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The neurobiology of cognitive control in successful cocaine abstinence

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ABSTRACT

Introduction: Extensive evidence demonstrates that current cocaine abusers show hypoactivity in anterior cingulate and dorsolateral prefrontal cortex and respond poorly relative to drug-naïve controls on tests of executive function. Relatively little is known about the cognitive sequelae of long-term abstinence in cocaine addicts.
Methods: Here, we use a GO–NOGO task in which successful performance necessitated withholding a prepotent response to assay cognitive control in short- and long-term abstinent cocaine users (1–5 weeks and 40–102 weeks, respectively).
Results: We report significantly greater activity in prefrontal, cingulate, cerebellar and inferior frontal gyrii in abstinent cocaine users for both successful response inhibitions and errors of commission. Moreover, this relative hyperactivity was present in both abstinent groups, which, in the presence of comparable behavioral performance, suggests a functional compensation.
Conclusions: Differences between the short- and long-abstinence groups in the patterns of functional recruitment suggest different cognitive control demands at different stages in abstinence. Short-term abstinence showed increased inhibition-related dorsolateral and inferior frontal activity indicative of the need for increased inhibitory control while long-term abstinence showed increased error-related ACC activity indicative of heightened behavioral monitoring. The results suggest that the integrity of prefrontal systems that underlie cognitive control functions may be an important characteristic of successful long-term abstinence.

1. Introduction

Addiction is characterized by an uncontrollable, compulsive drive to obtain and consume an abused drug, despite the profound negative health and social consequences likely to ensue (Everitt et al., 2001; Garavan and Stout, 2005; Goldstein and Volkow, 2002). Substance dependent individuals preferentially select actions that yield short-term gains, though they may lead to long-term losses (Bechara and Damasio, 2002). They are more likely to engage in risky behavior (Lane and Cherek, 2000) and show less consideration of the consequences of their actions (Petry et al., 1998). Arguably, these traits are related to executive dysfunction (Lyvers, 2000) wherein chronic cocaine users show deficits in the brain structures implicated in cognitive control of behavior, in particular, in regions thought to be the seat of higher executive brain functions (Miller and Cohen, 2001). Indeed, chronic cocaine users consistently demonstrate impairments on neuropsychological tests of executive function (Ardila et al., 1991; Di Sclafani et al., 2002; Yücel et al., 2007).

Two important aspects of executive control implicated in addiction are inhibitory control and performance monitoring (Garavan and Hester, 2007). Performance monitoring processes (e.g., error detection and conflict monitoring) have been ascribed to the anterior cingulate cortex (ACC) (Botvinick et al., 1999, 2001; Kiehl et al., 2000; MacDonald et al., 2000; Menon et al., 2001; Ruchsow et al., 2002; Ullsperger and von Cramon, 2001; van Veen and Carter, 2002).

One model of cognitive control asserts that when erroneous or conflicting behavior is detected by the ACC, it signals to lateral prefrontal cortex (PFC) regions responsible for maintaining goal-oriented behavior that greater levels of control are necessary to successfully perform a task (Botvinick et al., 2001 see Silton

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et al., 2010 for an alternative interpretation). Increased top-down control should reduce conflict by biasing the system away from the incorrect, conflict-causing response and towards the correct, conflict-reducing response (Botvinick et al., 2001; Fassbender et al., 2009). With regard to addiction and specifically abstinence, this monitoring process may be important in detecting risky situations or behaviors that increase the likelihood of relapse (Garavan and Stout, 2005).

Previous investigations of inhibitory control in cocaine addicts have shown reduced prefrontal activity relative to controls (Fillmore and Rush, 2002; Goldstein et al., 2001; Kaufman et al., 2003) and there is evidence that cocaine addicts appear to rely more heavily on a suboptimal cerebellar pathway to successfully inhibit a prepotent response (Hester and Garavan, 2004). These findings are consistent with theories implicating cocaine-induced damage to the mesencephalic dopamine (DA) system (Franken et al., 2005; Spanagel and Weiss, 1999). It is thought that blockade of dopamine transporters produces elevated synaptic DA levels, chronic exposure to which may account for both the reduced DA receptors and metabolism seen in users (Koob and Le Moal, 1997; Volkow et al., 1993). Inhibitory control has also been identified as a risk factor for addiction that precedes drug use (Dalley et al., 2007; Tarter et al., 2003; Verdejo-García et al., 2008). Performance and neuroimaging data on Stroop and decision-making tasks have been shown to predict likelihood of completing treatment in substance abusers (Brewer et al., 2008; Paulus et al., 2005; Streeter et al., 2008) as has cognitive functioning (Aharonovich et al., 2006; Turner et al., 2009). As these tasks are known to activate the neuronal circuits underlying cognitive control, this indicates that these circuits may play an important role in abstinence.

