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Hyperactivation of the Cognitive Control Network in Cocaine Use Disorders During a Multisensory Stroop Task*

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Abstract

Background—It has been suggested that individuals with cocaine use disorders (chronic cocaine abusers, CCA) have impairments in cognitive control, which likely contribute to impairments in decision making around drug use and relapse. However, deficits in cognitive control have currently only been studied under conditions of unisensory stimulation, which may not be reflective of more realistic multisensory drug cues.

Methods—The current study employed functional magnetic resonance imaging (fMRI) to measure neuronal activity during a multisensory numeric Stroop task.

Results—Despite few differences in reaction time, recently abstinent CCA (N = 14) exhibited increased activation in prefrontal cortex, striatum and thalamus during cognitive control relative to a group of carefully matched controls (N = 16). Importantly, these neuronal differences were relatively robust in classifying patients from controls (approximately 90% accuracy) and evident during conditions of both low (slow stimulus presentation rate) and relatively high (faster stimulus presentation rate) cognitive demand. In addition, CCA also failed to deactivate the default-mode network during high frequency visual trials.

Conclusions—In summary, current results indicate compensatory activation within the cognitive control network in recently abstinent CCA to achieve similar levels of behavioral performance.

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Keywords

Cocaine; cognitive control; functional magnetic resonance imaging; Stroop

1. Introduction

Chronic cocaine use is associated with impairments in inhibitory control and attention (Garavan and Hester, 2007; Goldstein et al., 2004; Goldstein and Volkow, 2002; Jovanovski et al., 2005), which likely contribute to compulsive drug seeking and loss of control of drug use (Baler and Volkow, 2006). Specifically, impulsivity and impaired cognitive control have been associated with increased cocaine use disorder severity as well as poorer treatment outcomes (Brewer et al., 2008; Moeller et al., 2001; Streeter et al., 2008). Defining the nature of impaired cognitive control will be an important step for the development of future therapeutic targets, a critical need given few treatment options (Sofuoglu, 2010; Vocci and Montoya, 2009). Neuroimaging studies have revealed several structures, including the dorsal medial frontal cortex (dmFC), dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), anterior insula and inferior parietal lobes, that are commonly activated across a variety (e.g., Stroop, the go/no-go, the flanker, and Simon tasks) of cognitive control paradigms (Ridderinkhof et al., 2004; Roberts and Hall, 2008). Previous studies have demonstrated that individuals with cocaine use disorders (CCA) exhibit decreased metabolism in prefrontal, frontal, and temporal areas relative to healthy controls (Adinoff et al., 2003; Bolla et al., 2003, 2004; Goldstein et al., 2004; Strickland et al., 1993). However, conflicting results have been reported in CCA during a variety of cognitive control tasks. While some studies have demonstrated hypoactivation in the anterior cingulate cortex (ACC), pre-supplementary motor area, insula, prefrontal cortex, superior frontal gyrus and striatum relative to controls during cognitive control (Hester and Garavan, 2004; Kaufman et al., 2003; Kubler et al., 2005; Li et al., 2008) including Stroop-like tasks (Barros-Loscertales et al., 2011), others have reported hyperactivation in prefrontal areas during visual attention and working memory tasks (Tomasi et al., 2007a, b). It is unclear if these divergent results are due to differences in the nature and difficulty of the tasks employed, or to disparities in sample characteristics (e.g., time abstinent, concurrent drug or medication use, etc.).

Impairments in brain networks involved in top-down cognitive control may contribute to increased attentional bias to cocaine cues and cue-induced craving. Increased cue reactivity and attentional bias to cocaine cues contribute to drug use and are associated with increased cocaine use disorder severity (Carpenter et al., 2006; Kosten et al., 2006). Lower levels of activity in right prefrontal cortex during a working memory task in conjunction with concurrent presentation of cocaine stimuli distractors was associated with higher attentional bias to cocaine cues in CCA (Hester and Garavan, 2009). Inhibition of craving and associated inhibition of orbitofrontal cortex (OFC) and ventral striatal activation to cocaine cues was found to be associated with increased neural activation in right inferior frontal regions (Volkow et al., 2010).

