fMRI Data Predict Individual Differences of Behavioral Effects of Nicotine: A Partial Least Square Analysis

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Abstract

■ Reorienting of visuospatial attention can be investigated by comparing reaction times to validly and invalidly cued targets (''validity effect''). The cholinergic agonist nicotine reduces the validity effect and neural activity in the posterior parietal cortex. Behavioral effects of nicotine in nonsmokers are weak and it has been suggested that differences in baseline behavior before nicotine exposure may influence the effect of nicotine. This study investigates whether individual differences in reorienting-related *neural* activity under placebo may be used to predict individual nicotine effects. Individual nicotine effects are defined as the behavioral effects under nicotine that cannot be predicted by the behavioral data under placebo. Fifteen nonsmoking subjects were given either placebo or nicotine gum (2 mg) prior to performing a cued target detection task inside a magnetic resonance imaging scanner. The results of a partial least square analysis suggest that neural data under placebo can be used to predict individual behavioral effects of nicotine. Neural activity in the left posterior cingulate cortex, the right superior parietal cortex, the right dorsal medial prefrontal cortex, and the left ventral medial prefrontal cortex significantly contributes to that prediction. We conclude that nicotine effects on reorienting attention depend on individual differences in reorienting-related neural activity under placebo and suggest that functional magnetic resonance imaging data can contribute to the prediction of individual drug effects. ■

INTRODUCTION

Several studies have documented the therapeutic potential of nicotine to improve attentional functions in lesioned animals or patients with Attention Deficit Hyperactivity Disorder (ADHD), Parkinson's disease, and schizophrenia (Levin, McClernon, & Rezvani, 2006; Poltavski & Petros, 2006; Smith et al., 2006; Bekker, Bocker, Van, van den Berg, & Kenemans, 2005; Newhouse, Potter, & Singh, 2004; Newhouse, Singh, & Potter, 2004; Singh, Potter, & Newhouse, 2004). However, behavioral effects of nicotine in healthy nonsmoking volunteers tend to be weak (Kleykamp, Jennings, Blank, & Eissenberg, 2005; for a review, see Newhouse, Potter, et al., 2004). It has been suggested that the effects of nicotine may differ from subject to subject dependent upon personal traits or ''baseline'' characteristics before drug exposure (e.g., Abreu-Villaca, Queiroz-Gomes, Dal Monte, Filgueiras, & Manhaes, 2006; Thiel, Zilles, & Fink, 2005; Newhouse, Potter, et al., 2004; Mirza & Bright, 2001; Perkins, Gerlach, Broge, Grobe, & Wilson, 2000; Perkins, 1999; Perkins, Grobe, Epstein, Caggiula, & Stiller, 1992). Several neuroimaging studies have shown that between-subject differences in behavior or personal traits are associated with differential neural network's activity (Cohen, Young, Baek, Kessler, & Ranganath, 2005; Eisenberger, Lieberman, & Satpute, 2005; Gibbs & D'Esposito, 2005; Gray et al., 2005). It is therefore reasonable to assume that such differences in task-related neural activity may also contribute to interindividual variability in drug effects. The present article deals with the question whether attention-related neural activity at baseline can be used to predict intersubject differences in the effect of nicotine on visuospatial attention. That is, can neural activity be used to predict the behavioral effect of nicotine that cannot be predicted by behavioral data. The understanding of the relationship between pre-exposure differences in neural network activity and the behavioral reaction to nicotine may also help to explain why many patients suffering from schizophrenia or ADHD, who employ differential networks to solve attentional tasks (when being compared to control subjects), use nicotine to ''self-medicate'' their cognitive dysfunctions (Levin et al., 2006; Poltavski & Petros, 2006; Adler et al., 1998).

Influential neuropsychological models of attention include those developed by Mesulam (1981) or Posner and Petersen (1990). These models highlight the role of parietal and cingulate areas for attentional processes. The model of Posner and Petersen assumes that differential neural networks, each associated with specific

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neurotransmitters, subserve different attentional functions, and that acetylcholine plays a crucial role in orienting and reorienting of visuospatial attention. Reorienting of attention can be investigated with cued target detection tasks in which a cue provides either correct or misleading information about the location of an upcoming target (Posner, 1980). The difference in reaction times to validly and invalidly cued targets is referred to as the ''validity effect'' and has been interpreted as the extra time needed for reorienting attention (e.g., Thiel et al., 2005; Posner, Walker, Friedrich, & Rafal, 1984). Prior neuroimaging studies have shown that posterior parietal areas, including the inferior and superior parietal cortex (Giessing, Thiel, Stephan, Rösler, & Fink, 2004; Yantis et al., 2002), the intraparietal cortex (Thiel, Zilles, & Fink, 2004; Small et al., 2003; Corbetta & Shulman, 2002), and the temporo-parietal junction (Corbetta & Shulman, 2002) are involved in reorienting attention to invalidly cued targets. Evidence in rats, monkeys, and humans suggests that the cholinergic agonist nicotine speeds reorienting of visuospatial attention and that this effect may be mediated by the parietal cortex (Giessing, Thiel, Rösler, & Fink, 2006; Thiel et al., 2005; Stewart, Burke, & Marrocco, 2001; Phillips, McAlonan, Robb, & Brown, 2000; Witte, Davidson, & Marrocco, 1997).

Interindividual variability in responsiveness to nicotine (and also other drugs) has been investigated previously on the behavioral level and has been related, for example, to genetic factors (Greenwood, Fossella, & Parasuraman, 2005; Parasuraman, Greenwood, Kumar, & Fossella, 2005; Parasuraman, Greenwood, & Sunderland, 2002; Gilbert & Gilbert, 1995). Here, we aim to investigate whether neural activity measured with functional magnetic resonance imaging (fMRI) can be used to predict drug (i.e., nicotine) responses, and thus, help to explain interindividual variability. In most fMRI studies, the variability between subjects adds to the error variance (Rawlings, Pantula, & Dickey, 2001) and is otherwise neglected. In contrast, the present approach aims to explore and make use of this variability to predict individual drug effects. Thus, although standard fMRI drug studies make valuable contributions to identifying the neural networks involved in drug effects common to all subjects, the present approach aims to complement prior work by identifying brain areas that contribute to individual drug effects. To our knowledge, this is the first fMRI study to systematically investigate brain regions responsible for individual drug effects.

