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Ventral Striatum/Nucleus Accumbens Activation to Smoking-Related Pictorial Cues in Smokers and Nonsmokers: A Functional Magnetic Resonance Imaging Study

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Abstract

Background—Converging evidence from several theories of the development of incentive-sensitization to smoking-related environmental stimuli suggests that the ventral striatum plays an important role in the processing of smoking-related cue reactivity.

Methods—Twenty-six healthy right-handed volunteers (14 smokers and 12 nonsmoking controls) underwent functional magnetic resonance imaging (fMRI) during which neutral and smoking-related images were presented. Region of interest analyses were performed within the ventral striatum/nucleus accumbens (VS/NAc) for the contrast between smoking-related (SR) and nonsmoking related neutral (N) cues.

Results—Group activation for SR versus N cues was observed in smokers but not in nonsmokers in medial orbitofrontal cortex, superior frontal gyrus, anterior cingulate cortex, and posterior fusiform gyrus using whole-brain corrected Z thresholds and in the ventral VS/NAc using uncorrected Z-statistics (smokers Z = 3.2). Region of interest analysis of signal change within ventral VS/NAc demonstrated significantly greater activation to SR versus N cues in smokers than controls.

Conclusions—This is the first demonstration of greater VS/NAc activation in addicted smokers than nonsmokers presented with smoking-related cues using fMRI. Smokers, but not controls, demonstrated activation to SR versus N cues in a distributed reward signaling network consistent with cue reactivity studies of other drugs of abuse.

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Keywords

Nucleus accumbens; smoking; nicotine; tobacco; cue reactivity; fMRI

A major contributor to relapse to tobacco smoking and other drugs of abuse is the development of craving or wanting when presented with environmental stimuli (visual, olfactory, tactile, and imaginal) associated with drug use (Niaura et al 1988, 1998; Rohsenow et al 1990). Drug-related cue reactivity is demonstrated not only by affecting drug wanting or craving but also through dopaminergically-mediated reductions in inhibition of the acoustic startle reflex (Hutchison et al 1999, 2000, 2003), cardiovascular reactivity (Niaura et al 1988), and altered skin conductance (Niaura et al 1988).

Functional neuroimaging has demonstrated that the very same types of environmental cues that evoke drug craving activate an integrated network of brain regions involving the motivational and appetitive processes of addiction to nicotine and other drugs of abuse (Breiter et al 1999; Koob and Le Moal 2001; Volkow et al 2003). Converging data from animal models and in vivo studies implicate several distinct neurological circuits, which, together, provide a model for the development of nicotine addiction. In particular, these circuits include: (1) a reward circuit including the ventral striatum, (2) a motivational/drive circuit including the orbitofrontal cortex and subcallosal cortex, (3) a memory and learning circuit including the amygdala and hippocampus, and (4) a control circuit including the prefrontal cortex and the anterior cingulate cortex (Breiter and Rosen 1999; O'Doherty et al 2000; Volkow et al 2003). Each of these circuits receive direct dopaminergic innervation and are connected to each other in a network through mostly glutamatergic projections (Volkow et al 2003). Moreover, multiple brain regions are involved with these circuits including the extrastriate visual pathways (caudate, ventral temporal cortex: inferior temporal gyrus, lateral and medial fusiform gyrus) (Courtney et al 1997; Due et al 2002; Ishai et al 1999).

Of all of the regions implicated in development of nicotine addiction, the ventral striatum is a region of major interest particularly because of its dual role in processing the hedonic effects of nicotine administration and in signaling the presence of nicotine-related environmental stimuli (Balfour 2002; Balfour et al 1998; Garavan et al 2000; Janhunen and Ashtee 2004; Stein et al 1998). Rat studies demonstrate that addictive drugs stimulate dopaminergic neurons in the midbrain tegmentum resulting in increased burst firing and release of dopamine in the shell of the nucleus accumbens (Benwell and Balfour 1992; Corrigall et al 1992). Dopaminergic projections to the shell signal the presence of a rewarding stimulus, facilitate the acquisition of behaviors related to obtaining the reward, and become desensitized with repeated drug exposure (Benwell et al 1995).

