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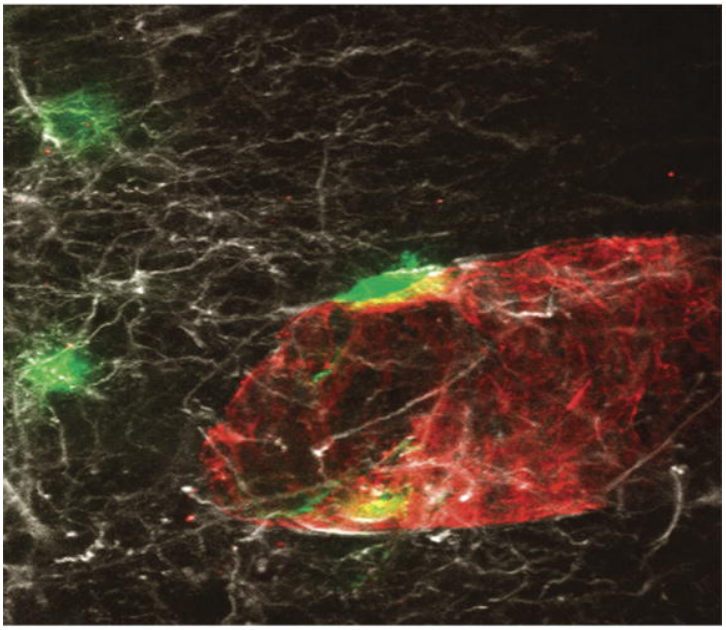

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Research Report

Widespread disruption in brain activation patterns to a working memory task during cocaine abstinence

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ABSTRACT

Cocaine abstinence is associated with impaired performance in cognitive functions including attention, vigilance and executive function. Here we test the hypothesis that cognitive dysfunction during cocaine abstinence reflects in part impairment of cortical and subcortical regions modulated by dopamine. We used functional magnetic resonance imaging (fMRI) to study brain activation to a verbal working memory task in cocaine abusers (n=16) and healthy controls (n=16). Compared to controls, cocaine abusers showed: (1) hypoactivation in the mesencephalon, where dopamine neurons are located, as well as the thalamus, a brain region involved in arousal; (2) larger deactivation in dopamine projection regions (putamen, anterior cingulate, parahippocampal gyrus, and amygdala); and (3) hyperactivation in cortical regions involved with attention (prefrontal and parietal cortices), which probably reflects increased attention and control processes as compensatory mechanisms. Furthermore, the working memory load activation was lower in the prefrontal and parietal cortices in cocaine abusers when compared with controls, which might reflect limited network capacity. These abnormalities were accentuated in the cocaine abusers with positive urines for cocaine at time of study (as compared to cocaine abusers with negative urines) suggesting that the deficits may reflect in part early cocaine abstinence. These findings provide evidence of impaired function of regions involved with executive control, attention and vigilance in cocaine abusers. This widespread neurofunctional disruption is likely to underlie the cognitive deficits during early cocaine abstinence and to reflect involvement of dopamine as well as other neurotransmitters.

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1. Introduction

Cocaine abuse is associated with disruption in cognitive operations that include attention, executive function and vigilance (Goldstein et al., 2004; Pace-Schott et al., 2005). Imaging studies of cocaine abusers tested during abstinence and protracted detoxification have reported reduced dopamine (DA) activity (Volkow et al., 1997b), which has been linked with long lasting decreases in activity of frontal cortical regions [i.e., dorsolateral prefrontal cortex (DLPFC), anterior cingulate gyrus (ACG) and orbitofrontal cortex] (Volkow et al., 2001). Since the mesocortical DA system

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facilitates executive function and attention via its projections to the PFC and ACG (Gaspar, 1992; Goldman-Rakic et al., 2000) and to the thalamus (Pinto et al., 2003; Sanchez-Gonzalez et al., 2005) and DA is necessary for the proper performance of cognitive functions that are modulated by frontal cortical regions (Nieoullon, 2002), we hypothesized that cocaine abusers tested during abstinence would have significant disruptions in the pattern of corticolimbic activation underlying the performance of these cognitive tasks. It has been previously hypothesized that frontal abnormalities may underlie the disruption in cognitive functioning in cocaine abusers during abstinence and detoxification (Bolla et al., 2000; Kufahl et al., 2005); however, this association has not been widely documented using functional magnetic resonance imaging (fMRI). To our knowledge there is only one published fMRI study that used inhibitory GO–NO/GO WM tasks; here the authors reported lower PFC activation in abstinent cocaine abusers than in control subjects (Hester and Garavan, 2004).

Therefore, in the current study we employ fMRI to characterize the functional significance of the abnormalities in the PFC of cocaine abusers that have been previously documented as decreases in metabolism, blood flow or volume (Adinoff et al., 2001, 2003; Goldstein et al., 2004; Goldstein and Volkow, 2002; Kosten et al., 2004; Volkow et al., 1992, 1988). Since we have previously shown that the decreases in PFC metabolism (including ACG and orbitofrontal cortex) in cocaine abusers were associated with depressed DA D2 receptor availability, we propose that the putative PFC abnormalities reflect in part dopaminergic dysfunction (Volkow et al., 1993). However recent preclinical studies documenting marked disruption in norepinephrine (NE) transporters in non-human primates exposed to chronic cocaine (Beveridge et al., 2005) suggest that the NE system also contributes to the cognitive dysfunction in cocaine abusers. We selected a verbal WM task because its processing is supported by a distributed neural system that is modulated by DA (Aalto et al., 2005) but also NE (Rossetti and Carboni, 2005). Specifically, this task engages DA modulated regions (the PFC, putamen, amygdala, parahippocampus and mesencephalon) and also the parietal and occipital cortices and the cerebellum. We hypothesized that the WM task would produce lower activation for chronic cocaine abusers than for control subjects in brain regions that are modulated by DA (PFC, striatum, amygdala/hippocampus and mesencephalon) and that these abnormal responses would be associated with impaired task performance. We further hypothesized that the abnormalities would be more accentuated during the earlier (<72 h) than later (>72 h) stages of abstinence.