Importantly, functional abnormalities within the cognitive control network also have clinical significance. Hypoactivation in the rostral ACC (rACC) during a go/no-go task is associated with impaired performance (Hester and Garavan, 2004) and correlates negatively with emotional regulation in cocaine users (Li et al., 2008). Improved clinical outcomes positively correlate with activation during incongruent compared to congruent trials during a Stroop task in the ventromedial prefrontal cortex (vmPFC), posterior cingulate cortex, and striatum but negatively with activation in the left DLPFC (Brewer et al., 2008).

Therefore, the current study compared evoked activity during a multimodal Stroop task (Mayer et al., 2011) in CCA relative to a matched sample of healthy controls (HC). Similar to previous results, we predicted that CCA would exhibit decreased evoked activity during the Stroop task. We also predicted measures of evoked activation in the cognitive control network would be negatively associated with clinical measures of craving.

2. Methods

2.1 Participants

Sixteen subjects with a confirmed diagnosis of chronic cocaine abuse and/or dependence and 16 gender, age, and education-matched HC were recruited for the current study. Results from this cohort on a cocaine cue task have been previously reported (Wilcox et al., 2011) such that methods and clinical results are abbreviated in the current manuscript. Two CCA were excluded from the study because of excessive head motion (three standard deviations over two parameters) compared to the rest of their cohort based on previously published algorithms (Mayer et al., 2007), leaving a total of 14 CCA (7 males; 37.14 +/- 8.97 years old; 12.5 +/- 1.98 years education) and 16 HC (7 males; 36.38 +/- 8.77 years old; 13.4 +/- 1.90 years education) in the final sample. Informed consent was obtained according to institutional guidelines at the University of New Mexico.

All CCA participants were abstinent from cocaine (negative urine screen) for a minimum of three days prior to their MRI scan to allow for elimination of the majority of active cocaine metabolites (confirmed by 6-drug urine screen including cocaine, marijuana, opiates, and amphetamine) and were therefore unlikely to be in significant acute withdrawal (Walsh et al., 2009). CCA participants were excluded from the study during screening if they had a history of DSM-IV opiate or sedative dependence, learning disorder, attention-deficit hyperactivity disorder, any major neurological condition, diagnosis of a schizophrenia spectrum disorder, or contraindications for MRI. HC were excluded based on similar criteria, with the additional criteria of any history of diagnosed psychiatric disorders or a substance use disorder in the last 10 years. As expected, CCA were more likely than HC to have a history or current diagnosis of a marijuana or alcohol use disorder as well as being prescribed psychoactive medications (4 CCA screened positive for benzodiazepines and one for THC).

2.2 Clinical Assessment

Participants completed a battery of measures, including the Fagerstrom Test for Nicotine Dependence (FTND), the Cocaine Craving Questionnaire (Brief-NOW and Brief-GENERAL forms: CCQ-N and CCQ-G), and the Structured Clinical Interview for DSM Disorders I Module E (SCID-I-E) for substance abuse and dependence. The Timeline Followback calendar was used to determine cocaine usage during the previous 30 days. A neuropsychological battery was also administered, and composite indices were calculated for the domains of memory, processing speed, executive functioning, and attention. The Wechsler Test of Adult Reading (WTAR) provided an estimate of pre-morbid intelligence. Measures of emotional status [State-Trait Anxiety Index (STAI) and Beck Depression Inventory-Second Edition (BDI)] were also assessed.

