Individual differences in smoking-related cue reactivity in smokers: An eye-tracking and fMRI study

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A B S T R A C T

Measures of cue reactivity provide a means of studying and understanding addictive behavior. We wanted to examine the relationship between different cue reactivity measures, such as attentional bias and subjective craving, and functional brain responses toward smoking-related cues in smokers. We used eye-tracking measurements, a questionnaire for smoking urges-brief and functional magnetic resonance imaging to assess the responses to smoking-related and neutral visual cues from 25 male smokers after 36 h of smoking abstinence. Regression analyses were conducted to determine the correlation between cue-evoked brain responses and the attentional bias to smoking-related cues. The eye gaze dwell time percentage was longer in response to smoking-related cues than neutral cues, indicating significant differences in attentional bias towards smoking-related cues. The attentional bias to smoking-related cues correlated with subjective craving ratings (r = 0.660, p < 0.001). The dorsolateral prefrontal cortex, the putamen, the posterior cingulate cortex and the primary motor cortex were associated with the attentional bias to smoking-related cues, whereas the orbitofrontal cortex, the insula and the superior temporal gyrus were associated with smoking-related cue-induced craving and smoking urges. These results suggest that attentional mechanisms in combination with motivational and reward-related mechanisms play a role in smoking-related cue reactivity. We confirmed a positive correlation between different smoking-related cue reactivities, such as attentional bias and subjective craving, and functional brain responses in various individuals. Further studies in this field might contribute to a better individualized understanding of addictive behavior.

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1. Introduction

Drug addiction is characterized by the motivational disturbances of compulsive drug taking and intense drug craving (Koob and Le Moal, 2001; Self, 1998). The cue-reactivity paradigm has been suggested as providing a means of measuring and extricating the concept of craving. Drug addiction can be studied experimentally using this paradigm; after providing a means of measuring and extricating the concept of craving, and functional brain responses in various individuals. Further studies in this field might contribute to a better individualized understanding of addictive behavior.

Abbreviations: ACC, anterior cingulate gyrus; BOLD, blood oxygen level-dependent; CO, carbon monoxide; DLPFC, dorsolateral prefrontal cortex; FTND, Fagerstrom Test for Nicotine Dependence; fMRI, functional magnetic resonance imaging; IAPS, International Affective Picture System; OFC, orbitofrontal cortex; PCC, posterior cingulate gyrus; QSU-Brief, Questionnaire on Smoking Urges-Brief; MT, primary motor cortex; SMA, supplementary motor area; STG, superior temporal gyrus.

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craving (Field and Cox, 2008; Hogarth et al., 2008; Robbins and Ehrman, 2004). Studies of attentional bias toward smoking-related cues have used selective attention tasks, such as the Emotional Stroop Task (Mogg and Bradley, 2002; Waters et al., 2003b) or the Visual Probe Task (Bradley et al., 2004; Ehrman et al., 2002). Depending on the task, different underlying attentional processes can be measured; the Emotional Stroop Task measures non-automatic attentional processes (higher-level executive/cognitive control), whereas the Visual Probe Task is more able to capture fast and automatic attentional processes (basic low-level/habit-strength behavior), although both levels of attentional processing are known to act similarly in nicotine addiction (Chiamulera, 2005; Kassel, 1997). Eye-tracking systems can be used to record the eye movements of subjects assessing shifts in visual selective attention, and either the initial shift in attention (first fixation) or maintained attention (longer gaze time=dwell time percentage) serves as markers of attentional bias. Studies have shown that maintained attention is best measured for longer durations (>2000 ms) when using the Visual Probe task and that it plays a greater role in cue-reactivity to smoking-related cues (Mogg et al., 2003).