Breiter and colleagues (Breiter and Rosen 1999), Koob and Le Moal (Koob and Le Moal 2001), Volkow and colleagues (Volkow et al 2003), and others have posited that drug-seeking behavior is a pattern of activity in the four integrated circuits (reward, memory, motivation, and control) that influences how an individual makes choices between behavioral alternatives. The response to a stimulus is influenced by its momentary salience (i.e., expected reward, which is processed in part by dopamine release in the nucleus

accumbens) in a hierarchical structure where the saliency value of the stimulus changes as a function of the previous experience and memory of the individual. Memories are stored in response to positive and negative experiences and the drug-related stimuli are weighted against the nondrug related stimuli. The stronger the saliency value of the stimulus, the higher the motivational drive to obtain the stimulus becomes. The cognitive decision to act to obtain the reward is processed in the prefrontal cortex and anterior cingulate cortex (Volkow et al 2003). With increasing use of a substance, the degree of control over the motivational drive to obtain nicotine or other drugs is diminished in a process termed "hedonic dysregulation" (Koob and Le Moal 1997). Over time the increasing reward value assigned to the drug leads to a resetting of reward thresholds with decreased sensitivity to naturally-occurring stimuli. Thus, drug seeking becomes the primary motivational behavior. In the view of Koob and Le Moal (Koob and Le Moal 2001), with diminishing negative feedback from control circuits, a positive feedback loop is established such that memory, reward, and drive perpetuate chronic drug use. Robinson and Berridge (Robinson and Berridge 2001) propose that positive and negative feedback are not at play per se, but that increased sensitivity to the negative consequences of drug abstinence (i.e., withdrawal symptoms and drug "wanting") are responsible for the observed difficulty in abstaining from drugs of abuse such as nicotine (Robinson and Berridge 2001).

Despite the complex nature of nicotine addiction and the neurological adaptations that accompany heightened salience to smoking-related environmental cues, the ventral striatum in particular is a brain region that is ubiquitously implicated in both the rewarding elements of nicotine administration and in the development of sensitization to aversive effects of the drug such as craving and wanting (Brody et al 2004b; Heinz et al 2004; Robinson and Berrridge 1993). While dopaminergic projections from the ventral tegmental area to the shell of the nucleus accumbens signal the presence of a rewarding drug stimulus, projections to the core become sensitized by repeated exposure to addictive drugs, including nicotine, and mediate the transition to drug dependence and subsequent conditioned responses to environmental cues repetitively paired with the positive reinforcing properties of addictive drugs (Balfour 2002).

In nicotine addiction in humans, environmental smoking-related cues reliably generate craving and trigger withdrawal symptoms (Niaura et al 1988). Functional neuroimaging studies using positron emission tomography (Brody 2002) and functional magnetic resonance imaging (fMRI) (Due et al 2002) have demonstrated that smoking-related cues activate regions associated with dopamine-dependent incentive sensitization processes in multiple cortical and subcortical limbic regions. A recent study by Heinz and colleagues demonstrated a significantly negative correlation between dopamine D2 receptor binding potential and alcohol craving in the ventral striatum in abstinent alcoholics (Heinz et al 2004). These findings are consistent with the incentive-sensitization model posed by Robinson and Berridge (Robinson and Berridge 1993, 2001) suggesting that low availability of D2 receptors in the ventral striatum mediates excessive attribution of incentive salience to drug-related stimuli, leading to a pathological "wanting" to consume drugs such as alcohol and nicotine. We therefore sought to explore the effect of smoking-related pictures compared with neutral pictures on BOLD signal in the ventral striatum using functional magnetic resonance imaging (fMRI). In addition, we sought to determine whether the fMRI

blood-oxygen-level-dependent (BOLD) response in the ventral striatum elicited by smoking-related cues would be greater in smokers than nonsmokers.