2.3 Tasks

A multisensory numeric Stroop task developed previously by our group (Mayer et al., 2011, 2012) was presented to all participants during whole-brain fMRI scanning¹. For each ten-

¹Please see Supplemental Materials for full details on image parameters by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

second block, multisensory (visual and auditory) congruent or incongruent numeric stimuli (targets) were simultaneously presented at either a low (0.33 Hz) or a high (0.66 Hz) frequency. Each block started with the cue word (exemplary visual angle = 7.69°) “LOOK”, “HEAR” or “NONE” followed by a stream of target numbers (“ONE”, “TWO”, or “THREE”; exemplary visual angle = 9.73°). If the cue word was “LOOK,” participants were instructed to press a button corresponding to the visual stimuli and ignore the number that was simultaneously presented aurally. If the cue word was “HEAR,” subjects attended to the aural number stream while ignoring visual targets. An additional passive condition (cue word “NONE”) was included (data not presented), during which participants were instructed not to respond to the targets. There was a 1325 ms delay between the presentation of the cue (175 ms duration) and the presentation of the first target number (200 ms duration) to maximize attentional focus.

Low frequency blocks included three trials and high frequency blocks included six trials. The inter-block interval was varied between 8, 10 and 12 seconds to decrease temporal expectations and permit modeling of the baseline (visual fixation plus baseline gradient noise). A total of 432 trials were presented across six separate imaging runs. Before being placed in the scanner, participants practiced the behavioral task until demonstrating competency.

The median reaction time of correct trials was selected as a more representative measure of central tendency for each subject and each trial-type due to skew. Two $2 \times 2 \times 2$ [Group (CCA vs. HC) $\times$ Modality (Auditory vs. Visual) $\times$ Condition (Congruent vs. Incongruent)] mixed-measures ANOVAs were conducted on median response time data for 0.33 Hz and 0.66 Hz frequency trials separately to assess behavioral performance under conditions of low and high attentional load.

2.4 MR Imaging and Analyses

High resolution anatomic images (T1) and whole-brain echo-planar images (TR = 2000 ms; TE = 29 ms; flip angle = 75°; FOV = 240 mm; matrix size = 64 $\times$ 64; voxel size: 3.75 $\times$ 3.75 $\times$ 4.55 mm; 33 slices) were collected on a 3 Tesla Siemens Trio scanner². Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996) was used to generate functional images using standard pre-processing techniques (time-slice correction, motion correction, outlier removal, blurred using a 6 mm Gaussian full-width half-maximum filter and spatial normalization to Talairach space). A voxel-wise deconvolution analysis was then performed to generate a single hemodynamic response function (HRF) that spanned the first 22 seconds post-stimulus onset for each trial-type. Error trials were modelled separately for each trial-type to eliminate associated variance (Mayer et al., 2011). Percent signal change (PSC) estimates were calculated based on the average of the beta coefficients for the images occurring six to fourteen seconds post-cue onset and then divided by the average model intercept.

Two MANOVAs were conducted to examine group differences in translational and rotational motion parameters, respectively. Two voxel-wise $2 \times 2 \times 2$ [Group (CCA vs. HC) $\times$ Modality (Auditory vs. Visual) $\times$ Condition (Congruent vs. Incongruent)] mixed-measures ANOVAs were performed on the spatially normalized percent signal change measure for the low and the high frequency conditions.

²Please see Supplemental Materials for details by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

For all voxel-wise results, false positives were corrected at $p < 0.05$ ($z > 2.6$) based on the Gaussian Random Fields theory as implemented in FSL (<http://www.fmrib.ox.ac.uk/fsl/feat5/programs.html>).

3. Results

3.1 Clinical Data

There were no significant differences ($p > 0.10$) between groups on major demographic variables (Table 1). CCA exhibited lower scores on the WTAR ($p < 0.01$) but otherwise were similar to HC in all other cognitive domains (all $p > 0.10$). Finally, as expected, CCA exhibited significantly increased cocaine craving severity ($p < 0.01$) and depressive symptoms ($p < 0.01$) relative to HC, with a non-significant trend for increased anxiety symptoms as well ($p = 0.06$).

