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Cerebral gray matter volumes and low-frequency fluctuation of BOLD signals in cocaine dependence: duration of use and gender difference

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Abstract

Background—Magnetic resonance imaging has provided a wealth of information on altered brain activations and structures in individuals addicted to cocaine. However, few studies have considered the influence of age and alcohol use on these changes.

Methods—We examined gray matter volume with voxel based morphometry (VBM) and low frequency fluctuation (LFF) of BOLD signals as a measure of cerebral activity of 84 cocaine dependent (CD) and 86 healthy control (HC) subjects. We performed a covariance analysis to account for the effects of age and years of alcohol use.

Results—Compared to HC, CD individuals showed decreased gray matter (GM) volumes in frontal and temporal cortices, middle/posterior cingulate cortex, and the cerebellum, at $p < 0.05$, corrected for multiple comparisons. The GM volume of the bilateral superior frontal gyri (SFG) and cingulate cortices were negatively correlated with years of cocaine use, with women showing a steeper loss in the right SFG in association with duration of use. In contrast, the right ventral putamen showed increased GM volume in CD as compared to HC individuals. Compared to HC, CD individuals showed increased fractional amplitude of LFF (fALFF) in the thalamus, with no significant overlap with regions showing GM volume loss.

Conclusions—These results suggested that chronic cocaine use is associated with distinct changes in cerebral structure and activity that can be captured by GM volume and fALFF of BOLD signals.

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Contributors

Drs. Ide, Sinha, Mazure, and Li contributed to the conceptualization and design of the study. Drs. Ide, Zhang, and Hu carried out the experiment and data analyses. All authors contributed to the writing and approved the final version of the manuscript.

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Conflict of Interest

We have no financial interests to disclose for the current study.

Keywords

stimulant; cerebral morphometry; prefrontal; low-frequency fluctuation; thalamus; gender difference

INTRODUCTION

Chronic cocaine exposure is known to influence cerebral structures and functions. Studies using magnetic resonance imaging (MRI) have highlighted these changes. For instance, functional MRI described altered regional activations in chronic cocaine users and individuals with prenatal exposure to drugs of abuse during a variety of behavioral challenges (Crunelle et al., 2012; Garavan and Hester, 2007; Li and Sinha, 2008; Roussotte et al., 2010). In particular, frontal cortical regions including the dorsolateral prefrontal and anterior cingulate cortices have consistently been implicated in deficits of cognitive control and decision making in association with cocaine misuse (Garavan and Hester, 2007; Lundqvist, 2010).

Voxel-based morphometry (VBM; Ashburner and Friston, 2000) analyses of high resolution MRI data examined changes in cerebral structures in neurological and psychiatric conditions as well as the neural bases of individual variation in personality traits and cognitive performance (DeYoung et al., 2010; Fusar-Poli et al., 2011; Haier et al., 2004; Kanai et al., 2010; Nickl-Jockschat et al., 2012; Raz et al., 2010; Selvaraj et al., 2012; Spencer et al., 2006; van Gaal et al., 2011). Investigators have used VBM to identify structural brain alterations in cocaine misuse. There was lower GM volume in bilateral premotor cortex, right orbitofrontal cortex, bilateral temporal cortex, left thalamus, and bilateral cerebellum in cocaine-dependent individuals, relative to the comparison group (Sim et al., 2007). Cerebellar GM volumes negatively correlated with duration of cocaine use as well as deficits in executive function and decreased motor performance. Another study reported lower gray matter (GM) volume in bilateral medial orbitofrontal cortex (OFC) in cocaine and amphetamine users, with the decrease associated with risk taking on a gambling task (Tanabe et al., 2009). More recently, Ersche and colleagues showed that cocaine dependence was associated with GM volume decrease in orbitofrontal, cingulate, insular, and temporoparietal cortices as well as the cerebellum, and increase in the basal ganglia (Ersche et al., 2011). Furthermore, longer duration of cocaine dependence was correlated with more severe GM volume reduction in orbitofrontal, cingulate and insular cortex. Many other studies similarly reported decreased GM volumes in cortical structures critical for goal-directed behavior (Fein et al., 2002; Franklin et al., 2002; Makris et al., 2008; Matochik et al., 2003; Moreno-Lopez et al., 2012; O'Neill et al., 2001; Rando et al., 2013; Weller et al., 2011) but some showed no (Narayana et al., 2010) or only a trend level difference (Lim et al., 2008) in association with cocaine misuse. Findings were also at odds regarding subcortical structures, with studies reporting both decreased (Barros-Loscertales et al., 2011; Hanlon et al., 2011) and increased volume in the putamen (Ersche et al., 2011), for instance. This variability in findings was summarized recently (Mackey and Paulus, 2013).