The neural responses to smoking-related cues in smokers have been investigated as changes in blood oxygen level-dependent (BOLD) signals in the brain using fMRI (Brody et al., 2007; Due et al., 2002; McBride et al., 2006; McClernon et al., 2005). Brain circuits involved in reward and motivation, as well as in learning, memory and control, are implicated in the processes of smoking addiction (Breiter and Rosen, 1999; David et al., 2005). It has been reported that cue-induced craving and brain activation responses to smoking cues are highly correlated in the components of the mesolimbic reward system and in memory circuits, whereas the severity of nicotine dependence is correlated with cue-induced activation of the circuits linked to visuo-spatial attention and motor function (Smolka et al., 2006; Yalcinov et al., 2009, 2010). The relationship between attentional bias and brain reactivity to smoking-related cues has not been sufficiently elucidated to date. Subjective craving and the urge to smoke have been suggested to be closely related to attentional bias for smoking-related cues (Mogg et al., 2005; Waters and Feyerabend, 2000). Correlations between subjective craving and smoking cue-induced changes in brain metabolism have also been reported in many studies with a large degree of agreement across studies (Brody et al., 2002; McClernon et al., 2005). Recent studies have also demonstrated the neural correlation between drug-related attentional bias and brain activation (Janes et al., 2010; Luijten et al., 2010). However, it would also be important to compare the different kinds of cue reactivity to see whether individual differences in these disparate types of cue responses are correlated.

In the current study, we aimed to look for a relationship between different measures of cue-reactivity; attentional bias was measured in smokers exposed to smoking-related cues through eye movements (behavioral cue reactivity), the functional activation of attention-, reward- and motivation-related brain areas (physiological cue reactivity) and subjective measures for craving (symbolic-expressive cue reactivity). Moreover, we looked for brain regions related to individual differences in brain activation to smoking-related cues.

In this study, we wanted to examine the following questions in smoking-addicted individuals: (i) whether the level of subjective craving was associated with attentional bias to smoking-related cues; (ii) whether individual differences in attentional bias score co-varied with functional brain activity responses to smoking-related cues; and (iii) whether individual differences in smoking urge and subjective craving score co-varied with functional brain activity responses to smoking-related cues.

2. Methods

2.1. Participants

Twenty-five right-handed male smokers, free of any medication, were recruited for this study if they smoked at least ten cigarettes per day for over three years. All participants had normal visual acuity, and those with psychiatric or neurological disorders were excluded. All psychiatric disorders were identified by a psychiatrist using the structured diagnostic tool, Diagnostic and Statistical Manual of Mental Disorder IV. The participants were originally recruited to receive acupuncture (or placebo) treatment for smoking cessation; however, all of the tests described in the current paper were carried out in a separate session before receiving any kind of acupuncture (or placebo) treatments (data regarding the efficacy of acupuncture for smoking cessation is in preparation for a separate manuscript). The subjects agreed to abstain from smoking for two days prior to the fMRI scanning session, and all sessions took place after approximately 36 h of smoking deprivation. To verify smoking abstinence, a carbon monoxide (CO) monitor (The Bedfont Instrument, Kent, UK) was used, and a CO value of less than 5 ppm indicated that the subjects had been compliant with the abstinence requirement. All participants gave informed consent for the study. This investigation was approved by the Institutional Review Board of University Hospital-Gangdong, Kyung Hee University, Seoul, Republic of Korea.

2.2. Smoking-related and neutral visual cues

The smoking-related and neutral visual cues were pictorial stimuli that were slightly modified from those we had used in our previous study (Chae et al., 2010). The smoking-related visual cues consisted of 15 color photographs of smoking-related scenes (e.g., a man holding a cigarette to his mouth). Each of the smoking-related visual cues was paired with neutral visual cues (e.g., a man holding a spoon to his mouth) that were matched as closely as possible for the visual characteristics (e.g., color, brightness, background scene). To check whether and to what degree the smoking-related visual cues induced a reaction in smokers, we obtained valence ratings to all smoking-related and neutral cues in a previous study. Whether the smoking-related pictures appeared on the left or the right side of the screen was counter-balanced. Five neutral picture pairs unrelated to smoking were taken from the International Affective Picture System (IAPS) and used in filler trials. The pictures were digitized and converted to an indexed 256-color palette. The pictures were approximately 14 cm wide and 10 cm high, and the distance between the inner edges of each picture in each pair was approximately 4 cm, as shown in Fig. 1A. The same smoking-related and neutral visual cues were used for the eye-tracking and the fMRI scanning sessions.