Previous studies of abstinent drug users have typically investigated short-term abstinence and have revealed many persistent deficits, which are more pronounced in heavy users, in the regions associated with cognitive control and reward anticipation (Bolla et al., 2004, 2003). Relative to controls, abstinent cocaine abusers have been shown to have reduced metabolism in left ACC and right dorsolateral prefrontal cortex (DLPFC), and greater activation in right ACC. Indeed, activity in some of these regions predicts relapse in both abstinent cocaine and methamphetamine abusers (Kosten et al., 2006; Paulus et al., 2005; Wexler et al., 2001) with individuals showing more ACC activity at the onset of abstinence being less likely to relapse subsequently. It has previously been suggested that the general pattern of prefrontal hypoactivity in drug users may ameliorate with increasing abstinence from drug consumption (Volkow and Fowler, 2000) and indeed abstinence from cocaine use has been shown to reduce high-risk responses on a gambling task (Bartzokis et al., 2000). GO/NOGO tasks in which the GO/NOGO ratio is low thereby creating a prepotent response that is difficult to inhibit on NOGO trials provide a useful assay of cortical activity underlying inhibitory control and action monitoring. Indeed cocaine addicts have shown impaired performance in these tasks (Fillmore and Rush, 2002; Fillmore et al., 2002). We hypothesized that such a task would be useful for evaluating any functional change that may occur in the cortical circuits underlying inhibitory control and action monitoring over abstinence.

Just as not all people with a propensity to develop addiction do so, not all addicts successfully complete treatment. Indeed, treatment programs typically have very high dropout rates (Carroll et al., 1994; Simpson et al., 1999) reflecting the relapsing nature of the disease. This means that very little is known about the neurobiology of successful long-term abstinence as the high attrition and relapse rates of longitudinal studies pose significant impediments to assessing long-term abstinence effects prospectively. Another research approach is to recruit and characterize individuals known to have been abstinent for varying durations. While this approach cannot reveal whether neurobiological differences in abstinent users preceded or arose from that abstinence, it can nonetheless characterize the functioning of those who have demonstrated the ability to abstain for either short or long periods. Here, we investigate what role cognitive control may play in abstinence, both short- and long-term. We hypothesized that any changes that may occur with prolonged abstinence or any pre-existing differences that might facilitate successful abstinence would be reflected in functional brain measurements of cognitive control.

2. Materials and methods

2.1. Participants and task design

Twenty-seven volunteers (21 male; mean age 33.2 years, range: 22–45) participated in this study, which was approved by the Institutional Review Board of the Nathan Kline Institute for Psychiatric Research (NKI). Participants gave informed written consent and were compensated for their participation.

Abstinent cocaine dependent (CD) users were patients in the Daytop Village Inc., a large therapeutic community with multiple treatment sites in the New York City area. Controls were recruited from the community via the NKI volunteer program and had no history of substance abuse disorders. Participants were recruited over the course of 5 months by a psychiatrist (JN) visiting the treatment site to make a presentation about the study. Interested participants were prescreened and signed a consent form to be enrolled in the study. The protocol described here was part of a larger study investigating the effects of abstinence on grey and white matter. All participants were screened with the Structural Clinical Interview for the DSM-IV – TR (SCID) by a psychiatrist (JN) or a SCID-certified research assistant (First et al., 2002). CD participants had no lifetime history of substance dependence (other than cocaine and nicotine) but were eligible for the study if they met criteria for abuse (lifetime or current) of other substances. Participants with any history of neurological disorders, psychiatric illness, head trauma, contra-indications for MRI, or HIV seropositivity were excluded. CD participants were excluded if they did not have continuous treatment or tested positive during the reported abstinence period. Participants early in treatment were monitored on a 24-h basis, were subject to periodic random urine toxicology screens, and were not permitted to leave the facility without an escort. Those later in treatment were allowed leave the facility on their own recognizance but were evaluated by clinical staff (including urine toxicology) upon their return. Subjective data on drug use and abstinence history (including date of last use) were collected from participants and corroborated with records from clinical charts, lab tests and interviews with clinical staff. On the day of scanning, representatives of the Daytop Village transported participants to and from NKI where all behavioral and MRI measurements occurred.

Abstinent CD participants were divided into two groups depending on length of abstinence from their last cocaine consumption. The long-term abstinent (LA) group ($n = 9$) had not consumed cocaine for on average 69 weeks (SD = 17.49, range: 40–102). The short-term abstinent (SA) group ($n = 9$) had refrained from consumption for on average 2.4 weeks (SD = 1.34, range: 1–5.1) prior to scanning. Average length of use prior to abstinence for the LA group was 10.67 years (SD = 7.63, range: 1.5–23) and for the SA group was 12.11 years (SD = 5.01, range: 1–18). This difference was not significant (Welch $t(13.81) = -0.47$, $p > 0.05$). A further group of nine cocaine-naïve participants constituted the control group (see Table 1).

Handedness (Oldfield, 1971) and socio-economic status (Hollingshead, 1975) of participants was assessed and participants were administered the Barratt Impulsivity test (Patton et al., 1995), the Buss Perry aggression test (Buss and Perry, 1992) and the Kreek–McHugh–Schluger–Kellogg (KMSK) scale (Kellogg et al., 2003) to assess drug use history. These assessments were included to characterize the participants and evaluate whether these traits would change with abstinence. Socioeconomic status (which includes educational status) has previously been linked with attrition rates from treatment programs (Alterman et al., 1996) and consumption of drugs of abuse (Miech and Chilcoat, 2007), as has aggression (Brook et al., 1995) and impulsivity (de Wit, 2009; Verdejo-García et al., 2008).

Participants completed a GO/NOGO task based on our earlier work (Garavan et al., 1999) and which has been shown previously to reveal functional hypoactivity in current cocaine users (Kaufman et al., 2003). The letters X and Y were serially presented, alternating at 1 Hz and participants were required to make a button press response to each letter. Responses and reaction times were recorded. Participants were instructed to withhold their response on NOGO trials, that is, trials in which the alternating pattern was broken. For example, in the stimulus train X Y X Y Y X, participants were to withhold their response to the fifth letter. The stimuli were presented for 900 ms followed by a 100 ms blank screen. Participants were instructed to respond while the letter was on the screen. Participants completed four runs each containing 315 GO and 20 NOGO stimuli totaling 1260 GO trials and 80 NOGO trials.

