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Differences in "bottom-up" and "top-down" neural activity in current and former cigarette smokers: evidence for neural substrates which may promote nicotine abstinence through increased cognitive control.

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Research highlights

- Drug-related stimuli acquire incentive motivational properties, possibly through increased "bottom-up" neural processing.
- Control, ex-smokers and smokers completed attentional bias and a go/no-go paradigm during fMR.
- Ex-smokers exhibited more neural activity than both control and smoker groups in prefrontal cortical regions.
- These findings may suggest that top-down control promotes abstinence in individuals formerly dependent on nicotine.

Introduction

Drug dependence is commonly associated with reactivity to drug-related stimuli (see Field and Cox, 2008 for a review). Brain imaging studies have demonstrated common neural substrates (e.g., amygdala, insula, cingulate and orbitofrontal cortex, thalamus and ventral striatum) for reactivity and

craving in response to substance-related cues (David et al., 2005; Due et al., 2002; Franklin et al., 2011; Franklin et al., 2007; Garavan et al., 2000; Goldstein et al., 2007; Grusser et al., 2004; Janes et al., 2010b; London et al., 1999; McBride et al., 2006; McClernon et al., 2007; Sinha et al., 2007; Smolka et al., 2006), with strong behavioural evidence for an attentional bias towards such cues among different drug-using populations (Bradley et al., 2008; Drobes et al., 2006; Field et al., 2008; Field et al., 2004, 2005; Franken et al., 2004; Franken et al., 2000; Hester et al., 2006; Lubman et al., 2000; Mogg et al., 2003; Munafo et al., 2003; Townshend et al., 2001; Vadhan et al., 2007; Waters et al., 2003a). There appears, therefore, to be evidence for the development of conditioned cue-induced attentional bias in response to drug-predictive stimuli. This bias may be implicit in maintaining addictive behaviours and provoking drug relapse among users attempting to remain abstinent (Carpenter et al., 2006; Cox et al., 2002; Rose, 2006; Waters et al., 2003b).

Examining neural responses to the salience of drug-related cues in addiction has particular value. First, theories on the underlying neurobiology of drug addiction argue that the reactivity of neural reward circuits to drug-related cues represents an “overvaluation” of drug reinforcers (Goldstein, 2002). Here it has been proposed that an attention to drug-cues results from, and further reinforces, their salience as a result of dopamine (DA) activation within reward circuitry. It has been suggested, for example, that DA systems mediate the incentive salience of rewards, such as drugs, by modulating their motivational value in a manner separable to that of their hedonic or reward value

(Robinson et al., 1993). Importantly, understanding if this incentive salience system operates similarly in current and former cigarette smokers is of particular interest, as smoking-related cues may increase attentional bias and expectancy of nicotine delivery irrespective of smoking status (i.e. current versus former user), potentially identifying a mechanism for smoking relapse risk. Second, understanding the mechanism by which attention is captured by salient smoking-related cues would appear critical to our understanding of nicotine addiction treatment. The neural mechanisms underlying a smoking-related attentional bias may reveal potential targets for therapies, cognitive (Attwood et al., 2008; Field et al., 2009; Muraven, 2010; Schoenmakers et al., 2010) and/or pharmacological (Franklin et al., 2011; Mei et al., 2010; Muraven, 2010; Rohsenow et al., 2008; Schnoll et al., 2010). This might be especially important if one can elucidate a distinct neural pattern which may reflect successful abstinence in former cigarette smokers.

Both nicotine and conditioned cues have been shown to maintain cigarette smoking and trigger relapse (Heishman et al., 2010; Henningfield et al., 1983; Janes et al., 2010a; Rose, 2006; Vollstadt-Klein et al., 2010). While the majority of cigarette smokers endorse the desire to quit, reported abstinence rates after twelve months are in the modest region of 5-17% (Hughes et al., 2008). Despite an increased understanding of its addictive properties, there is a scarcity of research examining the relationship between nicotine use and abstinence, and bottom-up/top-down neural responses to smoking-predictive stimuli in current and ex-smokers. Ex-smokers trying to remain abstinent, for example, may attempt to control their intrusive smoking-related cognitions,

either by diverting their attention away from smoking-related stimuli (Schoenmakers et al., 2010;) or suppressing their subjective craving (Brody et al., 2007), an effect which may be facilitated by increased top-down neural processing. This may suggest that in successful abstainers, there will be increased top-down processing in areas responsible for cognitive control, error/risk detection and avoidance behaviour, such as the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC) and insula (Bechara, 2005; Bush et al., 2000; Janes et al., 2010a; Preuschoff et al., 2008; Whalen et al., 1998). Similarly, individuals currently dependent upon nicotine may demonstrate inferior neural responses in these regions, concomitant with increased bottom-up activity in the nucleus accumbens (NAcc) and amygdala (David et al., 2005; Due et al., 2002; McClernon et al., 2007), which trigger the affective and appetitive signals of immediate drug outcomes (Bechara, 2005). Therefore, the failure to develop, or a loss of previously developed cognitive control in nicotine addiction, may affect the ability to restrain cigarette smoking upon the presentation of smoking-related cues, thus triggering relapse. To this end, inferior top-down cognitive control neural processing, may be an important factor in provoking smoking relapse, as a result of increased, overriding bottom-up neural functioning.

Therefore, based on the concept of exaggerated bottom-up and compromised top-down neural processing in addiction, the current study was divided into two separate experiments. These explored in demographically matched control, ex-smoker and current smoker samples 1) the neural responses during the presentation of smoking-related stimuli and 2) the neural correlates of cognitive control functioning. Experiment 1 utilized an attentional bias

paradigm, in which individuals were required to make stimulus-response selections in the presence of neutral, evocative and smoking-related stimuli. Experiment 2 used a go/no-go paradigm to examine motor response inhibition and error-monitoring in the same samples. We hypothesized that current smokers would demonstrate an attentional bias through slower reactions times in the presence of smoking-related cues; increased cue-reactivity in mesolimbic dopamine (DA) regions (i.e. amygdala, NAcc, caudate and putamen) and reduced prefrontal neural activity during response inhibition and error monitoring compared to controls and ex-smokers. Further, we hypothesized that ex-smokers would show either normal levels of activity in prefrontal regions or, given the high levels of relapse amongst smokers, greater-than-normal levels of control-related prefrontal activity, concomitant with reduced cue-reactivity in mesolimbic DA regions in response to smoking-related stimuli compared to current smokers. To this end, we endeavoured to characterise the cortical and subcortical responses of the ex-smokers, and hoped to provide evidence for the neural mechanisms which may promote successful abstinence from cigarette smoking.

Experiment 1

Material and Methods

Participants

13 current cigarette smokers, 10 ex-smokers and 13 controls completed Experiment 1. A semi-structured interview, as used in previous behavioural and functional imaging studies (Hester et al., 2009; Nestor et al., 2010; Nestor

et al., 2008; Roberts et al., 2009) was conducted to screen participants for past or present histories of psychiatric or neurological illness. Information pertaining to any form of treatment (counselling, psychological, psychiatric), past or present, was carefully detailed, with any potential participant describing any major life-time psychiatric event or brain injury (e.g., head trauma resulting in a loss of consciousness, seizure or stroke) considered ineligible for the study. People were also considered ineligible if they reported any familial psychiatric history (i.e., sibling, parent, grand parent). Prior to scanning, all participants completed an inventory for drug use (questionnaire taken from the Addiction Severity index Lite-CF; see questionnaires section below) to screen for past or concurrent abuse of substances; participants were considered ineligible if they reported concurrent or past dependence on other drugs (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, hallucinogens, MDMA and opiates) at the interview. Ex-smokers were additionally considered ineligible if they reported past or current use of products to facilitate nicotine abstinence (e.g., gum, patches, lozenges, nasal spray and inhalators). Information concerning alcohol and nicotine use in each participant was indexed in years (life-time) and recent (last 30 days). Other drug use information for each participant was indexed by the total number of separate occasions (life-time) and the total number of recent separate occasions (last 30 days).

Current smokers were required to have regularly consumed nicotine (=/> 10 cigarettes/day) for the previous 2 years in order to be eligible, with ex-smokers also having to have met this requirement prior to abstinence (see

Table 1). Ex-smokers must also have been abstinent from nicotine for a minimum of twelve months prior to enrolment in the study. Control participants must never have smoked cigarettes. Current smoking abstinence in controls and ex-smokers was confirmed by measuring expired carbon monoxide (CO) in parts per million (ppm) prior to scanning. All participants were required to provide a negative urine sample for various drugs of abuse prior to scanning, specifically screening for the presence of amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine, MDMA, methadone, opiates and tricyclic antidepressants (Cozart RapiScan, UK). Because previous research has shown that smokers demonstrate state-dependent (abstinence vs. satiety) differences during their performance on cognitive tasks (Hatsukami et al., 1989; Parrott et al., 1999; Powell et al., 2002; Pritchard et al., 1992; Rusted et al., 2000; Shiffman et al., 1995) and that acute abstinence from cigarettes impairs concentration (Heishman, 1999; Newhouse et al., 2004), and increases BOLD activity during fMRI (Azizian et al., 2010; David et al., 2007; Xu et al., 2005; Xu et al., 2007), cigarettes smokers each smoked *ad lib* approximately 15 minutes prior to scanning in order to avoid the potential confounds of withdrawal and/or craving on cognitive performance. Consequently, any differences in current smokers regarding cognitive performance or brain function could be attributable to the acute effects of their recent nicotine use. Given their frequent daily use, this is deemed desirable as it reveals the typical functioning of their cognitive systems.

All participants were right-handed as confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971) during the screening process. All participants

completing the study were neurologically normal (as confirmed by a registered radiologist who examined each structural MRI). All research participants provided informed consent and were financially compensated.

Questionnaires

The National Adult Reading Test (NART) (Nelson et al., 1978) was administered to all participants prior to scanning to assess verbal intelligence, as was the Beck Depression Inventory (BDI) to assess mood (Beck et al., 1996). Information concerning alcohol and drug use (see Table 1) was obtained from all participants using a questionnaire taken from the Addiction Severity Index *Lite*-CF (McLellan et al., 1992). Prior to scanning, the Fagerström test of nicotine dependence (FTND) was administered to participants in the smoking group. The FTND (Heatherton et al., 1991) is a 6-item questionnaire that measures the degree of nicotine dependence in an individual smoker. The Shiffman-Jarvik smoking withdrawal questionnaire (SJWQ) and the urge to smoke (UTS) scale were administered to both the smoker and ex-smoker groups prior to the scanning procedure. The 25-item SJWQ (Shiffman et al., 1976) asks individuals to respond to questions using a 7-point Likert-type scale that ranges from “very definitely” (7) to “very definitely not” (1) with respect to how they feel at that moment regarding separate withdrawal symptoms. These withdrawal symptoms are comprised of *craving*, *physical*, *psychological*, *sedation* and *appetite* constructs. Each construct is given a mean score, with the mean for each construct summed to provide an overall withdrawal score for an individual. The 10-item UTS scale (Jarvik et

al., 2000) assesses responses to craving-related questions, using a 7-point Likert-type scale ranging from “very definitely” (7) to “very definitely not” (1).