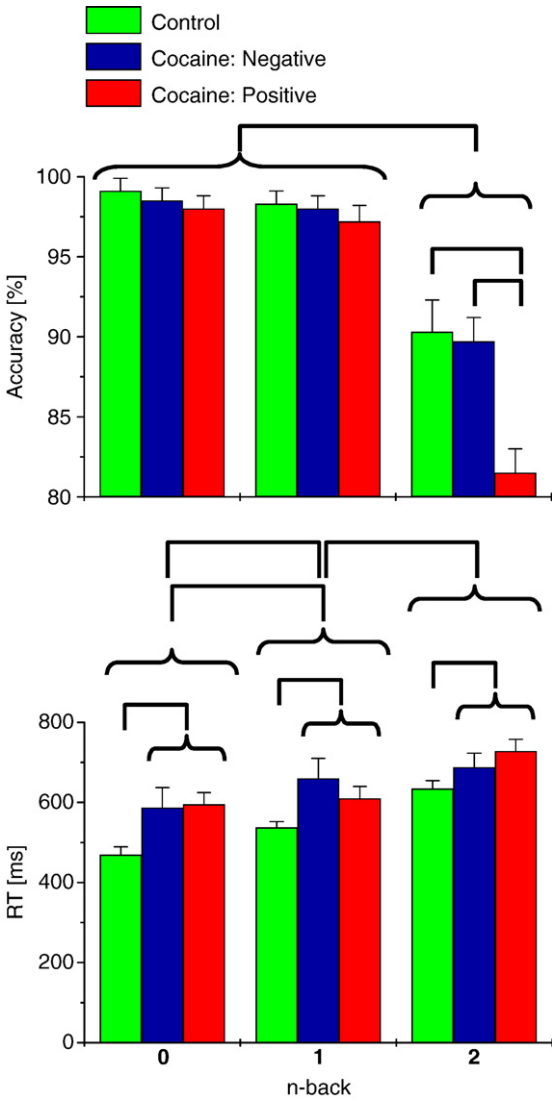

Fig. 1 – Average performance accuracy and reaction times during fMRI of verbal working memory (WM, *n*-back) for control subjects ($n=16$; green bars) and cocaine abusers with negative ($n=8$; blue bars) and positive ($n=8$; read bars) urine toxicology screening for cocaine. The numbers indicate the levels of difficulty of the 0-, 1- and 2-back conditions. Cocaine abusers, when compared with controls, had longer RT for all task levels and lower performance accuracy for the 2-back task ($p<0.006$). Symbols (⊓) highlight statistically significant differences ($p<0.05$) between groups and conditions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2. Results

2.1. *Behavioral data*

Fig. 1A shows that performance accuracy during the fMRI tasks was high (>80%) and similar for cocaine and control subjects. For both groups, accuracy was significantly lower for the more demanding 2-back task as compared to the 0- and 1-back tasks ($p<0.0001$; paired *t*-test). Accuracy on the 2-back task was lower for cocaine than for control subjects ($p=0.02$; two-sample *t*-test) and for subjects that had positive-cocaine urine screening than for those that had negative-cocaine urine screening ($p<0.007$; two-sample *t*-test). Reaction times (RT) were longer for cocaine than for control subjects across all conditions; and for 2-back than for 1-back, and for 1-back than for 0-back across all subjects ($p<0.006$). Reaction times were not different for subjects who

Table 1 – Coordinates of major activation clusters in the Talairach frame of reference and average t-scores in 0.73 cm³ isotropic ROI centered at these coordinates

