PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

Phil. Trans. R. Soc. B (2008) **363**, 3267–3276
doi:10.1098/rstb.2008.0106
Published online 24 July 2008

Acute effects of cocaine on the neurobiology of cognitive control

Hugh Garavan[1,2,*], Jacqueline N. Kaufman[2,3] and Robert Hester[1,4]

[1]*Institute of Neuroscience, School of Psychology, Trinity College Dublin, Dublin 2, Ireland*
[2]*Department of Psychiatry and Behavioral Neuroscience, Medical College of Wisconsin, Milwaukee, WI 53226, USA*
[3]*Department of Physical Medicine and Rehabilitation, University of Michigan, 325 East Eisenhower Suite 100, Ann Arbor, MI 48108, USA*
[4]*Queensland Brain Institute and School of Psychology, University of Queensland, St. Lucia, QLD 4072, Australia*

Compromised ability to exert control over drug urges and drug-seeking behaviour is a characteristic of addiction. One specific cognitive control function, impulse control, has been shown to be a risk factor for the development of substance problems and has been linked in animal models to increased drug administration and relapse. We present evidence of a direct effect of cocaine on the neurobiology underlying impulse control. In a laboratory test of motor response inhibition, an intravenous cocaine administration improved task performance in 13 cocaine users. This improvement was accompanied by increased activation in right dorsolateral and inferior frontal cortex, regions considered critical for this cognitive function. Similarly, for both inhibitory control and action monitoring processes, cocaine normalized activation levels in lateral and medial prefrontal regions previously reported to be hypoactive in users relative to drug-naive controls. The acute amelioration of neurocognitive dysfunction may reflect a chronic dysregulation of those brain regions and the cognitive processes they subserve. Furthermore, the effects of cocaine on midline function suggest a dopaminergically mediated intersection between cocaine's acute reinforcing effects and its effects on cognitive control.

Keywords: cocaine; impulsivity; functional magnetic resonance imaging; addiction

1. INTRODUCTION

There is a growing appreciation that the compulsive behaviour of drug-dependent individuals may result, in part, from compromise in the cognitive processes that control behaviour (Moeller *et al.* 2001; Lubman *et al.* 2004). For example, among the core behaviours associated with drug abuse are disinhibition and an apparent loss of self-control (Lyvers 2000). Diagnostic criteria for substance dependence emphasize behavioural patterns of diminished control and drug use exceeding intended levels, consistent with compromised monitoring and inhibition of potentially harmful behaviour. Compromised impulse control might be expected to have significant consequences for an individual as it is a fundamental control process. Impulse control follows a developmental trajectory demarcating important cognitive milestones early in life and its diminution has been proposed to underlie many aspects of cognitive decline in the elderly (Diamond 1990; Perry & Hodges 1999). It represents an important element of individual differences in personality (Patton *et al.* 1995) and its dysfunction is associated with many clinical conditions including attention-deficit hyperactivity disorder (ADHD) (Barkley 1997; Rapport *et al.* 2001), schizophrenia (Carter *et al.* 2001) and mania (McGrath *et al.* 1997; Clark *et al.* 2001). The many manifestations of impulse control hint at it being a multifaceted construct. Typical measures of impulsivity include perseverative behaviours, inability to delay gratification, inability to suppress prepotent responses, lack of premeditation prior to action, insufficient sampling of relevant information prior to decision making, resistance to extinction and more. As a consequence, investigations into the role of impulse control in addiction need to be cognizant of which particular aspect of the construct they are addressing as it is not yet clear to what extent these deficits are related, share common cognitive or neurobiological mechanisms or might coalesce to form a broad impulsive phenotype (Grant 2004).

Despite these conceptual uncertainties, there is evidence of addiction-related impairment in many of these different aspects of impulsivity suggesting that common (disrupted) mechanisms may be at play. For example, cocaine users show higher delayed discounting rates (Coffey *et al.* 2003; Simon *et al.* 2007), are slower or poorer at motor inhibition (Fillmore *et al.* 2002; Hester & Garavan 2004; Colzato *et al.* 2007), make riskier decisions on various gambling tasks (Bartzokis *et al.* 2000; Monterosso *et al.* 2001; Bolla *et al.* 2003; Fishbein *et al.* 2005; Verdejo-García *et al.* 2007) and amphetamine users sample less of the

* Author and address for correspondence: Institute of Neuroscience, School of Psychology, Trinity College Dublin, Dublin 2, Ireland (hugh.garavan@tcd.ie).

Electronic supplementary material is available at http://dx.doi.org/10.1098/rstb.2008.0106 or via http://journals.royalsociety.org.