Attentional Bias Paradigm

Participants performed an attentional bias paradigm during fMRI scanning. Participants viewed pictures of three different stimulus categories, including neutral (musical instruments), evocative (negative valence) photographs taken from the International Affective Picture System - (Lang et al., 1999) and smoking-related pictures. Each picture was surrounded by one of four different coloured borders (i.e., blue, yellow, green and red). During the presentation of each stimulus, participants were required to respond to the colour of each border with a button press (Fig 1). Here participants responded by pressing a blue or yellow button on the left hand-held key pad with their left middle or index fingers upon the presentation of a blue or yellow border respectively, and pressed a green or red button on the right hand-held key pad with their right middle or index fingers upon the presentation of a green or red border respectively. Participants were first trained with respect to these responses outside the scanner during the practice session. Participants also performed one practice run of the task while in the scanner, during which they responded to the presentation of the four different coloured borders without the pictures. There were two functional runs, each of which lasted 340 seconds. Each run began with a 20 second rest period and contained two blocks of each stimulus category (e.g., neutral-evocative-smoking-evocative-smoking-neutral) with each block followed by 20 second rest periods. There were ten different pictures within a block, with each picture presented for 1.5

seconds, followed by a pseudo-randomized inter-stimulus interval of 1, 1.5 or 2 seconds, such that each block was exactly 30 seconds in duration. The block order was the same for each participant. Dependent measures for the task were the mean percentage correct response and the mean reaction time for each stimulus category. The task was programmed using E-Prime (Psychology Software Tools, Pittsburgh, USA). Analyses of the dependent measures were conducted using 3 (Condition: neutral, evocative, smoking) x 3 (Group: control, ex-smoker, smoker) ANOVAs in the Statistical Package for the Social Sciences (SPSS).

-Insert figure 2 about here-

fMRI acquisition

All scanning was conducted on a Philips Intera Achieva 3.0 Tesla MR system (Best, The Netherlands) equipped with a mirror that reflected the visual display, which was projected onto a panel placed behind the participants' head outside the magnet. The mirror was mounted on the head coil in the participants' line of vision. Each scanning sequence began with a reference scan to resolve sensitivity variations. A parallel Sensitivity Encoding (SENSE) approach (Pruessmann et al., 1999) with a reduction factor of 2 was utilised for all T1-weighted image acquisitions. 180 high-resolution T1-weighted anatomic MPRAGE axial images (FOV 230 mm, thickness 0.9 mm, voxel size 0.9 x 0.9 x 0.9) were then acquired (total duration 325 seconds), to allow subsequent activation localization and spatial normalization. Functional data were collected using a T2* weighted echo-planar imaging sequence that

acquired 32 non-contiguous (10% gap) 3.5 mm axial slices covering the entire brain (TE = 35 ms, TR = 2000 ms, FOV 224 mm, 64 x 64 mm matrix size in Fourier space).

Data processing and analyses

All analyses were conducted using AFNI software (Cox, 1996). Following image reconstruction, the 3-D time series (runs 1 and 2) were concatenated and motion-corrected using 3-D volume registration (least-squares alignment of three translational and three rotational parameters). Activation outside the brain was removed using edge detection techniques. A block analysis was performed to estimate the activation for each separate stimulus category. These ON-OFF block regressors were first convolved with a standard haemodynamic response to accommodate the lag time of the blood oxygen level-dependent (BOLD) response. Multiple regression analyses were then used to determine the average level of block activation as a percentage change relative to the rest period baseline.

The percentage change, block activation voxels were re-sampled to 1 mm^3 resolution, then warped into standard Talairach space (Talairach et al., 1988) and spatially blurred with a 3-mm isotropic rms Gaussian kernel. Group activation maps for each condition of the task (neutral, evocative and smoking) were determined with one-sample *t*-tests against the null hypothesis of zero activation change (i.e., no change relative to the rest period baseline). Due to the very robust BOLD response observed across all groups during the task, we opted for a whole-brain corrected threshold of $p \leq 0.01$. Here,

significant voxels which passed a voxelwise statistical threshold (t = 4.6, p=0.001) were required to be part of a 328μl cluster of contiguous significant voxels. This cluster size criterion was determined through Monte Carlo simulations resulting in a 1% probability of a cluster surviving due to chance.

To compare activations between the control, ex-smoker and smoker groups, thresholded group *t*-test maps for each condition (neutral, evocative, smoking) in all groups were combined to form a single map (this combined map contained voxels that were significant in any of the conditions in each group). The mean activation for each cluster in this combined map was calculated for each subject and for each condition to enable a cluster level, functionally-defined, region-of-interest analysis.

We also performed small-volume correction analyses on the dorsolateral prefrontal cortex (DLPFC), amygdale, caudate and putamen (anatomically defined masks taken from the AFNI anatomy toolbox), given an *a priori* interest in BOLD responses in these regions. Previous research has demonstrated atypical DLPFC activity in smokers (Loughead et al., 2008; Musso et al., 2007; Xu et al., 2005; Xu et al., 2006), with the amygdala, caudate and putamen also shown to respond to drug and evocative stimuli (Britton et al., 2006; Due et al., 2002; Franklin et al., 2007; Garavan et al., 2000; Hariri et al., 2002; McClernon et al., 2009; Paradiso et al., 1999; Rasia-Filho et al., 2000; Volkow et al., 2006; Wang et al., 2007). For the DLPFC, a small-volume threshold was applied for voxels that fell within anatomically defined left and right hemispheres (BA 9 and 46 combined). Significant voxels

which passed a voxelwise statistical threshold (t = 3.4, p=0.005) were required to be part of a 284μl (DLPFC), 26μl (amygdala), 65μl (caudate) and 82μl (putamen) of contiguous significant voxels ($p \leq 0.05$ corrected). The cluster-size values used here were smaller than that used for the whole-brain analysis (328μl) due to there being fewer voxels within the small volumes (DPFC, amygdala, caudate and putamen). The combination of voxel-wise statistics and cluster size criteria resulted in a 0.05 probability of a cluster surviving by chance.

Finally, activity in the nucleus accumbens (NAcc) was also investigated given this region's role in attributing incentive salience to reward stimuli (Berridge et al., 1998; Gottfried et al., 2002). Due to its small size (left =130ul; right = 157ul), and the resolution of our acquisition voxels (1 mm^3), we treated the NAcc as an anatomically-defined ROI, averaging over all the voxels in this ROI to calculate a mean BOLD percentage change score during the neutral, evocative and smoking conditions in both the left and right NAcc in all three groups. For between-group comparisons involving the whole brain and small-volume correction (SVC) analyses, we conducted 3 (Condition: neutral, evocative, smoking) x 3 (Group: control, ex-smoker, smoker) ANOVAs on the mean percentage change scores extracted from these regions. For the ROI comparisons in the NAcc, we conducted 2 (Hemisphere: left, right) x 3 (Condition: neutral, evocative, smoking) x 2 (Group: control, ex-smoker, smoker) ANOVAs on the mean percentage change scores in this region. All analyses were conducted in SPSS.

Results

Demographics and drug use

Table 1 shows the demographic, nicotine and drug use histories for the control, ex-smoker and smoker groups. The groups did not significantly differ on age, years of education, verbal intelligence, BDI, gender distribution or alcohol and other drug use. Furthermore, there were no differences between smokers and ex-smokers with respect to nicotine use characteristics, such as years of use, pack-years and the number of cigarettes smoked per day. Expired CO levels were significantly lower in controls and ex-smokers compared to smokers, confirming nicotine abstinence in both these groups prior to testing. Table 2 shows that on the withdrawal and craving measures, only on the appetite construct of the SJWQ did the smoker and ex-smoker groups differ. Ex-smokers appeared to have less appetite compared to smokers. Smokers demonstrated a significantly greater UTS score at the testing session prior to scanning.

-Insert table 1 about here-

Attentional Bias Paradigm Performance

The first 3 (Condition: neutral, evocative, smoking) x 3 (Group: control, ex-smoker, smoker) ANOVA showed that for mean percentage accuracy, there was no effect of condition ($F=2.3$, $df=2, 99$, $p=0.1$), there was an effect of group ($F=3.2$, $df=2, 99$, $p<0.05$) but no condition by group interaction ($F=0.2$,

df=4, 99, *p*=0.9). Follow up pair-wise comparisons suggested that the group effect was driven by the difference between current and ex-smokers, but this difference only approached significance (*p*=0.06). For the second ANOVA exploring mean reaction time, there was no effect of condition (F=0.8, df=2, 99, *p*=0.5), no effect of group (F=0.4, df=2, 99, *p*=0.7) and no condition by group interaction (F=0.2, df=4, 99, *p*=1.0).

Table 3 lists the brain regions with significant BOLD activation during the neutral, evocative and smoking conditions across the three groups and the respective group, interaction and condition effects, with appropriate pair-wise statistical results.

-Insert table 2 about here-

There was a main effect of condition for the right thalamus, where the smoking stimulus condition elicited a greater BOLD response compared to the neutral stimulus condition. There were main effects of group in a number of regions. These included the right precentral gyrus/BA4, the left posterior cingulate cortex (PCC)\BA30 (Fig 2a), the left dorsolateral prefrontal cortex (DLPFC) small volume correction (Fig 2b), the right anterior cingulate cortex (ACC)/BA32 (Fig 2c), the right insula/BA13 (Fig 2d) and the left amygdala small volume correction (Fig 3a). Pairwise comparisons showed that smokers had lower BOLD activation compared to controls in the precentral gyrus, and lower activation compared to controls and ex-smokers in the posterior cingulate and DLPFC. Ex-smokers demonstrated a greater BOLD response compared to both controls and smokers in the anterior cingulate and insula.

Only for the nucleus accumbens (NAcc) region of interest analysis (Fig 3b and c) was there a condition by group interaction, in which smokers had significantly greater BOLD activation compared to ex-smokers during the smoking stimulus condition. We also performed within group analyses in current smokers to demonstrate greater BOLD activation in the NAcc and amygdala in response to smoking-related compared to neutral cues, and hence increased salience attribution in current nicotine dependence. Here, greater activation was observed in the left (t=2.15, df=12, p<0.05) and right (t=3.9, df=12, p<0.01) NAcc, and in the left amygdala (t=2.41, df=12, p<0.05) when comparing the two conditions. For the caudate and putamen small volume correction analyses, no voxels survived thresholding.

-Insert figure 2 about here-

-Insert figure 3 about here-

Experiment 2

Material and Methods

Participants

10 current cigarette smokers, 10 ex-smokers and 13 controls completed Experiment 2. These were the same subjects used in experiment 1 except for three smokers, who did not complete experiment 2.

