inter-individual response heterogeneity. *Neuroimage, 45,* 549–561.

Fell, J. (2007). Cognitive neurophysiology: Beyond averaging. *Neuroimage, 37,* 1069–1072.

First, M. B., Spitzer, R. L., Giddon, M., & Williams, J. B. (1995). *The structured clinical interview for DCM-IV axis I disorders research version (SCID-1)*. New York: American Psychiatric Press.

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. *Magnetic Resonance in Medicine, 33,* 636–647.

Friston, K. J., Worsley, K. J., Frackowiak, R. S. J., Mazziotta, J. C., & Evans, A. C. (1994). Assessing the significance of focal activations using their spatial extent. *Human Brain Mapping, 1,* 214–220.

Giessing, C., Thiel, C. M., Rösler, F., & Fink, G. R. (2006). The modulatory effects of nicotine on parietal cortex depend on cue reliability. *Neuroscience, 137,* 853–864.

Goldman, R. I., Wei, C.-Y., Philiastides, M. G., Gerson, A. D., Friedman, D., Brown, T. R., et al. (2009). Single-trial discrimination for integrating simultaneous EEG and fMRI: Identifying cortical areas contributing to trial-to-trial variability in the auditory oddball task. *Neuroimage, 47,* 136–147.

Grinband, J., Wager, T. D., Lindquist, M., Ferrera, V. P., & Hirsch, J. (2008). Detection of time-varying signals in event-related fMRI designs. *Neuroimage, 43,* 509–520.

Gur, R. C., Turetsky, B. I., Loughead, J., Waxman, J., Snyder, W., Ragland, J. D., et al. (2007). Hemodynamic responses in neural circuitries for detection of visual target and novelty: An event-related fMRI study. *Human Brain Mapping, 28,* 263–274.

Halgren, E., Baudena, P., Clarke, J. M., Heit, G., Liégeois, C., Chauvel, P., et al. (1995). Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. *Electroencephalography and Clinical Neurophysiology, 94,* 191–220.

Halgren, E., Baudena, P., Clarke, J. M., Heit, G., Marinkovic, K., Devaux, B., et al. (1995). Intracerebral potentials to rare target and distractor auditory and visual stimuli. II. Medial, lateral and posterior temporal lobe. *Electroencephalography and Clinical Neurophysiology, 94,* 229–250.

Halgren, E., Marinkovic, K., & Chauvel, K. (1998). Generators of the late cognitive potentials in auditory and visual oddball tasks. *Electroencephalography and Clinical Neurophysiology, 106,* 156–164.

Hariri, A. R., & Weinberger, D. R. (2003). Imaging genomics. *British Medical Bulletin, 65,* 259–270.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K. O. (1991). The Fagerstrom test for nicotine dependence: A revision of the Fagerstrom tolerance questionnaire. *British Journal of Addiction, 86,* 1119–1127.

Heishman, S. J., Kleykamp, B. A., & Singleton, E. G. (2010). Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology, 210,* 453–469.

Huster, R. J., Eichele, T., Enriquez-Geppert, S., Wollbrink, A., Kugel, H., Konrad, C., et al. (2011). Multimodal imaging of functional networks and event-related potentials in performance monitoring. *Neuroimage, 56,* 1588–1597.

Jacobsen, L. K., D'Souza, D. C., Mencl, E. W., Pugh, K. R., Skudlarski, P., & Krystal, J. H. (2004). Nicotine effects on brain function and functional connectivity in schizophrenia. *Biological Psychiatry, 55,* 850–858.

Jenkinson, M., Bannister, P., Brady, J., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage, 17,* 825–841.

Kaping, D., Vinck, M., Hutchison, R. M., Everling, S., & Womelsdorf, T. (2011). Specific contributions of ventromedial, anterior cingulate, and lateral prefrontal cortex for attentional selection and stimulus valuation. *PLoS Biology, 9,* e1001224.

Karch, S., Feuerecker, R., Leicht, G., Meindl, T., Hantschk, I., Kirsch, V., et al. (2010). Separating distinct aspects of voluntary selection between response alternatives: N2- and P3-related BOLD responses. *Neuroimage, 51,* 356–364.

Kiehl, K. A., Stevens, M. C., Laurens, K. R., Pearlson, G., Calhoun, V. D., & Liddle, P. F. (2005). An adaptive reflexive processing model of neurocognitive function: Supporting evidence from a large scale (n = 100) fMRI study of an auditory oddball task. *Neuroimage, 25,* 899–915.

Kumari, V., Gray, J. A., Ffytche, D. H., Mitterschiffthaler, M. T., Das, M., Zachariah, E., et al. (2003). Cognitive effects of nicotine in humans: An fMRI study. *Neuroimage, 19,* 1002–1013.

Lawrence, N. S., Rose, T. J., & Stein, E. A. (2002). Cognitive mechanism of nicotine on visual attention. *Neuron, 36,* 539–548.