2.3. Eye tracking task design

The tasks were presented in a dimly lit, sound-proofed room using a 1700-MHz PC with a 17 in. LCD-TFT monitor. Participants’ eye movements were recorded during the experiment with a computerized eye-tracking system (iView XTM RED, SensoMotoric Instruments, Germany). In the eye-tracking task, each trial started with fixation for 2000 ms on a central cross, which was replaced on the display with a pair of pictures for 6000 ms. The stimulus exposure time was chosen according to previous studies, which showed that longer exposure duration was better to measure maintenance of attention compared to initial attention and resulted in more differences in attentional bias between smokers and nonsmokers (Bradley et al., 2004; Mogg et al., 2003). Participants were seated at a desk at a constant distance of 1 m from the monitor and were instructed to look at the fixation cross at the start of each trial and to be motionless and refrain from moving their heads during the task.

2.4. Preparation of eye movement data

The eye-tracking data were analyzed using the Eye Tracking Data Analysis Program (BeGaze, SensoMotoric Instruments, Germany). The direction of gaze was measured in degrees once every 17 ms.
was composed of each subject in a block design with three blocks per category. Each block

2.6. fMRI task design and scanning parameters

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and smoking urge. We used questions based on the Questionnaire on Smoking Urges-Brief (QSU-Brief), which is the shorter version of the

each in a block design with three blocks per category, whereas each block was composed of alternating five smoking-related and five neutral stimuli. Each image was shown for 6 s, with each block lasting for 30 s. After each block, a fixation cross was presented on a white background for 30 s.

The dwell time percentage for each picture for each participant was calculated from the total presented time. The dwell time percentage for each image was analyzed using a paired t test. The attentional bias score was calculated for each subject as the difference in mean dwell time percentage between smoking-related and neutral pictures. Pearson correlation tests were also conducted to assess the correlation between the attentional bias score and the craving for smoking cues. Significance levels for all statistical tests were set at \( p = 0.05 \).

2.5. Subjective measures

The Fagerstrom Test for Nicotine Dependence (FTND) was conducted to check for the level of subjects’ nicotine dependency. Immediately after the eye-tracking task, all subjects were requested to assess their craving and smoking urge. We used questions based on the Questionnaire on Smoking Urges-Brief (QSU-Brief), which is the shorter version of the Questionnaire on Smoking Urges that has been tested and confirmed for its validity and reliability (Tiffany and Drobes, 1991; Toll et al., 2006). Answers were given as ratings on a 7-point scale.

2.6. fMRI task design and scanning parameters

The 15 smoking-related and 15 neutral visual cues were presented to each subject in a block design with three blocks per category. Each block was composed of five smoking-related or five neutral visual cues. Each image was shown for 6 s with a block lasting for 30 s. After each block, a fixation cross was presented on a white background for 30 s. As shown in Fig. 1B, all fMRI experiments were conducted using a 3.0 T whole-body scanner (Philips Achieva, Best, the Netherlands) with an 8-channel phase array head coil. To minimize movement artifacts, the head of each subject was fixed by a head holder. To investigate blood oxygenation level-dependent (BOLD) effects, a transverse gradient-echo echo-planar imaging sequence was performed. The corresponding imaging parameters were repetition time (TR = 3000 ms), echo time (TE = 35 ms), flip angle = 90°, field of view (FOV) = 230 × 230 mm, imaging matrix = 64 × 64, slices = 30, slice thickness = 4.5 mm and gap between slices = 0 mm, and voxel size = 3.6 mm × 3.6 mm × 4.5 mm. In addition, a three-dimensional anatomic image was also acquired to reconstruct functional areas into brain regions (TR = 9.9 ms, TE = 4.6 ms, imaging matrix = 240 × 240, FOV = 240 × 240 mm, slices = 120, flip angle = 7°, slice thickness = 1 mm, voxel size = 1 mm × 1 mm × 1 mm).