Cocaine misuse is frequently comorbid with heavy alcohol drinking, which is associated with changes in cerebral morphometry (Buhler and Mann, 2011). However, only a handful of studies have controlled for or examined the effects of alcohol use on structural brain changes in chronic cocaine users (Alia-Klein et al., 2011; Makris et al., 2008; O'Neill et al., 2001; Sim et al., 2007). Indeed, the decreased GM volume of the dorsolateral prefrontal cortices may be driven by life time alcohol use in cocaine addicts (Alia-Klein et al., 2011). An earlier study of alcohol dependent individuals also demonstrated that comorbid cocaine use disorder did not account for any independent variance in volumetric measures (Bjork et

al., 2003). Similarly, only a few studies considered the effects of aging (Alia-Klein et al., 2011; Bartzokis et al., 2000; Konova et al., 2012; Tanabe et al., 2009). An earlier work reported an increased age-related decline in temporal but not frontal cortical GM in stimulant dependent individuals as compared to healthy controls (Bartzokis et al., 2000).

While VBM examines structural changes, an alternative approach that allows investigators to probe cerebral integrity is to make use of low frequency blood oxygenation level dependent (BOLD) signals, which can be derived from the fMRI time series when participants perform a cognitive task (Hu et al., 2013; Zhang and Li, 2010) or are at rest (Margulies et al., 2010; Rosazza and Minati, 2011). There is growing evidence that the low-frequency BOLD signal, the “spontaneous” activity, is critical to functional connectivity of the brain (Biswal et al., 1995; Fair et al., 2007; Fox and Raichle, 2007), and organized in anatomical circuits, including the motor, visual, auditory, default mode, memory, language, dorsal and ventral attention systems (Fox and Raichle, 2007). Such low-frequency BOLD signals, as reflected in the fractional amplitude of low-frequency fluctuations (fALFF; (Zhang and Li, 2010; Zou et al., 2008)), may, therefore, inform task-independent activity changes and complement morphometric analysis of structural changes.

The current study aimed to describe the changes in cerebral GM volume and fALFF of BOLD signals in cocaine dependent individuals. With a relatively large cohort of cocaine dependent and healthy individuals, we controlled for age and years of alcohol use and examined whether GM volume and fALFF of BOLD signals share a similar pattern of changes and whether these changes are associated with the duration of cocaine use.

2. METHODS

2.1 Subjects and Assessment

Eighty-four treatment-seeking individuals (29 women) with cocaine dependence (CD) between 18 and 55 years of age were recruited from the greater New Haven area through advertisements to participate in the study. CD volunteers met criteria for current cocaine dependence, as diagnosed by the Structured Clinical Interview for DSM-IV (SCID; First et al., 1995). Recent cocaine use was confirmed by urine toxicology screens upon admission. Participants were drug-free while residing in the Clinical Neuroscience Research Unit (CNRU), a monitored treatment unit at the Connecticut Mental Health Center, for two to four weeks prior to imaging. CD volunteers were assessed with the Beck Depression Inventory (BDI; Beck et al., 1961) and the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970) at admission. The average BDI (mean $\pm$ standard deviation = 13.1 ± 9.7) and STAI state (38.4 ± 11.1) and trait (43.5 ± 11.9) scores were within the range reported previously for CD individuals (Falck et al., 2002; Karlsgodt et al., 2003; Lopez and Becona, 2007; Rubin et al., 2007). All subjects were physically healthy with no major medical illnesses or current use of prescription medications. None reported having a history of head injury or neurological illness. Other exclusion criteria included a history of or current dependence on another psychoactive substance (except nicotine), major depression, and current or past history of psychotic disorders. Pregnant or lactating women were not recruited. Eighty-four healthy control (HC) individuals participated in the study. Table 1 summarizes the demographics of CD and HC participants.

All subjects provided written informed consent prior to study participation, according to a protocol approved by the Human Investigation Committee at Yale University School of Medicine.