Methods and Materials

The Oxfordshire Research Ethics Committee approved the study and written informed consent was obtained from all subjects following an introductory letter, screening for MRI contraindications, and a full explanation of the study. Twenty-six right-handed healthy volunteers (smokers $n = 14$, nonsmokers $n = 12$) underwent brain fMRI during which they viewed pictures showing either neutral or smoking-related scenes. Non-smokers were defined as "never smokers" such that they had never been regular, daily smokers or casual smokers of more than 100 cigarettes in their lifetime. An event-related fMRI design was employed as follows (Due et al 2002). Stimuli were standardized color pictures of people smoking (smoking-related) or engaged in a neutral activity (neutral) matched in frequency for gender. Smoking-related and neutral images were drawn from the International Smoking Image Series (Gilbert and Rabinovitch 1998). These images were shown on a projection screen placed below the subjects' feet, viewed with prism glasses. Using Presentation™ software (Neurobehavioral Systems, Inc., San Pablo, California), 75 pictorial images were presented for 5 seconds at a frequency of 1 image each 6 seconds with a one-second rest period. Fixation crosses were presented during rest periods. Pictures consisted of faces of individuals smoking cigarettes (smoking-related) or not smoking cigarettes (neutral) with equal numbers of male and female pictures per condition. Smoking-related and neutral cues were randomized for presentation sequence, resulting in approximately 28% smoking-related and 72% neutral pictures. All images were color photographs, subtending approximately 20° by 16° of visual angle. Participants were required to indicate with a keypress whether they thought the subject of the photograph was male or female. Smokers were asked to abstain from smoking overnight, and abstinence from smoking overnight was confirmed by demonstration of low exhaled carbon monoxide (<11 parts per million [ppm]). In addition to sociodemographic questions, smokers completed the Fagerström Test of Nicotine Dependence (FTND) (Heatherton et al 1991), a highly reliable measure of the severity of nicotine dependence-prior to entry into the scanner. All subjects were administered well-validated self-report assessment scales (Shiffman et al 2004) for nicotine craving (Shiffman-Jarvik Craving Scale [5 items rated 0–100]) (Shiffman and Jarvik 1976) and withdrawal [Minnesota Withdrawal Scale (8 items rated 0–4)] (Hughes and Hatsukami 1986) while situated in the scanner before and after the stimulus presentation.

Whole brain functional MRI data were acquired continuously through the period of visual stimulus presentation with a 3 Tesla whole-body scanner (Siemens, Erlangen, Germany) with a quadrature birdcage head coil. Before the first presentation of stimuli, sagittal localization (two-dimensional Turbo FLASH, time for repitition (TR) = 30 ms, time to echo (TE) = 5 ms, Flip angle = 50°) was performed. For functional imaging during stimulus presentation, echo planar T2*-weighted images were acquired (slices coplanar to structural images: TR = 3000 msec, TE = 30 msec, flip angle = 90°, field of view (FOV) = 256 × 192, Matrix size = 64 × 64, slice thickness 5 mm, 25 slices). Analysis of echo planar imaging (EPI) data is limited to the first 150 volumes (reduced from original protocol of 200 volumes) as initial piloting demonstrated a trend of excessive head motion in both groups of

subjects after the first 450 seconds (150 volumes) in the experiment. Following functional imaging, three-dimensional, high resolution T_1-weighted structural images were obtained with 128 axial slices (TE = 5 msec, flip angle = 12°, TR = 15 msec, slice thickness = 1.5mm).

Data pre-processing was conducted using FEAT (fMRI Expert Analysis Tool) Version 5.42 from the FMRIB Software Library (www.fmrib.ox.ac.uk/fsl), developed by the Analysis Team at the Centre for Functional Magnetic Resonance Imaging of the Brain, John Radcliffe Hospital, Oxford, United Kingdom. Pre-statistical processing was as follows: motion correction utilizing Motion Correction using FMRIB's Linear Image Registration Tool (MCFLIRT) (Jenkinson and Smith 2001); nonbrain removal using Brain Extraction Tool (BET) (Smith 2002); spatial smoothing with a Gaussian kernel of 5 mm full-width half maximum; mean-based intensity normalization; nonlinear high-pass temporal filtering (Gaussian-weighted least squares straight line fit, with sigma = 25.0 sec). Time series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al 2001). Statistical analysis was performed by modeling smoking versus neutral conditions (boxcar functions convolved with the hemodynamic response function) as explanatory variables within the context of the general linear model on a voxel-by-voxel basis. *Z* (Gaussianized T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and corrected cluster significance level of $p = .05$. Registration to high resolution structural images of each individual subject was carried out using FLIRT (Jenkinson et al 2002) and all high-resolution structural images were co-registered to standard (Montreal Neurological Institute) space. Higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) (Beckmann et al 2003; Woolrich et al 2004). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $p = .05$ (Worsley et al 1992). Region of interest anatomical masks were created for the ventral striatum using FSL View software (www.fmrib.ox.ac.uk). The brain atlas by Duvernoy (Duvernoy 1999) was used as a guide for defining anatomical landmarks, which ranged from (X: ±4 to 10; Y: +6 to +18, 0 to −10) consistent with the landmarks of the "limbic-related" striatum as defined by Fudge and Haber (Fudge and Haber 2002)—including the nucleus accumbens proper, the medial tail of the ventral caudate, and the medioventral putamen (sharing amygdalostriatal afferents).