To predict individual behavioral effects of nicotine on visuospatial attention from neural activity, we applied a partial least square (PLS) approach (McIntosh, Chau, & Protzner, 2004; McIntosh & Lobaugh, 2004; McIntosh, Bookstein, Haxby, & Grady, 1996; Geladi & Kowalski, 1986; Wold, 1966). PLS analyses of fMRI data assume that brain regions solve cognitive tasks as a *network of voxels* (McIntosh et al., 1996). The analysis used here consisted of two steps. First, we used the behavioral data under placebo and estimated the individual behavioral effects of nicotine by regressing out individual behavioral differences before nicotine exposure. In a second step, we investigated whether neural data under placebo can be used to further predict the individual behavioral nicotine effects (i.e., to reduce the remaining error which is independent from the behavioral data under placebo) using a PLS approach. In PLS, the overall goal is to predict a data matrix Y (in our case, the behavioral data) from a data matrix X (in our case, the neural data). If Y is a vector and the number of predictors in X is small compared to the number of observations in Y, the prediction can be done with an ordinary multiple regression approach. However, if the number of predictors is large, multiple regression is inappropriate and multivariate approaches such as principal components regression (PCR), maximum redundancy analysis (MRA), or PLS have to be applied (Abdi, 2003; van den Wollenberg, 1977). These techniques try to extract latent factors which account for a large proportion of variation in the data in order to predict the responses. Differences between these techniques arise in the way these factors are extracted. Although PCR, for example, searches for factors that explain much of the variation in the predictor space (X), these factors may not be associated with the responses. MRA, on the other hand, considers the variation in the responses (Y) but neglects the variation in the predictor space (X). In contrast, PLS is a *robust* form of redundancy analysis, which seeks for directions in the predictor space which explain both, variations in the predictor and response variables (Abdi, 2003; Höskuldsson, 1996). Thus, the PLS analysis is more appropriate to find stable factors that can be used to predict behavioral responses in independent datasets.

Up to now it is unclear whether brain regions involved in the ''common effect'' of nicotine on visuospatial attention *over* subjects are also responsible for ''differential nicotine effects'' *between* subjects. We hypothesized that individual behavioral effects of nicotine on reorienting visuospatial attention are related to interindividual differences in neural activity in brain networks consistently activated over subjects during visuospatial attention tasks. Individual differences in brain networks involved in reorienting attention, such as the parietal cortex, might constitute the ''basis'' (i.e., an individual neural signature) on which nicotine exerts its neural and/or behavioral effect.

METHODS

Subjects

Fifteen right-handed nonsmokers (12 men, 3 women; age range: 20–36 years, mean: 26.5 years) with no history of acute or chronic medical disease gave written informed consent to participate in the study. No subject

was on medication (except for contraceptives). All subjects had normal or corrected-to-normal vision. A clinical evaluation was first carried out to ensure that subjects had no conditions contraindicative for nicotine administration. Ethics approval was obtained from the local ethics committee. Nonsmokers were used to avoid confounding effects of nicotine abstinence on cognitive effects, that is, the possibility of reversing a deprivation-induced attentional deficit, rather than increasing attentional processes per se. No subject had used nicotine during the last 2 years and most subjects (13 of 15) had never smoked regularly at all. Subjects were asked to abstain from alcohol 12 hours before each session and from caffeine 3 hours prior to testing. One volunteer (male) was excluded from further analysis due to a high amount of missed responses in invalid trials (65%) and one volunteer (female) was excluded because her behavioral data were classified as an outlier (see Results section), leaving 13 subjects whose data were further analyzed.

Drug Administration

We used a within-subjects design. Scanning involved two sessions, separated by at least 3 days. The order of drug administration was counterbalanced over subjects. Nicotine was delivered in the form of a polacrilex gum (NICORETTE mint taste 2 mg, Pharmacia). A taste- and size-matched gum served as placebo (Pharmacia, Helsingborg, Sweden). Subjects were asked to chew the gum for 30 min at a rate of one chew per 3 sec. A dose of 2 mg was chosen as higher doses (4 mg) lead to adverse effects in nonsmokers (Nyberg, Panfilov, Sivertsson, & Wilhelmsen, 1982). Scanning started immediately after chewing had finished. In nonsmokers, nicotine plasma levels are, on average, 1.3 ng/ml at this time point (Heishman & Henningfield, 2000). The half-life of nicotine is about 2 hours (Benowitz, Porchet, Sheiner, & Jacob, 1988). Pulse oximetry was performed throughout the experiment.

Stimuli and Experimental Paradigm

A cued target discrimination task was used with central predictive cuing. Stimuli were projected onto a screen in front of the participant in the MRI scanner. Viewing distance was approximately 29 cm. The baseline display was composed of a central diamond (1.3° eccentric in each visual field) and two peripheral boxes (3° wide and 9.6° eccentric in each visual field). The cue stimulus consisted of the central diamond brightening for 100 msec, cueing the subject to either the left or right hemifield. In the cue–target interval, subjects were presented for 400 or 700 msec with a bilateral checkerboard array within the peripheral boxes, which alternated in black and white polarity at 10 Hz (3° wide and 9.6° eccentric in each visual field). The target stimulus (1.3° wide circle, red or green color) appeared for 100 msec on one side within the alternating checkerboard; the other, irrelevant stimulus occurred simultaneously on the other side (see Figure 1 for illustration). Subjects were instructed to maintain fixation on the central diamond throughout the experiment and to decide via button press whether the red (half of the subjects) or green circle (the other half of the subjects) occurred in the right or left hemifield. Responses to targets were made with the right index and middle fingers on a button of a keypad placed on the right side of the subjects' body. Cues were either validly (80%) or invalidly indicating the side of target appearance. Trials were presented every 2 sec. The order of trial types was randomized, as was the occurrence of left and right targets and cue–target intervals. The total number of events was 300 with 160 validly cued trials, 40 invalidly cued trials, and 100 ''null events'' (Josephs & Henson, 1999), where a baseline display (see above) was presented. The use