2.2. Scanning parameters and data analysis

Functional images were acquired in contiguous 5 mm transverse slices using a blipped gradient-echo echo-planar pulse sequence (TE = 50 ms, TR = 2000 ms,

Table 1
Demographic characteristics for the control and abstinent cocaine groups. Entries are of the form: mean/standard deviation (min-max). The (optional) number in square brackets indicates the number of participants with no data. All observations were compared by ANOVAs. For the pair-wise contrasts (Tukey's Honest Significant Difference test) C = control, LA = long and SA = short and $p \leq 0.05$. Drug use information was compiled from a combination of SCID, KMSK, and clinical records.

Characteristic	Control	Short	Long	Signif.	Pairwise differences
Number of participants	9	9	9		
Gender M/F	7/2	7/2	7/2		
Age at time of scanning (years)	30.5/6.7 (22.8–44.4)	36.4/6.6 (25.8–45.8)	32.8/8.3 (22–44.1)		
Edinburgh handedness (1 = right)	0.7/0.6 (−0.7–1) [1]	0.8/0.4 (−0.2–1)	0.9/0.1 (0.8–1)		
Years of education	16/3.6 (12–20)	12.4/1.8 (10–16)	10.2/2 (7–13)	***	LA < C; SA < C
Years of use	Not applicable	12.1/5.0 (1–18)	10.6/7.6 (1.5–23)		
Lifetime usage (g)	Not applicable	3911/1937 (1924–8008)	10712/12213 (243–33310)		
Avg. weekly use just prior to treatment (g)	Not applicable	11.3/7.4 (2–25)	29.2/37.3 (1–105)		
Typical usage (g/week)	Not applicable	12.8/19.2 (2–63)	19.3/21.2 (3–70)		
Task performance					
Percent correct responses	50.6/13.1 (30.5–68.3)	56.1/11.6 (36.3–76.5)	52.4/9.3 (41.5–69.5)		
Incorrect inhibitions (ERRORS) RTs	272.9/54.2 (202.1–352.2)	278.5/47.4 (216.7–359.7)	307.3/76.2 (215.3–451.8)		
GO Trial RTs	315.7/56.1 (239.6–404.4)	339.7/52.6 (271.7–411.1)	352.1/50 (282.5–423.6)		
Socioeconomic status					
Parental socioeconomic status	2.1/1.2 (1–5)	2.9/1.1 (2–5)	2.4/1.2 (1–5)		
Participant socioeconomic status	2.2/1.1 (1–4)	2.6/0.7 (1–3)	3.7/0.9 (2–5)	**	LA > SA; LA > C
Barratt's impulsiveness scale					
Total	56.3/6.4 (46–64)	70.4/13.7 (57–88)	57.7/8.5 (48–70)	*	LA < SA; SA > C
Motor subscale	17.6/3.8 (13–24)	23.2/4 (17–30)	20.1/4.2 (14–27)	*	SA > C
Attention subscale	19.2/3.2 (14–23)	22.8/6.6 (13–31)	19.6/2.8 (14–23)		
Non-planning subscale	19.6/1.3 (18–22)	24.4/5.7 (18–32)	18/3.9 (11–22)	**	LA < SA; SA > C
Buss Perry aggression scale					
Total	45.3/8.4 (34–60)	74.2/25.4 (41–120)	83.3/16.3 (59–109)	***	LA > C; SA > C
Physical subscale	13.4/3.8 (9–20)	21/8.1 (11–37)	25.8/7.3 (15–33)	**	LA > C
Verbal subscale	10/2.6 (8–15)	13.3/4.2 (9–20)	15.3/3.6 (9–20)	*	LA > C
Anger subscale	10.8/2.4 (8–16)	18.4/8 (9–33)	21/5.5 (13–28)	**	LA > C; SA > C
Hostility subscale	11.1/4.3 (8–21)	21.4/9.2 (10–36)	21.6/5.1 (13–28)	**	LA > C; SA > C

* $p \leq 0.05$ refers to the corresponding ANOVA.
** $p \leq 0.01$ refers to the corresponding ANOVA.
*** $p \leq 0.001$ refers to the corresponding ANOVA.

FOV = 224 mm, 64 × 64 matrix, 3.5 mm × 3.5 mm in-plane resolution). All scanning was conducted on a 1.5T Siemens VISION scanner (Erlangen, Germany) equipped with a 30.5-cm i.d. three-axis local gradient coil and an end-capped quadrature birdcage radio-frequency head coil. High-resolution T1-weighted MPRAGE anatomical images (TE = 4.9 ms, TR = 11.6 ms, flip angle 8°, FOV 256 mm, slice thickness 1 mm, matrix 256 × 256 × 180) were acquired after functional imaging to permit subsequent activation localization and spatial normalization. Stimuli were back-projected onto a screen at the participants' feet and were viewed with the aid of prism glasses that were attached to the head coil.