2.7. fMRI data analysis

Pre-processing and statistical analysis were conducted using the Statistical Parametric Mapping software (SPM5, http://filion.ac.uk). All functional images underwent correction for acquisition time and for head motion. Six motion regressors (three rotation and three translation) characterizing the subjects’ movements during the scan were included in the model for each subject as nuisance covariates. Pre-processing included motion correction, normalization to the Montreal Neurological Institute stereotactic space based on Talairach coordinates, and spatial smoothing with an 8-mm full-width-at-half maximum isotropic Gaussian kernel to decrease the spatial noise. At the individual subject level, we computed statistical maps of regressor coefficients estimated for the valence ratings convolved with the canonical hemodynamic response function, which were then taken to a random effects level by including the statistical images from each subject in a one-sample \( t \)-test. Each cue was modeled as a boxcar function convolved with a canonical hemodynamic response function that began at the onset of each cue. Contrast maps were generated between smoking-related and neutral regressors for the smoking-related cue reactivity. Individual contrast images (smoking-related minus neutral images) were subsequently included in a second level random effects analysis. Brain activation for smoking-related cues relative to neutral cues was considered significant \( p < 0.001 \) (uncorrected) with a minimum cluster extent threshold of 10 contiguous voxels.

A multiple linear regression analysis was conducted to evaluate the association of cue-evoked brain responses with (1) the attentional bias and (2) smoking urges to smoking-related cues. Specifically, first level contrast maps reflecting the cue-induced brain activity (i.e., the difference between the smoking-related and neutral images) were entered into a regression analysis at the second level with a regressor, the attentional bias characterizing dwell time percentage to smoking-related cues. In addition, first level contrast maps reflecting the cue-induced brain activity were entered into a regression analysis at the second level with a regressor, smoking urges to smoking-related cues measured by the QSU-Brief. For the regression analysis, activation was
considered significant at $p<0.005$ (uncorrected) with a minimum cluster extent threshold of 10 contiguous voxels.

3. Results

3.1. Subject demographics

All subjects were right-handed adult males (25.0±1.2 years; all results are represented as the mean±standard error of the mean). All of the subjects reported to have smoked more than 10 cigarettes per day for more than 3 years, and the average of all the subjects was 17.6±0.8 cigarettes smoked per day and 6.0±1.1 years smoking. The subjects’ smoking behavior and smoking abstinence were confirmed by breath CO levels and were 13.2±1.5 ppm in the non-abstinent at the screening visit and 3.1±0.3 ppm in the abstinent condition. The mean FTND score of 5.5±0.3 also indicated nicotine dependency. Two subjects dropped out during the eye-tracking task because of technical problems, and the data from the remaining twenty-three participants were further analyzed.

3.2. Correlation between attentional bias and craving

The attentional bias score was calculated for each subject as the difference in mean dwell time percentage between smoking-related and neutral pictures. Eye gaze dwell time percentage on the smoking-related cues was significantly longer than that on the neutral cues (paired t-test, 43.5±2.5 vs. 34.3±2.0%, $p<0.05$), as shown in Fig. 2A and B. When controlling for the dwell time percentage with both neutral pictures on the left and the right, there was no significant difference in eye gaze dwell time percentage (37.9±2.2 vs. 38.4±2.1%, $p>0.887$).

The subjective craving score measured after the eye-tracking task by the QSU-Brief was 37.2±2.2. A significant correlation was found between the subjective measures of craving and the attentional bias score ($r=0.660$, $p<0.001$). Subjects reporting a stronger craving exhibited a longer gaze dwell time on smoking-related cues (Fig. 2C, D).