Results

One smoker, who suffered a stroke after completing the study and developed a cerebral vascular accident in the weeks following the study, was excluded from the analysis because of concerns about her health at the time of the scanning. One smoker and one nonsmoker were excluded because of computer malfunction with paradigm presentation. Three smokers were excluded because of exhaled CO ≥ 11 ppm indicating cigarette smoking in the previous 12 hours. The final sample for analysis therefore consisted of 9 smokers and 11 nonsmokers.

Smokers did not differ from nonsmokers in mean age (34.4 years vs. 28.3 years respectively, t [1, 18] = 1.43, $p = .2$) or sex distribution (56% female vs. 73% female respectively, X^2 [1]

= 1.8, p = .2). Seventy-eight percent of smokers were of European ancestry compared with 100% of nonsmokers, and 78% of smokers had a college education compared with 100% of non-smokers (for both comparisons: X^2 [1] = 2.78, p = .1). Amongst smokers, the mean score of the Fagerström Test of Nicotine Dependence was 4.7 (SD = 1.7), which is similar to reported population means of regular smokers (Benowitz 1999; Heatherton et al 1991; Prokhorov et al 1996), mean number of cigarettes per day was 18.3 (SD = 8.7) and the mean exhaled carbon monoxide indicated overnight abstinence (mean = 2.9 ppm, SD = 2.9) (Javors et al 2005; Sato et al 2003). Mean craving scores in the smokers were [145.2 (SD = 170.3) pre-scan; 250.2 (SD = 205.4) post-scan, paired-sample *t*-test, t = .98, df = 8, p = .357]. Mean withdrawal scores in the smokers were [6.8 (SD = 5.4) pre-scan; 9.1 (SD = 6.5) post-scan, paired-sample *t*-test, t = 1.15, df= 8, p = .285].

Whole brain group analysis using mixed effects and corrected cluster statistics ($Z > 2.3$, cluster $p < .05$) demonstrated bilateral activation in smokers in three large clusters with centers of gravity in the anterior cingulate cortex (ACC)/orbitofrontal cortex (OFC), superior frontal gyrus (SFG), and occipital cortex (Table 1 and Figure 1). Within the ACC/OFC cluster were local maxima in the medial orbitofrontal cortex (8, 56, −12; z-statistic 3.60), and ACC (−6, 50, 0; *Z*-statistic 3.73). The SFG cluster demonstrated several local maxima on the left with peak at (−14, 56, 28; Z-statistic 3.28). The occipital cluster included local maxima in the posterior fusiform gyrus (32, −86, −20; Z-statistic 3.23), and lingual gyrus (−6, −82, −12; Z-statistic 3.06). Group activation was not observed in nonsmokers.

We were particularly interested in activation in ventral striatum/nucleus accumbens (VS/NAc) and so carried out a secondary analysis restricted to this area in all subjects using an uncorrected z threshold of 2.3. This revealed group activation in smokers (peak voxel coordinates ventral striatum: right 8, 14, −2, *Z*-statistic = 2.8; left −4, 14, −2, *Z*-statistic = 3.2) (Figure 2).

Whole-brain group comparisons did not reveal differences between smokers and nonsmokers. However, our prior hypothesis concerned activity in the VS/NAc. Therefore, the effect size for the contrast between smoking and neutral cues expressed as the contrast of the parameter estimates (COPE) was determined within a group VS/NAc region of interest (ROI) mask for smokers and nonsmokers. As there were no significant differences in mean COPE by hemisphere in smokers or nonsmokers, we restricted between-group comparisons of BOLD contrast to the global (bi-hemispheric) VS/NAc. Global VS/NAc activation was greater in smokers than nonsmokers [mean COPE = 33.6 (SD = 29.6) vs. −7.9 (SD = 24.3), student *t*-test, t = 3.45, df = 18, p = .003] (Figure 3).

