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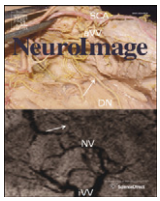

Neurobiological substrate of smoking-related attentional bias

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ABSTRACT

Substance-dependent patients automatically and involuntarily allocate their attention to drug cues in the environment, a process referred to as attentional bias. Attentional bias is increased during periods of subjective craving and predictive of treatment outcome and relapse in substance dependence. Despite recent theoretical and clinical advances with regard to attentional bias, the underlying neurobiological mechanisms are largely unknown. The objective of the current study was to investigate the neural substrate of attentional bias and associated subjective craving in smokers. A group of smokers ($n=20$) and a group of age- and gender-matched nonsmoking controls ($n=22$) were recruited from the general population and participated in a single session of fMRI scanning while attentional processes were manipulated. Main outcome measures were blood oxygen level-dependent (BOLD) fMRI activation during an attentional bias paradigm and self-reported cigarette craving. Results of the current study show that the dorsal anterior cingulate cortex, the superior parietal gyrus, and the superior temporal gyrus were more strongly activated in smokers, as compared to controls, when they had to pay attention to task-relevant information (line counting) while smoking cues were present as distracters (attentional bias). Subjective craving measures during attentional bias correlated with brain activation in the insula and putamen. To our knowledge, this is the first controlled study that shows the brain regions involved in attentional bias in smokers. The current study demonstrates that brain regions contributing to top-down attentional processing are implicated in attentional bias in smokers, suggesting that smokers have to employ more attentional resources to focus on a standard cognitive task when smoking cues are present.

Introduction

Substance abuse and addiction are commonly associated with enhanced reactivity to substance-related cues. Attentional bias is one of the key cognitive processes involved in cue reactivity and involves the tendency of substance-dependent patients to automatically and involuntarily allocate and maintain their attention to conditioned drug cues (Field and Cox 2008). Attentional bias for drug cues is thought to result from acquired motivational and attention-grabbing properties of these cues due to sensitization of dopamine systems in the brain (Robinson and Berridge 2008). For substance-dependent patients, drug cues become extremely salient, become the focus of attention, and elicit behaviors like drug seeking and consumption. Attentional bias has consistently been found in various types of addiction (for reviews, see Field and Cox, 2008; Franken, 2003; Robbins and Ehrman, 2004) utilizing a wide range of experimental paradigms including attentional tasks such as the emotional Stroop and visual probe task. Smokers, for example, are slower to name the color of smoking-related words when compared to neutral words during the smoking Stroop task (Munafo et al., 2003), and they are faster to respond to probes replacing smoking pictures than to probes replacing nonsmoking pictures (Bradley et al., 2004; Ehrman et al., 2002; Mogg et al., 2005) during the visual probe task. Eye-tracking and event-related potential studies (Field et al., 2004; Littel and Franken 2007; Mogg et al., 2003) have also indicated enhanced attentional processing of drug cues in smokers. As predicted by theoretical models, attentional bias is associated with current craving, the strong subjective urge to consume a substance of abuse (Field et al., 2009; Franken 2003). Recently, attentional bias has been proven to be a clinically relevant construct that is associated with relapse rates or treatment outcome in smokers (Waters et al., 2003), alcohol (Cox et al., 2002), cocaine- (Carpenter et al., 2006), and heroin-dependent patients (Marissen et al., 2006). Further, preliminary evidence has been provided that attentional bias extinction training

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reduces conditioned cigarette craving in smoking males (Attwood et al., 2008) and drinking behavior in alcohol-dependent patients (Attwood et al., 2008; Fadardi and Cox 2009; Field and Eastwood 2005; Field et al., 2007; Schoenmakers et al., 2007, 2010). Despite these theoretical and clinical advances, the neurobiological mechanisms of attentional bias are largely unknown.