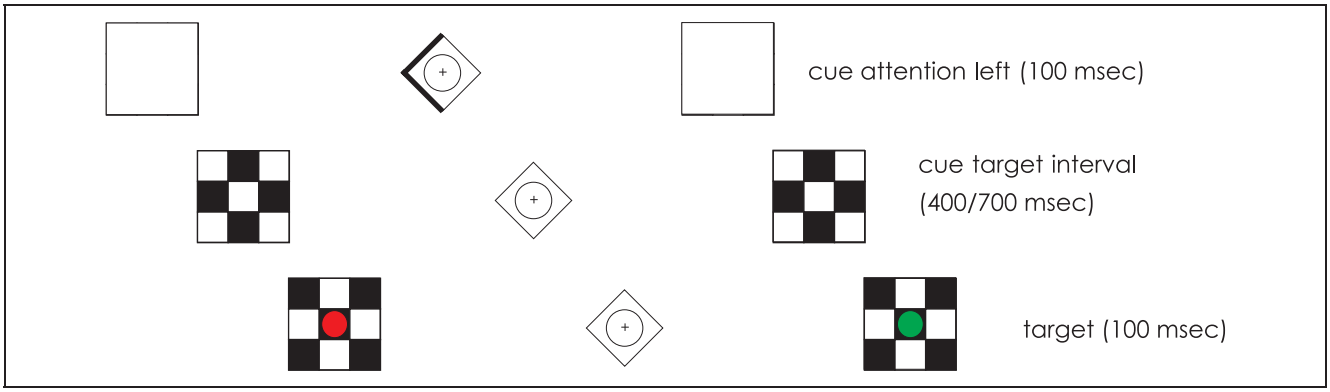

Figure 1. Experimental paradigm. A trial consisted of a cue (central diamond, 100 msec) and a target stimulus (red or green circle appearing within a checkerboard 100 msec). The cue–target interval was 400 or 700 msec. Trials were presented every 2000 msec. Subjects were asked to indicate whether the respective target stimulus occurred in the right or left hemifield. The example here shows a validly cued trial with the red circle being the target stimulus.

and random inclusion of null events leads to variable trial onset asynchronies. Prior to scanning, subjects were informed about the different trial types. They were told that spatial cues were highly informative and they were encouraged to use these cues to improve task performance. A 2-min training was performed before each scanning session.

Data Acquisition

A SONATA MRI system (Siemens, Erlangen, Germany) operating at 1.5 T was used to obtain T2*-weighted echo-planar images (EPI) with blood oxygenation level dependent (BOLD) contrast (matrix size: 64 × 64, pixel size: 3.12 × 3.12 mm^2). Two hundred fifty volumes of 24 four-mm-thick axial slices were acquired sequentially with a 0.8-mm gap (repetition time = 2.5 sec, echo time = 66 msec). The first five volumes were discarded to allow for T1 equilibration effects. The time series of each voxel was realigned temporally to the middle slice to correct for differences in slice acquisition time. Images were normalized to a standard EPI template (resampled to 3 × 3 × 3 mm^3 voxel). The data were then smoothed with a Gaussian kernel of 8 mm full-width half-maximum to accommodate intersubject anatomical variability. A high-pass filter (using a cutoff of 128 sec) and a correction for temporal autocorrelation in the data (AR 1 + white noise) were applied to accommodate serial correlations.

Behavioral Analysis: Estimation of Individual Nicotine Effects

The aim of this step in the data analysis was to estimate the individual behavioral effects of nicotine from behavioral data under placebo (i.e., baseline) using a regression analysis. According to the statistical model used, the behavioral validity effect of subject i under nicotine is equal to $y_i = x_i + bx_i + a + r_i$ where x_i is the behavioral validity effect of subject i under placebo, bx_i is a percentage effect of nicotine, a is a constant nicotine effect, r_i is the sum of the error and the *individual nicotine effect* d_i [$r_i = d_i$ + error]. Put into words, we hypothesized that three nicotine effects may influence the observed behavioral data in the nicotine condition: (i) a constant nicotine effect [a], which is independent from the validity effect under placebo (e.g., a reduction of reaction times which is the same for each individual); (ii) a nicotine effect which is dependent on the validity effect under placebo [bx_i], that is, a so-called percentage nicotine effect (e.g., ceiling effects in which subjects with high performance levels could not improve their performance); and (iii) an individual nicotine effect d_i, which is independent from the behavioral data under placebo but might be further predicted with the individual neural network activity of each subject (see next paragraph). The statistical model is equal to a standard linear regression analysis in which we predict the behavioral validity effect under nicotine with the behavioral validity effect under placebo: $\hat{y}_i = x_i + bx_i + a = (1 + b)x_i + a$. This behavioral analysis was done to ensure that the PLS approach does not detect neural networks which are, in general, involved in speed differences between subjects (see the next paragraph for further details). Within our statistical model, we assumed that the validity effect under nicotine depends on the validity effect under placebo (Perkins, 1999). Due to our previous results (Thiel et al., 2005), we expected that nicotine causes a percentage *decrease*. Therefore, we tested within the linear regression analysis [$\hat{y}_i = x_i + bx_i + a = (1 + b)x_i + a$] whether the slope $(1 + b)$ of the regression is significantly smaller than unity, which means that b is smaller than zero (this approach is described in more detail in Perkins, 1999).

Behavioral Analysis: Motivation for Controlling General Speed Effects

To control for general speed effects under placebo, we used the residuals of the regression model as a measure of individual nicotine effects rather than using individual difference scores (i.e., ''validity effect placebo'' minus ''validity effect nicotine''). To explain our approach consider, for instance, the following theoretical example: If nicotine induced a 50% reduction of reaction times (e.g., Subject 1: 20 msec validity effect under placebo and 10 msec validity effect under nicotine; Subject 2: 40 msec under placebo and 20 under nicotine; and Subject 3: 60 msec under placebo and 30 msec nicotine), the difference between validity effect under nicotine and placebo (10 msec, 20 msec, 30 msec) would highly correlate with the general speed under placebo (20 msec, 40 msec, 60 msec). Therefore, a PLS analysis using difference scores would identify brain regions involved in general speed differences under placebo. In contrast, the regression model used here eliminates nicotine effects which linearly depend on the validity effect under placebo (compare also Mayerl, Sellke, & Urban, 2005).