Functional analyses were conducted using AFNI (Cox, 1996). After reconstruction, differences in slice acquisition timing were corrected using Fourier interpolation. The time-series was then motion corrected (least-squares alignment using three translational and three rotational parameters). Separate hemodynamic response functions for successful inhibitions (STOPS) and errors of commission (ERRORS) were then calculated using deconvolution based on each participant's behavioral data. A γ-variate function was then fitted voxelwise to these hemodynamic response functions using non-linear regression (Murphy and Garavan, 2005). Brain activation was operationally defined as the area under these event-related response functions expressed as a percentage of the area under the baseline. For this task, the baseline is implicit and reflects tonic task-related activity. The whole-brain activation maps were then warped into a standard stereotaxic ($1\ mm^3$) space (Talairach and Tournoux, 1988) and spatially blurred using a 4.2 mm isotropic FWHM Gaussian filter kernel. For each of the two trial types, whole-brain one-sample *t*-tests against the null hypothesis of no event-related activity determined within-group activation maps separately for each group. Significant voxels passed a voxelwise statistical threshold ($t = 3.83$, $p < 0.005$) and, to control for multiple comparisons, were required to be part of a larger 270 μl cluster. The volume threshold was determined by means of a Monte-Carlo simulation and resulted in 5% probability (corrected) of a cluster surviving due to chance.

In order to conduct between-group comparisons, the group activation maps were then combined to create separate OR maps for STOPs and ERRORs. An OR map included the voxels in clusters indicated as significant from any of the three constituent group maps. Mean activation levels of the clusters in the combined maps were calculated for each participant to allow a series of between-group ANOVAs to be conducted, using R (R Development Core Team, 2010), on these functionally defined ROIs. Due to significant differences (described below), total scores for the Buss Perry aggression scale and Barratt's impulsiveness scale, and scaled participant socioeconomic status were included as covariates in all fMRI regions of interest ANOVAs for STOPS, ERRORS and aggregate regions described below. Unless otherwise stated, pairwise *post hoc* differences between groups were assessed using Tukey's Honest Significant Difference test (HSD).

3. Results

3.1. Demographics

There were no significant between-group differences in age ($F_{(2, 24)} = 1.52$, $p > 0.05$) or handedness ($F_{(2, 23)} = 0.66$, $p > 0.05$) (one subject was omitted from the latter ANOVA due to missing information; see Table 1 for complete demographic information).

An analysis of variance revealed a significant difference on Barratt's impulsivity scale (BIS) (total) ($F_{(2, 24)} = 5.42$, $p \leq 0.05$). Tukey's HSD revealed that the control group differed significantly from the SA group ($p \leq 0.05$), the SA and LA groups also differed significantly ($p \leq 0.05$), and the control and LA groups were not significantly different ($p > 0.05$). ANOVAs of the Buss Perry (BP) aggression test also revealed significant differences ($F_{(2, 24)} = 10.81$, $p \leq 0.001$). Tukey's HSD showed that the control group differed significantly from the LA ($p \leq 0.001$) and SA ($p \leq 0.01$) groups but that the LA and SA groups did not differ ($p > 0.05$). The groups did not differ on parental socioeconomic status (SES) ($F_{(2, 24)} = 1.02$, $p > 0.05$) but did on participant SES ($F_{(2, 24)} = 6.24$, $p < 0.01$) with the LA group being greater than both SA and control groups ($p < 0.05$).

3.2. Behavioral results

There were no significant between-group differences in reaction times (RTs) for incorrect inhibitions ($F_{(2, 24)} = 0.83$, $p > 0.05$) or GO stimuli ($F_{(2, 24)} = 1.09$, $p > 0.05$). Similarly, no between-group differences were observed in the percentage of successful inhibitions ($F_{(2, 24)} = 0.53$, $p > 0.05$).

3.3. Event-related fMRI results

3.3.1. Stops. The regions observed for STOPS (Table 2) were consistent with meta-analyses of this and similar tasks (Buchsbaum

Table 2
Correct inhibitions (STOPS). BA is Brodmann's area, volumes are in micro-liters and center-of-mass coordinates are in the Talairach & Tournoux atlas. RL: right–left, AP: anterior–posterior, IS: inferior–superior. For the pair-wise contrasts (Tukey's Honest Significant Difference test) C = control, LA = long and SA = short and $p \leq 0.05$.

Structure	Hemisphere	BA	Volume	RL	AP	IS	Significance	Pairwise differences
Limbic system								
Cingulate gyrus	R	24	323	−1	−8	31		
Posterior cingulate	R	23	367	−4	27	23		
Frontal lobes								
Inferior frontal gyrus	L	47	707	34	−24	−4	*	LA < SA
Inferior frontal gyrus	R	47	254	−45	−27	4	***	LA > C; LA > SA
Medial frontal gyrus	R	6	423	−1	−34	34		
Middle frontal gyrus	R	9	983	−42	−9	35	***	LA > C; SA > C; LA < SA
Middle frontal gyrus	R	10	292	−38	−52	5		
Middle frontal gyrus	R	46	276	−43	−39	23		
Precentral gyrus	L	6	381	42	2	31		
Precentral gyrus	R	6	295	−47	1	46	*	LA > C; SA > C
Superior frontal gyrus	L	10	421	31	−51	22	**	LA < SA
Superior frontal gyrus	R	9	523	−36	−34	33	**	SA > C
Superior frontal gyrus	R	6	425	−4	−14	48	*	
Temporal lobes								
Middle temporal gyrus	R	22	308	−58	49	9	*	SA > C; LA < SA
Middle temporal gyrus	R	37	276	−50	40	−4		
Superior temporal gyrus	L	22	275	54	8	−5	**	LA < C; LA < SA
Superior temporal gyrus	R	13	283	−57	42	21		
Parietal lobes								
Inferior parietal lobule	R	40	2307	−48	50	38		
Precuneus	R	39	1315	−31	59	39	*	
Subcortical								
Cerebellar tonsil	L		513	35	39	−41	**	LA > C
Insula	R	13	2125	−38	−17	−1		
Thalamus	R		471	−12	14	9	*	LA > SA
Cerebellar tonsil	R		326	−37	55	−32	*	LA > C; LA > SA
Caudate	L		273	10	−6	11		