Go/No-go Inhibitory Task

The go/no-go task (Garavan et al., 2005) performed by the three groups consisted of alternating target stimuli (the letters X and Y), each of which were presented for 900 milliseconds, immediately followed by a 100 millisecond inter-stimulus interval. Participants were instructed to make a response (on a

hand-held key pad) as quickly as possible to each stimulus ("go" trials). Participants were additionally instructed to inhibit their response ("no-go" trials) when the target stimuli did not alternate (i.e. the second of two identical, successively presented target stimuli - e.g., respond to all stimuli except the fifth in the sequence XYXYYX). Participants recommenced responding to alternating stimuli once again, following the presentation of the "no-go" stimulus. There were a total of 250 stimuli presented in each run of the task, of which 25 were "no-go" trials. Participants completed a total of two runs of the task, with each run lasting 254 seconds. Therefore, the average stimulus-onset-asynchrony (SOA) of interest (i.e. the intervals between the "no-go" trials) was 10 seconds. Dependent measures for the task were the mean "go" and "no-go" (STOP) accuracy, together with mean "go" and mean ERROR response times. The task was programmed using E-Prime (Psychology Software Tools, Pittsburgh, USA). Between-group comparisons using a one-way analysis of variance (ANOVA) were performed on the dependent measures. Bonferroni-corrected *post hoc* analyses were conducted upon the observation of a significant ANOVA group effect. All analyses were conducted in SPSS.

fMRI acquisition

The same scanning acquisition parameters as Experiment 1 were used for Experiment 2.

Data processing and analyses

All analyses were conducted using AFNI software (Cox, 1996). Following image reconstruction, the two time series datasets were concatenated and motion-corrected using 3-D volume registration (least-squares alignment of three translational and three rotational parameters). Activation outside the brain was also removed using edge detection techniques.

To examine neural activations in response to successful inhibitions (STOPs) and ERRORs in all groups, an event-related analysis was performed. Here, separate regressors identifying the locations of STOPs and ERRORs within the time-series were used in a deconvolution analysis to calculate impulse response functions (IRFs) for each regressor (Murphy et al., 2005). Using a nonlinear regression programme, we determined the best-fitting gamma-variate function for each IRF (Cohen, 1997) as described previously (Garavan et al., 1999). The area under the curve of the gamma-variate function was expressed as a percentage of the area under the baseline. The baseline for both the STOP and ERROR measures reflected tonic task-related processes ("go" trials) of the task.

The percentage area (event-related activation) voxels were re-sampled at 1 mm^3 resolution before being warped into standard Talairach space (Talairach et al., 1988) and spatially blurred with a 3-mm isotropic rms Gaussian kernel. Group activation maps for each measure were determined with one-sample *t*-tests against the null hypothesis of zero activation change (i.e. no change relative to the ongoing "go" trial period baseline). For ERRORs, significant voxels passed a voxelwise statistical threshold ($t = 3.4$,

$p \leq 0.005$) and were required to be part of a 274µl cluster of contiguous significant voxels. This cluster size criterion was determined through Monte Carlo simulations and resulted in a posterior statistical threshold of $p \leq 0.05$, corrected. Due to the very robust BOLD response observed across all groups for STOPs, we opted for an omnibus threshold of 0.01. Here, significant voxels which passed a voxelwise statistical threshold ($t = 3.6$, $p \leq 0.001$) were required to be part of a 328µl cluster of contiguous significant voxels. The activation maps for the control, ex-smoker and smoker groups were combined by condition (i.e., separate combinations for STOPs and ERRORs) as OR maps (either/or maps in which a voxel was included if significant in any of the separate group maps). Between-group comparisons using a one-way analysis of variance (ANOVA) were performed on the mean activations of the resulting clusters of activation within the OR maps. Bonferroni-corrected *post hoc* analyses were conducted upon the observation of a significant ANOVA group effect. All analyses were conducted in SPSS.

Results

Demographics and drug use

Table 1 (see Experiment 1) shows the demographic, nicotine and drug use histories for the control, ex-smoker and smoker groups. Experiment 2 produced very similar results to Experiment 1 with respect to demographic, nicotine and drug use histories, as well as nicotine withdrawal and craving measures (see Table 1 in Experiment 1).

Go/No-go Task Performance

For behavioural responses, a between-group one-way ANOVA revealed significant group differences for STOP accuracy ($F_{(2,30)}$ =7.6, p<0.01). *Post hoc* analyses showed that smokers were poorer at inhibiting (Fig 4a) compared to controls (p<0.05) and ex-smokers (p<0.01). For percentage omission errors (Fig 4c), there was no significant difference between the groups ($F_{(2,30)}$ =0.4, p=0.7). For GO trial reaction time (Fig 4d), there was a significant difference between the groups ($F_{(2,30)}$ =4.6, p<0.05). *Post hoc* analyses revealed that ex-smokers were significantly slower than both controls and smokers. There was a similar difference (Fig 4b) between the groups for ERROR trial reaction time ($F_{(2,30)}$ =4.6, p<0.05), with *post hoc* analyses revealing that ex-smokers were significantly slower than both controls and smokers.

-Insert Figure 4 about here-

fMRI

STOP analyses

Activated areas were predominantly in the right hemisphere, but also included some bilateral activity (see Table 3). Between-group, one-way ANOVAs revealed that the smoker group had less BOLD activation than controls in almost all areas where significant group differences were observed. Particularly significant, given their role in cognitive control, was the observation of group differences in the right anterior cingulate (ACC)/BA32 ($F_{(2,30)}$ =7.1, p<0.01) and the left middle frontal gyrus (i.e. 9/46 - DLPFC) ($F_{(2,30)}$ =5.0, p<0.05) where smokers showed significantly lower activation than controls in both regions (Fig 5a and b). Similar effects (i.e., smokers showing reduced activation compared to controls) were observed in the superior frontal

gyri and bilateral inferior parietal lobule. There was also a group difference in the left ACC ($F_{(2,30)}$ =4.4, p<0.05), where ex-smokers showed greater activation compared to smokers (Fig 5c). Areas in which both smokers and ex-smokers showed lower activation than controls included the left inferior frontal gyrus(IFG)/BA44 (Fig 5d), the right middle and superior temporal gyrus (STG); pre- and post-central gyri, left parahippocampal gyrus and bilateral anterior insula/BA13.

-Insert Table 3 about here-

-Insert Figure 5 about here-

ERROR analyses

Medial wall and bilateral activation, predominantly in the left hemisphere, was observed during ERROR trials across the three groups (see Table 4). Between-group, one-way ANOVAs revealed a number of significant group differences. There was a group difference in the right superior frontal gyrus (SFG)/BA10 ($F_{(2,30)}$ =6.9, p<0.05 - Fig 6a), where smokers had significantly lower activation than controls, and in the right middle frontal gyrus (MFG)/BA46 ($F_{(2,30)}$ =3.6, p<0.05 - Fig 6b), where ex-smokers had significantly higher activation than controls. Group differences also emerged in the left posterior cingulate cortex (PCC)/BA24 ($F_{(2,30)}$ =3.7, p<0.05) and anterior cingulate cortex (ACC)/BA24 ($F_{(2,30)}$ =3.5, p<0.05), where ex-smokers also showed greater activation than smokers (Fig 7a and b). One other pattern observed was for greater ERROR-related activation in ex-smokers compared

to both controls and smokers. This was observed in right and left superior frontal gyri (Fig 7c and d), bilateral parahippocampal gyri, left insula, middle temporal gyrus and the cerebullum. Other regions where there was less activation in smokers relative to controls and greater activation in ex-smokers relative to controls are listed in Table 4.

-Insert Table 4 about here-

-Insert Figure 6 about here-

-Insert Figure 7 about here-

Correlations

We did not observe any correlations between nicotine use demographics (i.e. usage, withdrawal, urge to smoke) and go/no-go behavioural performance in either the ex-smoker or smoker groups. Furthermore, there were no correlations between nicotine use demographics and mean BOLD activation change during motor response inhibition in either the ex-smoker or smoker groups or between nicotine use and mean BOLD activation change during ERRORs in the ex-smoker group. We did, however, observe a significant negative correlation between the Fagerström test of nicotine dependence (FTND) score and mean BOLD activation change during ERRORs (Fig 8a and b) in the right superior frontal gyrus/BA10 ($r= -0.72$, $p<0.05$) and the left insula/BA13 ($r= -0.86$, $p=0.01$) in the smoker group. There was also a significant negative correlation between urge to smoke (UTS) score and mean ERROR-related BOLD activation change in the left parahippocampal gyrus/BA35 ($r= -0.78$, $p<0.01$) in the smoker group.

-Insert Figure 8 about here-

Discussion

Experiment 1 investigated behavioural and neural responses during an attentional bias paradigm in current cigarette smokers, ex-smokers and controls. Behaviourally, there were no significant differences between any of the groups, contravening the hypothesis that current smokers would demonstrate an attentional bias through slower reactions times in the presence of drug-related cues. While smokers have been shown to demonstrate state-dependent (abstinence vs. satiety) alterations in arousal (Parrott & Kaye, 1999), motivation (Powell et al., 2002) and sustained attention (Rusted et al., 2000), which might bestow an acute beneficial effect of nicotine on task performance, it is may be that this lack of behavioural effect represents the small sample size used in Experiment 1, compared to previous studies (Domier et al., 2007; Munafo et al., 2003; Rzetelny et al., 2008). Experiment 2 investigated neural activity during motor response inhibition and error monitoring in the same sample using a go/no-go task. Behaviourally, smokers demonstrated significantly poorer motor response inhibition compared to both the ex-smoker and control groups. Smokers have been shown to exhibit higher rates of impulsivity than non-smokers (Mitchell, 1999; Waldeck et al., 1997), with the current findings appearing to corroborate existing evidence (Mitchell, 2004) of poorer motor response inhibition. The number of omission errors was not significantly higher nor response times significantly faster in the smoker group, suggesting that their increased commission error rate was not confounded by an overall inability to perform

the task or confounded by faster responses. The current study also revealed that ex-smokers were significantly slower to respond, possibly suggesting a more conservative or cautious response style.

Reduced BOLD activation in smokers

In Experiment 1, smokers showed, overall, significantly less neural activity compared to controls in the right precentral gyrus/BA4. The attentional bias paradigm in Experiment 1 required participants to make stimulus-response selections in the presence of neutral, evocative and smoking-related stimuli. These responses required the use of both hands, therefore, likely to activate the left and right primary motor cortices. Nicotinic receptors are particularly abundant in the primary motor cortex (Perry et al., 1992; Sihver et al., 1998), with past research in cigarette smokers demonstrating reduced motor cortex excitability (Lang et al., 2007). The reduction observed here, therefore, may potentially indicate reduced neural functioning within neuronal circuits of the motor cortex in current nicotine addiction. Current cigarette smokers also showed an overall reduction in BOLD activation, compared to controls and ex-smokers, in the left posterior cingulate cortex (PCC). The PCC has been described as the “evaluative region” of the cingulate (Vogt et al., 1992), and is anatomically linked to the prefrontal cortex (PFC) and striatum. The PCC been shown to respond under conditions of sensory arousal (Garavan et al., 2000; Kosten et al., 2006), motivationally-linked attention (Mohanty et al., 2008) and the evaluation of emotional memories (Maddock, 1999); with additional evidence indicating that neuronal responses in the PCC signal subjective spatial biases that guide orienting toward certain stimuli (McCoy et

al., 2005). Therefore, reduced BOLD activation in this region, in the absence of any behavioural deficit, may suggest atypical neural activity in relation to the evaluation of stimulus-response selections in current smokers.