2.2 Imaging protocol, spatial preprocessing and modeling of brain images

Conventional T1-weighted spin-echo sagittal anatomical images were acquired for slice localization using a 3T scanner (Siemens Trio). Anatomical images of the functional slice locations were obtained with spin-echo imaging in the axial plan parallel to the Anterior Commissure-Posterior Commissure (AC-PC) line with TR=300 ms, TE=2.5 ms, bandwidth=300 Hz/pixel, flip angle=60°, field of view=220×220 mm, matrix=256×256, 32 slices with slice thickness=4 mm and no gap. A single high-resolution T1-weighted gradient-echo scan was applied on each participant. One hundred and seventy-six slices parallel to the AC-PC line covering the whole brain were acquired with TR=2530ms, TE=3.66ms, bandwidth = 181 Hz/pixel, flip angle = 7°, field of view = 256×256 mm, matrix = 256×256, 1mm³ isotropic voxels. Functional blood oxygenation level dependent (BOLD) signals were then acquired with a single-shot gradient-echo echo-planar imaging (EPI) sequence. Thirty-two axial slices parallel to the AC-PC line covering the whole brain were acquired with TR=2000 ms, TE=25 ms, bandwidth=2004 Hz/pixel, flip angle=85°, field of view=220×220 mm, matrix=64×64, 32 slices with slice thickness=4 mm and no gap. Three hundred images were acquired in each run for a total of 4 runs of the stop signal task, as described in details in our earlier work (Li et al., 2009a, 2005).

Data were analyzed with Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, University College London, U.K.). Images from the first five TRs at the beginning of each run were discarded to enable the signal to achieve steady-state equilibrium between radio frequency pulsing and relaxation.

2.3 Voxel-based morphometry (VBM)

The aim of VBM is to identify differences in the local composition of brain tissue and its association with behavioral and cognitive measures, while discounting large scale differences in gross anatomy and position. This can be achieved by spatially normalizing individuals' structural images to the same stereotactic space, segmenting the normalized images into distinct brain tissues, smoothing the gray-matter images, and performing a statistical test to localize significant associations between anatomical and behavioral measures (Ashburner and Friston, 2000).

Voxel-based morphometry was performed using the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>) packaged in Statistical Parametric Mapping 8 (Wellcome Department of Imaging Neuroscience, University College London, U.K.). T₁-images were first co-registered to the Montreal Neurological Institute or MNI template space (1.5 mm³ isotropic voxels) using a multiple stage affine transformation, during which the 12 parameters were estimated. Co-registration started with a coarse affine registration using mean square differences, followed by a fine affine registration using mutual information. In this step, coefficients of the basis functions that minimize the residual square difference (between individual image and the template) were estimated. Tissue probability maps (TPM) constructed from 471 healthy subjects were used in affine transformation. After affine transformation, T₁-images were corrected for intensity bias field (kernel size FWHM = 60mm) and a local means denoising filter (Manjon et al., 2010) with default parameter 1 was applied, to account for intensity variations (inhomogeneity) and noise caused by different positions of cranial structures within MRI coil; and, finally, they were segmented into cerebrospinal fluid, gray and white-matters, using an adaptive maximum a posteriori (MAP) method (Rajapakse et al., 1997) with k-means initializations, as implemented in VBM8, generating tissue class maps (which included the grey matter or GM maps). In segmentation, partial volume estimation (PVE) was performed with default parameter 5, with a simplified mixed model of at most two tissue types (Tohka et al., 2004). Segmented and the initially registered tissue class maps were normalized using Dartel (Ashburner,

2007), a fast diffeomorphic image registration algorithm of SPM. As a high-dimensional non-linear spatial normalization method, Dartel generates mathematically consistent inverse spatial transformations. We used the standard Dartel template in MNI space, constructed from 550 healthy subjects of the IXI-database (<http://www.brain-development.org/>), to drive the Dartel normalization. Normalized GM maps were modulated (i.e., scaled by the amount of expansions and contractions) so the absolute GM volume remains identical to the original volumes in individual native space. Finally, the GM maps were smoothed by convolving with an isotropic Gaussian kernel. Smoothing helps to compensate for the inexact nature of spatial normalization and reduces the number of statistical comparisons (thus making the correction for multiple comparisons less severe); however, it reduces the accuracy of localization. Most VBM studies used a kernel size of FWHM=12mm. We used a smaller kernel size of FWHM=8mm to achieve localization accuracy.