One contribution of 17 to a Discussion Meeting Issue 'The neurobiology of addiction: new vistas'.

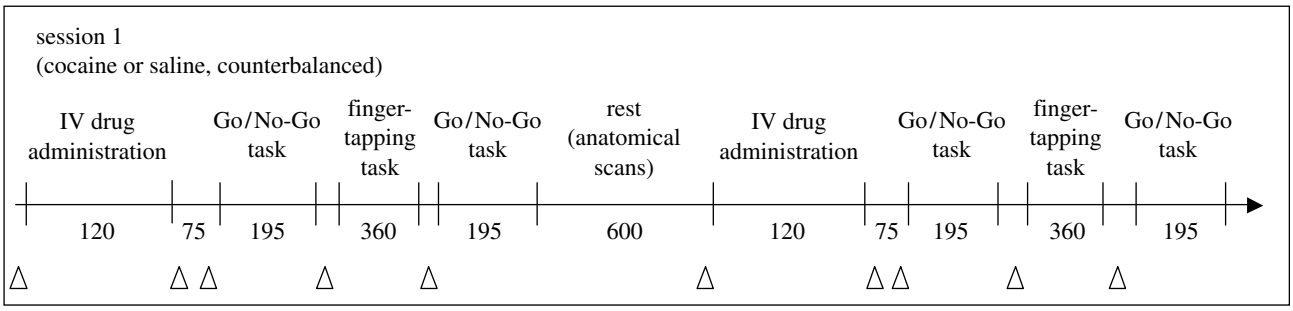

Figure 1. Experimental design. The durations of the components are given in seconds and triangles represent the time points in which physiological measurements were made.

available information prior to making decisions (Clark *et al.* 2006). A growing literature suggests both anatomical changes and functional dysregulation in lateral, ventral and medial prefrontal cortex in chronic cocaine users (Volkow *et al.* 1993; Franklin *et al.* 2002). Anterior cingulate cortex (ACC) hypoactivity for performance monitoring processes has been demonstrated in chronic cocaine users (not currently under the influence of cocaine) when compared with non-using control participants (Kaufman *et al.* 2003); a similar effect has also been reported for opiate-dependent individuals (Forman *et al.* 2004) and cannabis users (Eldreth *et al.* 2004). Poor motor response inhibition in cocaine users has been associated with reduced activity in dorsolateral prefrontal cortex, insula and the ACC, and increased activity in the cerebellum (Kaufman *et al.* 2003; Hester & Garavan 2004; Li *et al.* 2007). Stroop task performance has been associated with changes in orbitofrontal cortex in cocaine users (Goldstein *et al.* 2001).

One approach to understanding cocaine-related impairments on these cognitive control processes and their underlying neurobiology is to study the acute effects of a cocaine administration. Cocaine's powerful reinforcing properties have been well documented both experimentally and anecdotally (Johanson & Fischman 1989; Kuhar *et al.* 1991; Ahmed & Koob 1998). While research has focused primarily on elucidating the neurobiological mechanisms of cocaine's effects on putative reward systems, less research has explored the functional neuroanatomical regions associated with the cognitive changes that accompany cocaine use. Inhibitory control and action monitoring during and immediately after the consumption of cocaine are of particular importance as cocaine's stimulatory effects paired with its short half-life produce a physiological urge to seek more cocaine shortly after initial consumption. This urge may be facilitated by compromise in those cognitive processes involved in controlling behaviour. The present study aims to investigate cocaine's effects by identifying the cortical regions and psychological functions affected by an acute cocaine administration. Using a motor response inhibition task in which both motor impulsivity and the brain's response to errors can be assayed allows us to determine whether cocaine directly affects these processes thought central to controlling behaviour. In addition, the acute effects of cocaine on both brain function and cognitive control may suggest likely candidates for long-term impairment. Frequent drug-induced activation of these regions may lead to their subsequently being functionally downregulated, with negative consequences for the cognitive functions they perform (Garavan & Stout 2005).

2. MATERIAL AND METHODS

(a) *Participants*

Thirteen otherwise healthy, right-handed, active cocaine users (two female; mean age of 37 years, range of 21–45 years) participated in this study after providing written informed consent according to the procedures approved by the Medical College of Wisconsin's Institutional Review Board. Details on the screening and pretesting medical procedures are provided in the electronic supplementary material. Urine samples returned positive screens for cocaine or its metabolites, indicating that participants had used cocaine within the previous 72 hours. All users were able to estimate their last use, which ranged from 11 to 80 hours (average 36 hours) before the scan session; no user displayed overt behavioural signs of cocaine intoxication. The average amount of money spent on the last use of cocaine was $84 (range: $10–$400). Years of cocaine use ranged from 5 to 20 (average 12 years), and educational level ranged from 8 to 14 years (mean 12 years). A secondary follow-up comparison was also conducted, which included the data from 14 drug-naive controls from a previous study (10 females; mean age 30 years; range 19–45 years; Kaufman *et al.* 2003). All non-drug users had negative urine tests for all drugs.