In order to test the null hypothesis that there was no difference in activation between smoking and neutral cues in each group, we conducted one-sample *t*-tests comparing the mean COPE in VS/NAc to zero. Mean VS/NAc COPE was significantly greater than zero in smokers (one-sample *t*-test, t = 3.41, df = 8, p = .009), but not in nonsmokers (one-sample *t*-test, t = −1.08, df = 10, p = .308). ROI analysis identified two controls with VS/NAc mean cope of greater than 2 standard deviations from the mean (Figure 3). Analysis excluding these outliers also demonstrated significantly greater relative activation in VS/NAc to the

smoking vs. neutral contrast [33.6 (SD = 29.6) vs. −5.7 (SD = 12.3), student *t*-test, $t = 3.68$ $df = 16$, $p = .004$] in smokers than non-smokers. There was no significant correlation between cigarette craving and VS/NAc mean COPE before or after the scan in smokers.

A 2 × 2 multivariate analysis of variance (MANOVA) of reaction times to smoking-related and neutral cues, with cue type (smoking-related, neutral) as a within-subjects factor and smoking status (smoker, nonsmoker) as a between-subjects factor indicated a main effect of smoking status on reaction time (F [1, 18] = 7.78, $p = .012$), with smokers demonstrating slower reactions times to all cues compared to nonsmokers. The main effect of cue type and the cue type × smoking status interaction were nonsignificant ($ps \geq .18$), suggesting that smokers' reaction times to smoking-related cues compared to neutral cues did not differ from nonsmokers.

Discussion

The observation of activation in ventral striatum, orbitofrontal cortex, anterior cingulate cortex, and fusiform gyrus in addicted smokers presented with smoking-related cues (versus neutral cues) is consistent with other studies examining drug-related cue reactivity. As in our study, Due and colleagues, using a similar design, observed activation in prefrontal gyrus and fusiform gyrus and a statistical trend toward activation in anterior cingulate cortex (Due et al 2002). We observed group-level activation in posterior fusiform and lingual gyrus, both extrastriate visual cortical areas and part of a visuospatial attention circuit including anterior cingulate cortex and prefrontal cortex (Kirino et al 2000; McCarthy et al 1997; Saito et al 2003; Yoshiura et al 1999). Despite differences in paradigm design, the convergence of findings amongst smokers in both studies reinforces the notion posed by Due and colleagues that mesocorticolimbic and visuospatial-attention circuits may work in concert to increase attention to stimuli of heightened salience such as the sight of a burning cigarette to an addicted smoker.

The observation of ventral striatum activation to smoking-related cues is also consistent with the findings of Heinz and colleagues (Heinz 2004) who demonstrated activation in ventral striatum (inclusive of NAc and ventral caudate) to alcohol-related picture cues. Although we observed a main effect of smoking status on global reaction times, which is likely to be the result of nicotine deprivation in abstinent smokers (Havermans et al 2003 Trimmel and Wittberger 2004), we did not observe any differential effect of cue type on reaction time in smokers compared to nonsmokers. However, there was substantial variability in reaction times, and any effect may have been masked by this. Studies demonstrating main effects of cue type of reaction time typically employ a greater number of trials and thus the brevity of our peresentation may have reduced sensitivity to detect effects of cue type (Bradley et al 2004; Hogarth et al 2003).

It is also interesting to note neither Due and colleagues (Due et al 2002) nor Heinz and colleagues (Heinz et al 2004) reported significant correlations between fMRI BOLD response in ventral VS/NAc and craving measures related to cigarettes or alcohol, respectively. While we did see an increase in craving during the experiment in smokers, this increase was not statistically significant. It may be that the short stimulus duration (5 sec)

and brevity of the experiment was not sufficient to induce an increase in tobacco craving. However, regions similar to those activating in our study have demonstrated activation when stimulus duration was sufficient to evoke heightened drug craving (Brody et al 2004a; Garavan et al 2000). Thus, the involvement of reward signaling brain regions in our experiment may represent preconscious processes indicative of heightened incentive salience while our paradigm was not sensitive enough to detect the conscious manifestation of tobacco craving or wanting.