Brain region		Coordinates [mm]			Control (C; n=16)			Cocaine (S; n=16)			S>C			WM load		
		x	y	z	0	1	2	0	1	2	0	1	2	C	S	S>C
IFG47	L	−33	18	−3	2.4	**3.5**	**5.0**			2.2			−2.2			
	R	33	18	−3	2.9†	**3.2**	**6.0**	**3.3**	**4.7**	**4.6**				2.2		
MFG9	L	−45	9	33		**6.2**	**9.4**		**9.7**	**11.5**	−2.1	2.6†		**2.7**		
	R	45	9	33		**4.6**	**8.5**		**7.1**	**6.5**				3.1†		−2.5*
MFG9	L	−45	27	21		**4.8**	**9.0**		**3.6**	**8.5**				**3.4**	3.4†	
	R	45	27	21		**2.5**	**5.8**		**4.7**	**8.1**				2.5†	2.5	
MFG6	L	−39	−6	51				3.1	**6.3**	**4.1**	2.6	**5.2**	**3.2**			
	L	−24	0	51			**3.2**		**4.5**	**10.2**		**3.3**	**4.7**	2.4†	**4.0**	
	C	−9	3	60	**2.5**	**2.4**	**3.3**	2.6	**9.9**	**7.6**		**5.4**	**2.8**			
SFG8	C	3	27	51					**3.7**	**6.3**		**3.2**	**4.4**			
medFG8	C	−6	18	45	**4.2**	**7.3**	**11**		**9.8**	**13.8**	−2.3			3.0*	2.8†	
ACG24	C	−6	24	21				−2.1	**−4.0**	**−5.8**	−2.1	−3.1*	**−4.7**			
Putamen	L	−24	12	−3					**−2.7**	**−4.7**		−2.8†	**−3.8**			
	R	24	6	15					**−2.6**	**−5.4**		−2.4*	**−4.4**		−2.0	
INS13	R	45	−6	6			**−3.7**		**−6.6**	**−9.9**		−3.7†	**−4.1**		−2.4	
Tha/Mes	C	−6	−15	−3	2.4	**3.8**	**3.4**					−2.1*	−2.5*			
PHG/Amy	L	−30	−3	−15					**−3.2**	**−6.8**			**−3.3**		−2.6*	
	R	30	−3	−15					**−3.4**	**−5.8**		−2.4†	**−3.4**			
PCG30	C	−6	−51	18	**−5.8**	**−8.5**	**−12**	−2.0†	**−6.0**	**−8.4**	2.2		3.0	**−3.1**		
PostCG5	L	−42	−24	54		**−2.4**		2.4	**3.5**	2.3	2.1	**4.1**	2.0			
PostCG3	R	39	−30	51			**3.0**	2.0	**5.7**	**6.7**		3.4	2.4			
IPC40	L	−30	−42	54				3.8†	**7.9**	**10.2**	3.2	**6.2**	**6.3**			
SPC7	L	−33	−57	51	2.2	**6.0**	**8.8**		**4.7**	**10.6**				2.5†	**4.2**	
	R	33	−48	57		**5.9**	**10**		**7.5**	**9.9**				**3.7**		
	L	−21	−54	54			**3.8**		**7.4**	**11.6**		**4.8**	**5.1**	2.3†	**3.0**	
PreCUN7	R	18	−63	42		**4.6**	**9.1**					−3.0†	**−6.5**	**3.5**		−2.7*
PreCUN39	L	−36	−66	39			**3.1**		**−4.0**	**−3.9**		−2.5	−4.9†	2.6†		
FusG19	L	−33	−66	−15		**4.2**	**5.1**		**8.8**	**10.6**		**3.3**	**3.5**			
	R	36	−78	−6					**2.8**	**3.5**						
LG17	L	−24	−81	−9					**4.9**	**4.9**		**3.1**	**3.2**			
CER	L	−12	−51	−18	2.7†	**2.9**			−2.6		−2.3	−3.9†			**6.2**	2.0*
	C	0	−72	−15	3.2†	**6.4**	**7.0**	2.0	**7.1**	**7.8**						

Statistical significance (corrected for multiple comparisons): $p_{corr}<0.001$ (**bold**); $p_{corr}<0.05$ (†). (*): $p_{corr}<0.05$ with small volume correction (spherical; searching radius=10 mm). S: cocaine. C: controls. The 0, 1 and 2 column labels indicate 0-, 1- and 2-back tasks. WM load: 2-back minus 1-back.

had positive or negative urine screening. The increased RT and the decreased performance accuracy for increased WM load (0-, 1- and 2-back) reflect the increased difficulty of the tasks.

2.2. *Brain activation*

For both groups, the 0-, 1- and 2-back tasks activated a bilateral network (Table 1 and Fig. 2, "Main activation") that included the PFC [inferior (IFG), middle (MFG), and medial (medFG) frontal gyri], and the superior parietal (SPC) and occipital [fusiform gyrus (FusG)] cortices, as well as the thalamus and the cerebellum (CER), in agreement with our previous studies (Tomasi and Caparelli, 2007; Tomasi et al., 2007a,b, 2006b); the tasks deactivated the posterior cingulate gyrus (PCG) and the posterior insula (INS). Differences between the groups were observed (Table 1 and Fig. 2) in (1) the precuneus (Brodmann areas, 7 and 39; PreCUN7 and PreCUN39), left cerebellum, thalamus (Tha) and mesencephalon (Mes) and the putamen (put), which were activated more in controls than in cocaine abusers; (2) the prefrontal [MFG6, MFG9 and the superior frontal gyrus (SFG8)], parietal [SPC7, inferior parietal cortex (IPC40) and the postcentral gyrus (PostCG3 and PostCG5)] and occipital [FusG19 and the lingual gyrus (LG17)] cortices, which activated more in cocaine abusers than in controls; and (3) in the ACG24, INS13, parahippocampal gyrus (PHG) and the amygdala (Amy), which deactivated more in cocaine abusers than in controls.

2.3. *Working memory activation*

Brain activation during the 1- and 2-back tasks was contrasted (intra-subject) to that during the 0-back task to remove the common sensory–motor effects associated to subjects' responses (button press events). This WM effect was evaluated for each group, conjunctively for the 1- and 2-back tasks [(1-back vs. 0-back) and (2-back vs. 0-back); Fig. 2, "WM"]. For both groups the WM effect on brain activation was significant in the MFG9, medFG8, SPC7, and the cerebellum; the WM effect on

