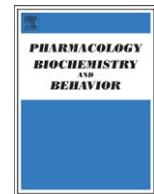




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## Neural mechanisms underlying drug-related cue distraction in active cocaine users

Robert Hester <sup>a,\*</sup>, Hugh Garavan <sup>b,c</sup><sup>a</sup> Queensland Brain Institute and School of Psychology, University of Queensland, St Lucia, Queensland, 4072, Brisbane, Australia<sup>b</sup> School of Psychology and Trinity College Institute of Neuroscience, Trinity College, Dublin, Ireland<sup>c</sup> Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, USA

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## ABSTRACT

Human drug dependence routinely features a difficulty with disengaging attention from drug-related stimuli, a symptom previously shown to be predictive of relapse during treatment. We examined the neural mechanisms underlying this attentional bias in cocaine users, varying working memory (WM) load to reflect the demands imposed by ruminative craving thoughts. Sixteen active users of cocaine were administered a WM task that manipulated the requirement for selective attention by varying the background contents, cocaine-related or neutral, upon which a recall probe item was shown. Behavioural and fMRI data were collected. Cocaine users had significantly poorer attentional control under high WM demands, suffering both increased response times and reduced recall accuracy, with this effect more pronounced for cocaine stimuli (when compared to neutral stimuli). The presence of background cocaine stimuli was associated with increases in occipital cortex activity, consistent with increased visual processing of the irrelevant stimuli for these trials. In addition, the cocaine stimuli were associated with increased right prefrontal activity with those participants with higher levels of right prefrontal activity having lower levels of attentional bias. Cocaine users under high cognitive demands had difficulty modulating the neural mechanisms underlying cognitive control which appear necessary for restricting the visual processing of task-irrelevant, but salient drug-related, stimuli, a finding that may be relevant to identifying those at most risk of relapse.

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Human drug addiction is a complex multifactorial phenomenon that features, with remarkable consistency, a difficulty controlling attention away from salient drug-related stimuli. The neural mechanisms of drug craving, and the process by which drug-related stimuli attain salience that is important to attention have been the focus of much recent research, however it remains unclear what neural mechanisms underlie the inability to ignore such stimuli.

Behavioural studies have shown that ignoring drug-related stimuli represents a significant difficulty for those dependent on drugs such as alcohol (Cox et al., 2003), and heroin (Franken et al., 2003) and nicotine (Bradley et al., 2004; Field et al., 2004b). Cocaine users demonstrate a strong attentional bias for cocaine-related stimuli (Copersino et al., 2004; Franken et al., 2000; Hester et al., 2006), with greater bias predicting poorer outcomes during drug-treatment programs (Carpenter et al., 2005). The basis of this attentional bias in cocaine users may lie in the reinforcing properties of cocaine and its influence on the mesocorticolimbic 'reward' network, and consequently, the influence of the limbic system on attention and cognitive control. The mesocorticolimbic neural circuit, which includes the nucleus accumbens, amygdala and hippocampus, has been associated with the acute reinforcing properties of cocaine (Kuhar et al., 1991; Koob et al., 1994; Everitt et al., 1999; Dackis and O'Brien, 2001;

Anderson and Pierce, 2005), whereby repeated administration of cocaine alters the responsiveness of these regions insofar as they become sensitized to the association between the drug, its many related stimuli (e.g., context and surroundings in which it is taken), and the euphoria that accompanies cocaine intoxication. Indeed, studies of cocaine craving where drug-related stimuli are presented to either active or abstinent users have demonstrated significant activation in regions such as the amygdala, nucleus accumbens and hippocampus (Grant et al., 1996; Maas et al., 1998; Childress et al., 1999; Garavan et al., 2000; Kilts et al., 2001; Wexler et al., 2001; Bonson et al., 2002), along with other regions in the mesocortical circuit (which includes the ACC, dPFC and orbitofrontal cortex). The type of conditioned associative learning is typically found with other reinforcing stimuli (e.g., food, pain), and items conditioned in this way are reinforced as salient to the individual (Berridge and Robinson, 1998).

Salience is also critical to attention (Driver and Frackowiak, 2001; Chun and Marois, 2002). The salience of a stimulus determines its capacity to hold attention, and to an extent, to direct attention. Learning the salience of stimuli and, in turn, allowing salience to reflexively direct our attention (particularly visual attention) appears to have a logical and evolutionary advantage, in that when navigating a complex multi-stimulus environment, our attention is captured by those items which we find rewarding (e.g., food) or might harm us (e.g., predators). As salience directs attention relatively automatically (Pessoa and Ungerleider, 2004), a greater level of cognitive control

\* Corresponding author. Tel.: +61 7 3346 6353; fax: +61 7 3346 6301.