We additionally observed, across all conditions, significantly less BOLD activation in the left dorsolateral prefrontal cortex (DLPFC) of smokers compared to controls, and to a greater degree, ex-smokers in Experiment 1. While smoking-related stimuli have previously been shown to increase neural activity in the DLPFC of smokers, this increase in activity has been shown to occur upon the expectation of an imminent opportunity to smoke (McBride et al., 2006; Wilson et al., 2004). The left DLPFC has previously been associated with the implementation of cognitive control processes in preparation for conflict (MacDonald et al., 2000), and may suggest that in current cigarette smokers, there is a failure to sufficiently activate this region, despite adequate behavioural functioning. Significantly, ex-smokers failed to demonstrate any deficit in task-related neural activity compared to controls in the precentral gyrus, PCC and DLPFC, which may identify important functional characteristics of successful abstainers. These effects may have pre-existed the cessation of nicotine use in ex-smokers (and, it might be speculated, may have facilitated abstinence) or may indicate a restoration of function following long-term abstinence.

During successful STOP trials of the go/no-go task in Experiment 2, we observed significant reductions in the right DLPFC BOLD response of smokers compared to controls, consistent with previous research findings of

differences in this region during cognitive processing (Loughead et al., 2008; Xu et al., 2006; Xu et al., 2007). Long-term nicotine use has been associated with reduced grey matter volume in the DLPFC (Brody et al, 2004; Gazdzinski et al, 2005; Gallinat et al, 2006), suggesting that changes in DLPFC structural integrity may affect top-down cognitive control in smokers. Compared to controls, cigarette smokers also showed a significant reduction in right ACC/BA32 neural activity during successful STOP trials. The ACC has previously been implicated in urgent inhibitions reflecting heightened performance monitoring processing (Garavan et al., 2002). Therefore, this finding, together with an apparent reduction in STOP accuracy, may suggest insufficient neural activity within the right ACC, which may relate to problems with response inhibition in nicotine addiction.

During ERROR trials in Experiment 2, current cigarette smokers also showed reduced neural activity, compared to controls, in the right superior frontal gyrus (SFG)/BA10. The SFG has previously been identified as a region responding to errors in behaviour during a go/no-go task (Garavan et al., 2003), with cocaine users similarly demonstrating a reduction in error-related neural activity in this region during error monitoring (Kaufman et al., 2003). Furthermore, ERROR-related BOLD activation in this region of smokers was found to be negatively associated with scores on the Fagerström test of nicotine dependence (FTND), provoking the notion that progressive dependence is associated with greater reductions in the integrity of prefrontal cortical neural functioning in relation to error monitoring; an effect which may serve to facilitate continued nicotine use.

Reduced BOLD activation in smokers & ex-smokers

During the go/no-go task, the present study also revealed reduced STOP-related neural activity in frontal, temporal, parahippocampal and insular regions of both current and ex-smokers. The left IFG has been implicated in the suppression of prepotent responses (Novick et al, 2005; Swick et al, 2008) and is known to play an important role in cognitive control (Aron et al., 2003; Ridderinkhof et al., 2004b). The insula has also been shown to respond during inhibitory functioning, as well as in the learning and acquisition of inhibitory avoidance behaviour (Blakemore et al., 1998; Buchsbaum et al., 2005; Garavan et al., 1999; Kaufman et al., 2003). Reduced neural activity observed in former cigarette smokers in these regions, following prolonged abstinence, may reveal the residual effects of chronic nicotine exposure on certain neural mechanisms of inhibitory control. Alternatively, any commonalities between current and former smokers may identify aberrant neural functioning that pre-existed the initiation of smoking in either group, which may have constituted a cognitive risk factor for the initiation of nicotine use (Reynolds et al., 2009; Verdejo-Garcia et al., 2008).

Increased BOLD activation in smokers

Individuals currently dependent upon drugs may, in addition to demonstrating reduced neural responses in top-down cognitive processing, elicit exaggerated bottom-up neural activity in structures which trigger the affective and appetitive signals of immediate drug outcomes (Bechara, 2005). The results of Experiment 1 showed that smokers demonstrated significantly more

positive BOLD activation in the nucleus accumbens (NAcc) in response to smoking-related stimuli compared to ex-smokers. Human fMRI studies have observed elevated neural responses in the NAcc during the presentation of nicotine cues (David et al., 2005; Due et al., 2002; Franklin et al., 2007), which may represent excessive attribution of incentive salience to drug predictive stimuli (Robinson and Berridge, 1993). Of interest, the difference between smokers and ex-smokers in Experiment 1 was driven by activation increases above baseline in smokers and deactivations below baseline in the ex-smoker group. The NAcc deactivation in ex-smokers may relate to the salience of nicotine-predictive cues following the successful cessation of smoking. Determining whether certain stimuli should be approached or avoided may define either a positive or negative valence for such stimuli, which in ex-smokers, is signified by NAcc deactivation in response to smoking-predictive cues. Overall, the observed NAcc responses may represent evidence for the positive versus negative valence that smoking cues may have for smokers and ex-smokers, respectively.

Smokers also exhibited, across conditions, significantly greater BOLD activation in the left amygdala compared to the control group. The animal and human literature has provided evidence that the amygdaloid nuclei respond to smoking-related stimuli (Due et al., 2002; Franklin et al., 2007; Janes et al., 2010), as well as aversive and appetitive stimulus properties (Davis, 1992; Gallagher et al., 1999; Holland et al., 1999; Paradiso et al., 1999; Rasia-Filho et al., 2000). The amygdala has also been shown to be involved in stimulus-reward associations (Kentridge et al., 1991) and is thought to be part of a

neural system involved in the identification of, and subsequent response to, emotionally salient stimuli (Phillips et al., 2003). There is also growing evidence documenting the relationship between uncertainly and increased amygdala activity (Belova et al., 2007; Dunsmoor et al., 2008; Herry et al., 2007; Rosen et al., 2006; Whalen, 2007), with uncertainty about the occurrence of aversive (evocative) and reward (drug) outcomes in cigarette smokers, potentially increasing the motivational salience of these stimuli upon exposure. This may be reflected in the greater neural activity elicited in smokers in response to the presentation of evocative and smoking-related (but not neutral) stimuli in Experiment 1. Taken together, increased subcortical neural activity in current cigarette smokers may reflect a combination of increased salience attribution and reactivity to smoking-related and emotional stimuli within ventral striatal and amygdaloid circuitry.

Increased BOLD activation in ex-smokers

The ability to monitor one's behaviour during drug abstinence may be especially important when there is a need to detect risky circumstances or behaviours, including those that might induce drug relapse (Garavan & Stout, 2005). Neural responses evoked during behavioural monitoring in addiction are of particular interest, especially during drug abstinence, as they may elucidate specific adaptations within neural regions which promote cognitive control over addictive processes.

We observed significantly greater BOLD activation, across conditions, in the right ACC/BA32 of ex-smokers compared to both control and smoker groups

during Experiment 1. The activation cluster observed here was located in the rostral portion of the ACC (rACC). There is evidence implicating the rACC in the assessment of emotional information (Bush et al, 2000), particularly where the suppression of task-irrelevant emotional information is required (Whalen et al, 1998), and during the presentation of emotionally evocative stimuli (Bishop et al., 2004; Mohanty et al., 2005; Vuilleumier et al., 2001). Experiment 2 additionally observed that ex-smokers demonstrated significantly greater ERROR-related BOLD activation in the left ACC compared to smokers, but not controls. We additionally observed that ex-smokers elicited more ERROR-related activation in the left posterior cingulate (PCC)/BA24, compared to smokers. The PCC has also been shown to respond to errors during a go/no-go task (Menon et al., 2001), with existing evidence for PCC hypofunctioning in cigarette smokers (Neuhaus et al., 2006). Therefore, cingulate functioning may improve following a protracted period of abstinence in ex-smokers, and/or potentially contribute to facilitating nicotine abstinence through heighted conflict and error monitoring in this region.

EX-smokers had, across all conditions, significantly greater BOLD activation than both controls and smokers in the right insula/BA13 in Experiment 1. The anterior, agranular regions of the insula are known to have reciprocal connections with the ACC, with proposals that the serial processing of interoceptive information occurs within the insula, particularly the right anterior portion, where the conscious awareness of interoceptive stimuli arises (Craig, 2002, 2003). We additionally observed that ex-smokers had significantly

greater go/no-go ERROR-related BOLD activation than both controls and smokers in the left insula/BA13 during Experiment 2. ERROR-related neural activity in the insula has previously been shown in healthy controls (Garavan et al., 2002; Hester et al., 2005; Klein et al., 2007), which may reflect a greater autonomic response, or heightened interoception (Bud Craig, 2009; Critchley et al., 2004) in response to errors in behaviour. The apparent incongruity between reduced insular neural activity during motor response inhibition and the heightened neural activity during error monitoring in ex-smokers relative to controls, may suggest that monitoring one's performance, especially during instances of high error likelihood, is an integral feature of initiating and sustaining nicotine abstinence. This effect may, therefore, evolve to compensate for reductions in neural inhibitory control. Interestingly, the negative correlation observed between FTND scores and ERROR-related BOLD activation in the left insula of smokers, may also suggest that the severity of dependence could confer a greater vulnerability to relapse, if neural activity in the insula is required for performance monitoring during abstinence. This may suggest, therefore, that heightened insula monitoring of conflict and errors in ex-smokers is an important aspect contributing to nicotine abstinence, representing an important characteristic of individuals who successfully refrain from smoking.

Ex-smokers additionally exhibited a greater neural response during ERROR trials in the right MFG/BA46, compared to controls, but not smokers. This finding of greater ERROR-related neural activity in and around the right DLPFC is curious, given that only smokers elicited a reduction in this region

during STOP trials. The DLPFC has been implicated in maintaining stimulus information against interference from competing non-target stimuli (Casey et al., 2001), with increased ERROR-related DLPFC BOLD activation in ex-smokers possibly suggesting a preparatory, hypervigilant neural response to competition between approach (go) and avoidance (no-go) stimuli. This DLPFC response in ex-smokers, which may not be a requisite response in controls, may provide a neural signature which contributes to ongoing successful nicotine abstinence, but which is deficient in individuals who are currently nicotine-dependent. Taken together, these findings may signify both poorer error-monitoring throughout the cingulate gyrus as a consequence of ongoing and chronic nicotine use; with an increase in neural activity within this region and the DLPFC of ex-smokers, concomitant with a greater attentiveness to one's behaviour during extended nicotine abstinence.