* $p \leq 0.05$ and refers to the corresponding ANOVA.
** $p \leq 0.01$ and refers to the corresponding ANOVA.
*** $p \leq 0.001$ and refers to the corresponding ANOVA.

et al., 2005; Garavan et al., 2006). We observed frontal activation in inferior, middle, superior, and medial frontal gyrii and non-frontal activation in temporal, parietal, cerebellar and subcortical regions. The analysis of group differences revealed a general pattern wherein LA and SA users had greater activation than control participants. Of those regions showing significant between-group ANOVA differences, relative to controls, the users showed greater activity in predominantly prefrontal and precentral cortex with the LA group also showing increased bilateral cerebellar activity. More specifically, pairwise *post hoc* tests showed the SA group with greater activity than controls in the right middle frontal gyrus (RMFG), right precentral gyrus, right superior frontal gyrus (RSFG), and one right middle temporal region. The LA group showed greater activity than controls in right inferior frontal gyrus (RIFG), RMFG, right precentral gyrus, left superior temporal gyrus (LSTG), and one region in each of the right and left cerebellar tonsils.

With respect to pairwise comparisons between the user groups, the LA group displayed greater activity than the SA group in the RIFG, right thalamus, and right cerebellar tonsil. Conversely, the SA group demonstrated greater activity than the LA group in LIFG, RMFG and LSFG, right middle temporal gyrus and LSTG regions.

Based on the observation of different patterns of group effects in the left and right IFG, a 2 × 3 (hemisphere × group) ANOVA was conducted on the mean activation in the left and right functionally-define IFG regions. Group was not significant ($F_{(2, 45)} = 1.28, p > 0.05$) but hemisphere ($F_{(1, 45)} = 5.52$, $p < 0.05$) and the interaction term ($F_{(2, 45)} = 12.51$, $p < 0.001$) were (see Fig. 1). *t*-Tests and one-way ANOVAs (and pairwise *t*-tests) were conducted to elucidate these observations. Within the SA group, LIFG was more active than RIFG ($p < 0.001$); in the LA group RIFG was more active than LIFG ($p < 0.05$). In the RIFG, a significant main effect of group was observed ($F_{(2, 21)} = 10.6$, $p < 0.001$); the LA group had more activity

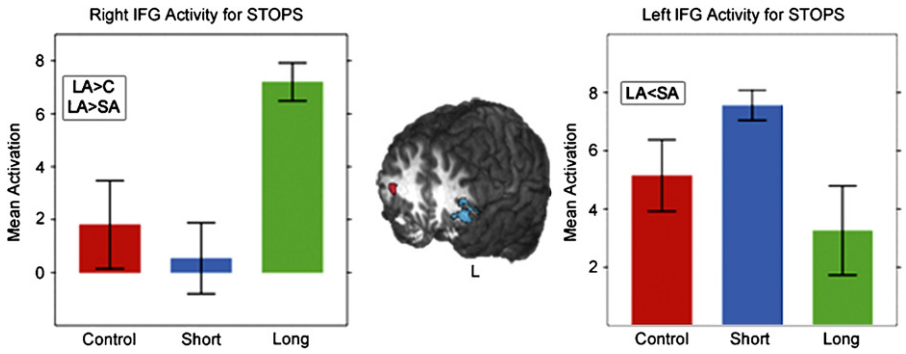

Fig. 1. Regions in the left and right inferior frontal gyrii for STOPS analysis. Group-wise differences are shown in the charts. Error bars represent standard error of the mean.

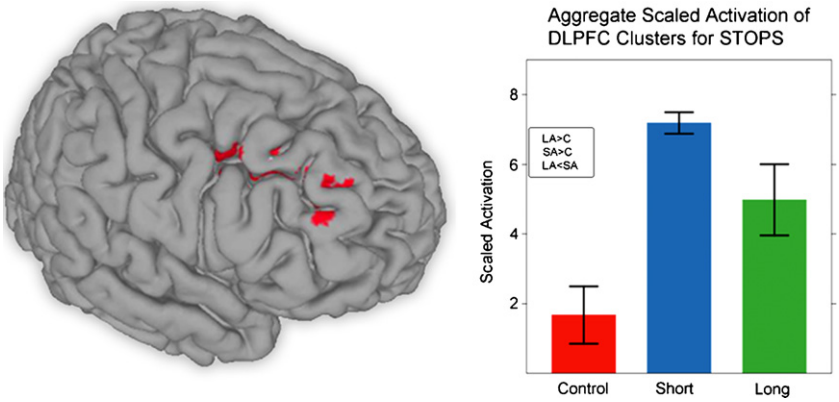

Fig. 2. Three regions, located in RMFG, and two in RSFG, used in the aggregate STOPS DLPFC cluster, the mean activity in which was aggregated and weighted by volume. Error bars represent standard error of the mean.

here than the SA and control groups ($p < 0.05$). In the LIFG, a marginal effect of group was observed ($F_{(2, 211)} = 3.41$, $p = 0.052$); the SA group had more activity than the LA group ($p < 0.05$).