3.2 Selective Attention Response Time Data

Accuracy data for both groups approached ceiling (CCA: 94.94 $\pm$ 5.67%; HC: 97.12 $\pm$ 2.22%) such that the data were not subjected to further analyses. Response time results from the low frequency (0.33 Hz) trials (see Figure 1A) indicated significant main effects of modality ($F_{1, 28} = 23.91$, $p < 0.001$) and condition ($F_{1, 28} = 28.56$, $p < 0.001$), with a significant modality $\times$ group interaction term ($F_{1, 28} = 9.72$, $p < 0.005$). Response times for congruent (mean = 622.43 ms $\pm$ 81.67) trials were faster than incongruent (mean = 675.63 ms $\pm$ 195.32) trials. Simple-effects testing indicated that HC responded significantly faster on visual (mean = 598.94 ms $\pm$ 52.67) compared to auditory (mean = 675.75 ms $\pm$ 67.96) trials, with no significant differences for CCA (visual = 652.22 ms $\pm$ 106.06; auditory = 669.21 ms $\pm$ 134.44). The remaining interaction terms and main effect of group were not significant ($p > 0.10$).

For high frequency (0.66 Hz) trials (see Figure 2B), results indicated both a significant modality $\times$ group ($F_{1, 28} = 9.81$, $p < 0.005$) and modality $\times$ condition ($F_{1, 28} = 8.50$, $p < 0.01$) interaction (Figure 1B). Simple effects testing (modality $\times$ group interaction) indicated that HC responded significantly faster on visual (mean = 555.42 ms $\pm$ 56.67) compared to auditory (mean = 594.62 ms $\pm$ 42.42) trials, with no significant differences observed in CCA (visual = 587.46 ms $\pm$ 90.48; auditory = 591.90 ms $\pm$ 88.24). For the modality $\times$ condition interaction, simple effects testing indicated that participants responded significantly faster when attending to incongruent visual (mean = 593.98 ms $\pm$ 86.08) compared to auditory (mean = 629.52 ms $\pm$ 79.54) stimuli, with no differences for congruent trials.

3.3 Functional data

MANOVAs indicated that there were no differences between the two groups in terms of the magnitude of rotational or translational motion parameters ($p > 0.10$).

3.3.1 Low Frequency Trials—A significant main effect of condition was observed within the left DLPFC, VLPFC (BAs 9/44/45/46), frontal eye fields (BAs 6/9), middle frontal and precentral gyri (BA6) and insula (BAs 13/21/22/39/40). Bilateral foci were observed in posterior parietal cortex, middle and superior temporal gyri, caudate and thalamus. For all regions, increased activation was observed for incongruent compared with congruent trials³.

³Please see Supplemental Materials, Table S1 by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

Several clusters also demonstrated a main effect of modality, which could generally be characterized by two different patterns of activation. Greater activation for the auditory compared with the visual modality was observed in the dMPC (BAs 6/8/32). Greater deactivation for the visual compared with the auditory modality was observed in the left precuneus (BA7), left posterior cingulate cortex (BAs 23/30/31), and bilateral cuneus (BAs 17/18/19).^{4,5}

During low frequency trials (see Figure 2A), CCA patients exhibited increased activation relative to HC within the bilateral VLPFC, superior temporal gyri, precentral gyri, insula (BA 13/22/38/44/45/47), basal ganglia, and thalamus. A significant cluster was also present in the left DLPFC/precentral gyrus (BA9)⁶.

3.3.2 High Frequency Trials—A significant main effect of condition during high frequency trials was observed within the bilateral medial frontal gyrus and premotor areas (BAs 3/4/5/6/7) with increased deactivation observed for incongruent compared to congruent trials⁷.