Significantly greater ERROR-related neural activity was also observed in the right (medial) and left (lateral) superior frontal gyri (BA8 and BA9 regions respectively) of ex-smokers compared to both the control and smoker groups in Experiment 2. As these regions have previously been implicated in general executive functioning (Duncan et al., 2000) and error monitoring (Garavan et al., 2002; Kaufman et al., 2003), it would appear that ex-smokers may be "super normal" in these prefrontal regions, given that their neural responses significantly surpassed those of nicotine naïve controls, as well as those individuals who are currently nicotine-dependent. Importantly, recent research has shown that varenicline, an effective smoking cessation medication, diminishes cue-induced ventral striatal neural activity, concomitant with

increased activity in the cingulate and dorsolateral prefrontal cortex (Franklin et al., 2011), as well as improving working memory performance and associated neural functioning within lateral and midline prefrontal regions in smokers (Loughead et al., 2010). Therefore, the ability to maintain long-term nicotine abstinence may arise from neural hyperactivity within an assemblage of cognitive control neural networks, which may be exploited in addiction recovery to encode and monitor error behaviour more effectively.

Limitations

There were a number of limitations in the present study, which may necessitate a cautious interpretation of the findings. First, we had a small number of participants in each group for both experiments. Furthermore, three cigarette smokers were not included in Experiment 3. Also, the current study did not employ a structured clinical interview for DSM-IV Axis I diagnoses when recruiting participants from any group, but rather a semi-structured interview used on previous occasions (Hester et al., 2009; Nestor et al., 2010; Nestor et al., 2008; Roberts et al., 2009). Despite the strong co-occurrence between lifetime prevalence of depression and smoking (Khlat et al., 2004; Kushnir et al., 2010), we observed no group differences in mood using the Beck Depression Inventory and when screening participants for self-reported personal and familial mental health history. Furthermore, we cannot disqualify the potential confound of nicotine withdrawal in smokers during the testing session. While smokers were permitted to smoke *ad lib* prior to testing, withdrawal from, and cravings for, nicotine may have had an effect on task performance, and consequently, the neural correlates of behaviour during the

latter stages of scanning. This possibility may be tempered, however, by previous research demonstrating that acute withdrawal from nicotine actually increases neural activity related to cognitive functioning in smokers (Xu et al., 2005; Xu et al., 2007).

The second, and a potentially more important limitation, relates to our method of fMRI data analyses in both experiments. The two step analysis method employed here, whereby the regions-of-interest used for the between-group comparisons, functionally-defined by the groups, may appear to fall foul of the criticism articulated by Kriegeskorte and colleagues (2009). Two features of the present analysis mitigate this concern, however. First, the functionally-defined regions were defined with *t*-tests vs. zero (i.e. against the null hypothesis of no significant activation) rather than with between-group *t*-tests; the latter approach is more likely to maximise between-group differences and exacerbate a possible selection bias. Second, the regions were defined by all groups rather than by just one; significantly active regions in each group were combined using an OR operation such that the final set of ROIs were those activated in any or all groups and were thus not inherently biased towards any one group.

Conclusion

Preliminary studies have provided evidence for neuroadaptations in the prefrontal cortex following prolonged drug (i.e. alcohol, cocaine, opiate, methamphetamine and nicotine) administration, which may contribute to a loss of control and compulsive drug-seeking *per se*. Alcohol abuse, for

example, is associated with decrements in cognitive inhibitory control (Vogel-Sprott et al., 2001; Weafer et al., 2008). There is also evidence for alterations in the PFC (Sullivan et al., 2003), OFC (Volkow et al., 2007) and ACC (Ridderinkhof et al., 2004a) in alcoholism, possibly as a result of neuroadaptations within frontostriatal circuitry. Individuals with a history of chronic cocaine use demonstrate dysfunctional inhibitory control (Fillmore et al., 2002; Kaufman et al., 2003), together with functional deficits in frontal regions (Garavan et al., 2008; Goldstein et al., 2004; Goldstein et al., 2010; Hester et al., 2004), which may provide evidence for a dysregulation of ACC and DLPFC functioning. The severity of global cognitive impairment has also been demonstrated to render cocaine addicts less amenable to behavioural treatment (Aharonovich et al., 2006; Aharonovich et al., 2003), with poorer response inhibition and impulsivity, also shown to predict poor treatment retention (Moeller et al., 2001; Patkar et al., 2004; Streeter et al., 2008).

Chronic opiate use is associated with risky decision-making (Brand et al., 2008) and problems with inhibitory control (Ersche et al., 2007), with irregular neural functioning in OFC (Botelho et al., 2006) and ACC regions (Forman et al., 2004). Decision-making performance in opiate users (Passetti et al., 2008) and neural activation patterns related to decision-making in methamphetamine users (Paulus et al., 2005) have also been shown to predict abstinence and relapse in these populations, perhaps suggesting that the integrity of top-down processing in areas responsible for inhibitory control, error/risk detection and avoidance behaviour, are imperative to maintaining drug abstinence in general. Cigarette smokers have been shown to exhibit

higher rates of impulsivity than non-smokers (Mitchell, 1999; Waldeck & Miller, 1997) with evidence for poorer motor response inhibition (Mitchell, 2004). The long-term use of nicotine has also been associated with reduced grey matter volume in the DLPFC (Brody et al, 2004; Gazdzinski et al, 2005; Gallinat et al, 2006), potentially suggesting that the integrity of DLPFC-top-down cognitive control in smokers may precipitate impulsivity and provoke relapse.

While recent research has shown that the social harms to the individual and others using alcohol, cocaine, opiates and methamphetamine are higher than nicotine (Nutt et al., 2010), there appears to be strong evidence for deficits in cognitive control and associated neural responses across these populations. As treatment adherence may rely upon addicted individuals exercising greater prefrontally-mediated, executive control over drug-seeking behaviours (Everitt et al., 2008; Goldstein et al., 2002; Jentsch et al., 1999), the continued exploration of neural systems in both current addiction and abstinence, therefore, may elucidate neural loci which help predict drug relapse and inform us with respect to treatment intervention targets.

Experiment 1 has demonstrated a number of BOLD activation differences between smokers, ex-smokers using this attentional bias model, which may explicate important adaptive mechanisms which contribute to remaining abstinent. Experiment 2 showed reductions in motor response inhibition and hypofunctioning in brain regions traditionally associated with inhibitory control in chronic cigarette smokers. While there was some evidence for the residual

effects of nicotine on neural circuitry associated with inhibitory control, ex-smokers demonstrated significantly more neural activity during error monitoring compared to current smokers and nicotine naïve controls. Neural activity within circuits critically involved in error and performance monitoring, it is suggested, may have evolved from the practice that these processes receive as the ex-smoker monitors his/her behaviour during prolonged periods of abstinence. Therefore, the current findings may help clarify important adaptive control mechanisms which contribute to remaining abstinent. Longitudinal studies, which assess pharmacological and behavioural treatment approaches to augment nicotine abstinence (and abstinence from alcohol and drugs in general), may be successful in revealing how reducing attentional bias and increasing cognitive control protect against drug relapse; particularly in relation to controlling intrusive drug-related cognitions, behavioural inhibition and error-monitoring.

Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

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Table 1. Mean and SEM for the control, ex-smoker and smoker groups on demographic, nicotine and drug use history, withdrawal, dependence and craving measures for Experiment s 1 and 2 ([a]also shows demographic data for the 10 smokers who completed Experiment 2; [b]denotes usage prior to abstinence; ***p*<0.01 smoker>ex-smoker on nicotine withdrawal and craving; ****p*<0.001 smoker>ex-smoker and control on expired carbon monoxide).

	Control (n=13)	**Ex-smoker (n=10)**	**Smoker (n=13)**	**Smoker (n=10)a**
Age	23.6 ± 1.3	25.4 ± 1.6	24.3 ± 1.2	23.0 ± 1.0
Years of Education	17.3 ± 0.8	17.9 ± 0.9	16.8 ± 0.6	17.0 ± 0.9
Verbal Intelligence Score (NART)	122.9 ± 1.2	123.2 ± 1.0	121.0 ± 1.0	120.0 ± 1.3
Females/Males	8/5	7/3	6/7	5/5
Beck Depression Inventory (BDI) Score	1.5 ± 1.2	2.5 ± 1.9	1.0 ± 1.9	1.3 ± 0.7
Years of Alcohol Use	6.3 ± 1.3	9.0 ± 1.5	8.0 ± 1.2	6.9 ± 0.8
Alcohol Use in the Last Month (no. days)	6.4 ± 1.2	6.6 ± 1.6	8.8 ± 1.3	8.9 ± 1.4
Alcohol Use Age Onset (Years)	16.4 ± 0.4	16.4 ± 0.6	16.3 ± 0.5	1 6.1 ± 0.5
Years of Nicotine Use	0.0 ± 0.0	7.1 ± 1.7	7.7 ± 1.4	6.7 ± 1.2
Pack-Years	0.0 ± 0.0	5.9 ± 1.5**b**	5.4 ± 1.7	6.3 ± 1.7
Number of Cigarettes/Day	0.0 ± 0.0	16.0 ± 2.5	15.0 ± 1.3	14.7 ± 1.5
Nicotine Use in the Last Month (no. days)	0.0 ± 0.0	0.0 ± 0.0	29.6 ± 0.4	29.5 ± 0.5
Number of Packs in the Last Month	0.0 ± 0.1	0.0 ± 0.0	21.3 ± 2.3	20.8 ± 2.8
Nicotine Abstinence (wks)		84.8 ± 13.6		
Subscales of Shiffman/Javik Withdrawal Scale				
Craving		3.4 ± 0.2	3.4 ± 0.3	3.4 ± 0.4
Physical Symptoms		2.0 ± 0.3	1.7 ± 0.2	2.0 ± 0.4
Psychological Symptoms		3.4 ± 0.1	3.0 ± 0.2	3.1 ± 0.2
Sedation		3.8 ± 0.2	3.1 ± 0.2	3.2 ± 0.3
Appetite		2.0 ± 0.3	3.4 ± 0.4**	3.5 ± 0.4**
Total Score		14.4 ± 0.7	14.5 ± 0.7	14.9 ± 0.9
Fagerström Score			3.2 ± 0.5	3.2 ± 0.5
Urge to Smoke Scale Score		12.3 ± 1.1	33.9 ± 5.2**	38.0 ± 6.1**
Expired Carbon Monoxide (ppm)	3.0 ± 0.0	3.0 ± 0.0	15.2 ± 0.9	14.6 ± 1.1***

Table 2. Regions of activation during the neutral, evocative and drug conditions of the attentional bias paradigm in the control, ex-smoker and smoker groups. Shown are the regions for whole brain, small volume correction and region of interest analyses. Statistics shown are for 3 (Condition: neutral, evocative, drug) x 3 (Group: control, ex-smoker, smoker). The *p* values in parentheses indicate separate *post hoc* Bonferroni pair-wise comparison results between groups. Positive values for *x*, *y* and *z* Talairach co-ordinates denote, respectively, locations that are right, anterior and superior relative to the anterior commissure. Table abbreviations indicate: BA=Brodmann area; HS=hemisphere; Vol=activity cluster volume in microlitres; DLPFC=dorsolateral prefrontal cortex.