(b) *Task and procedure*

Task stimuli consisted of a 1 Hz serial visual stream of alternating X and Y (Garavan *et al.* 2002; Kaufman *et al.* 2003). Participants were instructed to press a button for each stimulus (Go trials) while still on screen. No-Go trials in which the stimuli did not alternate required inhibition of the response (i.e. participants would respond to each stimulus except the fifth in the sequence …XYXYYX…). No-Go trials represented 6% (80 No-Go trials) of the total number of trials over four runs with task difficulty tailored for each participant by manipulating stimulus presentation rates (details in the electronic supplementary material). Go/No-Go runs were alternated with a simple event-related visuomotor finger-tapping task to be used as a measure of the effects of cocaine on the shape and size of the haemodynamic response function (Murphy *et al.* 2006). Cocaine-using participants completed both drug imaging sessions on the same day (drug order was counterbalanced), separated by approximately 2 hours. Each session comprised four Go/No-Go task runs alternated with two finger-tapping runs (see timeline in figure 1).

Cocaine-using participants were manually injected over 120 s through a catheter port with either cocaine at 40 mg/70 kg body weight, or normal saline; administration

order in the two separate scanning sessions was counterbalanced across participants. Infusions occurred at rest points prior to task runs 1 and 3 of each session. The dose used was based on previous work in administering cocaine to users conducted at the Medical College of Wisconsin, and was of a reinforcing quality (producing a high and rush) comparable with the users' reported typical use. The rate of administration over 2 min was chosen from pilot data that demonstrated this rate to minimize the rush experience (important for keeping subjects 'on-task' and avoiding head movements during magnetic resonance imaging (MRI) acquisition) and to prolong the high period (to enable completion of the task during a drug-active window). Scanning of the Go/No-Go task was initiated approximately 75 s following completion of the injection (time required to obtain baseline physiological measures). The 3 min 15 s task run was followed by a 6 min event-related finger-tapping task. There then followed another 3 min 15 s task run and then a rest period during which the high-resolution anatomical images were collected. Vital statistics (blood pressure (BP) and heart rate (HR)) were measured between each run; the exact timings of these measurements varied between subjects due to small variations in data copying and scanner preparation time between runs. Approximately 40 min after the first injection, the second injection was administered and the three aforementioned functional runs were repeated. HR and BP were monitored for safety and to assess physiological responses to cocaine administration.

(c) *Image acquisition and analysis*

High-resolution anatomical images and standard gradient-echo, echo-planar functional images were acquired (functional images were 7 mm contiguous sagittal slices: repeat time, 2000 ms; echo time, 40 ms; field of view 240 mm; 64×64 matrix; 3.75×3.75 mm in-plane resolution; see the electronic supplementary material). Imaging data were analysed using the AFNI software package (Cox 1996; http://afni.nimh.nih.gov/afni) and comparisons were carried out between the saline and cocaine conditions (full details in the electronic supplementary material). In brief, event-related changes in activation were calculated using deconvolution and curve-fitting techniques for successful inhibitions (STOPS) and commission errors (ERRORS) for each condition (cocaine and saline). Statistically significant activation maps were created for both STOPS and ERRORS for each condition based on the one-sample *t*-tests against the null hypothesis of no activation changes with thresholds ($p\leq0.05$, corrected) determined through data simulation procedures (Garavan *et al.* 1999). Functionally defined region of interest maps were defined for each event type (STOPS and ERRORS) by combining the activated regions of both the intravenous (IV) cocaine and saline conditions as OR maps (e.g. for STOPS, a voxel was included in the region of interest if significant, in either the cocaine or the saline condition) and between-condition comparisons were performed on the mean activations of the resulting functionally defined regions.

Additionally, data from healthy control participants were available from a previous study (Kaufman *et al.* 2003) in which drug-naive participants completed four runs of the same inhibitory control task using similar stimulus duration tailoring procedures as described above. In a secondary follow-up analysis, data from cocaine users following cocaine and saline injections were compared with these healthy controls using the regions identified in our original study. Although the procedures were not identical for the two studies (e.g. there were no IV lines for the controls) this follow-up analysis was deemed a worthwhile initial investigation of a cocaine administration's impact on those areas previously observed to be functionally hypoactive in users. Finally, details of the event-related finger-tapping control task analyses are reported in-depth elsewhere (Murphy *et al.* 2006).