Previous studies have shown that conditioned drug cues elicit a response in substance-dependent patients in a general network of brain regions mainly consisting of the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), and ventral striatum, as well as superior parietal and temporal brain areas (for review, see Wilson et al., 2004). Although these studies have provided important information regarding the neurophysiology of addiction, they do not clarify the contribution of brain structures within this network to specific processes that occur during exposure to drug-related stimuli, such as attentional bias and craving. Several brain regions activated during cue exposure are known to be involved in attentional processing and may be involved in attentional bias for alcohol, drug, and smoking cues as well. Although empirical studies are largely lacking, an important role for the ACC in attentional bias has been hypothesized (Franken 2003). The ACC is a heterogeneous brain region consisting of several functionally distinct areas and regulates attention that serves both cognitive and emotional processing (Bush, Luu, Posner 2000; Bush and Geer 2001; Vogt et al., 2005; Weissman et al., 2005). A widely supported view of ACC functioning is that cognitive and emotional information is processed separately in two major subdivisions (Bush et al., 2000). The rostral–ventral zone of the ACC (rvACC) is involved in emotional processing, more specifically in emotional conflict, salience attribution, and emotional response (Bishop et al., 2004; Compton et al., 2003; Etkin et al., 2006; Fujiwara et al., 2009). Other brain structures supposed to be involved in the bottom-up process of salience attribution are the OFC, ventral striatum, and amygdala; areas that are anatomically connected to the rvACC (Goldstein and Volkow 2002; Volkow et al., 2004). Together, they may constitute a ventral attentional system involved in attentional bias that operates in a stimulus-driven fashion by directing attention to salient stimuli. In contrast, the dorsal ACC (dACC) has been implicated in top-down attention (Silton et al., 2009). Activity in the dACC contributes to focused attention on relevant stimuli, especially when the achievement of behavioral goals is threatened by distracting events (Weissman et al., 2005) (i.e., salient stimuli). In addition to the dACC, superior parietal and dorsolateral prefrontal brain regions are involved in attention and executive control (Cavanna and Trimble 2006; Kompus et al., 2009; Liu et al., 2004; Silton et al., 2009). The dACC, superior parietal, and dorsolateral prefrontal regions may thus be involved in attentional bias and constitute a more dorsal top-down attentional system. Currently, there is some evidence that these regions are hypoactive in substance-dependent patients during performance of nonaffective cognitive paradigms (Forman et al., 2004; Kaufman et al., 2003; Volkow et al., 2004). On the other hand, it has been suggested that these regions may become overactive during cue exposure as a result of increased effort to maintain cognitive control (Lubman et al., 2004).

To the best of our knowledge, there are no controlled studies in the literature that are explicitly designed to examine brain regions involved in substance-related attentional bias. Although several fMRI studies have been published in which substance abusers perform an attention demanding task while being exposed to drug cues (Goldstein et al., 2007, 2009a, b; Hester and Garavan 2009; Tapert et al., 2004), the results of these studies are difficult to interpret with regard to brain processes involved in attentional bias for several reasons. First, two studies employing the drug Stroop task did not report drug cue-specific activations; therefore, it is unclear if differential processing of drug cues relative to neutral cues occurred (Goldstein et al., 2007; Goldstein et al., 2009a). Second, modifications of the Stroop task paradigm (Goldstein et al., 2009a,b; Tapert et al., 2004), such as the addition of a reward component (participants could earn money as a function of task performance in Goldstein et al. 2009a,b) tend to confound interpretation in terms of attentional bias. Besides these conceptual issues, some of these studies suffer from methodological problems, such as low power (Goldstein et al., 2007; Tapert et al., 2004) or the lack of a control group (Goldstein et al., 2007; Hester and Garavan 2009), the latter precluding conclusions regarding involvement of specific brain regions in substance abuse patients. Although the results of these studies most likely do not reflect the neural substrates of attentional bias *per se*, they suggest that substance-dependent patients show deviant brain activation in both subregions of the ACC (Goldstein et al., 2007, 2009b; Tapert et al., 2004), the dorsolateral prefrontal (Tapert et al., 2004) and inferior frontal gyrus (Hester and Garavan 2009), the superior parietal lobe (Goldstein et al., 2009b; Tapert et al., 2004), and the brainstem (Goldstein et al., 2009a). In addition to the above-reviewed methodological issues, there is also an important conceptual issue that is likely to be present in standard (nonadapted) attentional bias paradigms like the drug word Stroop task. Notably, it cannot be ruled out that differential brain activation in these task paradigms is the result of differences in simple cue reactivity to drug cues between substance-dependent patients and controls. Therefore, in the present study, we developed a new pictorial task paradigm to elicit brain activations specifically associated with attentional bias in smokers while controlling for nonspecific activations resulting from other processes involved in cue reactivity (i.e., picture viewing), including arousal and familiarity.