In group analyses, we performed two-sample t tests with age and years of alcohol use as covariates and without these covariates to compare cerebral gray matter volumes between CD and HC. The results were examined at a corrected threshold (see Section 2.5). We derived GM volume of ROIs, by computing the mean GM volume across voxels, for individual subjects for correlation with the years of cocaine use and for gender comparison of the slope of the linear regression (Zar, 1999).

2.4 Fractional amplitude of low-frequency fluctuation (fALFF)

In the pre-processing of BOLD data, images of each participant were realigned (motion-corrected) and corrected for slice timing. A mean functional image volume was constructed for each participant for each run from the realigned image volumes. These mean images were co-registered with the high resolution structural image and then segmented for normalization to an MNI (Montreal Neurological Institute) EPI template with affine registration followed by nonlinear transformation (Friston et al., 1995a). Finally, images were smoothed with a Gaussian kernel of 8 mm at Full Width at Half Maximum.

In general linear models (GLM) events of interest were employed as regressors to explain task-related activities as described in our previous work (Farr et al., 2012; Hendrick et al., 2010; Winkler et al., 2012). Briefly, four main types of trial outcome were distinguished: go success (G; response within a one-second time window in a go trial), go error (F, no response or response beyond the one-second window in a go trial), stop success (SS; no response in a stop trial), and stop error (SE; response in a stop trial). A statistical analytical design was constructed for each individual subject, using the GLM with the onsets of go signal in each of these trial types convolved with a canonical hemodynamic response function (HRF) and with the temporal derivative of the canonical HRF and entered as regressors in the model (Friston et al., 1995b). Additional regressors with the go trial RT and stop trial SSD were also included for parametric modulation. Realignment parameters in all 6 dimensions were also entered in the model. The data were high-pass filtered (1/128 Hz cutoff) to remove low-frequency signal drifts. Serial autocorrelation was corrected by a first-degree autoregressive or AR(1) model. The GLM estimated the component of variance that could be explained by each of the regressors. Based on previous studies that suggested a linear superposition of task activity and spontaneous BOLD fluctuations (Arfanakis et al., 2000; Fox et al., 2006a, 2006b), task-residual time series was obtained by removing task-related activity with the GLM (Fair et al., 2007).

As discussed earlier, as a measure of spontaneous neural activities, fALFF was extracted from the task time series by removing task-related signals with the GLM. To account for the power spectrum density of the low-frequency fluctuation, Zang (2007) developed an index – the amplitude of low frequency fluctuation (ALFF) – in which the square root of power spectrum was integrated in a low-frequency range in order to examine the regional intensity

of spontaneous BOLD fluctuations. Because the ALFF appeared to be sensitive to the physiological noise (Zou et al., 2008), we carried out a fractional ALFF (fALFF) analysis on the task-residual data as in a previous study (Zhang and Li, 2010). Briefly, filtered task-residual time series were transformed into the frequency domain using the fast Fourier transform (FFT). Since the power is proportional to [amplitude]² at a given frequency, the power spectrum obtained by FFT was square rooted to obtain the amplitude. A ratio of the amplitude averaged across 0.009–0.08 Hz to that of the entire frequency range (0–0.25 Hz) was computed at each voxel to obtain the fALFF, creating an amplitude map for the whole brain, which was then normalized: normalized fALFF = (fALFF – global mean fALFF)/standard deviation of global mean.

In group analyses, similarly, we performed two-sample t tests with age and years of alcohol use as covariates and without these covariates to compare fALFF between CD and HC. The results were examined at a corrected threshold (see Section 2.5). We derived fALFF of ROIs, averaged across voxels, for individual subjects for correlation with the years of cocaine use and for gender comparison, as with the analyses for GM volume.

2.5 Statistical analysis

We analyzed brain imaging data in SPM and employed a threshold $p < 0.05$ corrected for family-wise error (FWE) of multiple comparisons to examine the results. Investigators have argued that the corrected voxel threshold of $p < 0.05$, based on the Gaussian random field theory, may be too restrictive and suggested the use of the cluster threshold (Hayasaka and Nichols, 2003; Poline et al., 1997). Thus, we present results that satisfy either peak voxel FWE $p < 0.05$ or a combined threshold of voxel $p < 0.0001$ and cluster FWE $p < 0.05$. These are referred to as voxel $p < 0.05$ FWE and cluster $p < 0.05$ FWE in the below.