3. RESULTS

(a) *Physiological analyses*

ANOVAs on each of the physiological measures revealed significant main effects for drug condition and time and significant interactions (all $p<0.01$). Physiological measures showed the anticipated effects of cocaine infusion (figure 2) with beats per minute, systolic and diastolic BP rising from pre- to post-injection ($F_{9,4}=50.0$, $p\leq0.001$; $F_{9,4}=19.18$, $p\leq0.006$ and $F_{9,4}=6.2$, $p\leq0.05$, respectively). Whereas HR significantly differed between the pre-injection time point 1 and each subsequent time point, systolic BP was significantly higher at time points 2, 3 and 7 compared with time point 1 ($p<0.05$) and diastolic BP was significantly higher at all time points except time point 6. For saline administration, ANOVAs revealed no significant variance for HR, systolic or diastolic BP over the course of the scan session (all $p>0.25$).

(b) *Performance analyses*

To examine behavioural effects of the drug manipulation, a 2×4 (drug condition$\times$scan run) repeated-measures ANOVA assessed changes in performance (percentage of successful inhibitions for all No-Go trials) across each scan session's four runs in the users. Both main effects were significant (drug: $F_{1,12}=11.7$, $p\leq0.005$; scan run: $F_{3,10}=4.8$, $p\leq0.025$), as was the interaction ($F_{3,10}=6.8$, $p\leq0.009$). The main effects indicate that the percentage of successful inhibitions was higher in the cocaine condition ($66.8\pm4\%$) than in the saline condition ($51.2\pm6\%$) and that accuracy declined over the duration of each session. Performance was significantly better in the cocaine condition relative to the saline condition during runs 1 and 3 (run 1: $F_{1,12}=23.8$, $p\leq0.001$; run 3: $F_{1,12}=5.5$, $p\leq0.04$), but was not different from the saline condition for runs 2 and 4 (run 2: $F_{1,12}=1.5$, $p\leq0.24$; run 4: $F_{1,12}=3.1$, $p\leq0.10$), indicating that the performance was significantly better in the scan runs that immediately followed cocaine administration. A 2×4 (drug condition$\times$scan run) repeated-measures ANOVA on omission errors across the four scan runs found a significant effect for drug ($F_{1,12}=7.9$, $p\leq0.02$), but not for run or the interaction (all $F<1$); participants made significantly more omission errors in the saline condition ($1.9\pm5\%$) than in the cocaine condition ($0.5\pm0.2\%$). Finally, there was no difference in the Go response time between the conditions ($F<1$) and there was no effect of the order of substance administration on any task performance measure (all $p>0.10$). The absence of a condition effect on response time helps rule out the possibility that the improved inhibitory performance in the cocaine condition was secondary to more cautious, slower responding following cocaine.