Based on the previous studies and theoretical accounts, we hypothesized that both subregions of the ACC are involved in attentional bias. Specifically, we expected that the dACC will be overactive in smokers during the attentional bias paradigm. This dACC activity will contribute to focused attention on the primary task, as smokers will be highly distracted by the conditioned smoking cues. In keeping with the other brain regions involved in salience attribution and top-down attention, we expected the OFC, ventral striatum, amygdala, superior parietal, and dorsolateral frontal cortex to be similarly hyperactive due to their involvement in attentional bias for smoking-related stimuli as well.

Materials and methods

Subjects

A total of 20 smokers and 22 nonsmoking controls participated in the study. Subjects were recruited via advertisements on the Internet and were screened by telephone for study eligibility. Exclusion criteria for both groups were (a) drug abuse other than nicotine, (b) current physical or psychological illness, (c) any use of medication, and (d) fMRI contra-indications. Data from two smokers and three nonsmoking controls were discarded due to scanner failure. The final sample consisted of 18 smokers (mean age = 23.6 years, SD = 4.1, 13 men) and 19 nonsmokers (mean age = 22.8 years, SD = 2.1, 12 men). Smokers smoked at least 10 cigarettes per day (mean = 16.7 cigarettes per day, range = 10–25) for a duration of at least 2 years (mean = 7.1 years, range = 2–14). The Fagerström test for nicotine dependence (FTND; Heatherton et al., 1991) served as a measure of nicotine dependence in smokers (mean score = 3.72, range = 0–7). Nonsmokers had smoked less than 5 cigarettes during lifetime, except for one nonsmoker who had smoked 20 cigarettes more than 10 years ago (mean = 2.1 cigarettes lifetime, range = 0–20). Although a study from Jacobsen et al. (2002) suggests that nicotine does not alter the coupling between BOLD signal and neural activity, smokers abstained from smoking for 3 hours before scanning to avoid direct pharmacological confounds without introducing marked withdrawal effects. Both smokers and nonsmoking controls abstained from alcohol for at least 24 hours before scanning. All subjects provided written informed

consent. The study was approved by the Ethics Committee of Erasmus Medical Center Rotterdam.

Paradigm

An experimental paradigm, the attentional bias line counting task, was developed to detect brain regions specifically involved in attentional bias. During each trial in this task, a picture with either smoking-related stimuli (people engaged in smoking behavior or smoking-related objects) or neutral stimuli (people engaged in nonsmoking behavior or neutral objects) was presented for 900 ms (Fig. 1). A fixation cross was shown for an average of 2100 ms (jittered from 1100 to 3100 ms, steps of 250 ms) before the presentation of the next picture stimulus. Two to five lines were displayed within each picture, with semirandomly distributed spaces between these lines. Instructions for participants varied over blocks. In one block (counting lines), participants were asked to count the number of lines presented in the picture and to press the corresponding button as fast as possible. Note that, for this task, the content of the picture is irrelevant to task performance. In the other block (naming pictures), participants had to indicate whether the content of the picture included smoking stimuli or neutral stimuli by pressing the corresponding button. This is an easy and straightforward task, with low cognitive demands. Before each block, task instructions were presented for 4 s. Within each block, smoking and neutral pictures were semirandomly presented. In total, 72 trials were presented in each of the following conditions: line-counting smoke picture (LCSP), line-counting neutral picture (LCNP), picture-naming smoke picture (PNSP), and picture-naming neutral picture (PNNP). Based on these conditions, three contrasts were defined for analyses. First, the LCSP and LCNP relative to baseline contrast (overall cognitive effort) was computed to assess the overall effects of line counting irrespective of picture content. Brain activation related to this contrast reflects overall cognitive effort during line counting in smoking and neutral pictures. Second, the LCSP minus LCNP contrast (attentional bias) represents brain activation associated with attentional bias for smoking stimuli, as all brain activation related to line counting is cancelled out. What remains is the brain activation reflecting the task-irrelevant (automatic) attentional bias for the smoking pictures. Third, the LCSP minus PNSP contrast (cue exposure-corrected attention) was computed. This contrast reflects attention to the smoking pictures during line counting while correcting for cue reactivity to these smoking cues and therefore serves as a check to ensure that group differences in brain activation in the attentional bias contrast (LCSP minus LCNP) does not solely reflect cue reactivity induced by the content of the pictures.