Three regions located in BA 9 and 46 (Fig. 2) were observed in right DLPFC. Given an interest in the role of DLPFC in abstinence, we aggregated their mean activity levels, weighted by cluster volume, and observed a significant main effect of group ($F_{(2, 21)} = 11.80$, $p < 0.001$). Pair-wise comparisons revealed that the LA and SA groups each displayed significantly more activity than the control group ($p < 0.05$).

3.3.2. Errors. In agreement with previous studies of error processing (Braver et al., 2001; Carter et al., 1998; Hester et al., 2004; Kiehl et al., 2000; Menon et al., 2001; Ullsperger and von Cramon, 2003), we observed error-related activation in dorsal ACC, insula, inferior and dorsolateral prefrontal cortex (PFC) (see Table 3). Significant group differences were found in prefrontal cortex, in the inferior, middle and superior frontal gyrii, in the anterior cingulate, the right supramarginal gyrus and the right culmen of the cerebellum. In general, the SA and LA groups each had greater activity in these regions relative to the control group, though LA < SA in the LIFG, LA > SA in the RIFG, and LA > SA in the right culmen.

A number of error-related activations located in BA 32 and 24, shown in Fig. 3, were observed in the cingulate gyrus. An aggregate of their mean activity, weighted by cluster volume, showed a marginally significant main effect of group ($F_{(2, 21)} = 3.19$, $p = 0.06$). Tukey's HSD ($p = 0.05$) showed this difference to be driven by the LA group having greater mean activity than the controls. A planned linear contrast in the ANOVA (control < SA < LA) showed a significant linear trend in the means of the groups ($F_{(1, 21)} = 6.30$, $p < 0.05$). Tukey's HSD also showed this effect to be driven by the LA group having greater mean activity than the controls ($p < 0.05$). The significant linear trend in group means was also present in this latter ANOVA ($F_{(1, 24)} = 6.73$, $p < 0.05$).

Although activated on error trials, some error-related activation in response inhibition tasks might reflect processes that are also present on successful inhibitions (such as conflict monitoring) or may contain activation associated with the unsuccessful attempt to inhibit; in accordance with the race model of response inhibition (Logan and Cowan, 1984), the response inhibition network may

Table 3
Errors of commission (ERRORS). BA is Brodmann's area, volumes are in micro-liters and center-of-mass coordinates are in the Talairach & Tournoux atlas. RL: right–left, AP: anterior–posterior, IS: inferior–superior. *p*-Values were derived from ANOVAs. For the pair-wise contrasts (Tukey's Honest Significant Difference test) C = control, LA = long and SA = short and $p \leq 0.05$.

Structure	Hemisphere	BA	Volume	RL	AP	IS	Significance	Pairwise differences
Limbic system								
Cingulate gyrus	R	32	1084	−3	−15	40		
Cingulate gyrus	L	32	1028	0	−32	26		
Cingulate gyrus	R	24	324	−1	5	46		
Cingulate gyrus	L	24	306	1	18	33	*	SA > C
Frontal lobes								
Inferior frontal gyrus♦	L	47	1185	35	−23	−6	**	SA > C; LA < SA
Inferior frontal gyrus	R	9	376	−46	−1	22	**	LA > C; LA > SA
Middle frontal gyrus	R	9	600	−38	−36	34	**	LA > C
Superior frontal gyrus	L	9	312	37	−43	30	**	SA > C
Temporal lobes								
Middle temporal gyrus	R	21	383	−62	33	−3		
Angular gyrus	R	39	390	−43	63	36		
Parietal lobes								
Supramarginal gyrus	L	40	461	59	48	24		
Subcortical								
Insula♦	R	13	1557	−40	−11	−3		
Thalamus♦	R		1419	−1	2	8		
Culmen	R		327	−22	52	−28	***	LA > C; LA > SA

♦ Activity was ERROR specific ($p \leq 0.05$) as determined by a series of 2 × 3 (event-type × group) ANOVAs conducted on the activation levels within the 14 ERROR regions in both the ERRORs and STOPs conditions.
* $p \leq 0.05$ refers to the corresponding ANOVA.
** $p \leq 0.01$ refers to the corresponding ANOVA.
*** $p \leq 0.001$ refers to the corresponding ANOVA.