E-mail address: [r.hester@uq.edu.au](mailto:r.hester@uq.edu.au) (R. Hester).

must be imposed to ignore the salient stimulus and instead attend to a less salient stimulus. Top-down cognitive control, the process whereby conscious internal goals take precedence over automatic processes (Norman and Shallice, 1986; Miller and Cohen, 2001), is critical to a number of psychological processes that may contribute to drug addiction (Lyvers, 2000), such as inhibitory control and selective attention. Exerting cognitive control is associated with activation in the ACC, PFC and inferior parietal regions (Carter et al., 1999; Garavan et al., 2002; Giesbrecht et al., 2003), during selective attention tasks such as the Stroop (Zysset et al., 2001; Milham et al., 2003).

Recent evidence indicates that active and abstinent users of cocaine have dysfunction in the cortical regions underlying cognitive control, displaying hypoactivity in the anterior cingulate cortex (ACC), prefrontal cortex (PFC) and orbitofrontal cortex (OFC) (Bolla et al., 2004; Goldstein et al., 2001; Hester and Garavan, 2004; Kaufman et al., 2003).

If a user's attentional system is sensitive to drug-related stimuli in their environment, encountering these stimuli will cue attention and potentially craving. The craving process also involves ruminative thoughts, which appear to activate a working-memory like network of cortical regions (Bonson et al., 2002; Grant et al., 1996), and can interfere with working memory (WM) performance, which has been interpreted as evidence that ruminative thoughts occupy WM capacity. WM activates a network of cortical regions including critical roles for the PFC and ACC; maintaining a WM load appears to place particularly high demands on these regions in cocaine users (Hester and Garavan, 2004). The involvement of WM in craving may also be of consequence due to the relationship between WM and cognitive control, as increasing WM demands result in poorer cognitive control performance (Kane and Engle, 2003). WM is argued to play a critical role in actively maintaining attentional priorities, so that when greater load demands are placed on WM, implementing these 'attentional priorities' suffers, and greater processing of irrelevant information occurs (Kane and Engle, 2003).

The aim of the current study was to examine the neural mechanisms underlying the attentional bias for drug-related stimuli under differing WM demands in active cocaine-users. In the presence of cocaine-related stimuli, we examined whether the previously reported deficits in cognitive control would make cocaine users especially vulnerable to the influence of salient drug-related stimuli under high WM demands. Given the previous reports of hypoactivity in the cognitive control regions of cocaine users being correlated with poorer performance on tasks requiring inhibitory control and selective attention, we hypothesised that the behavioural interference effect of drug-related stimuli would be compounded by increased WM demands, and be related to lower levels of activity in cognitive control regions such as lateral prefrontal cortices.

## 1. Materials and methods

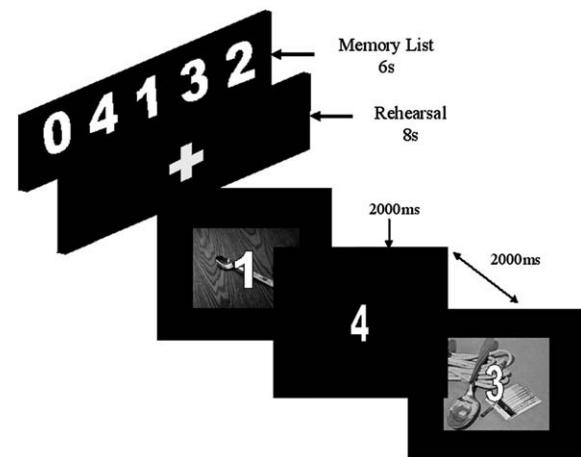
### 1.1. Participants

Sixteen active cocaine users (6 female; mean age=41, range=22–48; mean education 11.6 years, range 9–14 years) participated in the current study. All participants were right-handed and were screened by staff psychiatrists for current or past history or neurological and psychiatric disorders, and dependence on any psychoactive substance other than cocaine or nicotine. Participants were fully informed of the nature of the research and provided written consent for their involvement in accordance with the Institutional Review Board of the Medical College of Wisconsin (MCW). Participants were included in the study upon returning positive tests for cocaine or its metabolites, indicating that they had used cocaine within the past 72 h, and were excluded if they returned positive tests for any of the 96 psychoactive substances tested for. The average time since last use of cocaine was reported at 50 h (range 12–66 h), and participants reported using an