Procedures

After arrival, participants approved participation by signing informed consent. Breath carbon monoxide concentration was measured in all subjects using a calibrated Micro + Smokerlyzer (Bedfont Scientific Ltd., Rochester, UK) to objectively define smokers and nonsmokers. In addition, smokers completed the FTND (Heatherton et al., 1991) to measure nicotine dependence and the Questionnaire of Smoking Urges (QSU; Cox et al., 2001) to indicate their current subjective craving for a cigarette.

All subjects completed several questionnaires, including the positive affect negative affect scale (PANAS; Watson et al., 1988) and the Snaith–Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995) to measure mood state and anhedonia. These questionnaires were administered to ensure that differences between smokers and nonsmoking controls were not the result of differences in mood states.

Participants performed two tasks during fMRI scanning. The attentional bias line counting task was administered after a cognitive paradigm (not addressed in this paper). Smokers completed the QSU again immediately after the scanning session.

Imaging acquisition and data analysis

Blood oxygen level-dependent (BOLD) fMRI data were acquired on a 3-T General Electric Healthcare (HDx platform, Milwaukee, WI) scanner. Functional T2*-weighted images were acquired in 26 axial slices (thickness = 3.5 mm, interslice gap = 0.5 mm) covering the entire supratentorial brain with a repetition time (TR) of 2000 ms, echo time (TE) of 30 ms, field of view (FOV) of 220 mm, and matrix size of 96 × 64. A structural 3-dimensional inversion recovery (IR) fast spoiled gradient recalled echo (FSPGR) T1-weighted image was acquired in 192 axial slices (thickness = 1.6 and 0.8 mm overlap) with TR of 10.6 ms, TE of 2.2 ms, FOV of 250 mm, and matrix size of 416 × 256 mm.

Imaging data were analyzed using SPM5 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK). Preprocessing of the functional data included realignment and slice time correction. Next, the anatomical scan was coregistered to the first T2*-weighted image. Data were normalized using a SPM T1 template and data were spatially smoothed using a full-width at half-maximum Gaussian kernel of 8 mm. The four conditions, namely LCSP, LCNP, PNSP, and PNNP, were modeled in the context of the general linear model, using delta functions convolved with a canonical hemodynamic response function. The three contrasts for overall cognitive effort, attentional bias, and cue exposure-corrected attention were first calculated at single-subject level and were subsequently fed into second-level (random effects) analyses for main effects (one-sample *t*-test) and between-group comparisons (independent-samples *t*-test). Differences between groups for all contrasts are reported at $p<0.001$ (uncorrected) masked inclusively with the appropriate main effect to reduce the number of comparisons. Finally, the increase in craving during task performance was calculated for each smoker and whole brain correlations were performed on the attentional bias (LCSP minus LCNP) contrast. Craving-related brain activation in attentional bias is reported at $p<0.001$ (uncorrected).

Demographics and task performance data were analyzed in SPSS (Version 16.0 for Windows; SPSSInc., Chicago, IL). We used repeated-measures ANOVA to analyze task performance (separately for accuracy and reaction times during line counting) with group as the between-subject factor and picture type (smoking picture or neutral picture) as the within-subject factor.

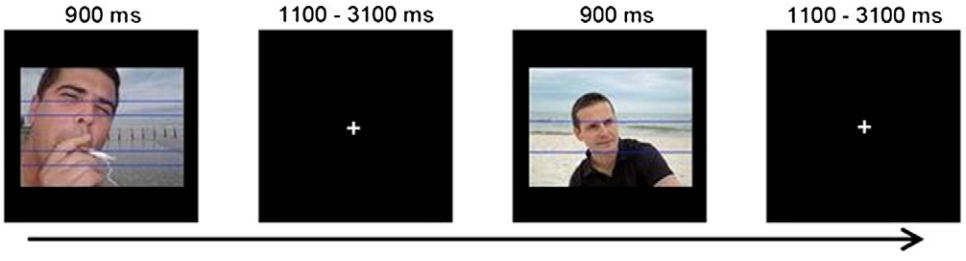

Fig. 1. The attentional bias line counting task.

Results

Questionnaires and breath analysis

As expected, smokers showed higher CO breath levels (mean = 8.3, range = 3–21) than nonsmoking controls (mean = 1.5, range = 0–5), $t(36) = 6.55$, $p < 0.001$. Groups did not differ on anhedonia and positive and negative affect scores (all p values > .05). Smokers differed in their changes in craving after the attentional bias line counting task. Of 18 smokers, 12 showed an increase in craving after the attentional bias line counting task. However, this increase was not significant for those smokers with all fMRI data available, $t(17) = 1.72$, $p = 0.1$. This nonsignificant result is probably due to the low statistical power because when all available smokers were included ($n = 20$), the p value was found to be 0.04.