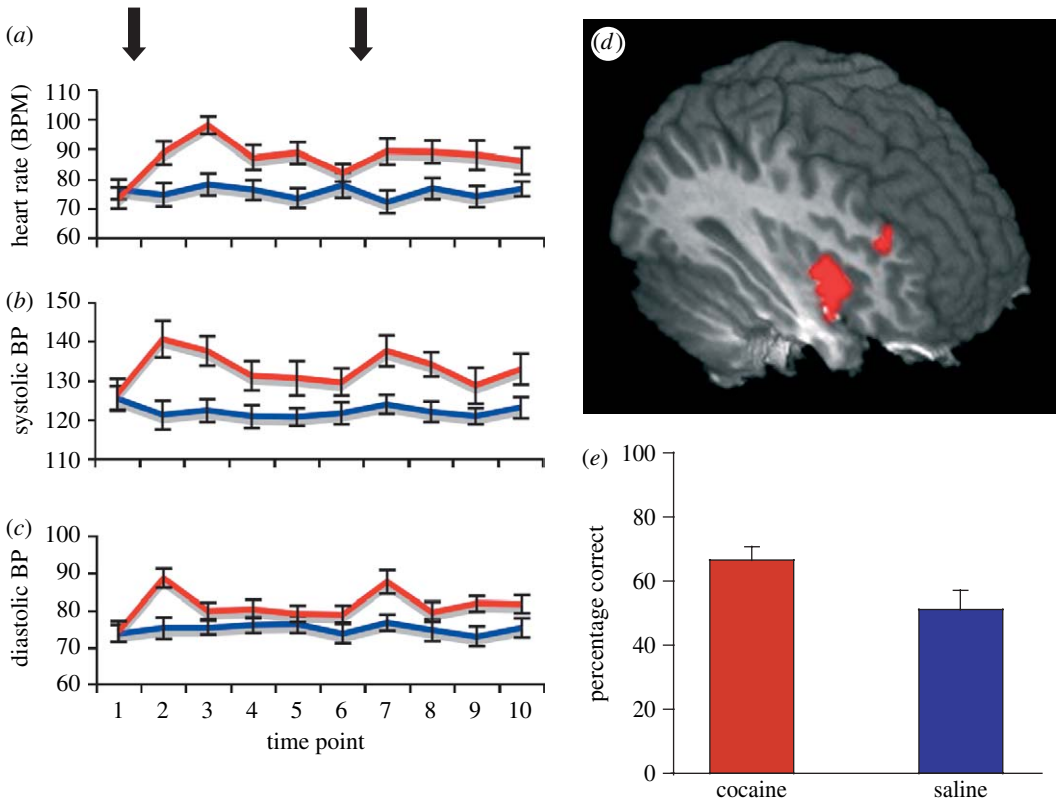

Figure 2. Physiological, behavioural and functional brain effects of cocaine in performing an inhibitory control Go/No-Go task. Cocaine administration increased (*a*) HR, (*b*) systolic BP and (*c*) diastolic BP and (*e*) improved the user's ability to inhibit a prepotent behaviour (all error bars are standard errors of the mean). Improved inhibitory control (successful inhibitions) was associated with increased activity in (*d*) right insula/inferior frontal gyrus (coronal section, $y=14$) and right dorsolateral prefrontal cortex. Drug infusions occurred between time points 1 and 2 as well as between time points 6 and 7. The four runs of the Go/No-Go task commenced following time points 3, 5, 8 and 10. The event-related finger-tapping control task was performed following time points 4 and 9. Red, cocaine; blue, saline.

Comparing performance with the control subjects from the previous investigation (Kaufman *et al.* 2003) revealed no significant difference between controls and users in the saline condition (51.2 versus 54.9%, respectively; $t=0.52$, $p\leq0.61$) and significantly better performance by users in the cocaine condition relative to controls (66.8 versus 54.9%, respectively; $t=2.23$, $p\leq0.03$).

(c) *Functional analyses*

For successful inhibitions (STOPS) in the saline and cocaine conditions of the users, activation was primarily bilateral with large clusters evident in bilateral insula extending rostrally into the inferior frontal gyrus, as well as the medial frontal/superior frontal gyri. Smaller clusters were evident in the right middle frontal gyrus, left middle frontal gyrus, and in the cingulate gyrus anterior to the precentral gyrus (table 1). Significant differences were observed for two regions, both of which produced higher blood-oxygen-level-dependent (BOLD) signal for the cocaine condition than the saline condition: the right insula/inferior frontal gyrus ($t_{(12)}=2.89$, $p\leq0.014$) and the right middle frontal gyrus ($t_{(12)}=3.81$, $p\leq0.003$; figure 2).

For commission errors (ERRORS), activation was bilateral and considerably more widespread, yet only five discrete regions showed significant differences between conditions, suggesting that differences observed were specific to both region and drug condition rather than a general effect of cocaine administration. In four of these five regions, users showed greater error-related activation following cocaine relative to the saline condition: right posterior cingulate/lingual gyrus ($t_{(12)}=3.4$, $p\leq0.005$); culmen of vermis/left lingual gyrus ($t_{(12)}=3.7$, $p\leq0.003$); left inferior parietal lobule ($t_{(12)}=3.1$, $p\leq0.01$); and right middle frontal gyrus ($t_{(12)}=3.9$, $p\leq0.002$). Conversely, participants were found to be hypoactive in the cocaine condition compared with the saline condition in the left posterior cingulate ($t_{(12)}=-6.4$, $p\leq0.001$).

Comparisons of neural activation for cocaine users in both the cocaine and saline conditions with that of non-using controls from a previous investigation (Kaufman *et al.* 2003) were carried out using regions of interest identified from the original study, i.e. regions in which users were previously shown to be hypoactive relative to controls. Confirming this previous result, the activation levels were significantly reduced in users ($p<0.05$, corrected) following the saline injection compared with non-using controls for STOPS; this hypoactivity was observed in right inferior parietal lobule, right insula into superior temporal gyrus and right middle frontal gyrus. Following IV cocaine, hypoactivity relative to controls persisted in just the right middle frontal gyrus. For ERRORS, similar to the original study, users in the saline condition demonstrated hypoactivity in an anterior cingulate cortex region; although less robust, this hypoactivity approached significance ($p\leq0.056$). By contrast, cocaine users in the cocaine condition showed no significant differences in activation compared