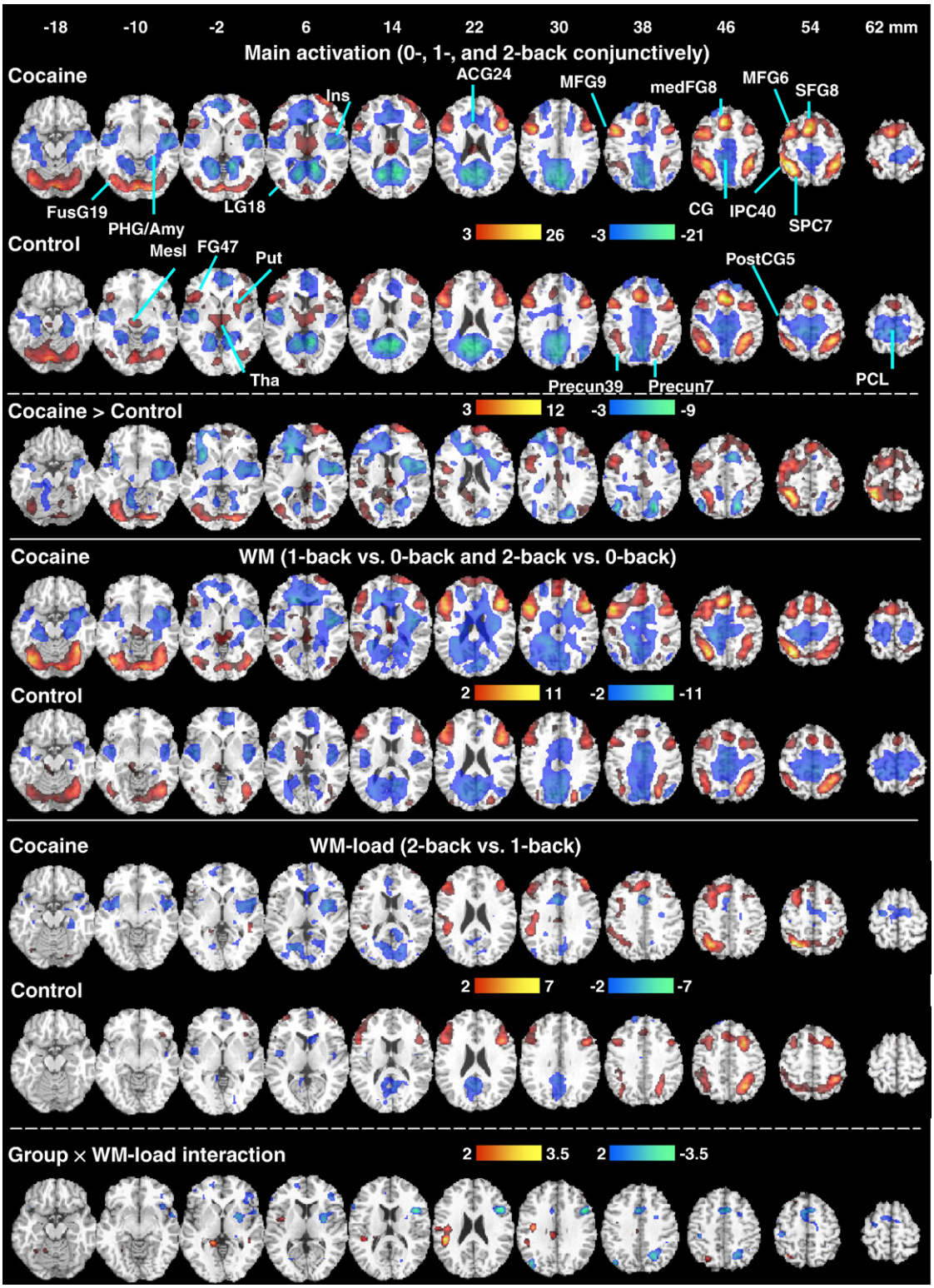

Fig. 2 – Statistical maps of BOLD signals during verbal working memory (WM, conjunction analysis: 0-back + 1-back + 2-back) for cocaine abusers ($n = 16$; positive and negative urines, combined; upper row), control subjects ($n = 16$; second row) as well as for the differential activation between the groups (group effect; third row), WM (conjunctive analyses of 1-back vs. 0-back and 2-back vs. 0-back; fourth and fifth rows, respectively for cocaine and control), WM load (2-back vs. 1-back; sixth and seventh rows, respectively for cocaine and control) and the for the group (Cocaine vs. Control) × WM load interaction effect (bottom row). White labels (top) indicate the *z*-coordinate of each slice in millimeters in the Talairach frame of reference. These two-way ANOVAs (random-effects) of brain activation were done using the "full-monty" SPM2 model. The statistics of the conjunction analyses (first and second rows) reflect the average activation across conditions after controlling for increased WM load. Red–yellow and blue–green color bars show the *t*-score windows for activation and deactivation, respectively.

brain deactivation was significant in the cingulate cortex and the INS. WM activation was larger for cocaine abusers than for controls bilaterally in the MFG9, medFG8 and in the left SPC7, LG17 and FusG19. WM deactivation was larger for cocaine abusers than for controls in the PHG/Amy and the left PreCUN39 and right PreCUN7.

2.4. *WM load activation*

Increased WM load from 1-back to 2-back produced larger positive fMRI signals in the PFC (MFG, and medFG) and SPC (Table 1 and Fig. 2). For cocaine abusers, increased WM load also produced larger activation in the left cerebellum and larger deactivation in the PHG/Amy (Table 1). For controls, increased WM load also produced larger activation in the PreCUN7 and 39 and larger deactivation of the PCG30. Group comparisons revealed that cocaine abusers had lower WM load activation in the MFG9 and PreCUN7 and higher WM load activation in the cerebellum than controls ($p_{corr}<0.03$; using a small volume correction with radius=10 mm; two-way repeated measures ANOVA in SPM2); these regions showed group activation differences (main WM and WM load effects).