Limitations of the Regression Analysis

One caveat of the regression approach is, however, that it relies on the reliability of behavioral data as error in the independent variable could result in a suboptimal control for intersubject differences before drug treatment and reduces the slope of the regression line (Kendall & Stuart, 1979, p. 438). Although there are statistical approaches that consider error in the independent variable (e.g., Jin, 1992; Myrtek & Foerster, 1986), we decided to use a normal regression approach to be consistent with the analysis of the neural data that also contain measurement error and to avoid arbitrary deci-

sions of the researcher (for a discussion on error variance estimations, compare Jamieson, 1998, p. 14).

fMRI Data Analysis

In contrast to a standard fMRI analyses, we were interested in individual differences between subjects and tested whether the fMRI data can be used to explain the variance of vector r, the residual variance, by predicting the individual nicotine effects d. If our statistical model (see above) is valid and x is reliable, d will represent the individual nicotine effects. Note that residuals r are independent from x, the behavioral validity effects under placebo (Mayerl et al., 2005; see the Discussion for further details). To explore the residual vector r (i.e., the differences between the measured validity effect under nicotine and the predicted validity effect obtained in the analysis above), we used a PLS analysis. If the model is valid, these residuals will represent the deviation from the ''general rule'' or functional relationship over subjects, and thus, represent the individual nicotine effects (plus an unpredictable error; Mayerl et al., 2005). The analysis performed on the fMRI data consisted of two levels. On the first level, we analyzed the fMRI data of each subject with a general linear model used in standard fMRI analysis. The first-level data analysis was conducted with the Statistical Parametric Mapping software SPM2 (www.fil.ion.ucl.ac.uk/spm2.html; Friston et al., 1995). Within each design matrix, 15 event types were used to model the placebo fMRI data. These event types consisted of eight effects of interest (all possible combinations of valid vs. invalid trials, right vs. left targets, and short vs. long target intervals) and 7 effects of no interest or confounds (missed or wrong responses and 6 head movement parameters coding the three rigid body translations and rotations). The event types were time-locked to the onset of the target by a canonical synthetic hemodynamic response function.

The second step of the fMRI data analysis is the PLS analysis. This second step identifies the brain network that significantly contributes to the prediction of individual behavioral effects of nicotine. The contrast images comparing invalid and valid trials entered into this second-level PLS analysis. By using contrast images, we averaged over the time dimension. This was done to reduce error variance and the dimensionality of our dataset (compare Caplan, Luks, Simpson, Glaholt, & McIntosh, 2006). The fMRI data were reorganized in one data matrix X in which each row represents one subject and each column one voxel. With this matrix, a linear combination of voxel values (by weighting the columns of the matrix) is identified that maximally covaries with the individual behavioral effect of nicotine (i.e., the deviations from the behavioral regression analysis). This linear combination can be thought of as the information derived from the neural network activity of each subject which, in a next step, can be used within a linear regression model to predict the behavioral data. Mathematically, the weights for the linear combination are given after mean correction by (Höskuldsson, 1996, p. 179):

$$\hat{\beta} = X'r/\mathrm{norm}(X'r),$$

where $\hat{\beta}$ represents the voxel weights, X the data matrix, r the residual vector, and ''norm(x)'' is the norm from x. fMRI data were scaled to mean zero and unit length because we had no prior information about the relative importance of the variables (Wold, Ruhe, Wold, & Dunn, 1984). To prevent error fitting, only those voxels entered into the PLS analysis which showed significant differential activation during invalid and valid trials in an analysis of an independent dataset (Giessing et al., 2004; the mask was constructed using an f-contrast on a level of significance of $p < .01$ and an extent threshold of $k \geq 20$ voxels).

Testing Significance of the Model: Cross Validation

To prove the significance of the model and account for overfitting, we used a leave-out-one-sample cross-validation procedure (Goutte, 1997) in combination with the randomization test of van der Voet (1994) using 500 randomizations (significance level: $p < .05$; similar to the statistic software SAS, compare http://support.sas.com/rnd/app/papers/pls.pdf). This test compares the capabilities of different models to predict responses by comparing the residuals of the cross-validation procedure. To check whether the neural data have predictive capability, we compared the PLS model with the so-called null factor model (similar to the statistic software SAS, compare also http://support.sas.com/rnd/app/papers/plsex.pdf). Within the ''null factor'' model, the reaction time, which is held out during the cross-validation approach, is predicted by the mean of the remaining reaction times. Therefore, the ''null'' model assumes that the linear combination of the PLS approach does not improve the prediction. In addition, we computed the root mean PRESS (mPRESS, *m*ean *p*redicted *re*sidual *s*um of *s*quares), a measure of the predictive power of the model (Wold et al., 1984; Cook & Weisberg, 1982, p. 33). The root mPRESS was calculated by the root of the mean sum of squares of the predicted residuals within the cross-validation procedure.

Testing Significance of Voxels: Bootstrapping

While the above testing was done to prove the significance of the model (including all voxels), the aim of the following step in the data analysis was to determine

those voxels/brain areas that show significant experimental effects and reliably contribute to the linear combination identified by the PLS analysis (compare McIntosh & Lobaugh, 2004). Significance was estimated with a bootstrap procedure, a statistical method in which the sampling distribution of an estimator is estimated by sampling with replacement from the original sample (Efron & Tibshirani, 1993). We assumed that $z = \hat{\beta}/SE_{\hat{\varepsilon}}(\hat{\beta})$ is distributed normal and reported only those voxels which reached a level of significance of $p < .001$ (two-tailed) and an extent threshold of $k \geq 10$ voxels ($SE_{\hat{\varepsilon}}(\hat{\beta})$: bootstrap standard error; Efron & Tibshirani, 1993). To estimate the bootstrap standard error, we used 1000 bootstrap replications. Furthermore, we plotted the bootstrap distribution of the most significant voxel in each cluster which is shifted above or below zero in case of a significant result (see Figure 6, Efron & Tibshirani, 1993, p. 171).

To summarize, our statistical analysis involves two major steps: (i) Using a linear regression analysis, we predicted the behavioral validity effect under nicotine by the behavioral validity effect under placebo. Differences between predicted and measured values (the residuals) represent the individual nicotine effects (plus error). (ii) Within a PLS analysis, we identified a brain network within the placebo data that shows differential activations between subjects which predict differential nicotine effects in the behavioral data.