3.3. Smoking-related cue-induced BOLD changes

The results from the statistical analysis of activation to smoking-related and neutral cues are shown in Table 1. When smoking-related and neutral conditions were presented to all subjects, the brain regions showing a BOLD signal change between smoking-related and neutral cues are listed. Smoking-related cues elicited greater activation than neutral cues in the left dorsolateral prefrontal cortex (DLPFC), the right anterior cingulate gyrus (ACC), the left posterior cingulate gyrus (PCC), the bilateral insula, the left thalamus, the right primary motor cortex (MI), the left supplementary motor area (SMA), the right superior temporal gyrus (STG), the left inferior parietal gyrus, the right superior parietal gyrus and the right superior occipital gyrus.

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**Fig. 2.** Differences in attentional bias score indicated by mean eye gaze dwell time percentages and its correlation with the subjective craving score. A: The mean eye gaze dwell time of the subjects on the visual stimuli is represented as a heat map. The green-to-red color map indicates the average dwell time spent on each pixel. B: The mean eye gaze dwell time percentage of all subjects on either smoking-related (orange) or neutral (blue) images. The dwell time percentage on smoking cues was significantly longer than that on neutral cues ($p<0.05$). C: The individual patterns of eye movements for the paired visual stimuli during one trial (6 s). The orange color represents the dwell time on the smoking-related stimulus, and the blue color represents the dwell time on the neutral visual stimulus. Empty or white space indicates that subjects were looking at neither of the two stimuli. D: Scatter plot illustrating the correlation between the subjective craving score and the attentional bias score to smoking cues ($r=0.660$, $p<0.001$). The attentional bias score was calculated for each subject as the difference in mean dwell time percentage between smoking-related and neutral pictures.
3.4. Correlation between attentional bias and smoking-related cue-induced BOLD changes

We determined whether individual differences in attentional bias score co-varied with functional brain activity responses to smoking-related cues (smoking-related vs. neutral). Brain areas in which the BOLD response correlated with the attentional bias to the smoking cues are summarized in Table 2 and Fig. 3. Higher attentional bias scores demonstrated significant co-variation with activities in the right DLPFC (x = 16, y = 38, Z = 3.16, r = 0.604, p < 0.001), the right putamen (x = 22, y = 22, z = 2, Z = 3.05, r = 0.663, p < 0.001), the left PCC (x = −20, y = −62, z = 8, Z = 3.41, r = 0.658, p < 0.001), the right PCC (x = 22, y = −60, z = 6, Z = 3.77, r = 0.635, p < 0.001), and the left MI (x = −34, y = −20, z = 44, Z = 3.45, r = 0.621, p < 0.001).

3.5. Correlation between smoking urges and smoking-related cue-induced BOLD changes

We determined whether individual differences in the QSU-Brief score co-varied with functional brain activity responses to smoking-related cues (smoking-related vs. neutral). Brain areas in which the BOLD responses correlated with smoking urges to the smoking cues are summarized in Table 3 and Fig. 4. Higher smoking urge scores demonstrated significant co-variation with activities in the left orbitofrontal cortex (OFC) (x = −25, y = 43, z = −6, Z = 2.96, r = 0.589, p < 0.01), the left insula (x = −42, y = −15, z = −10, Z = 3.21, r = 0.628, p < 0.001), and the left STG (x = −53, y = −22, z = −2, Z = 3.63, r = 0.688, p < 0.001).

4. Discussion

The present study focused on the relationship between different measures of smoking-related cue reactivity. In this study, we tried to examine the relationship between craving, attentional bias and the neural responses in the brain to smoking-related cues in smokers using a questionnaire, an eye-tracking system, and fMRI. We found that attentional bias to smoking-related cues measured in the eye-tracking task significantly correlated with brain activation in several brain areas, including the DLPFC, the putamen, the PCC, and the MI. We also demonstrated that smoking urges to smoking-related cues significantly correlated with brain activation in the OFC, the insula, and the SFG.