2.5. *ROI analyses*

Fig. 3 shows the average amplitude of BOLD responses in the brain. Compared to controls (green bars) and independently for the 1- and 2-back tasks (compared to baseline), the positive BOLD responses in cocaine abusers (positive and negative urines combined) were lower in the Tha/Mes, PreCUN7 and CER ($p<0.04$; two-sample t-test) and larger in the prefrontal (MFG6 and 9 and SFG8), parietal (IPC40, SPC7, PostCG3 and 5) and occipital (LG17 and FusG19) cortices ($p<0.01$); for cocaine abusers the negative BOLD responses (i.e., deactivation) in the ACG24, INS13, PHG/Amy and PreCUN39 were larger than for controls ($p<0.05$). These abnormalities were larger in cocaine abusers with positive urine toxicology screening (red bars;

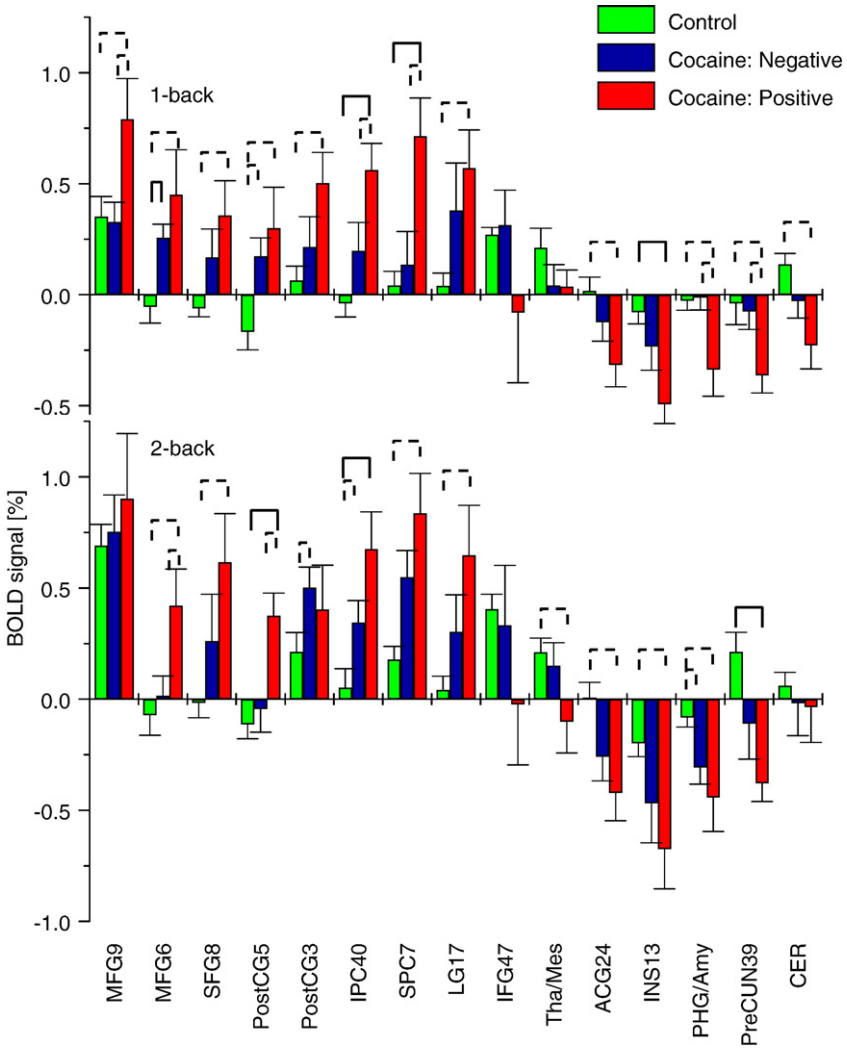

Fig. 3 – Average BOLD signals at specific ROIs (Table 1) for the 1-back (top) and 2-back (bottom) conditions and for controls ($n=16$; green bars) and cocaine subjects with negative ($n=8$; blue bars) and positive ($n=8$; red bars) urines for cocaine. ROI volume=27 voxels (0.73 cm^3). Solid ($p<0.001$) and dashed ($p<0.05$) symbols (□) highlight statistically significant differences. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 3). Only the PostCG5 (1-back), PostCG3, IPC40 and PHG/Amy (2-back) demonstrated statistically significant differences between cocaine abusers with negative urine results and controls. The cocaine abusers with positive urines had larger activation in the PFC (MFG9 and MFG6) and parietal cortex (PostCG5, IPC40, SPC7 and PreCUN39) and larger deactivation in the PHG/Amy than cocaine abusers with negative urines.

For cocaine abusers compared to control subjects, the ROI analyses demonstrated that the differential effect of WM load on BOLD responses (2-back – 1-back; Supplementary Fig. 2) was lower in the PFC (MFG6 and 9, $p<0.01$), parietal cortex (SPC7 and PreCUN7 and 39, $p<0.03$) and the putamen ($p=0.02$); only the cerebellum exhibited higher WM load responses in cocaine abusers than in control subjects ($p=0.02$). Cocaine subjects with positive urines had lower WM load responses in the MFG9, PostCG3 and the putamen than those with negative urines ($p<0.03$). Cocaine subjects with negative urines had lower WM load responses in the MFG6 and the PostCG5 than control subjects ($p<0.008$).

2.6. *Behavior vs. brain activation*

For cocaine abusers (positive and negative urine results combined), (1) higher performance accuracy during the 2-back task was associated with increased activation of the cerebellum (Fig. 4) and lower activation of the PostCG5 ($p_{corr}<0.05$) and (2) longer RT during the 2-back task was associated with increased activation of the PostCG5 ($p_{corr}<0.001$, Fig. 4).