Behavioral performance

Both groups performed the line counting task accurately: overall accuracy was 92%. Repeated-measures analysis of accuracy performance did not show a main effect for group. A main effect of picture content on accuracy was found ($F(1,35) = 4.82$, $p < 0.05$), with both groups performing less accurately at counting lines in smoking pictures than in neutral pictures (91% versus 92%). The picture × group interaction was not significant. With regard to reaction times, no main effect for group or picture was found. However, a trend for the main effect of picture ($F(1,35) = 3.98$, $p < 0.1$) could be observed indicating that reaction times to smoking pictures were slightly faster (791 ms versus 796). No picture × group interaction was found ($F(1,35) = 0.82$, $p < 0.05$). Although the interaction was nonsignificant, we observed that the difference in reaction times between smoking and neutral pictures was significant in controls ($t(17) = 2.43$, $p < 0.05$) but not in smokers. Nonsmoking controls were significantly faster on indicating the number of lines in smoking pictures than in neutral pictures.

fMRI results

Overall cognitive effort (LCSP and LCNP) was associated with robust brain activation in bilateral occipital, parietal, and prefrontal brain regions, as well as in motor areas, the ACC and several subcortical regions (Table 1). Smokers showed less brain activation associated with overall cognitive effort than controls in the rvACC, the left caudate nucleus, left intraparietal lobe, left lingual gyrus, and the left parahippocampal gyrus (Table 1). Both groups showed attentional bias (LCSP minus LCNP)-related brain activation in visual brain regions (Table 2). Most importantly, smokers showed significantly more attentional bias-related brain activation as compared to controls in the rostral zone of the dACC, extending into supplementary motor area (as functionally defined by Ridderinkhof et al., 2004), the right superior parietal lobe (SPL), and the left superior temporal gyrus (STG) (Table 2 and Fig. 2). Both groups showed more activation in visual, parietal, and motor areas (Table 2) during cue exposure-corrected attention (LCSP minus PNSP). Importantly, smokers, as compared to controls, showed more brain activation related to cue exposure-corrected attention for smoking cues in the rostral zone of the dACC ($x = 15$, $y = 30$, $z = 33$, $Z = 3.13$; Table 2) confirming that attentional bias related brain activation in this region does not arise from mere cue exposure effects.

Self-reported craving in smokers during the attentional bias paradigm was significantly associated with activation in the right putamen ($x = 24$, $y = -6$, $z = 24$, $Z = 3.63$) and the left insula ($x = -36$, $y = -39$, $z = 18$, $Z = 3.52$; Fig. 3).

Discussion

To our knowledge, this is the first controlled study showing the neural correlates of attentional bias in smokers. In line with our hypothesis, we observed greater brain activation in smokers relative to healthy controls in the dACC and right SPL during an attentional bias task paradigm. Unexpectedly, a similar effect was also observed in the left STG. Importantly, we showed that dACC hyperactivation in smokers could not be attributed to processes arising from mere cue exposure or cue exposure-related phenomena, including enhanced familiarity to smoking cues and arousal. In addition, activations in the left insula and the right putamen were found to be associated with attentional bias related craving. Further, in line with the cocaine study of Goldstein et al. (2009b), we found that smokers showed hypoactivation in the rvACC during the overall cognitive effort.

Current theories of ACC function suggest that the dorsal region of the ACC is involved in conflict monitoring (Botvinick et al., 2004; Egner et al., 2008; Etkin et al., 2006; Fan et al., 2008; Haas et al., 2006) and reducing possible interference effects from distracting stimuli, by boosting attention toward task-relevant stimuli (Fan et al., 2008; Weissman et al., 2004, 2005). Therefore, the current finding that

Table 1
Main and group effects for overall cognitive effort (LCSP and LCNP).