Clusters exhibiting a main effect of modality could generally be characterized by either greater activation in the visual modality or greater deactivation in the auditory modality. Areas showing greater activation during the attend visual condition included the left medial and lateral prefrontal cortex (BAs 8/6/24/31) extending into DLPFC (BA 46), bilateral primary and secondary visual cortex (BAs 7/17/18/19/37/39), bilateral parahippocampal gyri and right fusiform gyrus (BAs 20/35/36), bilateral striatum, bilateral thalamus, and bilateral cerebellum (declive and culmen). Areas exhibiting greater deactivation during the auditory modality included the bilateral medial and superior frontal gyri (BAs 6/8), right cingulate gyrus and precentral gyrus (BAs 6/24), bilateral vMPC (BAs 9/10/32) and the bilateral posterior cingulate cortex/precuneus (BAs 7/23/29/30/31)⁸.

The analysis of high frequency data indicated a significant group by modality interaction within several clusters, with simple effects (independent samples t-tests) indicating three patterns of findings (see Figure 3). For the first pattern, CCA showed greater activation than HC within the dMPC (cingulate/medial frontal gyri/SMA) and bilateral paracentral lobules (BAs 6,24,31,32), the right DLPFC, right middle frontal/precentral gyrus (BAs 8,9,10), and the right middle frontal/premotor cortex (BAs 3,4,6) for visual but not auditory trials. For the second pattern, HC had greater deactivation compared to CCA during the attend visual condition with no group differences during the attend auditory condition. The regions involved in this pattern included the bilateral posterior (medial frontal gyri, paracentral lobules, postcentral gyri, precuneus, and superior parietal lobules; BAs 4,5,6,7) and anterior (bilateral vMPC; BAs 9,10,32) hubs of the default-mode network. Finally, although the interaction term was significant within the bilateral visual cortex (precuneus, cuneus, superior parietal lobe and middle occipital gyrus) and right lingual gyrus (BAs 7/18/19/31), a simple effects test suggested that the group differences within these regions were significant only at a trend level for both visual and auditory conditions⁹.

⁴Please see Supplemental Materials; Table S2, by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

⁵Please see Supplemental Materials for functional results for the modality by condition interaction by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

⁶Please see Supplemental Materials; Table S3, by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

⁷Please see Supplemental Materials; Table S1 Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

⁸Please see Supplemental Materials; Table S2, by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

⁹Please see Supplemental Materials; Table S4, by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

Similar to the low frequency analyses, CCA again exhibited significantly increased activation than HC (Figure 2B) within the right insula (BA 13), bilateral basal ganglia and left thalamus (main effect of group), and the left VLPFC/superior temporal gyrus (BA13/44/45/47). In addition, HC exhibited deactivation within the bilateral vmPC extending into the rostral anterior cingulate gyrus (BA 6/8/9/10/24/32) whereas CCA exhibited little activation¹⁰.

3.4 Clinical significance of evoked activation

Four linear regressions were performed using group differences in functional activation (low and high frequency trials) to predict the degree of craving for cocaine (CCQ-G or CCQ-N). Brain activation within the clusters exhibiting a group difference at low frequency predicted scores on the CCQ-N at a trend level (overall model: $p = 0.055$). Activation within the right superior temporal lobe, inferior frontal gyrus, and insula (BAs 13/22/38/47) ($\beta = 1.94$), left basal ganglia and thalamus ($\beta = 1.55$), and right basal ganglia and thalamus ($\beta = -3.22$) contributed significantly to the model ($p < 0.05$). None of the other three models were significant ($p > 0.10$). In addition, the ability of functional activation to classify individuals as CCA and HC was examined using binary logistical regression. Regions exhibiting group differences during high frequency trials were able to accurately classify 15/16 HC and 13/14 CCA patients (93.3% accuracy). Similar classification results were obtained for the low frequency condition, with clusters correctly predicting group membership for 15/16 HC and 12/14 CCA patients (90.0% accuracy). The Wald statistics were not significant for either analysis ($p > 0.10$), suggesting that no one region contributed unique variance to the model.