4.1. Neural substrates for smoking-related cues

Drug urges play an important role in mobilizing drug-seeking behaviors and eliciting attentional biases for drug-related cues according to Tiffany’s model (Mogg et al., 2003; Tiffany, 1990). In the incentive sensitization model of Robinson and Berridge (1993), the rewarding properties of drug-use based on past conditioning history induce drug urges and therefore make drug-related cues highly salient or attention-grabbing (Robbins and Ehrman, 2004; Robinson and Berridge, 1993). Previous studies have related craving or an increased urge to smoke with enhanced attentional bias to smoking-related cues, referring to both models (Ehrman et al., 2002; Field and Cox, 2008; Mogg and Bradley, 2002; Robbins and Ehrman, 2004). In our study, we were also able to replicate this bias by showing a significant correlation between higher craving and an enhanced attentional bias to smoking-related cues.

Previous neuroimaging studies have shown that BOLD responses to smoking-related cues in smokers result in activation of the corticomesolimbic network in regions subserving reward and goal-directed behavior, but also attention (David et al., 2005; Due et al., 2002; McClernon et al., 2009). Our fMRI results are also mostly in agreement with the results of these previous studies. When comparing brain activation patterns to smoking-related cues vs. neutral cues, we also found a broad activation of the abovementioned brain circuits (see Table 1). In the current study, we found that smoking cues elicited greater activation than neutral cues in the mesocorticolimbic reward circuits, such as the DLPFC, and in the visuospatial attention circuits, such as the ACC. These findings are consistent in showing that smoking-related visual stimuli produce activation in the mesolimbic dopamine reward circuits and in areas related to visuospatial attention in anticipation of both the reinforcing effects and the incentive salience of the drug cues (David et al., 2005; Due et al., 2002; McClernon et al., 2009).

4.2. Individual differences in neural substrates for attentional bias to smoking cues

Attentional bias to smoking-related cues measured in the eye-tracking task significantly correlated with the activation of brain responses in several brain areas, including the right DLPFC, the putamen, the bilateral PCC, the left MI, and the left claustrum. The majority of these structures have been implicated previously in addiction models and play a crucial role in expectancy (DLPFC), attentional motivation (PCC), habit-based craving (dorsal striatum) and motor preparation for goal-directed actions (MI) (Belin and Everitt, 2008; Chiamulera, 2005; Everitt and Robbins, 2005; Volkow et al., 2006; Valachich et al., 2009, 2010). In previous studies, brain activation in the DLPFC and PCC correlated with the intensity of smoking cue-induced craving, suggesting a close association between expectancy and attentional processes and the subjective experience of craving (Field and Cox, 2008; Franklin et
The dorsal striatum has been known to be involved in the selection and initiation of actions and also to mediate the habitual and automatized nature of compulsive drug-seeking (Graybiel et al., 1994; McClernon et al., 2009; Tiffany, 1990; Volkow et al., 2006). The MI has been known to be associated with the severity of nicotine dependence assessed with the FTND, indicating that motor preparation and imagery are more pronounced in smokers who are severely dependent on nicotine (Smolka et al., 2006). Furthermore, it has been reported that the activation of motor regions in the brain is strongly correlated with the individual degree of nicotine dependence and that automatized motor behavior also plays an important role in addiction (Yalachkov et al., 2009, 2010). Overall, attentional bias to smoking-related cues is...
Secondly, the choice of subjects was also different; only male subjects were used. This choice may be a better indicator of the allocation of visuospatial attention compared to visual cues (Mogg and Bradley, 2002; Waters et al., 2003a). However, they differ from our study in a few points. Firstly, our study used more naturalistic, environmental pictorial stimuli and a counting and picture-naming task. These tasks assess the competition for processing resources between different features of a stimulus (perceptual vs. semantic) presented within the focus of attention, whereas our study uses more naturalistic, environmental pictorial stimuli and therefore may be a better indicator of the allocation of visuospatial attention to visual cues (Mogg and Bradley, 2002; Waters et al., 2003a). Luijten et al. (2010) also remark that their behavioral measure might not be ideally suited for attentional bias to smoking cues in smokers. In conclusion, the eye-tracking methodology and recording gaze dwell time are more direct and specific for measuring visuospatial selective attention (Field et al., 2004; Mogg et al., 2005; Van Rensburg et al., 2009). Secondly, the choice of subjects was also different; only male subjects associated with greater neural responses to smoking cues in brain regions engaged in the mesocorticobasal reward system, as well as in the neural circuits linked to visuospatial attention.