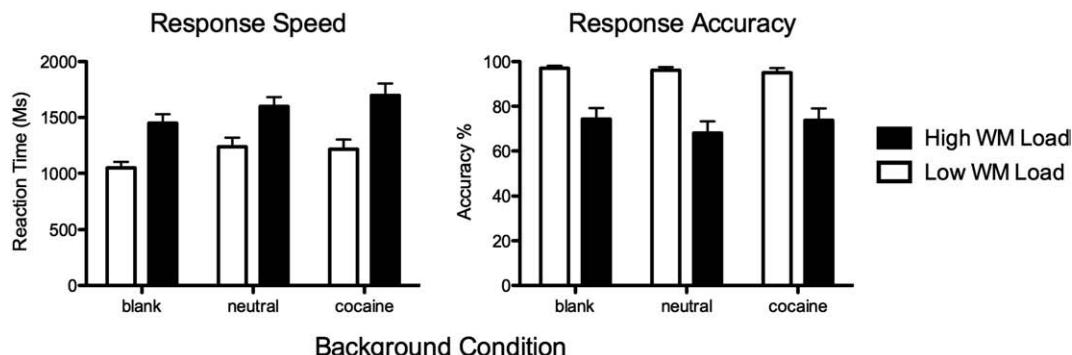
average of 5 times a week (range=1–7) for the past 13 years (range=3–27 years), spending an average of \$239 (range=25–500) per week. Smoking 'crack' cocaine was the preferred route of administration for all participants. Seven participants reported occasional use of cannabis, with the average duration since last use 11 days and none had consumed in the 72 h prior to testing. Seven participants also reported regular use of tobacco (mean=10.5 cigarettes per day). Participants were excluded for present or past dependence on alcohol, and recorded zero blood alcohol levels prior to testing. Regression analyses confirmed that a participant's status as either a cannabis or nicotine user was not related to the measures of behavioural performance or neural activity described below.

### 1.2. Behavioural task

The current task modified the paradigm used by de Fockert et al. (2001) to examine the influence of working memory demands on selective attention (see Fig. 1). Participants were required to remember the sequence of five random (high-load) or sequential (low-load) numbers. Recall trials presented a single memory list digit on a randomised background, with either a blank (black) screen (50% of trials), or interference conditions that included either neutral or cocaine-related pictures (a picture of home-made crack cocaine smoking device is presented). Participants responded to the recall probe with the number that had followed it in the memory list. Ten cocaine-related pictures were drawn from internet sites including the U.S. Drug Enforcement Agency and the Alcohol and Drug Information Clearinghouse. The neutral pictures were drawn from the International Affective Picture System (Lang et al., 1998), and were selected to match (where possible) the visual properties of the cocaine-related stimuli (see Fig. 1) (a list of the IAPS item numbers for the pictures used can be obtained from the corresponding author). The average normative arousal rating for the neutral pictures was 2.5 (range=1.72–2.93). All pictures were presented in black and white to eliminate visual processing differences due to colour. The pictures measured 320×480 pixels in size, and were presented centrally behind the probe item. Each scanner run consisted of two high and two low



**Fig. 1.** Working memory load task design. Participants were presented with an encoding screen that presented a list of five digits (between 0 and 4), vertically, for 6 s (see Fig. 1). They were instructed to remember the order of the digits. A series of 20 'probe' trials was then presented. Each probe trial consisted of a 2 s presentation of a single memory list digit (in 50 point font), to which the participant was required to respond with the digit that had followed it in the memory list, and followed by a 2 s inter-stimulus interval that showed a blank screen. Responses were made on a four-button response box, with each button corresponding to a particular digit (the 0 digit was always the first item in memory lists and therefore did not require a response button). Participants were instructed to respond as quickly and accurately as possible. Following the last probe trial a 16 second rest screen was presented prior to the presentation of the next encoding screen. Four blocks, or repetitions of this cycle, were completed during a single run of 416 s, and two runs were completed during a single imaging session.



**Fig. 2.** Mean reaction time (panel A), accuracy (panel B) and standard error estimates for cocaine users recall responses to target WM items. The data are separated by condition, with WM load (high, low) and the background stimuli condition (blank, cocaine, neutral) upon which the target item was presented. Statistical analysis of both data sets revealed similar result: significant main effects for WM load (high WM load > low WM load) and background condition (blank < cocaine, neutral), and a significant interaction between these factors.

working memory blocks, whose order was interleaved within runs and counterbalanced across runs. An equal distribution of cocaine-related and neutral backgrounds were presented within and across runs, resulting in 20 trials per condition (e.g., 20 low WM demand, cocaine-related background trials).

### 1.3. FMRI procedures and analysis

Scanning was conducted on contiguous 7 mm sagittal slices covering the entire brain from a 3T General Electric Signa scanner using a blipped gradient-echo, echo-planar pulse sequence ( $TE=40$  ms;  $TR=2000$  ms). High resolution anatomical images were acquired following the functional imaging to allow subsequent activation localisation and spatial normalisation. All MRI data analyses were conducted using AFNI software (<http://afni.nimh.nih.gov/afni/>).

A mixed event and block analysis was performed that estimated the activation separately for each of the four trial types of interest. Separate hemodynamic response functions at 2-second temporal resolution were calculated using deconvolution techniques for successful recall at each load size and each background type (designated low load/cocaine, high load/cocaine, low load/neutral, high load/neutral). Due to the small number of error events, the deconvolved hemodynamic response for incorrect recall included the errors committed for all trial types. A non-linear regression program determined the best-fitting gamma-variate function for these impulse response functions, with the area under the curve of the gamma-variate function expressed as a percentage of the area under the baseline. The baseline for this task was the blank background recall trials, which represented 50% of all probe trials. The encoding period that began each block was also modelled in the deconvolution as a boxcar function, as was tonic activity related to WM-demands with high demand considered the 'on' period and low demand the 'off' period.