We used Pearson regression to examine the correlation between GMV and years of cocaine use across participants. To compare men and women in this correlation, we tested for a difference in slope in the regressions using Student's t (Zar, 1999):

$$t = \frac{\beta_1 - \beta_2}{s_{\beta_1 - \beta_2}}$$

where $s_{\beta_1 - \beta_2}$ is the standard error of the difference between the regression coefficients β_1 and β_2 .

3. RESULTS

3.1 Voxel-based Morphometry: differences in gray matter (GM) volume between CD and HC

The results of a two-sample t test with age and years of alcohol use as covariates showed decreased GM volume in a number of cortical regions and the cerebellum in CD, as compared to HC, at voxel $p < 0.05$ FWE (Figure 1A).

We derived the GM volume for each of these regions of interest (ROIs) for individual subjects for gender comparison and correlation with years of cocaine use. Because there were a total of 12 ROIs, we used an alpha of $0.05/12 \sim 0.004$ to guard against type I error. The results of a group by gender analysis of variance (ANOVA) showed that there was not a group by gender interaction effect (p 's > 0.031) except for the precuneus, which showed a trend toward higher GM volume loss in men ($p = 0.010$). The results of linear regression showed that the GM volume of the left superior frontal gyrus (SFG, $r = -0.307$, $p < 0.004$), middle/posterior cingulate cortex ($r = -0.460$, $p < 0.00002$), and right SFG ($r = -0.472$, $p < 0.000001$) was inversely correlated with years of cocaine use. Furthermore, the slopes of

regression were significantly different between men and women for the right SFG, with women showing a steeper decline in GM volume loss with years of cocaine use ($p < 0.016$; Figure 2), but not for the left SPG or middle/posterior cingulate cortex (p 's > 0.05).

At cluster $p < 0.05$, FWE, the results demonstrated most of the same brain regions with diminished GM volume in CD, as compared to HC. In addition, the ventral putamen ($x=24$, $y=15$, $z=-11$, $Z=4.47$, 447 voxels, Figure 1B) showed increased GM volume in CD as compared to HC. Table 2 summarizes the coordinates and voxel Z values of these brain regions.

A group by gender ANOVA showed that the GM volume increase in the ventral putamen did not differ between men and women ($p=0.974$, interaction effect). The GM volume of the ventral putamen did not show a significant correlation with years of cocaine use ($r=-0.171$, $p=0.121$).

We also compared CD and HC with a two-sample t test without the covariates. The comparison showed results very similar to those of covariance analysis (Figure S1 and Table S1¹).

3.2 Fractional amplitude of low-frequency fluctuation (fALFF) of BOLD signals

At voxel $p < 0.05$ FWE, a single cluster in the thalamus ($x=0$, $y=-13$, $z=10$, $Z=5.82$, 36 voxels) showed greater fALFF of BOLD signals in CD as compared to HC subjects (Figure 3A). At cluster $p < 0.05$ FWE, in addition to the thalamus, the supplementary motor area, the right pallidum showed greater fALFF of BOLD in CD as compared to HC subjects; and the right middle frontal gyrus, anterior cingulate cortex, the middle occipital, and the right angular gyrus showed increased fALFF of BOLD in HC as compared to CD subjects (Figure 3B). Also, there was not any overlap between these findings in fALFF and VBM, even when examined at a threshold of $p < 0.001$, uncorrected.

We derived the effect size of fALFF for all subjects and performed an analysis of variance with group and gender as between-subject factors. The results showed that men and women did not differ in the change of fALFF ($p=0.941$, interaction effect). The fALFF of the thalamus cluster did not correlate with years of cocaine use across subjects ($p=0.447$, $r=0.08$) in linear regression.

Likewise, we compared CD and HC with a two-sample t test without the covariates. The results showed that, compared to HC, CD showed increased fALFF in the thalamus, supplementary motor area, and right pallidum (Figure S2 and Table S1²). Compared to HC, CD also showed decreased fALFF in anterior middle frontal gyri, left middle occipital gyrus, and right angular gyrus (Figure S2 and Table S1³).