Table 1. Regions activated for failed inhibitions (ERRORS) and successful inhibitions (STOPS). (Asterisks identify brain regions in which comparisons revealed significant differences (with modified Bonferroni at $p \leq 0.05$) between activation in the cocaine and saline conditions.)

structure	Brodmann area	hemisphere	volume (ml)	centre-of-mass (x, y, z)		
ERRORS						
frontal lobe						
middle frontal gyrus	46*	R	118	38	31	18
medial frontal gyrus	6/24	R	111	20	1	51
	6/24/32	R	3993	1	−1	52
post-central gyrus	3	L	407	−36	−25	47
			148	−22	−29	58
pre-central gyrus	4	L	126	−48	−14	38
	3/4	R	116	47	−14	48
cingulate gyrus	32	R	475	7	26	29
	29/30*	L	121	−16	−46	13
parietal lobe						
inferior parietal lobule	40*	L	156	−54	−43	25
	7	R	131	31	−51	52
temporal lobe						
parahippocampal gyrus	27	R	460	16	−36	2
	36	L	109	−22	−43	−5
middle temporal gyrus	39	R	121	53	−54	10
	37	R	107	52	−61	9
occipital lobe						
lingual gyrus	19/30	L	183	−12	−46	−3
	18/30*	R	169	11	−55	6
	18*	L	157	−4	−67	−1
declive	19	L	105	−20	−60	−12
subcortical						
putamen		R	3043	21	4	4
		L	1776	−24	−3	2
		L	111	20	1	51
thalamus			2739	0	−19	8
insula/claustrum	30	L	261	−30	16	2
STOPS						
frontal lobe						
middle frontal gyrus	9*	R	192	36	40	35
	6	L	101	−20	−7	57
superior frontal gyrus	6	R	472	1	6	55
cingulate gyrus	24/32	R	101	3	9	40
subcortical						
insula	*	R	1800	34	13	4
		L	1636	−30	11	3

with controls, with the exception of the left thalamus that had significantly more activation ($p \leq 0.02$) in users for ERRORS.

Because the results comparing users and controls in the ACC, a region shown previously to be significantly hypoactive, were only marginally significant, we examined this region further. The functionally defined region of interest (ROI) that we used was not only largely right hemispheric but also incorporated the interhemispheric space and some left ACC. To limit activation measures to the parenchyma, we masked the functional ROI with an anatomically defined map of the ACC, thereby only including the right hemisphere in the ROI. The resulting right hemisphere ACC ROI showed a significant difference between control participant data and the IV saline condition in users ($p \leq 0.05$), which disappeared following the IV cocaine administration (controls versus IV cocaine in users: $p \leq 0.66$).

Given cocaine's potent vasoactive effect, it was important to determine that any observed BOLD effects were due to changes in the neural level rather than being due to changes in vascular functioning or neuronal–vascular coupling. While a vascular basis for the observed effects is unlikely, given the regional specificity of the cortical effects, this was confirmed with the finger-tapping control data that showed no differences in the haemodynamic response in either amplitude (area under the curve) or shape (individual parameters of a gamma-variate model: $y = k\ t^{\mathrm{r}} \mathrm{e}^{-t/b}$) that was fit voxelwise to the haemodynamic response between the IV cocaine and saline conditions. Additional data also confirm no differences in event-related haemodynamic properties between the users and the cocaine-naive controls (Murphy *et al.* 2006).

4. DISCUSSION

The present study has addressed the effects of an IV cocaine administration on neurocognitive function in cocaine-dependent individuals. The results demonstrate that a cocaine-induced improvement in

inhibitory control was accompanied by increased activation in two frontal areas, right dorsolateral prefrontal cortex and right insula extending into right inferior frontal gyrus. The importance of these regions for inhibitory control, and particularly the more ventral region, has been demonstrated by functional imaging, human lesion studies and, more recently, by transcranial magnetic stimulation (Aron *et al.* 2004; Buchsbaum *et al.* 2005; Chambers *et al.* 2006, 2007; Garavan *et al.* 2006). That improved performance should be associated with increased activity in these regions adds further support to their central role in inhibitory control. Similarly, the cocaine administration was observed to increase activation levels in fron-tal and parietal areas that responded to performance errors. Previously, we have shown that the subjective awareness of errors in one's performance is associated with increased frontoparietal activity (Hester *et al.* 2005) and that cocaine users have poorer awareness of their errors (Hester *et al.* 2007). Thus, an increase in error-related activity may be functionally significant insofar as error-related activation levels tend to be greater in better, more attentive performers (Hester *et al.* 2004) and when errors are made more salient through within-subject manipulations (Taylor *et al.* 2006).