4. Discussion

For CCA, a conflict may arise upon exposure to an external sensory drug cue. Maintaining a decision to remain drug-free during cue exposure requires intact top-down processing networks, which recruit brain networks mediating working memory (maintaining the potential negative consequences of drug use), selective attention (response inhibition during conflict) and inhibitory control. Although previous data suggest decreased activation within these networks in CCA (Hester and Garavan, 2004; Kjome et al., 2010), current findings suggest a pattern most likely associated with compensatory activation (hyperactivation in conjunction with similar behavioral performance).

All participants exhibited the expected pattern of faster reaction times for congruent relative to incongruent trials during low and higher stimulation frequencies. Consistent with a large body of literature regarding cognitive control (Barros-Loscertales et al., 2011; Brewer et al., 2008; Leung et al., 2000; MacDonald et al., 2000; Mayer et al., 2011), incongruent trials resulted in increased activation within several lateral prefrontal areas and posterior parietal cortex relative to the congruent trials. However, the magnitude of the difference between incongruent and congruent trials was much greater during low frequency trials, suggesting that the higher frequencies of stimulation may have more generally increased the demands on the cognitive control network.

In addition, CCA demonstrated increased activation during both congruent and incongruent conditions (i.e., main effect of group) within regions (thalamus) involved in sensory gating (McCormick and Bal, 1994), the cognitive control network (VLPFC extending into anterior insula, DLPFC and dmPC), and other prefrontal and temporal regions implicated in top-down attention control. These results were fairly robust, with very high levels of classification accuracy (sensitivity and specificity) regardless of the frequency of

¹⁰Please see Supplemental Materials; Table S3, by accessing the online version of this paper at <http://dx.doi.org> and by entering doi: ...

stimulation, and could be investigated in future work as a possible marker of dependence severity. Both the lateral (VLPFC/DLPFC) and dMPC (dorsal ACC/pre-SMA) have been specifically implicated in resolving conflict and exerting cognitive control (Carter and Van Veen, 2007; Kim et al., 2011), suggesting that compensatory activation occurs within the cognitive control network and thalamus to achieve a similar level of performance in CCA.

Several interactions with the diagnosis term were also present in both the behavioral and functional data. During high frequency trials, CCA showed hyperactivation relative to HC in several prefrontal and medial frontal regions that was significant only during trials when attention was focused on the visual modality (i.e., ignore auditory). HC responded significantly faster on visual compared to auditory trials, whereas CCA exhibited similar reaction times for both auditory and visual trials. Considered collectively, current results suggest that CCA likely experienced equal amounts of interference on attend-visual and attend-auditory trials whereas HC experienced less interference (faster reaction times and decreased activation in cognitive control network) for the visual trials. Consistent with previous work (Tomasi et al., 2007b; Wilcox et al., 2011), CCA patients also exhibited a relative lack of deactivation in more posterior areas (BAs 4,5,6,7) as well as in regions of the DMN compared to controls. These results suggest that CCA are less capable of efficiently reallocating attentional resources from internal mental states during demanding cognitive tasks.

In contrast to our results, previous studies using response inhibition tasks (go/no-go and stop signal) and traditional cognitive control tasks (Stroop) have more consistently reported hypoactivation in CCA (Barros-Loscertales et al., 2011; Hester and Garavan, 2004; Kaufman et al., 2003; Kubler et al., 2005; Li et al., 2008). However, other studies have reported hyperactivation within the prefrontal cortex (BA6, BA9) during a visual attention and/or working memory task in CCA relative to HC in conjunction with decreased thalamic activation (Tomasi et al., 2007a, b). There are several potential explanations for the divergent findings obtained in current versus previous research. First, the multisensory tasks may have placed differential demands on cognitive resources. Specifically, multisensory Stroop, working memory, and visual attention tasks may recruit a broader array of brain networks involved in a variety of executive functions relative to response inhibition tasks (Roberts and Hall, 2008), which may have also influenced current results.