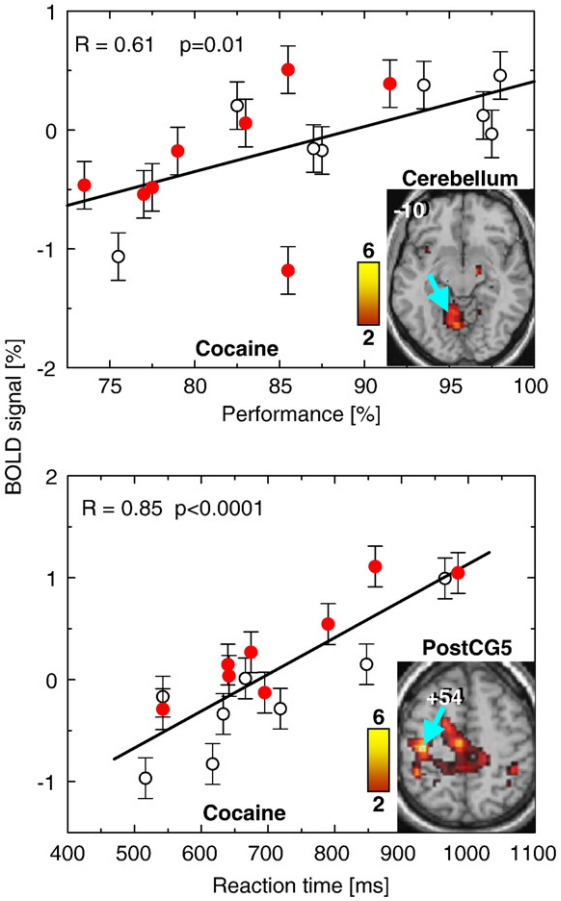

Fig. 4 – Linear correlations between behavioral measures (performance accuracy and RT) during the 2-back condition and average BOLD responses at specific ROIs in the cerebellum and the PostCG5 (Table 1) for cocaine subjects with negative (open circles) and positive (solid red circles) urines for cocaine. Solid lines are linear fits, and R is the correlation factor. Inserted activation maps show the pattern of significant voxel-wise correlation of brain activation with accuracy in the cerebellum (top panel) and with RT in the PostCG5 (bottom panel). White labels are z-coordinate of the slices in millimeters in the Talairach frame of reference. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Discussion

Here we document widespread abnormalities in the pattern of brain activation to a WM task in cocaine abusers compared with non-drug abusing controls. Specifically compared to controls, cocaine subjects had (1) lower activation in regions where DA nuclei are located (Mes) or known targets of DA pathways [ACG, putamen, PHG/Amy and thalamus (Sanchez-Gonzalez et al., 2005)] and the cerebellum (posterior lobe/declive); (2) higher activation in parietal and occipital cortices; and (3) lower WM load responses in the PFC, parietal cortex and the putamen.

3.1. *Behavior*

Cocaine abusers were significantly slower during fMRI for all WM loads, and their accuracy was lower during the 2-back task than that of controls. Note that as load increased and performance accuracy decreased, RT increased possibly to compensate for the perceived higher task demands. The cocaine subjects with positive urines performed significantly worse than those with negative urines, who in turn performed at the same level than controls; these cognitive abnormalities may reflect the effects of early abstinence (Kelley et al., 2005).

3.2. *Hypoactivation*

Findings on lack of activation in the mesencephalon, which is the brain region where DA neurons are located, and the thalamus (Table 1, Fig. 2), which is a main target of DA pathways (Sanchez-Gonzalez et al., 2005), are likely to reflect dopaminergic deficits in cocaine abusers. We recently reported similar hypo-activation findings in the thalamus in cocaine abusers performing a visual attention task (Tomasi et al., 2007a). Since the mesocortical DA system facilitates WM function via direct inputs to the PFC (Gaspar, 1992; Goldman-Rakic et al., 2000), the higher activation of the PFC by the dysfunctional mesocortical DA pathway might be associated with the observed impaired performance on the WM task in the cocaine subjects. In addition, cocaine subjects failed to activate the cerebellum (posterior lobe/declive), which is a brain region with minimal direct modulation by DA but for which there is evidence of indirect DA modulation (Anderson et al., 2006; Volkow et al., 1997a) and of involvement in the

performance of other verbal WM tasks (Desmond et al., 2005). Our findings on positive correlations between BOLD responses in the cerebellum and accuracy during the 2-back task in cocaine abusers provide further support for its involvement in WM tasks (Desmond et al., 2005). Although we report that these changes are likely to reflect the documented abnormalities in dopaminergic neurotransmission in cocaine abusers they could also reflect disruption in other neurotransmitters (i.e., glutamatergic, noradrenergic, cholinergic and GABAergic).

3.3. *Hyperactivation*

Previous fMRI studies on attentional (GO–NO/GO) tasks found reduced activation in the superior PFC in cocaine abusers (Hester and Garavan, 2004; Kaufman et al., 2003). The WM task, however, elicited larger activation in the PFC (MFG6 and MFG9) for the cocaine abusers than for control subjects (Table 1). For a different task (visual attention), we recently reported similar hyper-activation in the cocaine abusers (Tomasi et al., 2007a,b). Similarly, neuroimaging studies on Parkinson's disease have shown larger PFC activation in other hypodopaminergic conditions (Cools et al., 2002; Mattay et al., 2002). Taken together with greater parietal activation (Table 1 and Fig. 2) in the cocaine abusers as compared to controls, results may represent the larger recruitment of these attention network resources to support WM and other cognitive functions (Tomasi et al., 2006a), possibly reflecting increased attention in cocaine subjects to compensate for deficits in executive function (Hester and Garavan, 2004). In contrast, the control subjects deactivated some of these regions (PostCG5), consistent with similar deactivations during a large variety of other cognitive tasks as previously reported (Raichle et al., 2001). In general, task-related deactivations of brain regions have been associated with the temporary suspension of the baseline state (default mode) of brain function and may be crucial for accurate performance on cognitive tasks (Hahn et al., 2007; Raichle et al., 2001). Indeed, the inability to deactivate the PostCG in the cocaine subjects compared to control subjects may have contributed to the lower accuracy in the former group during the 2-back task. This hypothesis that cocaine subjects failed to suspend the default mode of brain function during the WM task in this region receives further support from the linear correlation between BOLD responses in the PostCG5 and RT (Fig. 4) or accuracy.