	MNI coordinates					MNI coordinates			
	x	*y*	*z*	*Z* value		*x*	*y*	*z*	*Z* value
Overall cognitive effort (LCSP and LCNP)									
Main effects smokers and controls					*Main effects smokers and controls continued*				
l- occipital	−42	−75	−6	>8	l- precentral gyrus	−27	−12	54	5.07
l- precuneus					l- precentral gyrus	−30	−15	66	4.95
l- SPL					r- culmen	9	−54	−9	4.96
r- MOG	27	−93	6	> 8	l- IFG	−51	3	33	4.93
r- SOG	30	−84	24	7.79	r- PHG	24	−30	−6	4.89
r- precuneus					r- thalamus	18	−36	0	4.71
r- SPL									
l- medial frontal gyrus	−3	0	57	6.32	*Smokers > Controls*				
l- ACC					- - -				
r- middle frontal gyrus	27	−12	63	5.95					
r- precentral gyrus	36	−18	63	5.43	*Smokers < Controls*				
l- PHG	−21	−36	−3	5.91					
l- caudate	−24	−42	6	5.43	r-rvACC	15	36	3	3.81
r- IFG	45	3	30	5.31	l-lingual gyrus	−12	−48	−3	3.64
r- IPL	45	−39	51	5.30	l-IPL	−63	−27	27	3.60
r- postcentral gyrus	48	−24	54	4.56	l-PHG	−18	−54	−9	3.39

Main effects are reported at $p < 0.05$ FEW-corrected. Group effects are masked for main effects and reported at $p < 0.001$ uncorrected.
Abbreviations: SPL, superior parietal lobe; MOG, middle occipital gyrus; SOG, superior occipital gyrus; ACC, anterior cingulate cortex; PHG, parahippocampal gyrus; IFG, inferior frontal gyrus; rvACC, rostro-ventral anterior cingulate cortex; IPL, inferior parietal lobe.

Table 2
Main and group effects on attentional bias (LCSP minus LCNP) and cue exposure corrected attention (LCSP minus PNSP).

	MNI coordinates					MNI coordinates			
	x	*y*	*z*	*Z* value		*x*	*y*	*z*	*Z* value
Attentional bias (LCSP minus LCNP)									
Main effects smokers and controls					*Smokers>Controls*				
l-OCC/ITG	45	−66	−3	5.16	l-STG	−60	−12	−3	3.71
l-MOG	−45	−81	3	4.54	r-dACC	9	21	48	3.63
l-MOG	−48	−75	−9	3.72	r-SPL	27	−75	39	3.18
r-MTG	51	−75	6	4.21					
r-MOG	45	−81	6	4.18	*Smokers<Controls*				
					- - -				
Cue exposure corrected attentions (LCSP minus PNSP)									
Main effects smokers and controls					*Smokers>Controls*				
r-middle frontal gyrus	27	−9	57	4.89	r-dACC	15	30	33	3.13
r- precuneus	27	−75	39	4.76					
r-IPL	42	−39	51	4.66	*Smokers<Controls*				
l-MOG	−30	−87	15	4.20	- - -				
r-IFG	51	3	24	4.16					
r-STG	54	−21	9	3.86					
l-lingual gyrus	−9	−87	2	3.81					
l-precuneus	−18	−72	51	3.42					
l-culmen	−6	−63	−12	3.41					

Main effects are reported at $p<0.05$ FDR-corrected. Group effects are masked for main effects and reported at $p<0.001$ uncorrected.
Abbreviations: OCC, occipital; ITG, inferior temporal gyrus; MOG, middle occipital gyrus; STP, superior temporal gyrus; dACC, dorsal anterior cingulate cortex.

attentional bias in smokers is associated with dACC hyperactivation suggests that smokers experience more cognitive conflict and need more focused (top-down) attention when performing a simple cognitive task (line counting) while smoking stimuli are present in the background. This enhanced activation in the dACC is probably needed to compensate the effects of the automatic (bottom-up) distraction by the conditioned smoking cues.

Attentional bias associated brain activation was also observed in the right SPL and the left STG. The SPL has been implicated in top-down attention processing (Szczepanski et al., 2010); more precisely, it has been suggested that the SPL is involved in directing attention in space (Cavanna and Trimble 2006). Therefore, the activation in the SPL is in accordance with our interpretation that smokers have to employ more attentional top-down resources to stay involved in the primary task. Hyperactivation in the STG is in line with previously observed temporal activation in several cue reactivity studies (David et al., 2007; Due et al., 2002; Garavan et al., 2000; Lee et al., 2005; McBride et al., 2006; Park et al., 2007; Schneider et al., 2001). Although speculative, we suggest that this effect is related to greater in-depth visual processing, in accordance with a theory of STG function proposed by Karnath (2001). The hypothesis of more elaborate visual processing receives some support from the fact that STG hyperactivation in smokers was not observed during cue exposure-corrected attention.