3.3 Correlation of VBM and fALFF measures to age and alcohol use

An important assumption underlying ANCOVA is that the dependent measure varies with the covariates similarly for the independent measures. That is, the slope of linear regression of GM volume and fALFF against age (or alcohol use) should not be statistically different between CD and HC. Thus, we confirmed that this is indeed the case by testing the difference in slope between CD and HC for GM volume of the left SFG ($p=0.802$); right SFG ($p=0.256$); middle/posterior cingulate cortex ($p=0.506$); ventral putamen ($p=0.444$), regressed against age. The results of regression against years of alcohol use were similarly

¹Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

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not significant for GM volume of the left SFG ($p=0.065$); right SFG ($p=0.086$); middle/posterior cingulate cortex ($p=0.753$); and ventral putamen ($p=0.715$). These regressions with GM volumes are shown in Figure S3⁴. The results of regression against age were not significant for fALFF of the thalamus ($p=0.072$); supplementary motor area (SMA) ($p=0.595$); pallidum ($p=0.805$); middle frontal gyrus ($p=0.607$); middle occipital gyrus ($p=0.552$); and angular gyrus ($p=0.135$). Similarly, the results of regression against years of alcohol were not significant for fALFF of the thalamus ($p=0.314$); supplementary motor area (SMA) ($p=0.925$); pallidum ($p=0.514$); middle frontal gyrus ($p=0.843$); middle occipital gyrus ($p=0.648$); and angular gyrus ($p=0.518$). As an example, the regression with fALFF of thalamus is provided in Figure S4⁵.

4. DISCUSSION

4.1 Cerebral morphometry in cocaine dependence

We showed that cocaine dependence is associated with decreased gray matter (GM) volumes in a number of cerebral structures, most notably right temporal cortex, middle and posterior cingulate cortex, cerebellum, and bilateral superior frontal gyri. Furthermore, the GM volume loss in the cingulate cortex and bilateral superior frontal gyri is correlated with years of cocaine use. While confirming some of the previous findings, these results also differ in a few important aspects. First, by controlling for age and years of alcohol use in group comparison, these findings are arguably more specific to cocaine misuse, in contrast to earlier studies. However, the analysis without these covariates yielded very similar results, suggesting that age and years of alcohol use may not contribute significantly to GM volume changes in chronic cocaine users. It is important to note that none of our CD participants are alcohol dependent (an exclusion criterion); thus, the finding of lack of influence of years of alcohol use by no means negate the effects of alcohol of cerebral morphometry (see Buhler and Mann, 2011 for a review). Second, while many previous studies reported GM volume loss predominantly in the orbitofrontal and ventromedial prefrontal cortices, the current findings appear to be most robust in the right temporal cortex, middle/posterior cingulate cortex, and bilateral superior frontal gyri, areas that were also projected in a recent meta-analysis (Mackey and Paulus, 2013). These findings thus contrast with earlier reports which have emphasized decreased GM volume in the prefrontal cortex (Ersche et al., 2013; Mackey and Paulus, 2013). Third, consistent with a recent work, there appeared to be a gender difference in GM volume loss in association with chronic cocaine use (Rando et al., 2013). Men showed a trend toward greater volume loss in the precuneus, while women showed a significantly steeper loss with years of use in the right superior frontal gyrus.

In accord with findings on the basal ganglia from earlier studies of stimulant users, we observed an increased GM volume in the ventral putamen in CD as compared to HC participants (Chang et al., 2005; Ersche et al., 2011; Jacobsen et al., 2001). This is intriguing because it is unlikely that cocaine-induced oxidative stress and vasoconstriction – effects commonly assumed to cause GM volume loss – could account for this finding. Indeed, a recent study showed that putamen is enlarged both in stimulant-dependent individuals and their non-dependent siblings, suggesting that this structural change in the striatum may be a neural marker of genetic predisposition to drug use rather than a consequence of chronic consumption of stimulants (Ersche et al., 2012). In a recent work we examined the cerebral structural correlates of alcohol expectancy in a large cohort of non-dependent adult alcohol drinkers and observed a negative correlation of the right ventral putamen volume and global

⁴Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

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positive alcohol expectancy in men (Ide et al., 2013). Earlier, in an fMRI study of neural responses to food stimuli, putamen showed greater activation when participants did not expect to eat as compared to when they expected to eat right after the experiment (Malik et al., 2011). Thus, one might speculate that greater GM volume in the putamen perhaps is related to CD participants' overall lower expectancy of rewarding experiences. Indeed, investigators have long posited a role of the dorsal striatum and altered dopaminergic signaling in the dorsal striatum in cocaine misuse (Volkow et al., 2006).