RESULTS

Behavioral Data: Effects of Nicotine Pooled over Subjects

Before investigating individual nicotine effects, data were pooled over subjects and an analysis of variance with the factors validity (valid/invalid) and drug (placebo/nicotine) was performed. The results revealed a significant validity effect [$F(1,13) = 16.17$, $p < .001$], but no significant drug effect [$F(1,13) = 1.48$, $p = .25$] or Drug × Validity interaction [$F(1,13) = 1.31$, $p = .27$; mean validity effect and standard error of mean (*SEM*) under placebo: 48.12 ± 12.92 msec, mean validity effect and *SEM* under nicotine: 38.60 ± 10.01 msec]. That is, nicotine numerically reduced the mean validity effect, however, this did not reach significance.

Behavioral Data: Outlier Detection

The behavioral data were checked for possible outliers before analyzing individual drug effects. We detected an extreme *x*-value (validity effect under placebo) which was located more than 2 standard deviations above the mean ($z = 2.35$; Cook & Weisberg, 1982). This data point was removed from the analysis because we cannot check whether the assumptions for the regression line seem reasonable for the intervening *x*-values.

Behavioral Data: Estimation of Individual Nicotine Effects

First, we tested whether the slope of the linear regression analysis was smaller than unity, and thus, indicates a baseline dependency. The *t* test revealed a significant result [$t(11) = 3.32$, $p < .005$, $(1 + b) = 0.39$; see Figure 2A]: That means, we found evidence for a percentage decrease of the validity effect under nicotine indicating that the nicotine-induced reduction of the validity effect was dependent on the validity effect under placebo, with subjects with a slower validity effect under placebo showing a bigger reduction (for a caveat of this regression approach, see the Methods section). Furthermore, we tested whether $(1 + b)$ is larger than zero. The *t* test was significant [$t(11) = 2.14$, $p < .05$], which shows that the validity effect under placebo significantly contributes to the prediction of the validity effect under nicotine. Note that the residuals of the linear regression analysis are equally distributed around zero and show no further relationship with the validity effect under placebo (see Figure 2B). This is important to document the validity of our statistical model. The relationship between the validity effect under placebo and nicotine is sufficiently described by a simple linear regression model and the prediction cannot be improved by further polynomial extensions. Differences in general reaction times between subjects before drug treatment had been widely regressed out (the residuals are uncorrelated with the validity effect under placebo).

Neural Data: Predicting Individual Behavioral Differences

The PLS analysis was conducted to investigate whether the neural data under placebo can be used to predict the individual effects of nicotine on reorienting attention, that is, those residual effects that cannot be explained by the behavioral data under placebo. We identified one linear combination which maximally covaried with the individual behavioral effects of nicotine (i.e., the residuals of the regression analysis; Pearson's $r = .86$). This linear combination can be thought of as a latent factor which accounts for both the variations in the neural and behavioral data. It represents the information in the neural data under placebo which can be used to predict the behavioral data in a following linear regression analysis. The results of the regression analysis are shown in Figure 3. The leave-out-one-sample cross-validation procedure, in combination with the randomization test of van der Voet (1994), documents that the results are significant and not due to overfitting (root mPRESS "0 factor model": 24.35, root mPRESS "1 factor model": 20.73, $p < .05$). This documents that neural activity predicts individual nicotine effects over and above a general percentage nicotine effect common to all subjects. Which voxels reliably contributed to this prediction was as-

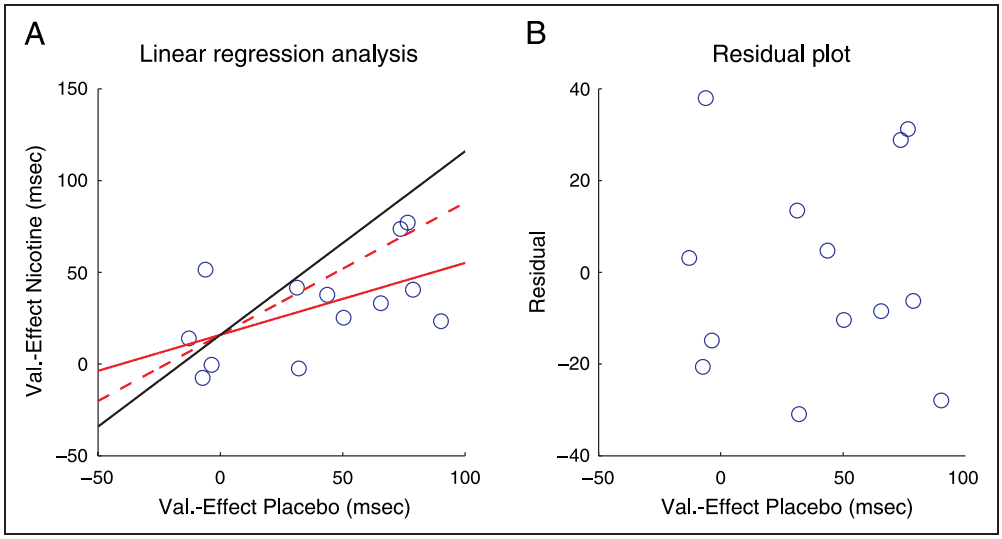

Figure 2. Individual effects of nicotine. (A) The validity effect under nicotine as predicted by the validity effect under placebo using a linear regression analysis (red solid line: regression line, black solid line: regression line with slope unity, red dashed line: 95% confidence interval of the regression slope). The slope of the regression line is smaller than unity which reveals evidence for a baseline dependent effect of nicotine: The reduction of the validity effect under nicotine is dependent on the validity effect under placebo. (B) Residuals of the regression analysis are plotted. The residuals represent the deviation from the "general" baseline-dependent nicotine effect over subjects and represent therefore the "individual" effects of nicotine (plus the error). Note that the residuals are equally distributed around zero.

sessed by a bootstrap procedure. This procedure revealed four significant clusters of voxels (extent threshold $\geq$ 10 voxels, $p < .001$). The cluster sizes, Z values, and MNI coordinates of these clusters are presented in Table 1 and illustrated in Figure 4. We found brain areas significantly contributing to the prediction of individual nicotine effects in the left ventral posterior cingulate cortex extending into the precuneus and the right superior parietal cortex. Within the frontal lobe, we found activations in the right dorsal medial prefrontal cortex and the left ventral medial prefrontal cortex. All bootstrap distributions of the most significant voxel in each of the clusters were shifted below zero. This further supports that these clusters of activations are indeed significant even if we do not assume normality of our test statistic (Figure 4, right side).