The most important finding in this study is the observation that ventral striatum activation to smoking-related (versus neutral) cues was greater in smokers than nonsmokers. This is the first time to our knowledge that such an observation has been reported using fMRI. The lack of significant between-group differences in whole-brain voxel-wise analysis may reflect the wide inter-individual variability in the size and precise location of activation changes in both groups but particularly so in the nonsmokers. Despite the wide variability in the COPE for smoking-related (versus neutral cues), ventral striatum activation was significantly greater in smokers than nonsmokers using a more sensitive region of interest approach. Consistent with these models, the observation of ventral striatum activation to smoking-related pictures would appear to be consistent with the notion that, as such stimuli can induce craving, the observed ventral striatum activation might be arising from neuroplasticity within the mesoaccumbens dopamine system with long-term smoking and may mediate conditioned cue reactivity. This hypothesis would be consistent with the observation by Heinz and colleagues of significantly negative correlation between striatal D2 receptor binding potential and cue-induced alcohol craving in abstinent alcoholics in withdrawal. As such, the observation of ventral striatum activation may be indicative of dopaminergic dysfunction. This suggestion is only speculative, as we do not have positron emission tomography data in these same subjects to examine D2 binding potential.

These findings should be interpreted with caution as the ventral striatum and the orbitofrontal cortex border on regions susceptible to signal loss due to susceptibility artifact (Ojemann et al 1997; Rogers et al 2004). We chose to include ventral striatum as a principal region of interest because of the strength of our a priori hypothesis implicating this region and because of the observation in other studies employing similar pulse sequences demonstrating activation. However, the reliability of future work might be enhanced by employing approaches such as coronal slices, special shimming pulse sequences and positioning, which have been shown to minimize the signal dropout due to susceptibility artifact (Rogers et al 2004).

Despite the limitations of our methods, this study does provide a comforting reinforcement of many of the current theories on development of smoking-related cue reactivity in humans. The ventral striatum appears to activate to smoking-related cues in our sample of smokers and this appears to be unique to smokers.

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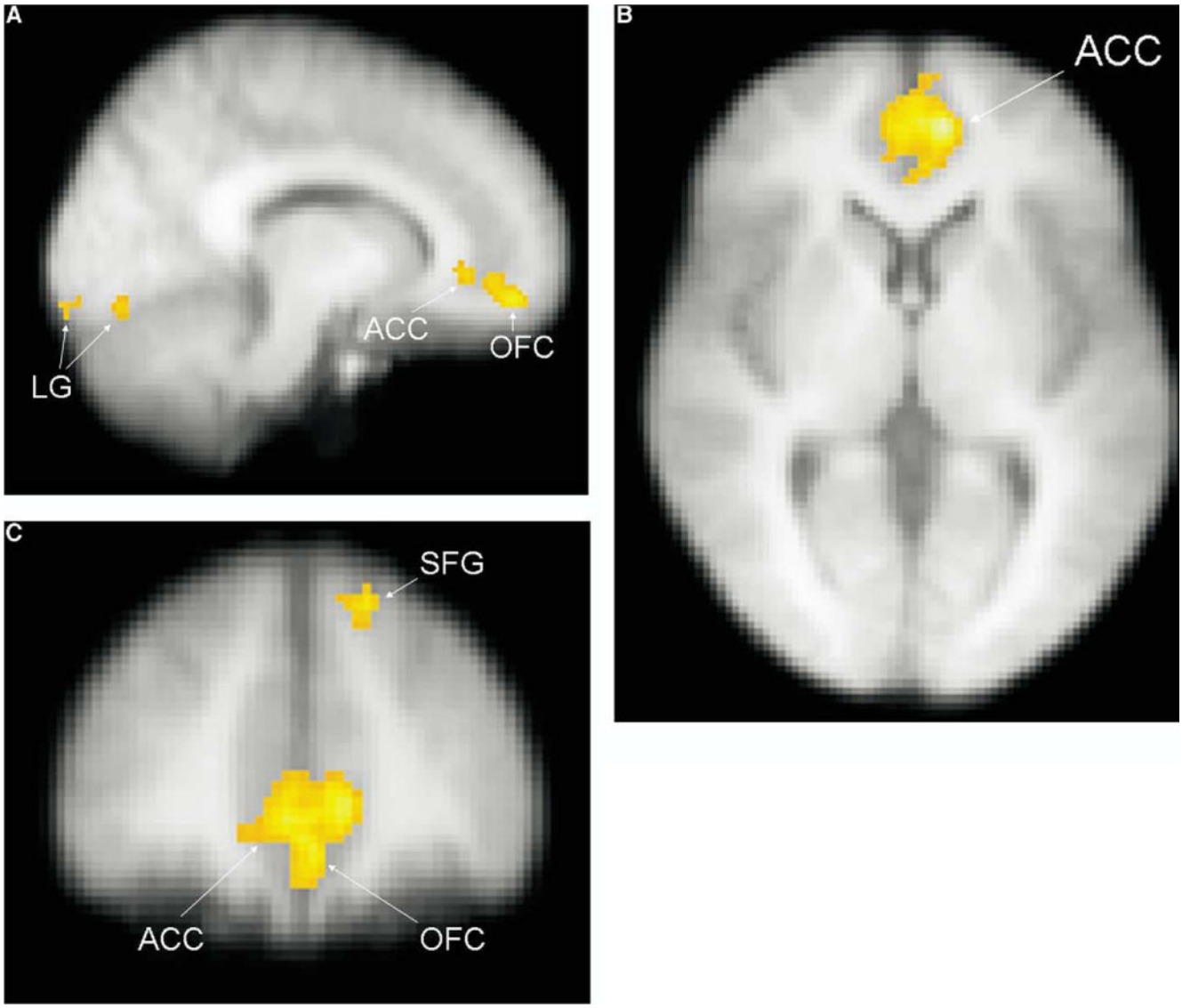