The percentage area (event-related activation) and percentage change (block-design activation) voxels were re-sampled at 1 mm<sup>3</sup> resolution, then warped into MNI space, and spatially blurred with a 3 mm isotropic rms Gaussian kernel. Group activation maps for each load size were determined with one-sample *t*-tests against the null hypothesis of zero event-related activation changes (i.e., no change relative to baseline). Significant voxels passed a voxelwise statistical threshold ( $t=4.14$ ,  $p\leq .001$ ) and a cluster-size statistical threshold of 142  $\mu$ l cluster of contiguous significant voxels. The cluster threshold was determined through Monte Carlo simulations (1000 iterations) and resulted in a 1% probability of a cluster surviving due to chance. The separate activation maps were then combined, deriving an 'OR' map of successful recall, which included all voxels of activation indicated as significant from any of the constituent maps. The mean activation for clusters in the OR map was calculated for the purposes of an ROI analysis, corrected for multiple comparisons using a modified Bonferroni procedure (Keppel, 1991).

## 2. Results

### 2.1. Behavioural data

A  $2\times 3$  repeated measures ANOVA was used to examine the within participant effects of load (low, high) and background type (neutral, cocaine-related, blank) on reaction times. Significant main effects for load,  $F(1,30)=220.4$ ,  $p<.01$ , and type,  $F(2,30)=15.2$ ,  $p<.01$ , highlighted the slower reaction times for the high WM load condition, and background distraction (cocaine and neutral conditions were significantly slower than the blank background condition ( $p<.001$ )), respectively (see Fig. 2). A significant interaction effect was found between load and type,  $F(2,30)=5.47$ ,  $p<.01$ , with the mean reaction times in the high WM condition indicating significantly longer RTs for the cocaine-related background condition when compared to either the neutral,  $t(15)=2.23$ ,  $p<.05$ , or blank background conditions,  $t(15)=-4.2$ ,  $p<.05$ . The attentional bias for cocaine-related stimuli was not evident at low WM demands, with RTs for low WM/cocaine-related background condition trials not significantly different to low WM/neutral background condition trials ( $p=.71$ ).

The pattern of results observed for accuracy performance also indicated a main effect of load,  $F(1,30)=36.0$ ,  $p<.01$ , and background type,  $F(1,30)=5.47$ ,  $p=.01$ . The interaction between load and type was significant,  $F(1,30)=5.62$ ,  $p<.01$ , with the mean accuracy data indicating that declines in recall accuracy under high WM demands were greatest for the cocaine picture/high load condition, when compared to either the neutral,  $t(15)=-3.5$ ,  $p<.01$ , or blank background conditions,  $t(15)=2.42$ ,  $p<.05$ . Accuracy in the low WM condition was above 95% for all three background conditions and did not show any significant condition-related differences.

### 2.2. Imaging data

Twenty-two regions of activation were identified for successful recall (see Table 1). The main effects analysis revealed significantly higher activity for the high WM load condition, when compared to the low WM condition, in right cerebellum (culmen region), and the opposite pattern in both the left inferior and right middle occipital gyri. Cocaine-related backgrounds were associated with greater activity in bilateral middle occipital, cerebellar (culmen), left inferior occipital, right inferior frontal (pars opercularis), left middle temporal and right precuneus regions. No region showed greater event-related activation for the neutral backgrounds.

Interaction effects between WM load and background type were seen in the left inferior occipital cluster (the largest cluster in the activation map), and right inferior frontal gyrus (IFG – pars opercularis) (see Table 1 and Fig. 3). During the high WM load condition, occipital region activity was significantly higher for cocaine-related stimuli than neutral stimuli, while no difference was

**Table 1**  
Regions of event-related activation for recall

Structure	HS	Volume ( $\mu$ l)	Centre-of Mass			Main Effects		Interaction effects	
			x	y	z	Load	Bkgnd		
<i>Frontal lobe</i>									
Inferior frontal	R	242	42	3	18		Cocaine ↑	*	
	R	168	43	22	25				
<i>Parietal lobe</i>									
Precuneus	R	264	6	-62	22		Cocaine ↑		
Cingulate (posterior)	L	271	-8	-54	31		Cocaine ↑		
<i>Temporal lobe</i>									
Middle temporal	L	265	-47	-66	3		Cocaine ↑		
Fusiform	R	271	28	-41	19				
<i>Occipital lobe</i>									
Inferior occipital	L	5918	-29	-83	-9	Low ↑	Cocaine ↑	*	
	R	543	25	-82	-8				
Middle occipital	R	521	23	-80	13				
	R	506	30	-69	33	Low ↑	Cocaine ↑		
	L	459	-30	-69	17		Cocaine ↑		
	R	506	39	-77	3				
	L	265	-47	-66	3				
	R	247	35	-17	16				
Lingual	R	264	5	-69	-10		Cocaine ↑		
	R	419	23	-62	-3				
<i>Cerebellum</i>									
Cerebellum	R	276	15	-49	-18	High ↑	Cocaine ↑		
	L	5183	-32	-48	-29		Cocaine ↑		
	R	433	31	-56	-25				
	R	662	20	-36	-34				
	R	211	29	-46	-29				
	R	647	10	-29	-20				

Positive values for x, y, and z MNI coordinates denote, respectively, locations that are right, anterior and superior relative to the anterior commissure. The main and interaction effects are represented in the three right-hand side columns, with main effects presentation including the condition and direction of difference (e.g., Cocaine↑ indicates that the cocaine-picture background condition had significantly higher BOLD activity than neutral background condition). Abbreviations include: hemisphere (HS), background condition (Bkgnd).