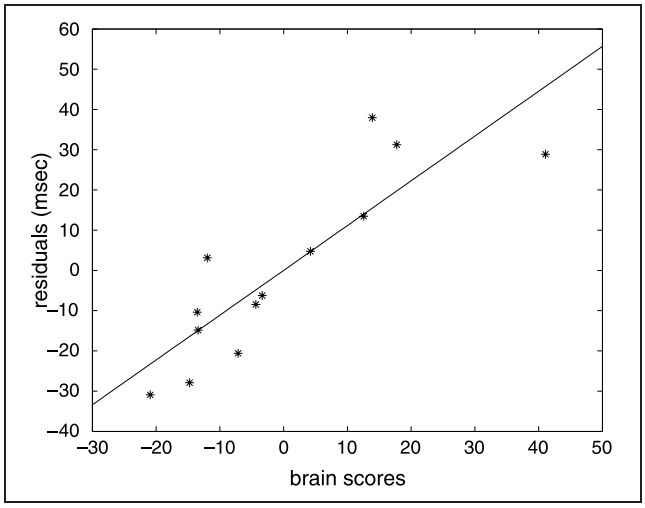

Figure 3. Predicting the individual nicotine effects with a partial least square (PLS) analysis. The PLS analysis reveals a weight for each brain voxel. Multiplying the voxel value of each brain voxel for each subject by the weight for that voxel, and summing across all voxels, gives a "brain" score for each subject constituting the latent variable. These "brain" scores maximally covary with the individual behavioral effects of nicotine (Pearson's $r = .86$).

Neural Data: Effects of Sex

Estrogen has been shown to modulate visuospatial attention via the cholinergic system (Dumas, Hancur-Bucci, Naylor, Sites, & Newhouse, 2006; Voytko, 2002). Previous studies provide evidence for differential effects of nicotine in men and women (Benowitz, Lessov-Schlaggar, Swan & Jacob, 2006; Perkins, Donny & Caggiula, 1999). Further, it was shown that the menstrual cycle may alter cortical circuitry involved in task performance (see, for example, Goldstein et al., 2005; Protopopescu et al., 2005). To test for possible sex effects, we reanalyzed our data including male subjects only. Consistent with our previous results, we found the same brain regions involved in the prediction

Table 1. Brain Regions which Reliably Contribute to the Prediction of Individual Nicotine Effects (Significance Level $p < .001$, Extent Threshold $k \geq 10$ Voxels)

	MNI Coordinates			*Num.*	
	x	*y*	*z*	*Voxels*	*Z*
L. ventral posterior cingulate cortex/precuneus	−9	−54	33	63	−7.00
R. dorsal medial prefrontal cortex	6	48	21	21	−6.26
R. superior parietal cortex	18	−60	54	12	−6.00
L. ventral medial prefrontal cortex	−3	36	−21	10	−5.14