Figure 1.

Mixed-effects group analysis in smokers. Group statistical map of three activation clusters within the mixed-effects group analysis of smokers only. Color of clusters corresponds to increasing *Z*-statistic from dark to light yellow. Structural image is a group-averaged T1 structural scan from all subjects in the study registered to standard space. **(A)** Clusters for lingual gyrus (LG), anterior cingulate gyrus (ACC), and orbitofrontal gyrus (OFC) are indicated with white arrows in sagittal slice (x = +12). **(B)** Bilateral ACC activation in axial slice (z = +2). **(C)** Bilateral ACC, OFC, and left superior frontal gyrus (SFG) activation in coronal slice (y = +42).

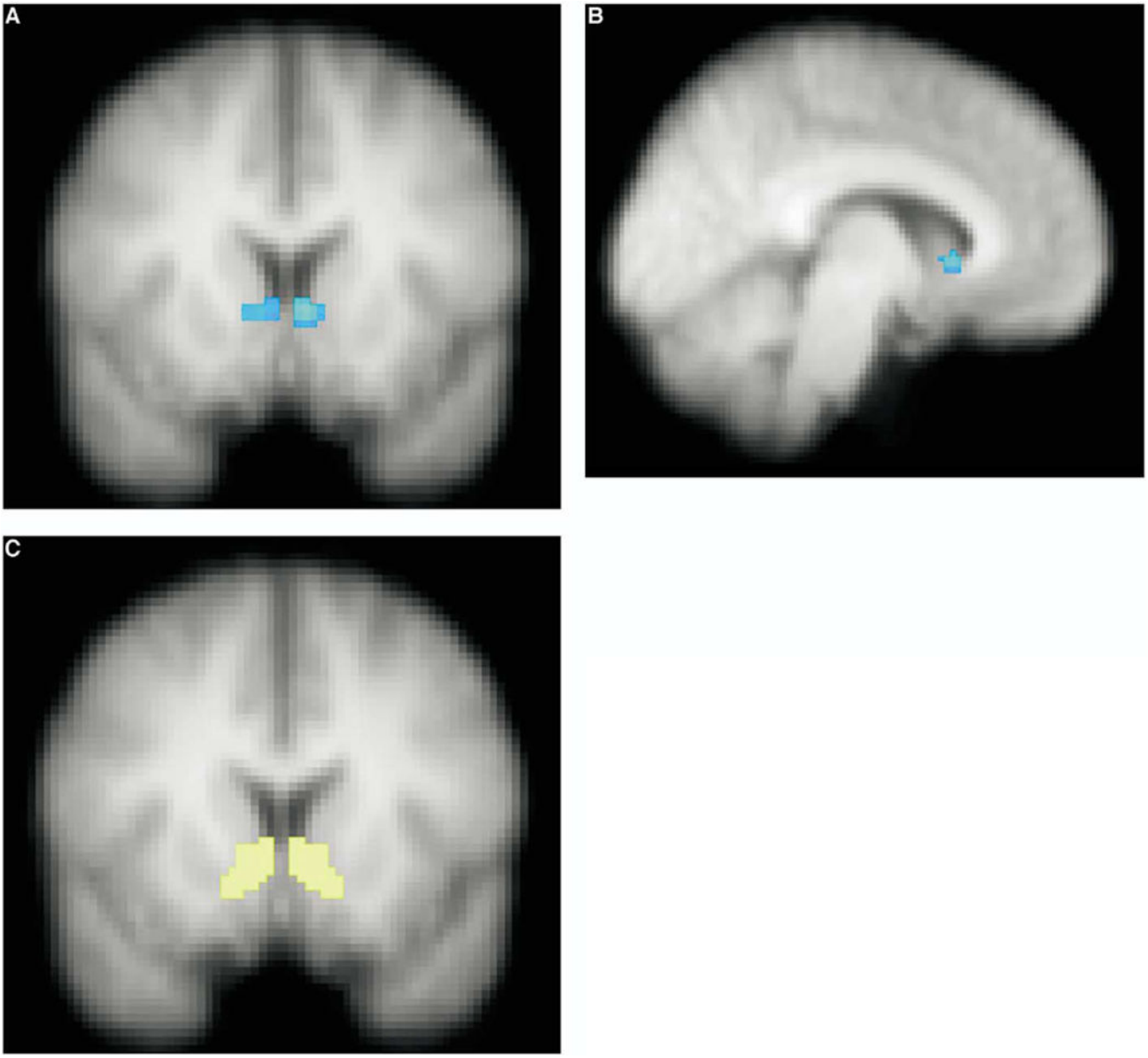

Figure 2.

Region of interest analysis of ventral striatum in smokers. Voxel-wise region of interest analysis of ventral striatum in smokers (n = 9) in coronal **(A)** and axial views **(B)**. Color of activation clusters corresponds to increasing Z-statistic from dark to light blue. Analysis was restricted to a bilateral anatomical mask of the ventral striatum **(C)** at an uncorrected Z-statistic threshold of 2.3.