\* Represents significant interaction effects ( $p < .05$ ) between WM Load and background content, whereby during the high WM load condition, occipital region activity was significantly higher for cocaine-related stimuli than neutral stimuli, while no difference was seen for the low WM condition.

seen for the low WM condition. The same pattern was seen in the right IFG cluster, with significantly higher levels of activity for cocaine-related stimuli (when compared to neutral stimuli) in the high WM load condition, and no difference for the low WM condition.

Given the similarity between the interaction effects for the occipital and right prefrontal regions, we calculated condition difference scores for neural activity (i.e., high WM-Cocaine minus high WM-Neutral), behavioural reaction time (i.e., high WM cocaine background RT minus high WM neutral RT) and accuracy measures. The difference scores were entered into a correlation analysis to examine the relationship between condition-specific effects in neural activity and behavioural interference effects. The responsiveness of a cocaine-user's right IFG to cocaine-related stimuli (when compared to neutral stimuli), was related to greater behavioural interference – both recall accuracy ( $r = -.55$ ,  $p < .05$ ), and response times ( $r = .47$ ,  $p < .05$ ) (Fig. 4). No interrelationship was observed between the neural activity difference scores or between the occipital activity and behavioural measures, and a moderate negative relationship was seen between the behavioural interference scores ( $r = -.64$ ,  $p < .05$ ), indicating that greater response time interference for cocaine-related stimuli was related to decreased recall accuracy.

The absence of limbic regions, such as the amygdala, from the whole-brain analysis limited our ability to test the hypothesis that

these regions are sensitive to the presentation of cocaine-related stimuli, and in turn, that this activity might be contributing to the attentional-bias demonstrated in reaction time and accuracy data. Given this interest, a right hemisphere amygdala ROI, which fell below the cluster-size threshold ( $x: 19$ ,  $y: -7$ ,  $z: -10$ ; size = 132  $\mu$ l) was used to derive mean BOLD activity estimates, which were then entered into a 2 (load)  $\times$  2 (background type) repeated measures ANOVA. The mean BOLD activity estimates (see Fig. 5) presented the expected trend of greater activity for trials with a cocaine-related background, an effect that appeared to compound during higher WM demands, however all statistical comparisons were non-significant ( $p > .49$ ).

The high level of individual variability in activity across the conditions, particularly in the high WM load/cocaine-related background condition, appears to have contributed to the lack of statistical significance in this comparison. Accuracy, reaction time and BOLD activity difference scores, calculated by subtracting the mean high load/neutral condition data from the equivalent high load/cocaine background trial mean, showed medium positive relationships between right amygdala activity and RT difference scores ( $r = .54$ ), but not accuracy ( $r = .04$ ). Amygdala activity in the high load/cocaine background condition showed a significant positive correlation with years of cocaine use ( $r = .58$ ), but negatively correlated with hours since last use ( $r = -.42$ ) and weekly spending on cocaine ( $r = -.41$ ), though the latter two correlations only approached significance ( $p = .12$ ).

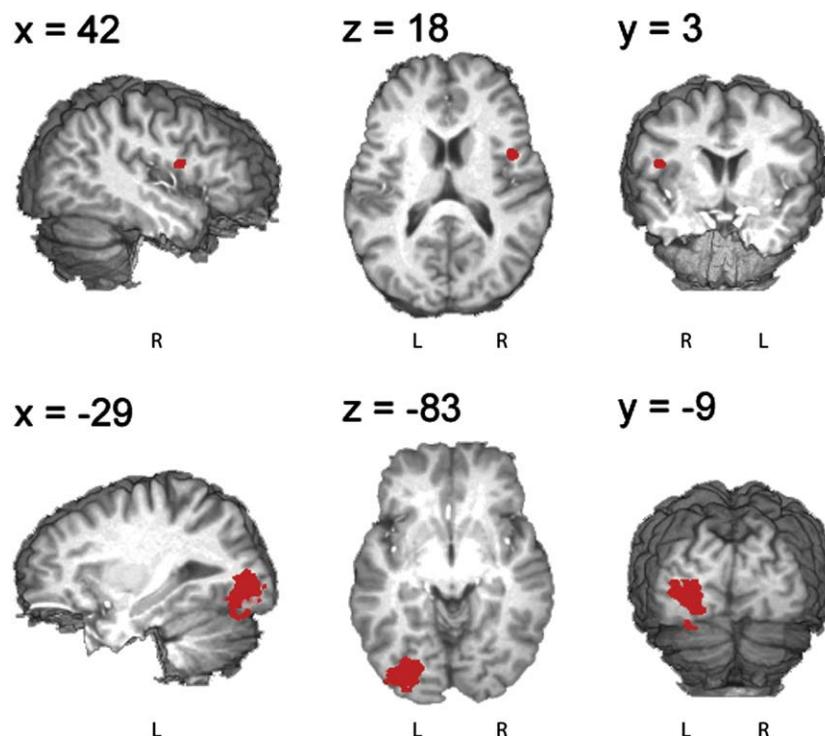
Activity in other functionally-defined regions of interest did not significantly correlate with self-report measures of cocaine use.