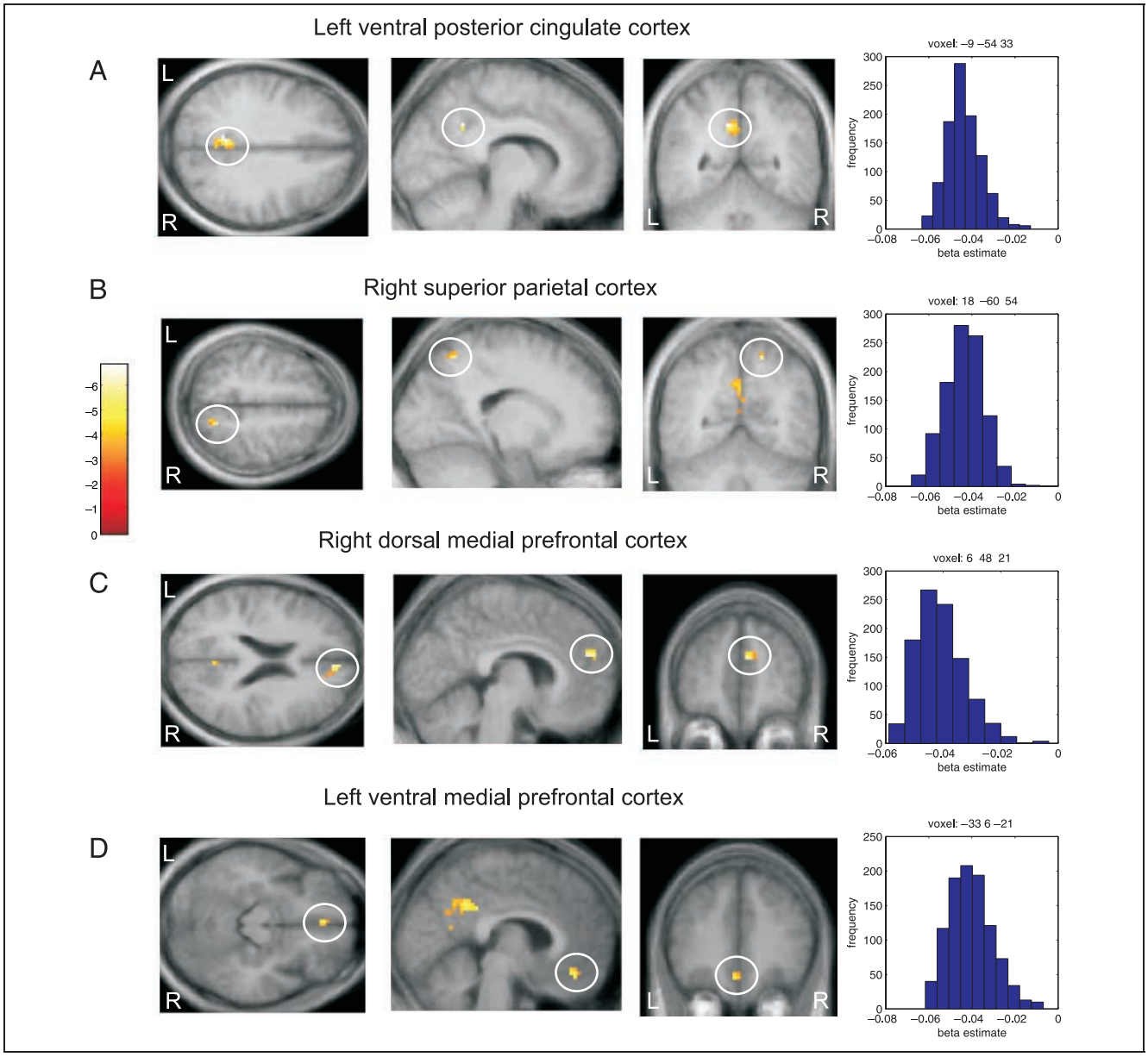

Figure 4. Brain regions involved in individual nicotine effects. Left side: Brain regions that reliably contribute to the prediction of individual nicotine effects are shown on the normalized mean structural MR image of the volunteers ($p < .001$, extent threshold $k \geq 10$ voxels). Right side: Bootstrap distribution of beta values of the most significant voxel. Note that the bootstrap distributions are shifted below zero which documents that these brain regions reliably contribute to the prediction.

of individual nicotine effects (root mPRESS "0 factor model": 25.51, root mPRESS "1 factor model": 20.31, $p < .01$, number of subjects = 11). Hence, the regions implicated in the present study seem to be related to individual behavioral effects of nicotine independent of sex.

DISCUSSION

The current study investigates whether fMRI data can be used to predict individual effects of nicotine on reorienting visuospatial attention. Our findings show that intersubject variability of reorienting-related neural activity under placebo is related to intersubject variability in the behavioral effects of nicotine. Brain regions that reliably contribute to the prediction of behavioral nicotine effects involved the left posterior cingulate cortex, the right superior parietal cortex, the right dorsal medial prefrontal cortex, and the left ventral medial prefrontal cortex.

Predicting Residuals—Speed-independent Effects of Nicotine

The regression analysis on the behavioral data revealed evidence for a percentage nicotine effect, that is, the amount of reduction of the validity effect under nicotine was dependent on the size of the validity effect under

placebo (compare also Perkins, 1999; see the Methods section for a critical comment on this analysis). Our results further showed that the residuals were equally distributed around zero, which means that the validity effect under placebo contains no further information (e.g., a quadratic relationship) that can be used to predict the validity effect under nicotine (see Figure 2B). This is an important finding because it documents the validity of our behavioral model and guarantees that brain areas identified in our PLS analysis are not related to general speed differences under placebo (see Methods section). The PLS approach used here therefore identifies brain regions which predict individual nicotine effects over and above a percentage nicotine effect common to all subjects.

Nicotine Effects Depend on Reorienting-related Neural Activity under Placebo

Previous studies have shown that behavioral effects of nicotine in animal and man depend on many influencing factors before drug treatment. According to Perkins (1999), subjects with slower reaction times under placebo are more strongly influenced by nicotine and show a stronger reduction of reaction times than subjects with faster reaction times under placebo. Mirza and Bright (2001) provided evidence that nicotine treatment affected attention strain-dependently: An improvement of performance was found in a rat strain with low baseline performance in a serial reaction time task, but not in rats with higher performance. In humans it has been shown that individuals high in traits of depression or nicotine dependency revealed stronger electroencephalogram (EEG) deactivations following nicotine abstinence (Gilbert et al., 2004). Thus, there is ample evidence that effects of nicotine treatment are not equal over subjects but may depend on pretreatment differences before nicotine exposure (Mansvelder, van Aerde, Couey, & Brussaard, 2006, p. 299).

Several neuroimaging studies demonstrate that between-subject differences in behavioral reaction times or personal traits are related to differential neural network activity (Cohen et al., 2005; Eisenberger et al., 2005; Gibbs & D'Esposito, 2005; Gray et al., 2005). It is therefore reasonable to assume that differences in neural activity may contribute to the behavioral outcome of drug treatment and improve the prediction of individual drug effects. Our results confirm that differential reorienting-related activity under placebo, as measured with fMRI, is related to individual behavioral effects of nicotine on reorienting visuospatial attention and that a network of medial fronto-parietal and posterior cingulate brain regions contributes to this prediction.

Network of Brain Regions Involved in Interindividual Differences

The PLS analysis revealed that the intersubject variability of neural activation within the left ventral posterior cingulate cortex, extending to the precuneus, the right superior parietal cortex, the right dorsal medial prefrontal cortex, and the left ventral medial prefrontal cortex, is reliably related to interindividual behavioral nicotine effects (see Figure 4). Mesulam's (1981, 1999) model of attentional orienting suggests that interconnected networks, including the parietal, frontal and the cingulate gyrus, contribute to selective attention and attentional impairments observed in neglect. It has also been suggested that the posterior cingulate cortex is important for anticipatory attention (Mesulam, Nobre, Kim, Parrish, & Gitelman, 2001). This brain region is more responsive to attention-directing cues than targets (Hopfinger, Buonocore, & Mangun, 2000) and is involved in the processing of cue reliability (Giessing et al., 2006). Recent neuroimaging studies further support the idea that the posterior cingulate cortex constitutes an important interface between emotion and top-down control of attention. Neural activity in the posterior cingulate cortex is increased for validly cued trials with behavioral benefit as compared to those without benefit and can be enhanced with monetary incentives (Small et al., 2003, 2005). Our study shows that neural activity in the posterior cingulate cortex predicts individual effects of nicotine upon visuospatial attention. Other regions contributing to the prediction of individual nicotine effects were found in the medial prefrontal cortex and the superior parietal cortex. The superior parietal cortex is a brain region that is activated when transient changes in the locus of attention are required (Yantis & Serences, 2003), and we have previously found evidence that activity in this brain region is increased when invalidly cued trials are detected (Giessing et al., 2004). Here, individual differences in superior parietal activity under placebo contribute to the prediction of the individual behavioral effects of nicotine.