While the present study focuses on cocaine users who are recently abstinent (< 4 weeks), the duration of abstinence is an important factor to consider in understanding and reconciling findings from other studies. For instance, a recent cross-sectional study demonstrated that duration of abstinence influences GM volume in a way that some cerebral structures approached and exceeded the level of control participants after 35 weeks of abstinence, suggesting that GM volume loss is not irreversible (Connolly et al., 2013). As much of reduction in GM volume occurs in areas critical for affective processing and self-control, longitudinal studies are warranted to examine show cerebral structures change as cocaine addicts are rehabilitated and how these changes contribute to long term abstinence.

4.2 FALFF in cocaine dependence

Compared to HC, CD participants showed increased fALFF in the thalamus, a structure critical to cognitive control. Many preclinical and clinical studies have suggested a role of the thalamus in performance monitoring, such as during matching sensory feedback with expected outcome of a motor response (Diamond and Ahissar, 2007; Monchi et al., 2001; Urbain and Deschênes, 2007), re-evaluation of a reinforcer (Mitchell et al., 2007), task planning on the basis of external information (Wagner et al., 2006), processing corollary discharge of an eye movement (Bellebaum et al., 2005; Sommer and Wurtz, 2004), and self-generating actions in response to predictability of stimuli (Blakemore et al., 1998). Anatomical studies have consistently established a link between the thalamus and prefrontal cortices in humans as well as non-human primates (Jones, 2002; Stepniewska et al., 2007; Yamamoto et al., 1992). Earlier we demonstrated a cerebellar thalamic cortical circuit for error-related cognitive control (Hendrick et al., 2010; Ide and Li, 2011).

Thalamic dysfunction has been implicated in stimulant misuse (Gu et al., 2010; Li et al., 2010; Moeller et al., 2010; Tomasi et al., 2007; Volkow et al., 2011). Thalamus showed diminished responses during a working memory task (Tomasi et al., 2007) and functional connectivity of a large circuit of cortical thalamic subcortical regions was altered in chronic cocaine users (Gu et al., 2010). In particular, in a recent study, we showed that decreased activation of the thalamus during error processing predicted relapse and time to relapse to drug use in cocaine dependent individuals (Luo et al., 2013). On the other hand, the relationship between fALFF and event-related BOLD signals are not entirely clear, and more work is needed to understand how fALFF interacts with error responses to impact self-control and other cognitive and affective processes of relevance to clinical outcomes.

Notably, findings from VBM and BOLD signal analysis did not overlap. Although largely interpreted to reflect neural activities, BOLD signals are known to be influenced by a number of other non-neural factors, such as local vasculature. Thus, the relationship between GM volume and BOLD signals are not entirely clear. To our knowledge, there is no systematic work to address this specific issue; however, many empirical studies have shown that task-related activation and GMV of a brain area are unrelated (Filippini et al., 2012; Keller and Menon, 2009; Maillet and Rajah, 2013; Wagner et al., 2008; Yan et al., 2010). This observation suggests that GM volume and fALFF represent distinct and complementary measures of cerebral functioning in cocaine dependence.

4.3 Gender differences

While a direct contrast between women and men did not reveal significant differences in GM volume loss and changes in fALFF, women appear to show a steeper decline in GM volume in the right superior frontal gyrus in association with years of cocaine misuse. Given that women generally consume cocaine less frequently and in lesser quantities (Berkowitz and Perkins, 1987; Huselid and Cooper, 1992; Thomas, 1995), this finding suggested that women may be particularly vulnerable to the influence of cocaine on cerebral structures, in accord with functional studies (Fox et al., 2009; Hu et al., 2004; Volkow et al., 2011). Women and men are known to show important differences in the clinical characteristics of drug and alcohol use behaviors. For instance, although women substance users typically begin using substances later than do men, they demonstrate an accelerated transition to addiction (Brady and Randall, 1999; Mann et al., 2005). Imaging studies have also suggested important gender differences in cerebral morphometry and regional activations in association with alcohol use and the risk of alcohol misuse (Pfefferbaum et al., 2001). Mann and colleagues showed that, despite lower amounts of alcohol consumption and a shorter duration of alcohol dependence in women, alcohol dependent women and men developed brain atrophy to a comparable extent (Mann et al., 2005). Thus, the current finding adds to the literature by highlighting a neural phenotype on the gender difference of substance misuse.