The current finding of hyperactivation in the dACC in smokers is in contrast with the observed hypoactivation of this region in Goldstein et al. (2009b) during performance of the cocaine word Stroop task. There may be several reasons for this discrepancy. First, the observed hypoactivation in the Goldstein et al. (2009b) study was not specific to drug cues and may therefore reflect a more general cognitive deficit in drug abusers and not a specific attentional bias process. Second, the cocaine Stroop task as employed in their study also included a monetary reward component, which may have biased dACC activation since this region is also involved in reward based decision making (Bush et al., 2002; Fujiwara et al., 2009). Third, the substance users in Goldstein et al. (2009b) consisted of cocaine users, who may not be comparable to our smoking group. It is known that cocaine users have more pronounced cognitive dysfunctions (Verdejo-Garcia and Perez-Garcia 2007; Verdejo-Garcia et al., 2007) as compared to smokers. Finally, we cannot unequivocally state that our smoking group is nicotine-dependent as FTND scores indicate medium dependence levels only. However, smokers in the current study smoked at least ten cigarettes per day, and half of our sample smoked at least 20 cigarettes per day. Still, it would be important to replicate the current finding of dACC hyperactivation in another population diagnosed with substance dependence.

In the present study, we did not observe attentional bias-related brain activation in brain regions involved in salience attribution or stimulus-driven attention including the OFC, ventral striatum, and amygdala. Activation in these brain regions was expected since environmental drug cues tend to capture the attention of drug users, due to the established salience of these cues (Robinson and Berridge 2008). The absence of activation in these regions is probably due to our fast event-related paradigm that was specifically designed to measure attentional bias and to keep other constructs such as prolonged cue exposure and emotional involvement to a minimum. In line with Goldstein et al. (2009b), we did find more pronounced hypoactivation in smokers in the rvACC during overall cognitive effort. This finding supports the notion that hypoactivation in this region is not related to specific drug cue processing or attentional bias in substance-dependent patients. The rvACC facilitates emotional processing, and is involved in emotional conflict, most likely by salience attribution and emotional responsiveness. It has been suggested that hypoactivation in the rvACC during focused attention contributes to the dynamic interplay between continuous cognitive and emotional processes (Gusnard et al., 2001; Raichle et al., 2001). The hypoactivation in smokers during overall cognitive effort in this region may therefore reflect a conflict between cognitive performance and emotional involvement as experienced by smokers.

We also found that subjective craving induced by the attentional bias paradigm was related to activation in the insula and putamen. This suggests that these regions are involved in the reciprocal relation between attentional bias and craving (Field et al., 2009). The insula has currently attracted attention as an important brain region in addiction by representing conscious urges to the drug of abuse via connections with the ventromedial prefrontal cortex and the amygdala (Naqvi et al., 2007; Naqvi and Bechara 2009). Furthermore, Paulus et al. (2005) demonstrated that activation in the insula, amongst other brain regions, predicted relapse in abstinent methamphetamine-dependent subjects. In addition, the putamen is supposed to play a role in addictive behavior through modulation of the mesolimbic dopaminergic system via D_1 and D_2 receptors (Ito et al., 2002; Naha et al., 2009).