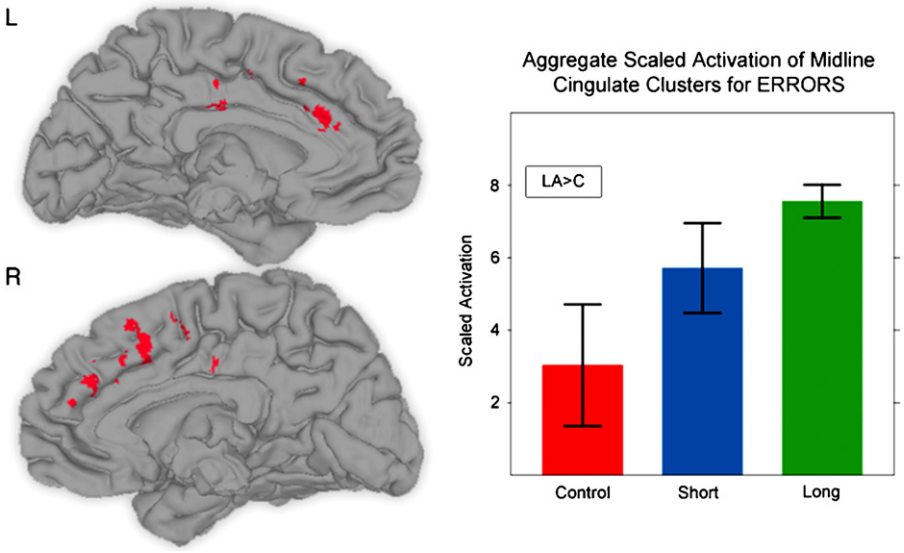

Fig. 3. Four regions, located in left and right cingulate gyrii, used in the aggregate ERROR cingulate gyrus cluster, the mean activity in which was aggregated and scaled by volume. Error bars represent standard error of the mean.

activate but may not do so sufficiently soon to countermand the response (Garavan et al., 2002). Consequently, to identify error-specific activations, a series of 2 × 3 (event-type × group) ANOVAs were conducted on the activation levels within the 14 regions listed in Table 3. These revealed greater error-related activation in the right insula ($F_{(1,45)} = 4.77$, $p < 0.05$), right thalamus ($F_{(1,45)} = 4.30$, $p < 0.05$), and left IFG (event type: $F_{(1,45)} = 5.62$, $p < 0.05$). There were no significant interactions and there was a significant group effect in the left IFG only ($F_{(2,24)} = 10.1$, $p < 0.001$) which was driven by control < SA and LA < SA ($p < 0.05$). Similar analysis conducted on the aggregate ACC region revealed no significant effects.

4. Discussion

The present study has revealed the neuroanatomical correlates of cognitive control in abstinent cocaine users. The results demonstrate comparable performance levels and greater activation associated with inhibitory control and performance monitoring processes in abstinent cocaine users relative to controls. This stands in contrast to the poorer performance and functional hypoactivity typical of current cocaine users (Kaufman et al., 2003) and indicates an important role for the neuroanatomical integrity of cognitive control in successfully maintaining abstinence. Moreover, the two abstinent groups also differed from one another in activation levels suggesting different cognitive control demands related to abstinence duration. Cocaine abstinence may be characterized by a three-stage symptomatology (Gawin and Kleber, 1986) and proceeds from initial symptoms of withdrawal to cocaine cessation. The initial phase, generally accepted as "the crash" by cocaine addicts and psychiatrists alike, is characterized as an exhaustion (including, but not limited to, intense depression, agitation, anxiety and intense cravings) and lasts from hours to 4 days (see Weddington et al., 1990 for an alternate view of early abstinence). This is followed by a withdrawal phase ranging in duration from 1 to 10 weeks and is characterized by an initial absence of cravings in the early weeks and their return by the middle weeks. Symptoms of anhedonia, anergia and intense cravings characterize the final weeks of withdrawal. Extinction lasts indefinitely and is typified by normal mood and recurrent (spontaneous or cued) cravings. The study described here demonstrates that the processes involved in the withdrawal phase of abstinence may be different from those involved in maintaining abstinence insofar as the underlying neural circuits recruited differ between the two groups with the LA group recruiting regions more typical of non-addicts though still displaying elevated activity patterns.

Overall, there was a general trend for the user groups to display greater levels of activity than the controls. For STOPS, the SA group activated more dorsal regions of the middle and superior frontal gyrii, whereas the LA group tended to recruit more inferior regions, such as bilateral inferior frontal gyrii, typically associated with response inhibition. Inhibitory control appears to be accompanied by greater activation in frontal regions including inferior frontal gyrus, cingulate gyrus, middle frontal gyrus and precentral gyrus. The role played by these regions in inhibitory control as has been revealed by lesion studies, functional neuroimaging and transcranial magnetic stimulation studies (Aron et al., 2003; Buchsbaum et al., 2005; Chambers et al., 2006; Menon et al., 2001; Rubia et al., 2003). Previous studies in cocaine addicts have shown many of these regions to be hypoactive relative to controls (Bolla et al., 2004; Kaufman et al., 2003). In contrast, the abstinent groups in this study show more elevated activity in the aggregate DLPFC cluster; a finding that has also been observed in abstinent marijuana users (Tapert et al., 2007). This, combined with the elevated precuneus activity (an integral component of the sensorimotor network, Luppino et al., 1999), may indicate increased fronto-parietal attentional, or response selection mechanisms being brought to bear on this cognitive task.

Hyperactivity in ACC relative to posterior cingulate cortex has been linked with greater likelihood of avoiding relapse with those participants showing this hyperactivity prior to scanning having longer periods of abstinence (Kosten et al., 2006). Abstinence may place extra demands on cognitive control and, specifically, the monitoring processes subserved by the ACC suggesting that the increased activity in this region, as indicated by the linear trend in the activity of the aggregate ACC region, may be a defining characteristic of successful abstinence.

The elevation of frontal activity appears to undergo a shift from the left to right hemisphere over the course of abstinence. Activation of the LIFG has been observed in children performing a task requiring both response inhibition and interference suppression (Bunge et al., 2002). Furthermore, the left IFG has recently been shown to be important for response inhibition (Swick et al., 2008) and in a task similar to that described here, older adults have been shown to rely more on left PFC (Garavan et al., 2006).