3.4. *Deactivation*

Findings on larger deactivation of the ACG, PHG/Amy and putamen/insula (Table 1 and Fig. 2), regions commonly associated with control and regulation of emotion, in cocaine compared to control subjects may reflect greater suppression of emotion (e.g., anxiety and discomfort, craving) in the MRI environment (Tomasi et al., 2006b) for cocaine abusers. This interpretation is consistent with a recent study where we showed the same (rostroventral) ACG region to be associated with performance accuracy by cocaine abusers on a newly developed emotional drug-related task (Goldstein et al., 2007).

3.5. *Cognitive load*

For control subjects, parametric increases of WM load enhanced brain activation bilaterally in the dorsolateral prefrontal and the parietal cortices (Table 1), in agreement with our previous studies (Tomasi et al., 2005). Of interest, increased WM load produced lower BOLD signal increases for cocaine abusers than for control subjects in these cortices (MFG9 and PreCUN7). Because the involvement of the PFC in higher-order cognitive functions and attention processing is well documented (Bolla et al., 2004), and evidence of PFC disruption in cocaine abusers has been consistent (Adinoff et al., 2001, 2003; Goldstein et al., 2004; Goldstein and Volkow, 2002; Kosten et al., 2004; Volkow et al., 1988), this finding probably reflects the limited capacity of the WM network (Tomasi et al., 2005), and the larger recruitment of network resources during the 1-back task, due to the inefficient neural processing in the MFG9, in the cocaine subjects. Since the parietal cortex is involved in processing of orienting responses in attention (Corbetta and Shulman, 2002), its disruption is also likely to contribute to the attention impairments in cocaine abusers.

3.6. *Abstinence*

The activation abnormalities were accentuated in cocaine abusers with positive urines suggesting that the imaging results might reflect acute effects of cocaine abstinence. Cocaine abstinence is associated with impaired performance in cognitive functions including attention, vigilance and executive function (Goldstein et al., 2004; Kelley et al., 2005; Pace-Schott et al., 2005) and imaging studies of cocaine abusers tested during abstinence have reported reduced DA activity (Volkow et al., 1997b). A limitation of our study is that even though we ascribe the differences between groups to cocaine abstinence we cannot rule out the contribution of nicotine withdrawal since the groups differed in their smoking histories and nicotine withdrawal is associated with cognitive impairment (Giannakoulas et al., 2003; Shoaib and Bizarro, 2005). However the fact that the cocaine abusers with positive urine who had the most recent last use of cocaine – and not the cocaine abusers with negative urines – were the ones that accounted for the neurocognitive abnormalities suggests that these are mostly driven by early cocaine abstinence and not nicotine withdrawal.

3.7. *Study limitations*

(1) fMRI is susceptible to white-matter activation artifacts. The BOLD responses arise from the capillary bed, which is localized at the neuronal gray-matter activation sites, but also from pial and draining veins that reflect neuronal activity several millimeters away from the fMRI activation site, reducing the localization of brain activation (Tomasi and Caparelli, 2007). Furthermore, fMRI is susceptible to geometrical distortion, especially at the vicinities of the sinus cavity and the temporal bone due to magnetic field gradients induced at air–tissue interfaces (Tomasi and Wang, in press) that can also result in white-matter activation artifacts. Finally, because the spatial smoothing enlarges the gray-matter activation clusters, overlapping activation with white-matter regions, part of the

white-matter activation artifacts may result from the fMRI imaging post processing. (2) Further studies are required to assess if the reported neurocognitive changes in cocaine addiction are recovered with protracted abstinence. Finally even though we are ascribing the abnormalities to cocaine abuse we cannot rule out the contribution of other substances (i.e., alcohol and marihuana), which are frequently co-abused by cocaine abusers.

In summary, using a WM task as a cognitive challenge we showed that, compared to healthy controls, cocaine abusers had lower activation of the mesencephalon, the thalamus and the cerebellum, which probably reflects dopaminergic deficits in the cocaine abusers; higher activation in parietal and prefrontal cortices, which probably reflects increased attention processing to compensate for inefficient executive functioning; and a lower WM load activation in prefrontal and parietal cortices, which might reflect the limited capacity and inefficient functioning of these regions. We also show in cocaine abusers larger deactivation of the ACG, putamen, parahippocampal gyrus and amygdala, which we interpret to reflect greater requirements to compensate for compromised emotional control while performing an unrelated cognitive operation. This study provides evidence of impaired integrative function of regions involved with executive control and attention in cocaine abusers and is likely to underlie the cognitive disruption in these subjects. Because these impairments encompass regions that are not modulated by DA, results further suggest involvement not just of DA but also of other neurotransmitters in the brain and cognitive abnormalities observed in cocaine abusers.