### 3. Discussion

Active cocaine users had significant difficulty controlling attention when required to ignore cocaine-related stimuli under high WM demands. The WM load implemented in the current study was an attempt to generate the type of cognitive demand previously associated, both at a behavioural and neural level, with the ruminative craving thoughts commonly reported in drug addiction (Bonson et al., 2002; Grant et al., 1996; Kilts et al., 2001) and other clinical conditions (Vreugdenburg et al., 2003; Watkins and Brown, 2002). The difficulty cocaine users experienced with ignoring drug-related stimuli, reflected in both their decreased recall accuracy and increased response times for this condition (when compared to neutral stimuli under the same load) was associated with higher levels of activity in the right inferior frontal gyrus (located in the pars opercularis), a region considered critical to the implementation of top-down cognitive control, and the left occipital cortex.

The right inferior frontal cortex (IFC) has been consistently linked to inhibitory control (Aron et al., 2004; Chambers et al., 2006; Garavan et al., 2006; Mayr et al., 2006), and has been argued to represent the suppression of an irrelevant response (Aron et al., 2004; Chambers et al., 2006). While it is not possible directly to ascribe this role here (because activity occurs during a working memory recall), previous data suggest that the IFC region has also been related to complex cognitive control performance more generally (Brass and von Cramon, 2004; MacDonald et al., 2000; Pochon et al., 2001; Sakai and Passingham, 2003), including during tasks measuring the capacity to ignore salient but irrelevant information (e.g., Stroop task) (Brass et al., 2005; Egner and Hirsch, 2005b; Taylor et al., 1997; Zysset et al., 2001). For example, Dolcos and McCarthy (2006) demonstrated in healthy controls that individual differences in the processing of emotional distractors during a demanding WM task was correlated with the level of right IFG activity.

The bias for drug-related stimuli is consistent with reports in other drug-abuse populations (Cox et al., 2002; Field et al., 2004a,b; Franken et al., 2004; Lubman et al., 2000), and clinical groups such as post-traumatic stress disorder, depression and obsessive compulsive disorder (Constans et al., 2004; Malhi et al., 2005; Moritz et al., 2004). The specificity of the drug-related attentional bias to cocaine



**Fig. 3.** Regions of event-related brain activity demonstrating significant interaction effects between WM load and background picture conditions. Interaction effects were seen in the right inferior frontal gyrus (panel A – top) and the left inferior occipital cluster (panel B – bottom). The MNI co-ordinates for the centre of mass of each cluster are presented.

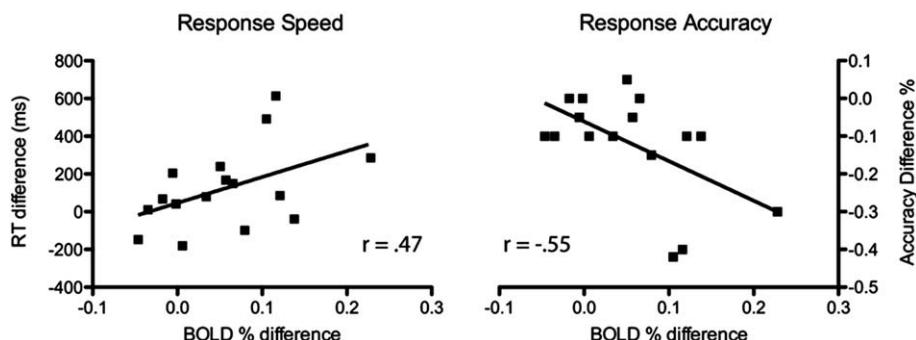
users has previously been demonstrated. Using the exact same cocaine-related and neutral stimuli in an emotional Stroop task (Hester et al., 2006), we demonstrated that while cocaine users had a significant attentional bias for the cocaine-related stimuli, equivalent to non-drug-related evocative stimuli, control participants did not. Given this finding, the relationship between neural activity and behaviour that we observed in the present study may not be specific to drug-related stimuli, but may generalise to other stimuli that cocaine users find evocative.