Lindenberg, A., Brinkmeyer, J., Dahmen, N., Gallinat, J., de Millas, W., Mobascher, A., et al. (2011). The German multicenter study on smoking-related behavior: Description of a population-based case-control study. *Addiction Biology, 16,* 638–653.

Mobascher, A., Brinkmeyer, J., Warbrick, T., Wels, C., Wagner, M., Gründer, G., et al. (2010). The P300 event-related potential and smoking—A population-based case-control study. *International Journal of Psychophysiology, 77,* 166–175.

Mulert, C., Seifert, C., Leicht, G., Kirsch, V., Ertl, M., Karch, S., et al. (2008). Single-trial coupling of EEG and fMRI reveals the involvement of early anterior cingulate cortex activation in effortful decision making. *Neuroimage, 42,* 158–168.

Musso, F., Konrad, A., Vucurevic, G., Schäffner, C., Friedrich, B., Frech, P., et al. (2006). Distributed BOLD-response in association cortex vector state space predicts reaction time during selective attention. *Neuroimage, 29,* 1311–1318.

Nature Neuroscience Editorial. (2010). The university student as a model organism. *Nature Neuroscience, 13,* 521.

Oostenveld, R., & Praamstra, P. (2001). The five percent electrode system for high-resolution EEG and ERP measurement. *Clinical Neurophysiology, 112,* 713–719.

Picton, T. W. (1992). The P300 wave of the human event related potential. *Journal of Clinical Neurophysiology, 9,* 456–479.

Polich, J., & Criado, J. R. (2006). Neuropsychology and neuropharmacology of P3a and P3b. *International Journal of Psychophysiology, 60,* 172–185.

Polich, J., & Ochoa, C. J. (2004). Alcoholism risk, tobacco smoking, and P300 event-related potential. *Clinical Neurophysiology, 115,* 1374–1383.

Pritchard, W., Sokhadze, E., & Houlihan, M. (2004). Effects of nicotine and smoking on event-related potentials: A review. *Nicotine & Tobacco Research, 6,* 961–984.

Rorden, C., Karnath, H. O., & Bonilha, L. (2007). Improving lesion-symptom mapping. *Journal of Cognitive Neuroscience, 19,* 1081–1088.

Rose, E. J., Rose, T. J., & Kurup, P. K. (2010). Nicotine modulation of information processing is not limited to input (attention)

but extends to output (intention). *Psychopharmacology, 209,* 291–302.
Sarter, M., Gehring, W. J., & Kozak, R. (2006). More attention must be paid: The neurobiology of attentional effort. *Brain Research Reviews, 51,* 145–160.
Smith, S. (2002). Fast robust automated brain extraction. *Human Brain Mapping, 17,* 143–155.
Stein, E. A., Pankiewicz, J., Harsch, H. H., Cho, J.-K., Fuller, S. A., Hoffman, R. G., et al. (1998). Nicotine-induced limbic cortical activation in the human brain: A functional MRI study. *American Journal of Psychiatry, 155,* 1009–1015.
Strobel, A., Debener, S., Sorger, B., Peters, J. C., Kranczioch, C., Hoechstetter, K., et al. (2008). Novelty and target processing during an auditory novelty oddball: A simultaneous event-related potential and functional magnetic resonance imaging study. *Neuroimage, 40,* 869–883.
Thiel, C. M., Zilles, K., & Fink, G. R. (2005). Nicotine modulates reorienting of visuospatial attention and neural activity in human parietal cortex. *Neuropsychopharmacology, 30,* 810–820.
Tiffany, S. T., & Drobes, D. J. (1991). The development and initial validation of a questionnaire on smoking urges. *British Journal of Addiction, 86,* 1467–1476.
Warbrick, T., Mobascher, A., Brinkmeyer, J., Musso, F., Richter, N., Stoecker, T., et al. (2009). Single-trial P3 amplitude and latency informed event-related fMRI models yield different BOLD response patterns to a target detection task. *Neuroimage, 47,* 1532–1544.
Warbrick, T., Mobascher, A., Brinkmeyer, J., Musso, F., Stoecker, T., Shah, N. J., et al. (2011). Direction and magnitude of nicotine effects on the fMRI BOLD response are related to nicotine effects on behavioural performance. *Psychopharmacology, 215,* 333–344.
Weissman, D. H., Roberts, K. C., Visscher, K. M., & Woldorff, G. (2006). The neural bases of momentary lapses in attention. *Nature Neuroscience, 9,* 971–978.
Winterer, G., Musso, F., Konrad, A., Vucurevic, G., Stoeter, P., Sander, T., et al. (2007). Association of attentional network function with exon 5 variations of the CHRNA4 gene. *Human Molecular Genetics, 16,* 2165–2174.
Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modelling of fMRI data. *Neuroimage, 14,* 1370–1386.
Worsley, K. J., Evans, A. C., Marrett, S., & Neelin, P. (1992). A three-dimensional statistical analysis for CBF activation studies in human brain. *Journal of Cerebral Blood Flow & Metabolism, 12,* 900–918.