There have been recent studies specifically looking for neural correlates of drug-related attentional bias (Janes et al., 2010; Luijten et al., 2010). However, they differ from our study in a few points. Firstly, our study used eye-tracking methodology as a behavioral measure of attentional bias whereas Janes et al. (2010) used an emotional Stroop task, and Luijten et al. (2010) used behavioral tasks, such as a line-counting and picture-naming task. These tasks assess the competition for processing resources between different features of a stimulus (perceptual vs. semantic) presented within the focus of attention, whereas our study uses more naturalistic, environmental pictorial stimuli and therefore may be a better indicator of the allocation of visuospatial attention to visual cues (Mogg and Bradley, 2002; Waters et al., 2003a). Luijten et al. (2010) also remark that their behavioral measure might not be ideally suited for attentional bias to smoking cues in smokers. In conclusion, the eye-tracking methodology and recording gaze dwell time are more direct and specific for measuring visuospatial selective attention (Field et al., 2004; Mogg et al., 2005; Van Rensburg et al., 2009).

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### Table 3

Activated regions: correlation between smoking urges and BOLD signal changes to smoking-related cues in smokers.

<table>
<thead>
<tr>
<th>Activated regions</th>
<th>Coordinates in Talairach's space</th>
<th>Z score</th>
<th>p Value (uncorrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(L) Superior temporal gyrus</td>
<td>−22 −53 −22 −2</td>
<td>3.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(L) Posterior insula</td>
<td>−42 −15 −10</td>
<td>3.21</td>
<td>0.001</td>
</tr>
<tr>
<td>(L) Orbitofrontal cortex</td>
<td>−25 −43 −6</td>
<td>2.96</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Mean stereotactic coordinates (mm) of peak voxel are listed according to the atlas of Talairach and Tournoux. BA: Brodmann area. All Z value thresholds are >2.96.

Associated with greater neural responses to smoking cues in brain regions engaged in the mesocorticobasal reward system, as well as in the neural circuits linked to visuospatial attention.

### 4.3. Individual differences in neural substrates for craving to smoking cues

Smoking urges in response to smoking-related cues, as measured by the QSU-Brief in the present study, significantly correlated with brain activation in the OFC, insula, and SFG. The OFC and the insula are anatomically and functionally associated with integrated autonomic control and are sensitive to interoceptive signals (Critchley, 2005). The OFC is known to play a crucial role in drug-seeking behavior (Kalivas and Volkow, 2005), which is partly through the action of reward-related decision-making and cognitive control (Rushworth et al., 2007). Previous studies have shown that the OFC is involved in cue-induced and abstinence-induced cigarette cravings (Franklin et al., 2007; Wang et al., 2007). Increased functional activity within the insula is associated with increased interoceptive awareness (Critchley, 2005). Smokers with brain damage involving the insula reported a greater ease of smoking cessation with minimal smoking urges, indicating that the insula is a critical neural substrate in the addiction to smoking (Naqvi, 2007; Wang et al., 2007). Increased functional activity within the insula is associated with increased interoceptive awareness (Critchley, 2005). Smokers with brain damage involving the insula reported a greater ease of smoking cessation with minimal smoking urges, indicating that the insula is a critical neural substrate in the addiction to smoking (Naqvi, 2007; Wang et al., 2007).