The availability of data from a previous control participant study allowed us to observe that an acute cocaine administration rendered activation levels in users largely indistinguishable with that of controls, seemingly 'normalizing' the cortical hypoactivity associated with chronic drug abuse. This normalization of function was observed in midline cingulate areas previously shown to be hypoactive for errors in cocaine users (Kaufman *et al.* 2003) and in right hemisphere parietal and insular regions. By contrast, the right dorsolateral prefrontal cortex region active for STOPS remained hypoactive relative to controls in both the IV cocaine and saline conditions, despite this region increasing in activity in the users following cocaine relative to the saline condition. Although the comparison between users and previously tested controls was imperfect experimentally and should be interpreted with some caution, it is also important to note that stable group differences between users and controls such as sex or education levels cannot account for the different patterns of results observed when comparing controls first to users in the IV saline condition and then to cocaine condition. Furthermore, although the user and control groups did differ in sex composition, we have previously shown that neither performance on the task nor error-related midline activity differs between males and females (Hester *et al.* 2004).

Much evidence exists for the capacity of stimulant drugs to enhance cognitive performance. This holds true not only for populations with known dysfunction in brain regions targeted by the mesolimbic dopamine system, such as ADHD (Vaidya *et al.* 1998; Aron *et al.* 2003; Bedard *et al.* 2003), but also for normal healthy control populations for whom no pre-existing cognitive deficits are identified (Sostek *et al.* 1980; Koelega 1993; Wiegmann *et al.* 1996). As stimulant medications are used in these populations to enhance cognitive performance, it is possible that one aspect of the reinforcing nature of chronic cocaine use is the drug's capacity to improve cognitive function through its action on cortical structures involved in cognitive control. A related possibility is that the cocaine administration alleviated a withdrawal or craving state in the users. While this or other motivational differences may have existed between the cocaine and saline conditions, it is important to note that a similar effect, an increase in electrophysiological error-related signal following d-amphetamine (de Bruijn *et al.* 2003), has been observed in drug-naive controls for whom withdrawal would not have applied. Furthermore, we found no relationships between the time since the users' last use, which may indirectly index their craving or withdrawal levels, and their performance or activation levels on the task or, most critically, on the change in activation between the IV cocaine and saline conditions.

The phasic modulation of activity levels in specific cortical regions is consistent with cocaine having either a direct or indirect long-term detrimental effect on those same cortical structures. For example, if drug use produces a phasic increase in activity in a brain region and the brain's homeostatic response is to down-regulate receptors in that region (Volkow *et al.* 2002) then, relative to a control condition, one may identify regions of possible downregulation by their increased phasic activity following a drug administration. Tonic downregulation of medial or lateral prefrontal regions may result from repeated exposure to a drug-induced hyperdopaminergic state, which has been suggested to account for decreased dopamine receptor levels in users, and consequently, decreased metabolism in response to stimuli other than the drug itself (Volkow *et al.* 1999). In this regard, the cognitive tests can serve as functional probes of cocaine's effects. The cognitive tests can also identify the profile of deficits, linked to specific brain structures, likely to accompany drug abuse. Although there is much evidence of impaired cognitive abilities in cocaine users (Fillmore & Rush 2002; Goldstein *et al.* 2004), the relationship between these behavioural impairments and their underlying neurobiology is not yet very well understood. In this regard, the present results nicely complement previous investigations that have demonstrated diminished inhibitory control in cocaine users (Fillmore & Rush 2002; Colzato *et al.* 2007). Identifying the neurocognitive profile of this group should inform therapeutic interventions and may also provide an assay of the efficacy of these interventions.

In the human model, it is unclear whether observed deficits reflect a consequence of drug abuse or a pre-existing difference. Neurofunctional deficits such as those observed may render an individual susceptible to the development of addiction (i.e. the transition from recreational to uncontrolled use; Tarter *et al.* 2003; Dalley *et al.* 2007; Verdejo-García *et al.* 2008) and may be related to the psychiatric comorbidities observed in drug-dependent users, or such deficits may result from the effects that prolonged cocaine use may have on the brain or a combination of both these factors. These uncertainties notwithstanding the present results demonstrate that an acute cocaine administration affects the functioning of brain areas critical for cognitive control, thereby showing a direct relationship between cocaine and impulse control, as mediated by

right prefrontal cortex, and performance monitoring as mediated by the ACC. Curiously, the results run counter to a hypothesis that acute cocaine would disrupt these control processes. Instead, the observation of improved performance and increased activation levels are consistent with similar ameliorative effects on inhibitory control that have been observed with methylphenidate in patients with ADHD (Scheres *et al.* 2003). By contrast, alcohol has been shown to impair error monitoring (Ridderinkhof *et al.* 2002), but this effect was observed in non-alcoholics and is thus in keeping with the neurofunctional effects of drugs of abuse being determined by a history of use and its associated brain changes (discussed further below). That said, as noted above, d-amphetamine increased an electrophysiological marker of error monitoring (but not performance) in drug-naive controls (de Bruijn *et al.* 2003); d-amphetamine improved information processing but had no effect on inhibitory control in drug-naive controls (Fillmore *et al.* 2005*a*,*b*), while d-amphetamine and cocaine administrations have also been observed to impair inhibitory control in users (Fillmore *et al.* 2002, 2003).