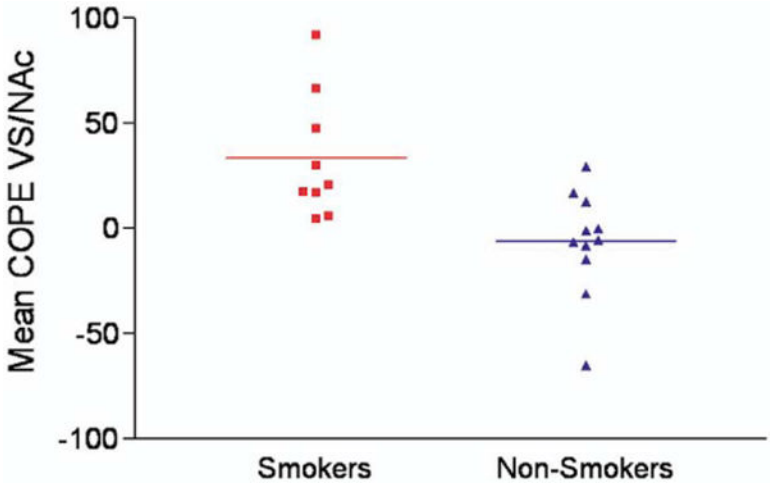

Figure 3.

Differences between smokers and nonsmokers in activation to smoking – neutral cues in ventral striatum. Scatter plot comparing smokers and nonsmokers in contrast of the parameter estimates (COPE) for smoking versus neutral picture cues. Region of interest analysis performed was within a bilateral mask of ventral striatum/nucleus accumbens (VS/NAc) (Figure 2).

Table 1

Corrected Mixed Effects Cluster Analysis in Smokers

Cluster	COG x (mm)	COG y (mm)	COG z (mm)	Max Z-statistic	Mean COPE	*p*
Anterior Cingulate Cortex/Orbitofrontal Cortex	1	44	−5	3.74	44.3	<.001
Superior Frontal Gyrus	−14	56	28	3.28	45.8	.008
Occipital Cortex	14	−78	−17	3.23	42.9	<.001

Group mixed-effects analysis of smoking–neutral contrast demonstrated significant activation in three main clusters consisting of multiple local maxima. COGx, y, z, are the coordinates of the centers of gravity (COG) for each cluster. *P* represents the *P* value corresponding to the maximum *Z*-statistic within each cluster. COPE, contrast of the parameter estimates.