**Fig. 4.** Smoking-related cue-induced BOLD changes and their correlation with subjective smoking urges measured by a questionnaire for smoking urges (QSU-B). Normalized SPM T-maps overlaid on the corresponding axial T1-weighted images showing statistically significant (p < 0.005, uncorrected with 10 continuous voxels) brain activation correlation between smoking urges and brain responses to smoking cues compared to neutral cues. Brain activation was observed in (A) the left OFC (x = −25, y = 43, z = −6, Z = 2.96, r = 0.589, p < 0.01) and (B) the left insula (x = −42, y = −15, z = −10, Z = 3.21, r = 0.628, p < 0.001). Talairach Z coordinates for slices are indicated below each figure. The Z value thresholds were above 2.96.
et al., 2007). Our findings support the notion that the OFC and the insula play an important role in nicotine dependence, specifically in cue-related cravings.

4.4. Limitations

Our study possesses several limitations. First, our measurement of attentional bias may not fully capture both types of attentional processing, specifically, automatic and non-automatic. Due to the length of cue presentation, our eye movement data predominantly shows an effect of smoking cue-related bias in attention maintenance, rather than a bias in automatic and initial orientation. However, based on previous findings, both levels of attentional processing seem to function similarly in nicotine addiction (Chiamulera, 2005; Kassel, 1997). Additionally, the attentional bias in attention maintenance seems to be a more robust effect, holding true across different experimental conditions (Bonitiz and Gordon, 2008; Bradley et al., 2003). Second, our present study lacks a normal control group. However, reactivity to visual smoking cues has been repeatedly shown to be specific to smokers vs. non-smokers and is not task-dependent (Mogg and Bradley, 2002). Third, the attentional bias scores were obtained before fMRI scanning, resulting in a time gap of approximately 30 min between measuring the BOLD signal and the attentional bias score. We cannot fully exclude the possibility of carry-over effects between the eye-tracking task and the fMRI task. Fourth, only evaluating breath CO measurements of the participants may not have been a perfect verification of their 36-hour smoking abstinence. Finally, due to the exploratory nature of this study, an α level of p < 0.005 was chosen, and corrections for multiple comparisons were not implemented. Additionally, due to the applied linear statistical models employed, we were only able to detect linear relationships between selective attention in the eye-tracking task and brain activation in the fMRI, thereby probably overlooking more complex relationships.

4.5. Implications

The results of this study have significant implications. It has been reported that cue reactivity predicts relapse and reinstatement of dependence (Abrams et al., 1988; Drummond, 2000; Drummond and Gaultier, 1994), although recent studies have noted that self-report-based cue reactivity is not necessarily related to smoking relapse (Perkins, 2009). Such measures as attentional bias towards smoking-related cues have been discussed as one of the most important underlying processes mediating drug-seeking behavior in drug-dependent patients. It has been known that attentional bias toward drug-related cues contributes to ongoing drug-taking or relapse and motivates instrumental drug-seeking behaviors among patients (Hogarth et al., 2008; Robbins and Ehrman, 2004). Moreover, attention paid to drug-related cues could distract individuals from effective therapies and prohibit them from the employment of abstinence-oriented coping skills (Waters et al., 2003b).

Measures of smoking-related cue reactivity are of high clinical importance because of their close relation to withdrawal and relapse. The concept of cue reactivity is a useful but broadly defined one, and the relationships between different measures of cue reactivity have not yet been fully elucidated (Chiamulera, 2005). Several processes are thought to be involved in cue reactivity, and to individualize patient treatment, it is important to study cue reactivity more in depth, especially at a more individualized level. We tried to accomplish this individualization by looking at individual differences encompassing different cue reactivity measures.

5. Conclusion

In summary, our study shows a positive correlation among behavioral, symbolic-expressive and physiological measures of smoking-related cue reactivity, such as attentional bias, subjective craving and functional brain responses, in different smokers. Attentional bias to smoking-related cues was associated with greater neural responses to smoking cues in several brain areas engaged in the mesocorticolimbic reward system, as well as in neural circuits linked to visuospatial attention. Smoking urges to smoking-related cues were correlated with the brain regions involved in reward-related decision-making and interoceptive awareness. Our results demonstrate that attentional, motivational and reward-related mechanisms may play a role in smoking-related cue reactivity. Further studies in this field might contribute to a better and more individualized understanding of addictive behavior.

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