Structure	BA	HS	Vol (µl)	Centre of Mass			Statistics
				x	y	z	
Smoker<Control							
Precentral Gyrus	4	R	1971	34	-14	51	F=7.6, df=2, 99, *p*<0.01
Smoker<Control+Ex-smoker							
Posterior Cingulate Cortex	30	L	1531	-18	-51	8	F=5.7, df=2, 99, *p*<0.01 - smoker<control (*p*<0.05) and <ex-smoker (*p*<0.01)
DLPFC	9/46	L	10404	-45	22	22	F=5.2, df=2, 99, *p*<0.01 - smoker<control (*p*<0.05) and ex-smoker (*p*=0.01)
Ex-smoker>Control+Smoker							
Anterior Cingulate Cortex	32	R	4432	5	40	-5	F=9.2, df=2, 99, *p*<0.001 - ex-smoker>control and smoker
Insula	13	R	7730	36	18	8	F=5.8, df=2, 99, *p*<0.01 - ex-smoker>control (*p*<0.05) and smoker (*p*<0.01)
Smoker>Control							
Amygdala		L	267	-20	-4	-15	F=4.6, df=2, 99, *p*<0.05
Smoker>Ex-smoker							
Nucleus Accumbens		L	130	-12	8	-8	F=6.9, df=4, 198, *p*<0.05 - smoker>ex-smoker, drug condition
Nucleus Accumbens		R	157	12	8	-8	F=6.9, df=4, 198, *p*<0.05 - smoker>ex-smoker, drug condition
Drug>Neutral condition							
Thalamus		R	2090	12	-13	3	F=3.4, df=2, 99, *p*<0.05 - drug condition>neutral condition

Table 3. Regions activated for STOP trials in the control, ex-smoker and smoker groups. Statistics shown are for one-way ANOVAs (*p* values in parentheses indicate separate *post hoc* Bonferroni pair-wise comparison results between groups). Positive values for *x*, *y* and *z* Talairach coordinates denote, respectively, locations that are right, anterior and superior relative to the anterior commissure. Table abbreviations: BA=Brodmann area; HS=hemisphere; Vol=activity cluster volume in microliters.

Structure	BA	HS	Vol (µl)	Centre of Mass			Statistics
				x	y	z	
Smoker<Control							
Superior Frontal Gyrus	9	R	5330	30	49	34	F=8.7, df=2, 30, *p*=0.001
Superior Frontal Gyrus	10	R	704	29	57	1	F=5.9, df=2, 30, *p*<0.01
Middle Frontal Gyrus	9/46	L	606	-41	38	34	F=5.0, df=2, 30, *p*<0.05
Anterior Cingulate Cortex	32	R	3520	6	31	26	F=7.1, df=2, 30, *p*<0.01
Inferior Parietal Lobule	40	R	13421	42	-48	38	F=5.0, df=2, 30, *p*<0.05
Inferior Parietal Lobule	40	L	5317	-44	-55	50	F=4.8, df=2, 30, *p*<0.05
Control>Ex-smoker+Smoker							
Inferior Frontal Gyrus	44	L	1765	-59	6	17	F=9.0, df=2, 30, *p*=0.001 - control>ex-smoker (*p*<0.05) and smoker (*p*=0.001)
Precentral Gyrus	4	R	494	62	-13	32	F=11.0, df=2, 30, *p*<0.001 - control>ex-smoker (*p*<0.01) and smoker (*p*<0.001)
Postcentral Gyrus	2	L	1987	-58	-23	35	F=7.4, df=2, 30, *p*<0.01 - control>ex-smoker (*p*<0.05) and smoker (*p*<0.01)
Superior Temporal Gyrus		R	2247	37	4	-22	F=7.9, df=2, 30, *p*<0.01 - control>ex-smoker (*p*<0.05) and smoker (*p*<0.01)
Middle Temporal Gyrus	21	R	493	64	-38	-4	F=9.7, df=2, 30, *p*=0.001 - control>ex-smoker (*p*<0.01) and smoker (*p*=0.001)
Insula	13	R	4208	31	16	-5	F=9.1, df=2, 30, *p*=0.001 - control>ex-smoker (*p*<0.05) and smoker (*p*=0.001)
Insula		L	1584	-36	1	0	F=7.7, df=2, 30, *p*<0.01 - control>ex-smoker (*p*<0.05) and smoker (*p*<0.01)
Parahippocampal Gyrus		L	467	-38	-24	-10	F=6.7, df=2, 30, *p*<0.01 - control>ex-smoker and smoker (*p*<0.05)
Ex-smoker>Smoker							
Anterior Cingulate Cortex	32	L	560	-1	35	24	F=4.4, df=2, 30, *p*<0.05
Smoker<Control+Ex-smoker							
Middle TG		L	3643	-59	-48	-5	F=5.5, df=2, 30, *p*<0.01 - smoker<control (*p*<0.01) and ex-smoker (*p*<0.05)

Table 4. Regions activated for ERROR trials in the control, ex-smoker and smoker groups. Statistics shown are for one-way ANOVAs (*p* values in parentheses indicate separate *post hoc* Bonferroni pair-wise comparison results between groups). Positive values for *x*, *y* and *z* Talairach coordinates denote, respectively, locations that are right, anterior and superior relative to the anterior commissure. Table abbreviations: BA=Brodmann area; HS=hemisphere; Vol=activity cluster volume in microliters.

Structure	BA	HS	Vol (µl)	Centre of Mass			Statistics
				x	y	z	
Smoker<Control							
Superior Frontal Gyrus	10	R	506	23	62	2	F=6.9, df=2, 30, *p*<0.05
Superior Temporal Gyrus	22	L	311	-62	-34	-8	F=3.6, df=2, 30, *p*<0.05
Ex-smoker>Control							
Superior Frontal Gyrus	9	L	5131	-24	-48	-33	F=4.8, df=2, 30, *p*<0.05
Middle Frontal Gyrus	46	R	2013	41	36	20	F=3.6, df=2, 30, *p*<0.05
Middle Frontal Gyrus		R	1890	40	21	40	F=4.9, df=2, 30, *p*<0.05
Insula	13	L	18558	-42	13	-2	F=6.7, df=2, 30, *p*<0.01
Superior Temporal Gyrus	39	R	12225	47	-57	26	F=5.3, df=2, 30, *p*<0.05
Superior Temporal Gyrus	39	L	4519	-54	-62	27	F=3.8, df=2, 30, *p*<0.05
Ex-smoker>Smoker							
Superior Frontal Gyrus		R	5339	19	50	30	F=3.8, df=2, 30, *p*<0.05
Anterior Cingulate Cortex	24	L	12687	-1	31	24	F=3.5, df=2, 30, *p*<0.05
Posterior Cingulate Cortex	24	L	7332	-1	-24	35	F=3.7, df=2, 30, *p*<0.05
Middle Temporal Gyrus		L	2002	-56	-46	-5	F=6.0, df=2, 30, *p*<0.01
Cerebellar Tuber		L	1197	-44	-61	-30	F=4.1, df=2, 30, *p*<0.05
Ex-smoker>Control+Smoker							
Superior Frontal Gyrus	8	R	1490	2	32	54	F=6.7, df=2, 30, *p*<0.01 - ex-smoker>control and smoker (*p*<0.01)
Superior Frontal Gyrus	9	L	621	-41	36	31	F=6.2, df=2, 30, *p*<0.01 - ex-smoker>control and smoker (*p*<0.05)
Middle Frontal Gyrus		R	2066	30	5	57	F=8.1, df=2, 30, *p*<0.01 - ex-smoker>control (*p*<0.01) and smoker (*p*<0.05)
Middle Temporal Gyrus	21	L	397	-51	5	-28	F=4.6, df=2, 30, *p*<0.05 - ex-smoker>control and smoker (*p*<0.05)
Middle Temporal Gyrus		L	1524	-56	-21	-14	F=6.7, df=2, 30, *p*<0.01 - ex-smoker>control and smoker (*p*<0.01)

Parahippocampal Gyrus	35	R	1840	28	-24	-22	F=10.3, df=2, 30, p<0.001 - ex-smoker>control (p=0.001) and smoker (p<0.01)
Parahippocampal Gyrus	35	L	512	-25	-23	-20	F=11.5, df=2, 30, p<0.001 - ex-smoker>control (p<0.01) and smoker (p=0.001)
Cerebellar Tonsil		L	330	-19	-57	-36	F=9.9, df=2, 30, p<0.001 - ex-smoker>control (p<0.001) and smoker (p<0.01)

Figure 1. Attentional bias paradigm where participants were required to make a response to the colour of a border (blue, yellow, green and red) surrounding neutral, evocative and smoking-related stimuli, with a button press using one of four different coloured keys (blue, yellow, green and red).

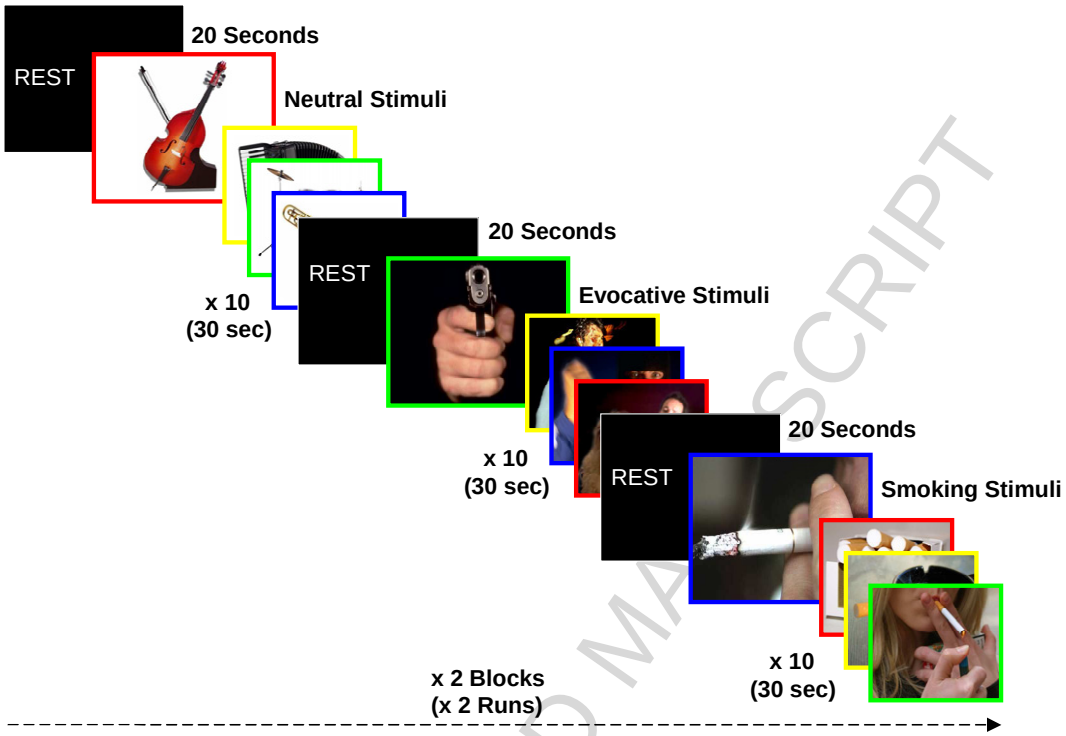

Figure 2. Percentage BOLD change for the control, ex-smoker and smoker groups in a) the left posterior cingulate cortex (PCC)/BA30 (smoker<control, p<0.05 and ex-smoker, p<0.01 across conditions; b) the left dorsolateral prefrontal cortex (DLPFC) small volume correction (smoker<control, p<0.05 and ex-smoker, p=0.01 across conditions); c) the right anterior cingulate cortex (ACC)/BA32 (ex-smoker>control and smoker, p<0.001 across conditions) and d) the right insula/BA13 (ex-smoker>control, p<0.05 and smoker, p<0.01 across conditions). Data expressed as means ± SEM.