4. Experimental procedures

4.1. *Subjects*

Sixteen healthy chronic cocaine abusers (9 men, 7 women; age=39.9±9.2 years; education=13.6±2.5 years; mean±SD) and 16 age-, gender-, and education-matched healthy control subjects (9 men, 7 women; age=34.0±8.7 years; education=15.0±1.8 years) participated in the study. Each subject provided a written informed consent approved by the Institutional Review Board at the Brookhaven National Laboratory. All subjects were carefully screened to ensure that they fulfilled study criteria. The inclusion criteria for both groups were: age 18 years or older, ability to read and speak English fluently and right-hand dominance. Subjects were excluded if they had any confounding chronic medical or neuropsychiatric illnesses (except for major depression associated with drug use), contraindicated metallic objects in the body, poor vision (worse than 20/80 without use of glasses and unable to wear contact lenses) or claustrophobia. Additionally, control subjects were excluded if they had history of drug dependence or positive urine toxicology screening on the day of the study. Cocaine subjects were included if they had DSM-IV diagnosis for Cocaine Dependence or Abuse and at least a 12 month (3.5 grams/week) history of cocaine use (predominantly by smoked route); they were excluded for current drug dependence other than cocaine or nicotine or positive urine toxicology screening for amphetamines, marijuana, benzodiazepines or opiates on the day of the study. Note that we did not exclude cocaine subjects for current or past alcohol or marijuana abuse (total $N=4$) or past alcohol or marijuana dependence ($N=2$), but dependence on other drugs was exclusionary. Eight cocaine subjects had a positive urine toxicology screening for cocaine on the day of the study and reported use of cocaine 1 ($n=4$), 2 ($n=3$) or 3 ($n=1$) days prior the study; the urine was negative for the remaining eight cocaine subjects, who reported use of cocaine 4 ($n=1$), 5 ($n=2$), 6 ($n=1$) or more than 30 ($n=4$) days prior the study. These results of urine toxicology screen were used to classify the cocaine subjects into the "positive" or "negative" subgroups, respectively. Six cocaine subjects were non-smokers and ten cocaine subjects were current cigarette smokers (mean daily use=8.8±6.8 cigarettes). Twelve control subjects were non-smokers and four control subjects were current cigarette smokers (mean daily use=11.0±6.2 cigarettes); smoking differences across the groups were not significant ($p=0.073$; Fisher's exact test). We did not exclude cigarette smokers as from our experience around 75% of cocaine subjects smoke cigarettes (vs. around 25% of controls).

4.2. *n-back working memory paradigm*

Others and we previously used this standard task to study working memory processing in controls (Tomasi and Caparelli, 2007; Tomasi et al., 2005, 2006b) and in HIV patients (Tomasi et al., 2006a). Briefly, it is of a blocked design ("Task" blocks: 30 s; "Resting" blocks: 30 s; 4 "Task"–"Resting" cycles) where alphabetical letters are sequentially presented in random order at a rate of one per second. The subjects were instructed to press a response button whenever they saw a letter (0-back) or the current letter was the same as the one (1-back task) or two (2-back task) before. MRI-compatible goggles connected to a personal computer were used to present the stimuli to the subjects. All response button events were recorded during the fMRI task to determine performance accuracy and RT.

4.3. *MRI sessions*

Subjects underwent MRI in a 4 T whole-body Varian/Siemens MRI scanner. A T2*-weighted gradient-echo planar imaging (EPI) pulse sequence (TE/TR=25/3000 ms, 4 mm thickness coronal slices, 1-mm gap, 35 slices, 48×64 matrix size, 20 cm square field-of-view, 84 time points) was used to collect the fMRI datasets, covering the whole brain. An acquisition bandwidth of 200 kHz was used to minimize both EPI image distortion and the acoustic noise emitted by the scanner during the fMRI study (Tomasi and Ernst, 2003). Padding was used to minimize motion. Task performance and subject motion were determined immediately after each fMRI trial to assure that performance accuracy was better than 80% and motion <1-mm translations and <1° rotations (Caparelli et al., 2003).

A T1-weighted 3D-MDEFT sequence (Lee et al., 1995) (TE/TR=7/15 ms, 0.94×0.94×3 mm spatial resolution, axial orientation, 256 readout and 192×48 phase-encoding steps, 8 min scan time) and a modified T2-weighted Hyperecho sequence (Hennig

and Scheffler, 2001) (TE/TR=42/10,000 ms, echo train length=16, 256×256 matrix size, 30 coronal slices, 0.86×0.86 mm in-plane resolution, 5 mm thickness, 1 mm gap, 2 min scan time) were used to obtain anatomical images to rule out gross morphological abnormalities.

4.4. *Statistical analyses*

The first four volumes in the time series were discarded to avoid non-equilibrium effects. Subsequent analyses were performed with the statistical parametric mapping package SPM2 (Welcome Department of Cognitive Neurology, London UK). The images were realigned to correct for head motion. Head motion was smaller than 1-mm translation and 1-degree rotation on all three planes for all subjects and fMRI runs. The realigned images were normalized to the Talairach frame and smoothed with an 8-mm full-width-half-maximum Gaussian kernel. The general linear model was used to estimate the BOLD signal amplitude; the blocked analysis was based on a box-car design convolved with a canonical hemodynamic response function (HRF). Maps of BOLD responses for each trial and subject were included in a two-way voxel-by-voxel repeated measures ANOVA model with three conditions (0-, 1- and 2-back) and two groups (cocaine, and control) to map brain activation across the main study groups. Additional linear regression analyses between BOLD responses and behavioral measures across subjects were conducted in SPM. The continuous random field calculation implemented in SPM2 was used to perform the cluster analyses. A threshold $p=0.005$ was used to display brain activations/deactivations. For all group analyses, a $p_{corr}<0.05$, corrected for multiple comparisons, was considered significant.

4.5. *Region-of-interest analyses*

Functional ROIs with a volume of 0.73 cm^3 were defined at the cluster centers of brain activation to extract the average statistical significance (*t*-scores) from the SPM activation maps for each group/condition as well as for within and between group comparisons of brain activation (Table 1); for this purpose we developed a program written in IDL (Research Systems, Boulder, CO). The average amplitude of the BOLD signals in these ROIs was similarly calculated from the estimated BOLD maps for each subject and for each condition. Separate ROI analyses of average BOLD responses were conducted for cocaine subjects with positive and negative urine toxicology screening (urine status) to rule out the potential effect of early cocaine abstinence on brain activation. *t*-tests were conducted for each ROI to validate the voxel-by-voxel statistical analyses described above. Statistical significance for these ROI analyses was defined as $p=0.05$.

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