The frontal cortex is involved in the processing of advance top–down information. For example, patients with lesions to the frontal cortex show a slightly diminished ability to benefit from directional as compared to neutral spatial cues (Koski, Paus, & Petrides, 1998). A medial prefrontal region (slightly inferior to the dorsal and superior to the ventral region identified in the present analysis) was found to increase neural activity dependent on the behavioral benefits of valid cues (Small et al., 2003). Animal evidence further supports the notion that the cholinergic input to the medial prefrontal cortex may facilitate the top–down regulation of attention by filtering distracting stimuli (compare, e.g., Sarter, Hasselmo, Bruno, & Givens, 2005; Sarter, Givens, & Bruno, 2001). Here we show that the action of the cholinergic agonist nicotine depends on medial prefrontal activation under placebo.

Within the current study, all brain regions which predicted individual nicotine effects revealed no significant differences between valid and invalid trials when pooling over subjects. However, in a prior target detection

paradigm with valid and invalid cues, all regions with the exception of the superior partial cortex revealed significantly stronger activations for valid in comparison to invalid trials or a correlation with the behavioral benefits of valid cues (e.g., Small et al., 2003, 2005; in the study of Giessing et al., 2004, all regions showed a significant effect at a threshold of $p < .005$ testing valid minus invalid trials). Therefore, we assume that the posterior cingulate, dorsal medial prefrontal, and ventral medial prefrontal cortex contribute to focusing attention during valid trials rather than reorienting attention during invalid trials. In contrast, the superior partial cortex seems to be involved in reorienting of visuospatial attention toward unattended targets by providing transient attentional control signals (e.g., Giessing et al., 2004, 2006; Yantis & Serences, 2003). In summary, the brain network, which contributes to the prediction of individual behavioral nicotine effects, seems to be involved in both the focusing and reorienting of spatial attention.

Relationship between Network Activity and Individual Nicotine Effects

Reorienting-related BOLD activity (i.e., invalid minus valid trials) under placebo was used to predict the individual behavioral effect of nicotine on reorienting visuospatial attention. Our results revealed that brain regions that reliably contributed to the prediction were negatively correlated with the individual effect of nicotine. This means that persons with larger BOLD signal differences contrasting invalid with valid trials (''invalid minus valid'') showed faster behavioral validity effects under nicotine when adjusted for predifferences in reorienting attention before drug treatment (by regressing out the validity effects under placebo). Thus, those subjects who did benefit from nicotine showed stronger activation for invalid compared to valid trials within a network of the left posterior cingulate cortex, the right superior parietal cortex, the right dorsal medial prefrontal cortex, and the left ventral medial prefrontal cortex. Subjects who did not benefit from nicotine, on the other hand, showed stronger activation for valid as compared to invalid trials.

The Default Mode

The network of regions described above (i.e., posterior medial parietal cortex activations extending to the posterior cingulate cortex and medial prefrontal cortex activations) is currently intensively discussed in the context of the so-called default mode of the brain. These brain areas show consistently transient decreases of activity during goal-directed actions when compared with passive stimulus viewing (see Cavanna & Trimble, 2006 for a recent review). This has led to the proposal that these brain areas might subserve a common function related to self-related intentions (Greicius, Krasnow, Reiss, & Menon, 2003; Gusnard, Raichle, & Raichle, 2001; Raichle et al., 2001). According to Drummond et al. (2005), the default network is associated with longer reaction times in a vigilance task, indicating disengagement from the task and related inattention after sleep deprivation. Lindgren, Molander, Verbaan, Lunell, and Rosen (1999) and Kadoya, Domino, and Matsuoka (1994) showed that nicotine increases EEG frequencies associated with arousal and reduces those associated with relaxed wakefulness. Because our analysis revealed brain regions similar to the ''default mode'' network, the effects of nicotine upon visuospatial attention might also be related to intersubject differences in controlling self-related thoughts and wakefulness. Nicotine might mediate the efficient utilization of top-down related resources necessary to detect violations in cue–target expectancies occurring in invalid trials, which would lead to a reduction of self-related processes and a shift to external stimuli.

Influences of cholinergic drugs on expectations or top-down influences have also been postulated by recent models of cholinergic effects on spatial attention. Yu and Dayan (2005) postulated that cholinergic modulation using nicotine might reduce the validity effect by influencing subjective cue predictability (i.e., increased levels of acetylcholine may reduce the ''certainty'' of top-down information; compare also Giessing et al., 2006). One could speculate that nicotine improves the detection of unattended targets especially in those individuals who rely on top-down information provided by the cue and do not adapt their expectations during invalid targets. Therefore, these individuals might show only small differences in neural activity between valid and invalid trials in the posterior cingulate cortex, the dorsal medial prefrontal cortex, and the ventral medial prefrontal cortex.

Conclusion

This study tries to fill a gap in the knowledge of cholinergic effects on visuospatial attention. Prior studies documented that behavioral effects of nicotine differ between subjects (e.g., Perkins et al., 2000; Perkins, 1999). However, although several fMRI studies described the ''common'' or ''general'' impact of nicotine on neural networks involved in visuospatial attention (e.g., Giessing et al., 2006; Thiel et al., 2005; Lawrence, Ross, & Stein, 2002), our study identifies brain regions involved in differential effects between subjects. Our results show that differential neural activity in brain regions involved in focusing and reorienting spatial attention predicts individual behavioral effects of nicotine.

Recently, different multivariate methodological approaches have been applied to predict changes in subjective experiences or therapeutic outcomes, the relapse of individuals with substance dependence, or to discriminate patients and nonpatients with fMRI (e.g., Richardson, Strange, Duncan, & Dolan, 2006; Haynes

and Rees, 2005; Paulus, Tapert, & Schuckit, 2005). Here, we used a PLS analysis to predict behavioral drug effects. The PLS analysis is a particularly useful approach in a context of many highly collinear predictors and uncertain predictor–response relationships in psychopharmacological research. Therefore, our study provides a basis for future studies with larger sample sizes and studies experimentally manipulating ''baseline levels of neural activity,'' which might lead to additional information and a deeper insight into individual effects of drugs. In the long term, establishing predictors for individual drug effects using fMRI analyses might lead into an import clinical application as this would enable the selection of patients who are likely to profit from a certain medication from those how do not.

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