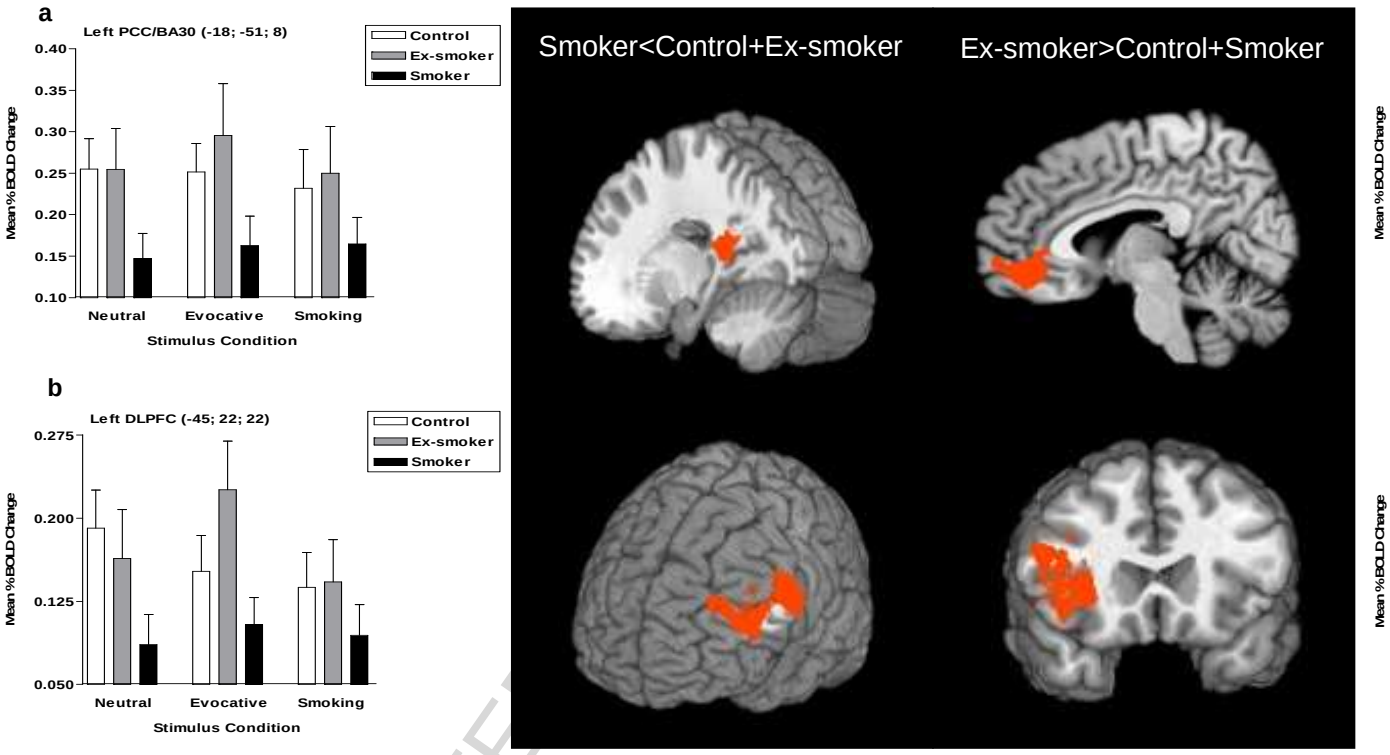

Figure 3. Percentage BOLD change for the control, ex-smoker and smoker groups in a) the left amygdala small volume correction (smoker>control, $p<0.01$ across conditions); b) right nucleus accumbens (NAcc) region of interest (ROI) average and c) the left NAcc ROI average (smoker>ex-smoker on the drug condition, $p=0.01$across hemispheres). Data expressed as means ± SEM.

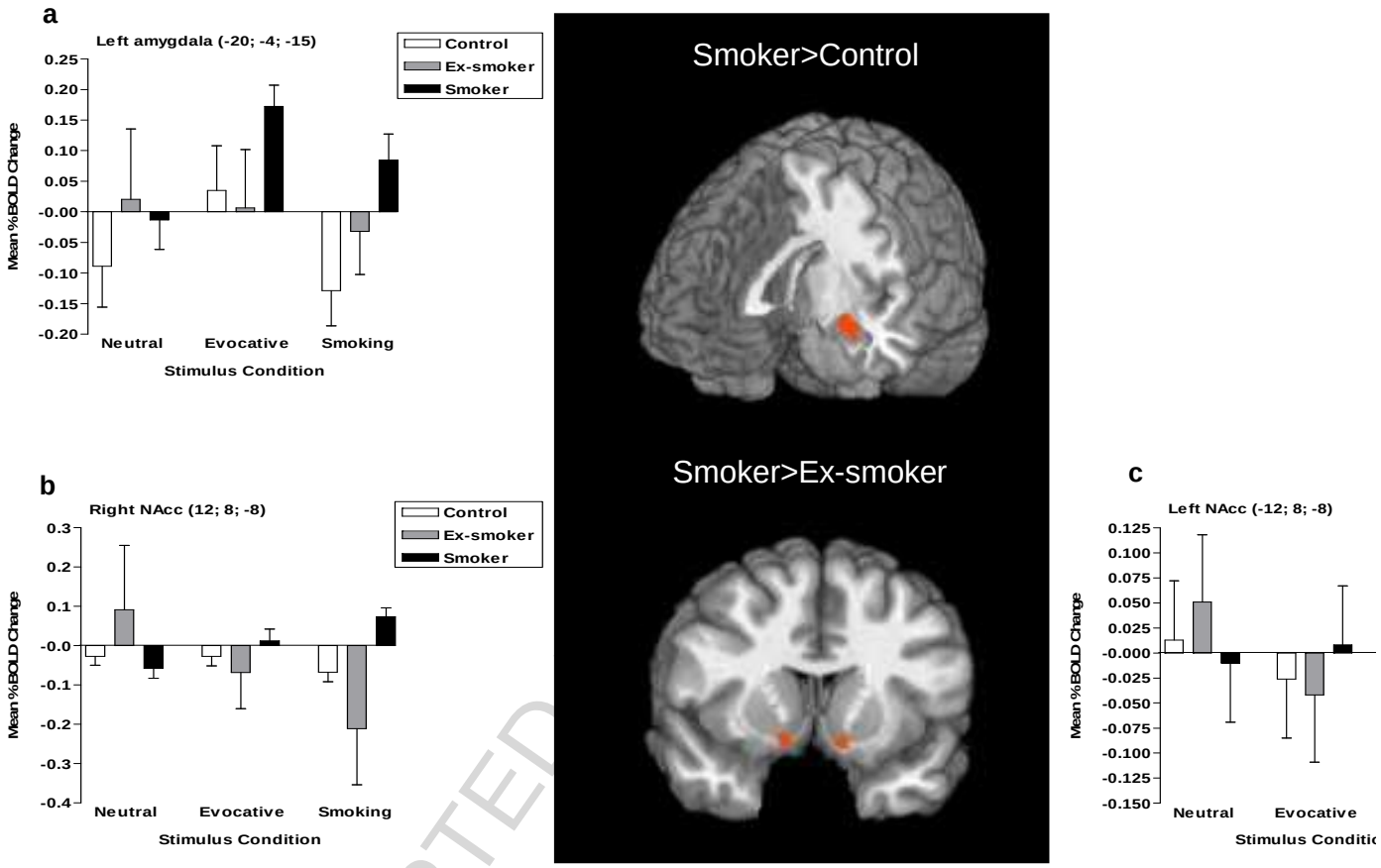

Figure 4. Control, ex-smoker and smoker groups performance scores on a) percentage STOP accuracy (*p<0.05 versus control, **p<0.01 versus ex-smoker); b) the mean ERROR reaction time (*p<0.05 versus control and smoker); c) mean percentage omission errors and d) mean GO trial reaction time (*p<0.05 versus control and smoker). Data expressed as means and SEM.

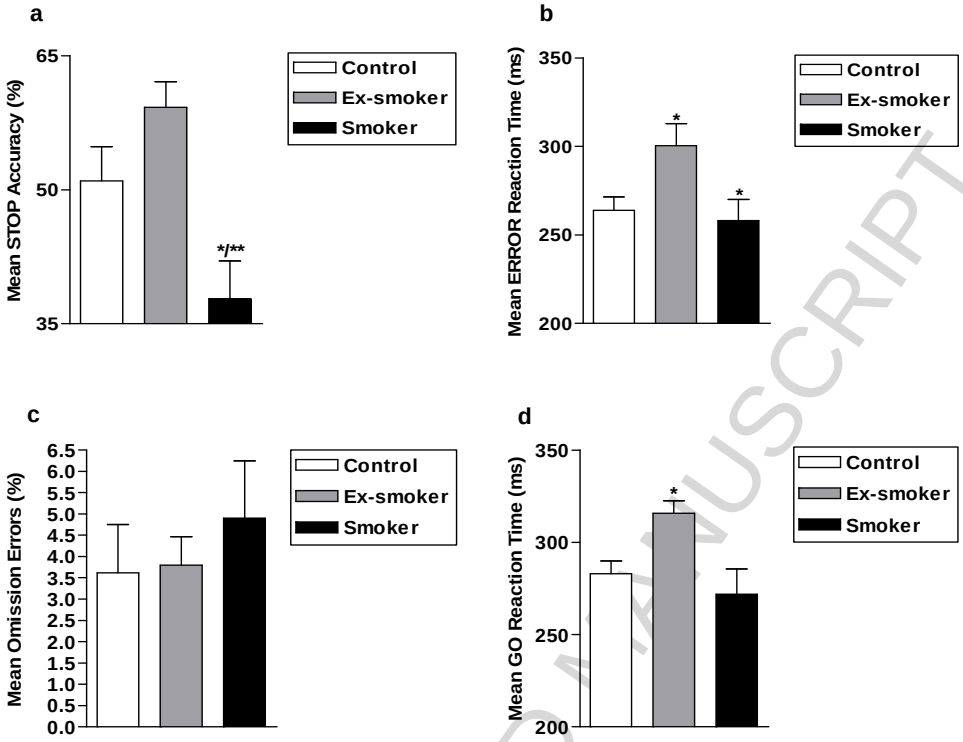

Figure 5. Percentage BOLD change for the control, ex-smoker and smoker groups during STOPs in a) the right anterior cingulate (ACC) (smoker<control, p<0.01); b) the right middle frontal gyrus (MFG)BA9/46 (smoker<control, p<0.05); c) the left anterior cingulate (ACC) (ex-smoker>control, p<0.05) and d) the left inferior frontal gyrus (IFG)/BA44 (control>ex-smoker, p<0.05 and smoker, p<0.01). Data expressed as means ± SEM.