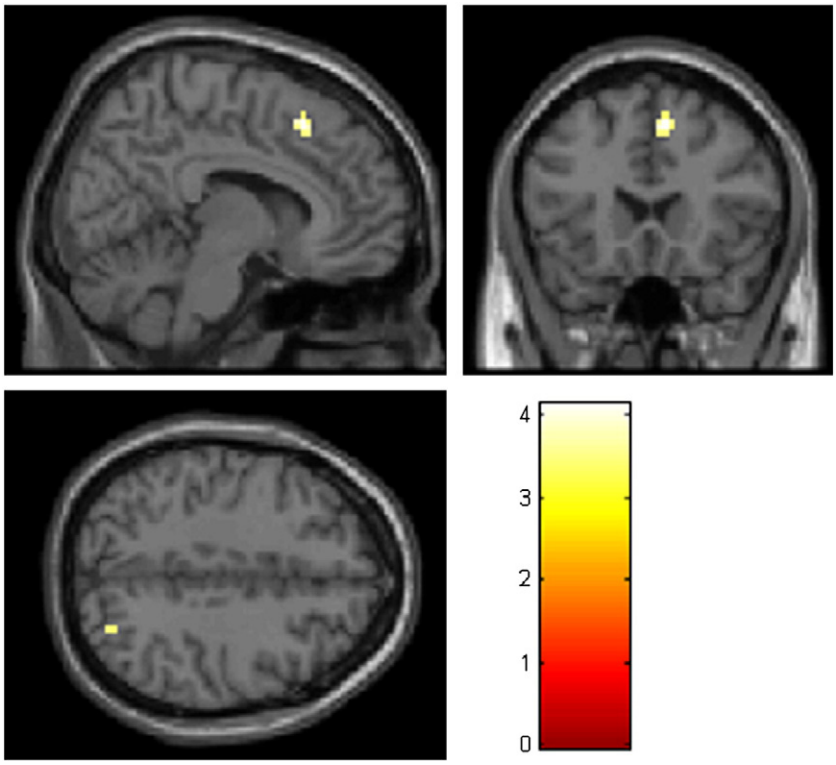

Fig. 2. Group effect in the dACC and the right SPL for the LCSP versus LCNP contrast; all effects and details are listed in Table 2.

A limitation of the current study is that behavioral measures are not fully supportive for attentional bias to conditioned smoking cues in smokers. However, reaction time data did show that nonsmoking controls were faster in counting the number of lines in smoking pictures than in neutral pictures, whereas this difference was not evident for smokers. These results suggest that nonsmoking controls are faster in counting lines in smoking pictures by ignoring the content of the picture, whereas smokers are less able to ignore the content of the smoking-related pictures. However, such an interpretation must be viewed with caution due to the lack of a significant omnibus interaction effect.

To conclude, we demonstrated, for the first time, hyperactivation in smokers compared to nonsmokers in the dACC, the right SPL, and the left STG associated with attentional bias. Furthermore, we demonstrated that brain activation related to attentional bias in the dACC cannot be attributed to other processes as a result of cue exposure. As converging evidence suggests that ACC dysfunction may be a biomarker for addiction (Goldstein et al., 2009b; Hong et al., 2009; Ma et al., 2010; Romero et al., 2010), it would be interesting to further investigate the differential contribution of the dorsal and ventral parts of the ACC in various specific task paradigms. It has also been hypothesized that dopamine plays an important role in attentional bias and craving (Franken, Booij, van den Brink 2005; Franken et al., 2004). The most important regions found to be implicated in attentional bias and craving in the current study, the dACC, the putamen, and the insula, all have efferent and afferent dopaminergic projections. It would therefore be a

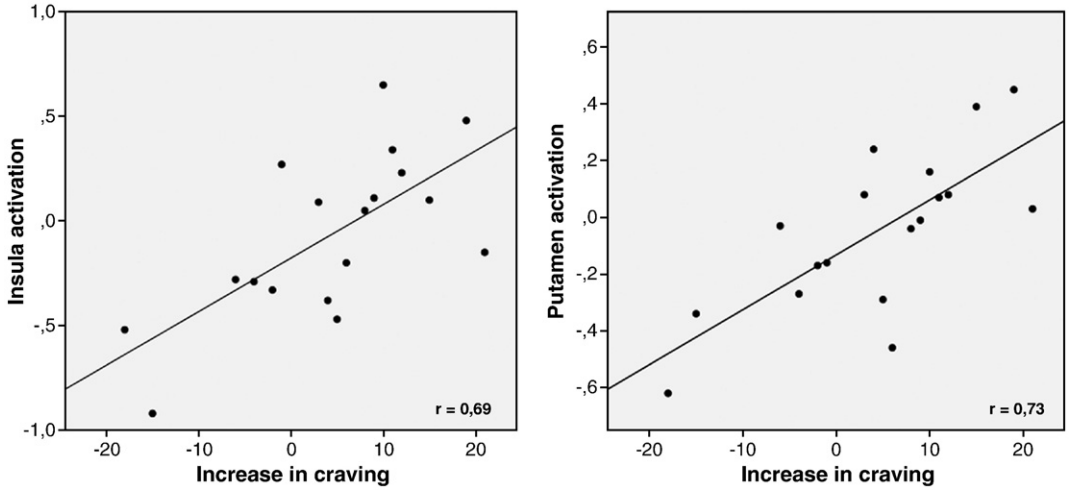

Fig. 3. Correlation between craving- and attentional bias-related brain activation in the left insula and right putamen.

future research agenda to examine the role of dopamine in attentional bias and craving-related brain activation.

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