Second, previous response inhibition tasks may have been more difficult than the current task, which is supported by the increased error rates in CCA relative to HC in previous studies (Hester and Garavan, 2004; Kaufman et al., 2003; Li et al., 2008). Some work suggests an 'inverted U' relationship between task difficulty and associated brain activation, with a leftward shift in the curve in illnesses (e.g., schizophrenia) associated with executive dysfunction (Callicott et al., 1999; Callicott et al., 2003; Fletcher, 2004; Whalley et al., 2004). A similar leftward shift may be present for CCA, with hyperactivation (CCA > HC) predicted on easier tasks (e.g., current task) and hypoactivation (HC > CCA) predicted on more difficult (e.g., previous response inhibition studies) tasks (Hester and Garavan, 2004; Kaufman et al., 2003; Li et al., 2008).

Finally, sample characteristics may have also contributed to the different observations across studies. First, abstinence time has the potential to influence patterns of functional activation (Connolly et al., 2012). All CCA in the current study had negative urine toxicology screens with a mean of 7 days since last use of cocaine. Length of abstinence has varied widely in previous studies, with some studies conducted at shorter abstinence times (Hester and Garavan, 2004; Kaufman et al., 2003; Tomasi et al., 2007a, b) and others at longer abstinence times relative to our study (Li et al., 2008). Thus, the effects of abstinence length remain to be elucidated in more carefully controlled studies. In addition, some of the CCA

were being prescribed antidepressants ($N = 2$), benzodiazepines ($N = 2$) or both ($N = 4$) at the time of the scan, all of which could interact with hemodynamic activity (Sperling et al., 2002; Vollm et al., 2006; Wagner et al., 2010).

Several limitations of the current study should be noted. First, although our sample size was similar to previous publications (Barros-Loscertales et al., 2011; Hester and Garavan, 2004; Kaufman et al., 2003; Li et al., 2008; Tomasi et al., 2007a, b), it may have reduced our ability to detect smaller effects and increased the likelihood of a biased sample. Thus, it is important that current findings of hyperactivation during multisensory cognitive control be replicated in an independent sample of CCA. In addition, our limited sample also precluded the analysis of gender specific effects in multisensory inhibition. Second, our sample was representative of a typical group of individuals with cocaine use disorders. Therefore, while current results are likely to be more generalizable, they do include the additional confounds of concurrent use of psychopharmacologic agents and higher rates of alcohol and other drug use. Finally, CCA differed from HC in terms of pre-morbid intelligence, and it is difficult to disambiguate differences in intelligence from the presence of a cocaine use disorder (Miller and Chapman, 2001).

In conclusion, the current study suggests that CCA are characterized by hyperactivation within the cognitive control network during a multisensory numeric Stroop task in combination with similar behavioral performance for the majority of conditions. These functional differences may be most suggestive of compensatory activation, and may mediate some of the common characteristics of cocaine use disorders, including loss of control and cocaine craving severity during recent abstinence. Future directions include further defining the relationship between hyperactivation and clinical severity and the relationship of hyperactivation to treatment outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Mean reaction times (RT) in milliseconds (ms) for the attend-auditory trials (Aud) and for the attend-visual trials (Vis) displayed according to group (HC = healthy controls; CCA = individuals with cocaine use disorders) and condition (C = congruent distractor stimuli; I = incongruent distractor stimuli). Error bars are equivalent to the standard error of the mean. Panel A presents results for low frequency trials, and Panel B presents results for high frequency trials.

Figure 2.