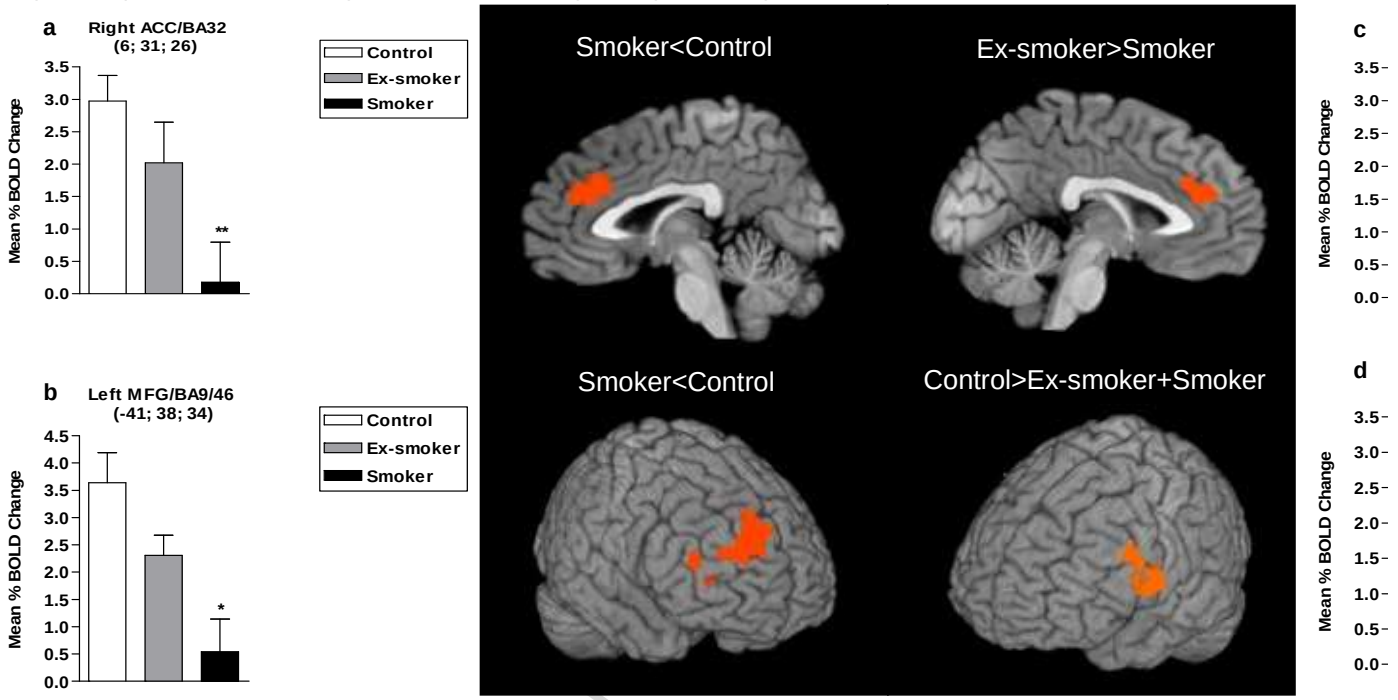

Figure 6. Percentage BOLD change for the control, ex-smoker and smoker groups during ERRORs in a) the right superior frontal gyrus (rSFG)/BA10 (smoker<control, $p<0.05$) and b) right middle frontal gyrus (MFG)BA46 (ex-smoker>control and smoker, $p<0.05$). Data expressed as means ± SEM.

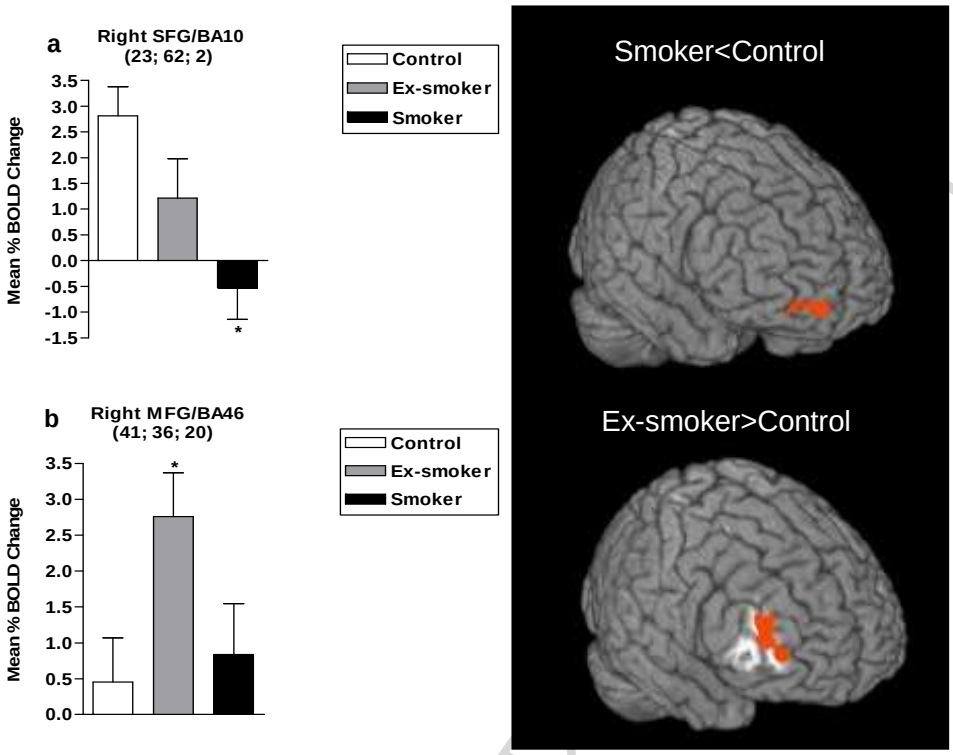

Figure 7. Percentage BOLD change for the control, ex-smoker and smoker groups during ERRORs in a) the left posterior cingulate (PCC)/BA24; b) the left anterior cingulate (ACC)/BA24 (ex-smoker>smoker, $p<0.05$); c) the right superior frontal gyrus (SFG)/BA8 (ex-smoker>control and smoker, $p<0.01$) and d) the left superior frontal gyrus (SFG)/BA9 (ex-smoker>control and smoker, $p<0.05$). Data expressed as means ± SEM.

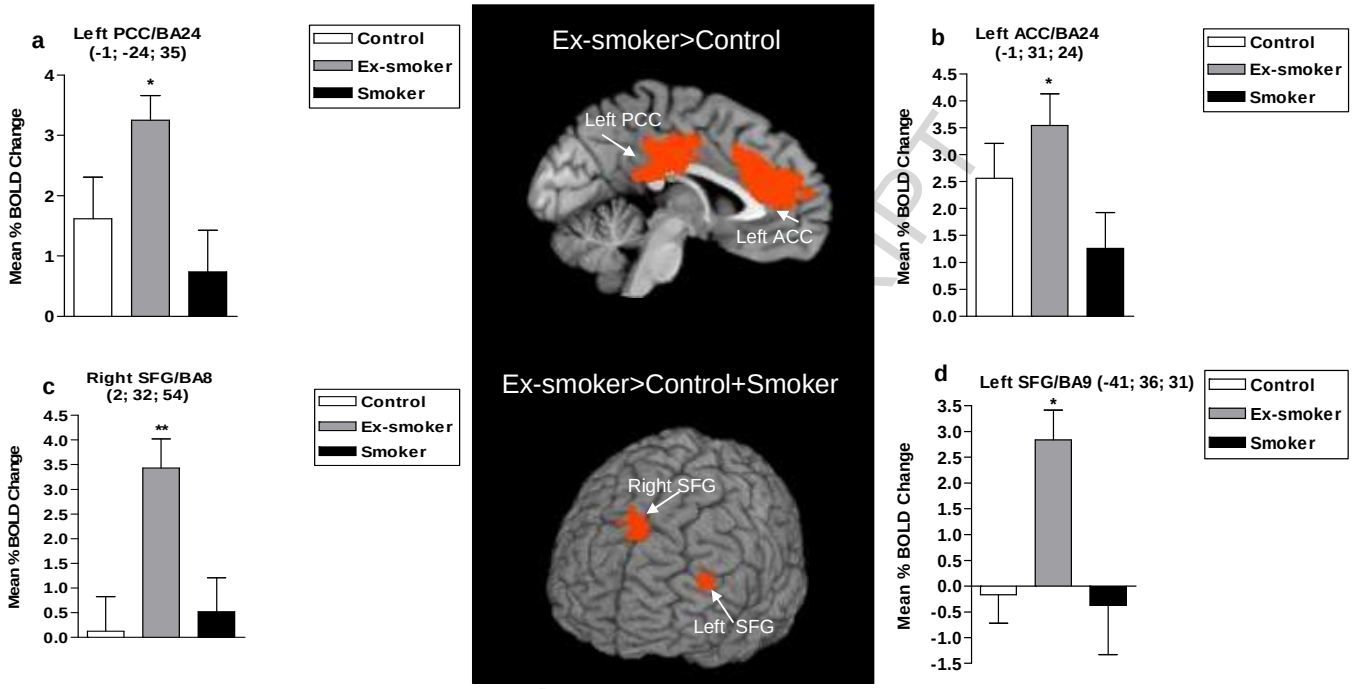

Figure 8. Correlations in the smoker group between Fagerström test of nicotine dependence (FTND) score and ERROR BOLD activity (mean percentage BOLD change) in a) the right superior frontal gyrus/BA10 and b) the left insula/BA13.