One important consideration in attempting to reconcile these findings is the role of dose on the observed patterns of cortical activation and behavioural performance. While the beneficial effects of stimulant medications such as methylphenidate to enhance cognitive performance in both children and adults have been demonstrated (Chelonis *et al.* 2002; Aron *et al.* 2003; Bedard *et al.* 2003, 2004), these benefits appear to vary by dose, with more unfavourable behaviours appearing at higher doses (Stein *et al.* 2003). Similar inverted U-shaped function curves for behaviour are observed in studies of chronic cocaine users (Johnson *et al.* 1998). A relevant series of studies by Fillmore and colleagues have demonstrated the importance of drug dose insofar as inhibitory control performance on a Go/No-Go task was found to be disimproved following oral cocaine administration in the 50–150 mg dose range (Fillmore *et al.* 2002), but improved following administration in the 100–300 mg dose range (Fillmore *et al.* 2005*a*,*b*; but see also Fillmore *et al.* (2006), in which performance was shown to increase with dose but with different dose–response effects on two different tests of motor response inhibition). Although full dose–response studies are difficult for both methodological and safety reasons, the present results, having established a drug-related enhancement effect, may warrant further study of dose-related effects in future neuroimaging studies.

A further consideration when interpreting a drug's beneficial or deleterious effects on cognitive performance is the drug use history of one's participants. The present study did not include a drug-naive control group. Even if one might surmount the significant ethical and safety issues involved in administering cocaine to drug-naive controls, it is likely the case that the response of controls, given, for example, their baseline levels of dopaminergic activity, might be quite different from those of experienced cocaine users. Individual variation of this kind can be observed in drug-naive controls who, based on working memory capacity measures thought to reflect tonic dopaminergic activity, can show widely divergent performance and brain activation responses following a dopaminergic challenge (Gibbs & D'Esposito 2005). Fillmore and colleagues note that earlier findings of improved inhibitory control following d-amphetamine in drug-naive controls (de Wit *et al.* 2000) were limited to those subjects who displayed poor inhibitory abilities (Fillmore *et al.* 2005*a*,*b*). These observations suggest that the effects of a drug administration will be modulated by where the recipient falls on that drug's dose–response function curve.

The present results showing ACC hypoactivity relative to controls to be present following saline but not cocaine, coupled with the similar effects of d-amphetamine (de Bruijn *et al.* 2003) and the evidence that ACC dysfunction in cocaine users may be related to D_2 receptor availability (Volkow *et al.* 1993), suggest that the neurotransmitter dopamine may be implicated in performance monitoring functions. This conclusion is supported by recent functional MRI and electrophysiological evidence linking the brain's error response to genetic markers of dopamine function (Frank *et al.* 2007; Klein *et al.* 2007; Krämer *et al.* 2007). Additionally, patients with Parkinson's disease show reduced ACC responses to errors that are partly moderated by dopaminergic medication (Frank *et al.* 2004). It has been proposed that the midline error-related signal is driven by the same mesocorticolimbic dopamine system that generates ventral striatal responses related to expected and unexpected rewards and losses (Holroyd & Coles 2002). Thus, the present results lead to a hypothesized intersection between cocaine's dopaminergically mediated reinforcing effects and a cognitive dysregulation, with dopamine function in the ACC hypothesized to be on the cognitive–affective interface. Disruption to the ACC may be of particular relevance for understanding the behaviour of cocaine users given that the performance monitoring functions of this region includes the assessment of risky behaviour and decision making (Magno *et al.* 2006; Bjork *et al.* 2007). Deficits in those cognitive processes central to the endogenous control of behaviour may render the behaviour of the drug-dependent individual inordinately influenced by habitual behavioural patterns or by environmental stimuli such as drug-related cues.

This work was supported by USPHS grant DA14100 and General Clinical Research Center grant M01 RR00058. We gratefully acknowledge the assistance of Veronica Dixon, Kevin Murphy, Stacy Claesges, Linda Piacentine, Robert Risinger, Tom Ross and Elliot Stein.

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