Activity observed in these regions is therefore likely to be response inhibition related. The reliance of the SA group on this region suggests that early in abstinence users may adopt an alternative cognitive strategy in that they may recruit the LIFG in a manner akin to children and older adults to achieve behavioral results similar to the other groups. Recruitment of the LIFG may be indicative of short-term abstinence whereas with prolonged abstinence a pattern topographically typical of normal, healthy controls may emerge, though with the LA group displaying elevated activity levels. Should the transition from relying on left to right IFG be a result of abstinence, it is likely this may only develop with protracted abstinence as short periods of abstinence followed by relapse may not allow this to occur (Volkow et al., 2001; Wang et al., 2004).

The involvement of the cerebellum in high-order executive functions is well documented. Focal cerebellar damage has been associated with dysexecutive impairments, personality disorders such as disinhibited and inappropriate behavior and working memory impairment (Desmond et al., 2003; Heyder et al., 2003; Parkins, 1997). We, and others, have previously hypothesized that drug abusers may develop increased cerebellar activity to compensate for reduced prefrontal activity in tasks demanding elevated levels of cognitive control (Desmond et al., 2003; Hester and Garavan, 2004). The two abstinence groups in the present study showed clusters of activity in cerebellar regions that are consistently elevated relative to controls. If, as active drug users, they came to rely on elevated cerebellar activity to compensate for reduced prefrontal activity, it appears to have been maintained into abstinence, possibly because it served a crucial role in the cognitive control system while prefrontal control system recovered from damage to the mesencephalic dopamine system inflicted by chronic cocaine use. For the STOPS, the left cerebellar regions encompass portions of Lobules VII and VIII, while the right region is located in part of Crus I of the cerebellum. These cerebellar regions have recently been shown to exhibit strong resting state functional connectivity (RSFC) correlations with contralateral DLPFC (Krienen and Buckner, 2009). Likewise the region from the ERRORs is located in Lobule VI of the cerebellum, which has been shown to exhibit strong RSFC correlations with the anterior prefrontal cortex (Krienen and Buckner, 2009).

One of the defining neurobiological characteristics of chronic cocaine consumption is cortical hypoactivity (Volkow and Fowler, 2000). Indeed, acute administration of cocaine can prompt a return to activity levels seen in controls, making cocaine abusers' activity almost indistinguishable from that of controls. This normalization occurred in cingulate regions previously shown to be hypoactive in cocaine abusers (Garavan et al., 2008). By contrast, the cohort of abstinent users in this study demonstrated hyperactivity relative to controls in midline cingulate performance monitoring regions (Ridderinkhof et al., 2004). It has previously been shown that fronto-parietal activity is associated with subjective awareness of errors (Hester et al., 2005) and that cocaine abusers are not as aware of their errors as drug-naïve controls (Hester et al., 2007). The elevated activity observed in this study may be functionally significant insofar as raised error-related activity tends to be present in better, more attentive individuals (Hester and Garavan, 2004). This may reflect a neuro-adaption, as increased awareness of erroneous behavior, particularly that leading to cocaine consumption, may allow more cognitive processing of error prone behavior to occur and prevent its execution, thus realizing the higher goal of maintaining abstinence. For STOPs, the SA group displayed greater activity in RDLPFC and LIFG but for errors the LA group displayed greater ACC activity that points to increased performance monitoring. Though the groups differed from one another only marginally in the aggregate ACC region, the pattern of activity in which SA is intermediate between controls and LA, revealed by the significant linear trend, is consistent with increased monitoring as abstinence proceeds. This suggests, in one possible interpretation, that in the acute phase of abstinence heightened inhibitory control is especially important and that latterly the error monitoring system plays a greater role. That is, the users may no longer need to inhibit behaviors/urges but need to actively monitor them to maintain abstinence.

Though we observed no performance differences between our three groups, this could be explained by a number of factors. The group sizes are small (nine in each), which may be too small to reveal behavioral differences between the groups. A previous application of this task to current users and controls observed significant group differences in performance (Kaufman et al., 2003). However, the groups in the present study have been abstinent for a significant period of time. The group differences revealed in the neuroimaging data above suggest that the comparable performance of the abstinent users relative to the controls may have been achieved by additional functional recruitment (Rajah and D'Esposito, 2005). Indeed, equivalent task performance may be a directly measurable consequence of this and may be facilitated by abstinence. The small sample size is a limitation of the current study (and one that is not easily corrected due to the subsequent decommissioning of the scanner) and although we have observed significant group functional differences, it will be important for future studies to replicate these effects with larger samples.

As with most studies on human clinical groups it is not possible to address the etiology of these activity pattern differences, that is, we cannot say whether the differential brain recruitment patterns reported above predate cocaine consumption and facilitate abstinence or arose as a consequence of abstinence. This ambiguity notwithstanding, the present results are one of the first to show the functional sequelae of prolonged abstinence in cocaine abusers. They demonstrate that successfully abstinent users display elevated activity in prefrontal and midline regions. Moreover, different cognitive control strategies may be required at different stages in abstinence. The withdrawal phase of abstinence may require increased inhibitory control whereas in the extinction phase this may not be as important as ongoing monitoring of behavior to prevent relapse. These results suggest that the neural systems involved in cognitive control may be apt for targeting during treatment and may increase the likelihood of prolonged successful abstinence.

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Contributors

CGC analyzed the data and wrote the article. HG, JJF and JN designed the study. HG co-wrote the article. MS collected the MRI data. JN recruited participants. All authors have approved the manuscript.

Conflict of interest

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

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