In the high WM condition, occipital cortex activity was greater for irrelevant cocaine-related stimuli compared to neutral stimuli, while the difference observed between the stimuli types during the low WM condition was not significant. Similar increases were observed by de Fockert et al. (2001) with the original version of the WM and selective attention task (in control participants), and this effect has been replicated by Egner and Hirsch in the absence of a working memory manipulation (Egner and Hirsch, 2005a). de Fockert et al. argued that the increased reaction times, along with greater occipital region activity, were consistent with the interfering stimuli receiving greater visual

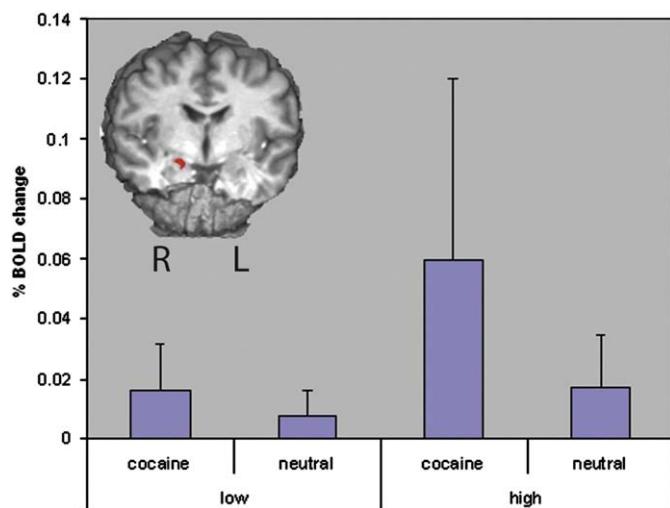
processing in the high WM demand condition. Given the longer reaction times and higher levels of occipital activity for cocaine users when attempting to ignore drug-related stimuli, this explanation would also appear consistent with our results.

Participants in the present study showed significantly greater activity in the cerebellum in response to high WM demands. Increased cerebellar activity during cognition has also been identified in schizophrenia (Meyer-Lindenberg et al., 2001), where poor working memory performance was accompanied by patterns of functional connectivity suggesting over-reliance on the cerebellum. Compensatory activity has also been demonstrated in alcoholics, where equivalent working memory performance was supported by relative increases in right cerebellar regions (Desmond et al., 2003), supporting reduced activity in the left prefrontal cortex. Similar compensatory effects have also been shown in chronic users of cannabis (Bolla et al., 2005), and our own findings with cocaine users (Hester and Garavan, 2004).

Previous evidence has highlighted the responsiveness of limbic regions, such as the amygdala, to the presentation of drug-related



**Fig. 4.** Correlation scatter plots for the relationship between the right IFG activity difference score and the behavioural interference scores calculated from reaction time (RT) and accuracy. Each difference score was calculated by subtracting the high WM load neutral condition score from the equivalent high WM load cocaine condition score.



**Fig. 5.** Percentage BOLD activity change in the right amygdala region of cocaine users during successful recall trials. The data are presented for the four trial types, divided by WM load (low, high) and background content (cocaine-related, neutral) conditions. Error bars represent 1 SE of the mean.

stimuli (Bonson et al., 2002; Breiter et al., 1997; Childress et al., 1999; Ciccioppo et al., 2001; Grant et al., 1996; Kilts et al., 2001; Makris et al., 2004). A pre-defined ROI-based analysis of activity in the right amygdala indicated that mean BOLD activity is consistent with previous studies – showing a trend of greater activity for trials with a cocaine-related background, an effect that appeared to compound during higher WM demands. However, all statistical comparisons were non-significant due to the high level of individual variability in activity across the conditions, particularly in the high WM load/cocaine-related background condition. Analysis of these individual differences indicated that amygdala activity was greater in those individuals who also had high scores on the behavioural measure of cocaine-related bias and more years of cocaine use. These relationships highlight the influence of sample heterogeneity on the relationship between limbic activity and drug-related attentional bias, but are consistent with the hypothesis that limbic responsiveness to drug-related stimuli contributes to the attentional bias observed in dependent drug users.

The relationship between an attentional bias for cocaine-related stimuli and greater activity in prefrontal and occipital regions is consistent with the hypothesis that cocaine-related stimuli hold visual attention and require greater levels of cognitive control, to avoid interfering with processing of the primary task. The dynamics of this relationship requires further clarification, as greater occipital activity may require higher levels of prefrontal activity to disengage from visual processing, or to continue performing the primary task in the presence of visual distraction. What is clear, however, is that individual differences in the ability to modulate prefrontal activity has a direct influence on attentional bias: those cocaine users who displayed the greatest increases in right IFG activity under the most demanding conditions (high WM load and cocaine-related backgrounds), showed the lowest levels of behavioural interference.