This figure depicts the regions showing significant (corrected at $p < 0.05$) differences in activation between individuals with cocaine use disorders (CCA) and healthy controls (HC) during all trials (main effect of group). Activation maps are color-coded according to the magnitude and the direction of the z score. Axial (Z) and sagittal (X) slice locations for both low (Panel A) and high (Panel B) frequency conditions are provided according to the Talairach atlas (L=left and R= right). Bar graphs present percent signal change (PSC) values for selected regions of interest (blue bars = CCA; red bars = HC; error bars = standard error of the mean). During low frequency trials, CCA exhibited increased activation compared to HC (CCA > HC) in the left dorsolateral prefrontal cortex (L DLPFC), left ventral lateral prefrontal cortex (L VLPFC), and left and right basal ganglia (L BG; R BG). Similar regions of hyperactivation were also observed in high frequency trials, with the addition of a lack of deactivation for CCA in the bilateral ventral medial prefrontal cortex (B vMPC).

Figure 3.

Panel A depicts the regions exhibiting a significant group x modality interaction during high frequency trials. Activation maps are scaled according to the magnitude of z scores and are presented in axial (Z) and sagittal (X) slice according to Talairach atlas (L=left and R=right). Bar graphs (panels B through D) present percent signal change (PSC) values for each cluster based on group (blue bars = individuals with cocaine use disorder (CCA); red bars = healthy controls (HC)) and modality (A = attend auditory; V = attend visual). Error bars are equivalent to standard error of the mean. For the first pattern (Panel B), CCA exhibited significantly (corrected at $p < 0.05$) increased activation compared to HC within the bilateral dorsal medial prefrontal cortex (dMPC), the right dorsolateral prefrontal cortex (DLPFC) and the right middle frontal cortex (MidF) for visual but not auditory trials. For the second pattern (Panel C), HC exhibited greater significantly (corrected at $p < 0.05$) greater deactivation compared to CCA during the attend-visual condition with no significant group differences during the attend-auditory condition. The regions involved in this pattern included the precuneus (PreCu), ventral medial prefrontal cortex (vMPC), and anterior and posterior hubs of the default mode network. Simple effects testing indicated that only a non-significant trend was present within the bilateral “where” visual pathways (Vis), suggestive of deactivation for CCA during the attend-auditory in contrast to deactivation for HC during the attend-visual trials.

Table 1

Demographic and clinical characteristics of chronic cocaine abuse/dependence (CCA) relative to healthy control (HC) participants.

	CCA		HC		
	Mean	SD (+/-)	Mean	SD (+/-)	Cohen's d
Demographic					
Age	37.14	8.97	36.38	8.77	$p > .10$
Education	12.5	1.98	13.44	1.90	$p > .10$
HQ	67.21	71.48	90.10	16.04	$p > .10$
Clinical					
BDI-II *	48.81	8.40	43.04	4.55	$p < .05$
STAI-State	49.61	10.54	45.53	8.02	$p > .10$
STAI-Trait	55.79	13.64	46.56	8.61	$p = .06$
FTND	2.63	2.07	1.71	2.22	$p > .10$
CCQ-G *	3.09	1.38	1.06	.16	$p < .01$
CCQ-N *	3.02	1.30	1.04	.15	$p < .01$
Neuropsych					
WTAR *	45.00	11.38	54.94	7.89	$p < .01$
Attention	44.16	4.22	46.07	4.81	$p > .10$
Memory	54.65	8.60	52.65	9.33	$p > .10$
PS	48.49	4.89	46.79	5.96	$p > .10$
EF	48.45	9.83	48.69	4.72	$p > .10$

Note: The current table is similar to a previous publication by Wilcox et al. (2011) secondary to overlapping samples. HQ = handedness quotient; BDI-II = Beck Depression Inventory-Second Edition; STAI = State-Trait Anxiety Index; FTND = Fagerstrom Test for Nicotine Dependence; CCQ-G = Cocaine Craving Questionnaire-General; CCQ-N = Cocaine Craving Questionnaire-Now; WTAR = Wechsler Test of Adult Reading; PS = processing speed; EF = executive function. Demographic data are raw scores (above solid line), whereas clinical and neuropsychological measures (below solid line) are T-scores.

* Denotes significant result

Means, standard deviations, and effect sizes for neuropsychological and some clinical indices reported following correction for WTAR as covariate at 50.30.