The latter result appears to link the present result with findings that suggest that attentional bias for drug-related stimuli is a predictor of treatment outcome (Carpenter et al., 2005; Cox et al., 2003). These studies indicate that while the majority of their drug dependent users display some level of attentional bias for drug-related stimuli, the greater the magnitude of attentional bias a user demonstrates, the higher their risk of relapse. Our results indicate that the magnitude of bias varies as a function of right prefrontal activity. That activity in a region thought critical to cognitive control, rather than within visual processing areas, predicted individual differences in the extent of bias is

consistent with the suggestion from a number of authors that cognitive control, or lack therein, may contribute to the maintenance of drug abuse (Goldstein and Volkow, 2002; Lubman et al., 2004; Lyvers, 2000). While dependent drug users are attracted to stimuli they associate with the reinforcing properties of a drug, and may continue to do so long after successful treatment for their addiction (Robinson and Berridge, 2003), the level of this bias appears to fluctuate as a function of cognitive control. Chronic use of cocaine has previously been linked with neuroanatomical and neurotransmitter dysfunction in the prefrontal cortices (Breiter et al., 1997; Franklin et al., 2002), with the present results indicating that such deficits may contribute to behaviour changes that increase the user's attention to drug-related stimuli.

The ability to measure, or potentially more importantly to augment, levels of prefrontally-mediated cognitive control appears a promising avenue for improving treatment outcomes. In addition to the behavioural findings linking cognitive control and treatment outcome (Carpenter et al., 2005), recent research with methamphetamine users has shown that low levels of right prefrontal activity during a cognitive decision making task predicted relapse outcome at 12 months (Paulus et al., 2005). Studies using repetitive trans-cranial magnetic stimulation on this region in patients with major depression has also shown benefits to both cognitive control performance and mood (Bermpohl et al., 2006), and pharmacotherapy agents for cocaine dependence treatment such as Modafinil have been shown to increase both cognitive control performance and activity in the cognitive control neural network (Turner et al., 2004). The exact procedure for increasing cognitive control is an area requiring further investigation; however studies attempting treatment interventions with drug users may obtain valuable information by tracking indicators of cognitive control.

Interestingly, no attentional bias for cocaine-related stimuli was observed during the low-working memory load condition of the present study. Previous studies utilising an emotional Stroop task have demonstrated significant attentional biases for drug-related stimuli in the absence of any working memory manipulation (Copersino et al., 2004; Franken et al., 2004). However, previous studies have also failed to show an attentional bias for emotionally salient words (in other clinical groups: Bipolar disorder, Depression and Schizophrenia) (Kolassa and Miltner, 2006; Mohanty et al., 2005; van den Heuvel et al., 2005), though on each occasion a 'compensatory' increase in right dPFC activity was detected.

Additionally, studies that have found attentional biases have typically capitalized upon the stimulus conflict effect: the presented stimulus word prompts the overlearned response of reading, thereby drawing attention to the salient (but task-irrelevant) drug-related semantic content of the word. While the present task required participants to focus attention centrally on the relevant stimulus and ignore the background picture, thereby requiring selective attention, it did not engender stimulus conflict between the relevant and irrelevant stimuli. Recent work (Egner and Hirsch, 2005a) suggests that attentional biases for evocative stimuli are most reliably produced when the task introduces both stimulus and response conflict. Given the lack of stimulus conflict in the present task, lower levels of cognitive control may have been sufficient to selectively attend to the relevant probe item stimulus. It is possible that only under conditions of high cognitive control demands, such as the high WM condition, that cocaine users' attentional control would have been vulnerable to evocative cocaine-related stimuli.

The absence of significant activity in the dorsal ACC region, previously associated with significant executive dysfunction problems in cocaine users (Bolla et al., 2004; Goldstein et al., 2007; Goldstein et al., 2001; Hester and Garavan, 2004), was noteworthy. These studies have identified a hypoactive response in the ACC region of cocaine users during tasks requiring cognitive control. The Goldstein et al. (2007) study identified a relationship between hypoactivity in the ACC and committing response errors during responses to colour-valenced

cocaine-related words, though their results did not show an attentional bias for cocaine-related stimuli. In general, the hypoactivity of the ACC region has been in comparison to healthy matched controls, rather than a within subject condition difference. The absence of a group comparison in the present study might account for why we did not observe a significant cluster of activity in the dorsal ACC region, as hypoactive responses in the ACC are likely to be missed after thresholding group MRI activity maps. The sensitivity of our paradigm may have also been limited by the administration of only 20 events or trials per condition, which represented a compromise between the desire for increased power afforded by higher trial numbers and the potential habituation of participants to repeated presentation of evocative stimuli.

The results of the present study support the hypothesis that cocaine users' attentional bias for drug-related stimuli is influenced by prefrontal cognitive control region activity. These resources appeared to be overwhelmed by the requirement to simultaneously maintain a high WM load and ignore a cocaine-related stimulus, highlighting the potential for negative outcomes to stem from ruminative thoughts and other sources of tonic cognitive demand. For example, the presentation of drug-related cues to dependent cocaine users has been shown to elicit anxiety responses (Sinha et al., 2000), which also have the potential to exacerbate the effects of WM demands on cognitive control (Ashcraft and Krause, 2007; Shackman et al., 2006). While the present study used a non-valenced WM load to represent ruminative thoughts, further research could examine how more ecologically valid methods of either eliciting, or measuring the extent of, ruminative thoughts in users might influence the level of attentional bias and the neural mechanisms underlying the bias.

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