4.4 Limitations of the study and conclusions

There are a few limitations to consider. First, we controlled for years of alcohol use in data analyses. However, individuals may use different amounts of alcohol on given occasions and vary in the total amount of alcohol consumed and its effects on cerebral structures and functions. The duration of use alone is unlikely to capture all of the variance associated with alcohol use. Further, although depression appears to implicate structural changes that are different from cocaine addiction (Bora et al., 2012; Du et al., 2012; Lai, 2013), we need studies to understand how depression interacts with cocaine misuse to disrupt cerebral structures and functions. Likewise, the two groups were not matched in race composition, education, cigarette and marijuana smoking, or psychiatric comorbidities. More studies, particularly those with a prospective design, with detailed clinical assessment are required to address the specific effects of cocaine misuse on cerebral structure and activity. Second, when men and women are compared separately or when gender was considered as an independent factor in group analyses, there were no differences that survived a statistical threshold with correction for multiple comparisons. We feel that this by no means suggested a lack of gender difference because, despite its moderate sample size, the study might not be powered to show this effect (Li et al., 2009b). In particular, the finding of a stronger correlation of GM volume loss and years of cocaine use in women is consistent with a body of literature and suggests gender as a critical issue to pursue in addiction neuroscience. Third, GM volume represents just one index of cerebral structure that may be altered in neuropsychiatric disorders. Additional analyses are required to examine cortical thickness and other parameters that have recently been used to characterize cerebral structures (Liu et al., 2013; Wheeler et al., 2013). Finally, this study is largely exploratory, with many of the mechanistic links between neural and clinical findings remaining to be established. With these considerations, we conclude that, accounting for the effects of age and alcohol, chronic cocaine use is associated with changes in cerebral GM volume and fALFF of BOLD signals, although such changes do not appear to predominate in the medial or orbital prefrontal cortex. Women seem to be particularly vulnerable to cocaine use, much like what has been observed for the effects of alcohol on cerebral morphometry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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REFERENCES

- Alia-Klein N, Parvaz MA, Woicik PA, Konova AB, Maloney T, Shumay E, Wang R, Telang F, Biegion A, Wang GJ, Fowler JS, Tomasi D, Volkow ND, Goldstein RZ. Gene x disease interaction on orbitofrontal gray matter in cocaine addiction. *Arch. Gen. Psychiatry*. 2011; 68:283–294. [PubMed: 21383264]
- Arfanakis K, Cordes D, Haughton VM, Moritz CH, Quigley MA, Meyerand ME. Combining independent component analysis and correlation analysis to probe interregional connectivity in fMRI task activation datasets. *Magn. Reson. Imaging*. 2000; 18:921–930. [PubMed: 11121694]
- Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage*. 2007; 38:95–113. [PubMed: 17761438]
- Ashburner J, Friston KJ. Voxel-based morphometry--the methods. *Neuroimage*. 2000; 11:805–821. [PubMed: 10860804]
- Barros-Loscertales A, Garavan H, Bustamante JC, Ventura-Campos N, Llopi JJ, Belloch V, Parcet MA, Avila C. Reduced striatal volume in cocaine-dependent patients. *Neuroimage*. 2011; 56:1021–1026. [PubMed: 21338692]
- Bartzokis G, Beckson M, Lu PH, Edwards N, Rapoport R, Wiseman E, Bridge P. Age-related brain volume reductions in amphetamine and cocaine addicts and normal controls: implications for addiction research. *Psychiatry Res*. 2000; 98:93–102. [PubMed: 10762735]
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch. Gen. Psychiatry*. 1961; 4:561–571. [PubMed: 13688369]
- Bellebaum C, Daum I, Koch B, Schwarz M, Hoffmann KP. The role of the human thalamus in processing corollary discharge. *Brain*. 2005; 128:1139–1154. [PubMed: 15758033]
- Berkowitz AD, Perkins HW. Recent research on gender differences in collegiate alcohol use. *J. Am. Coll. Health*. 1987; 36:123–129. [PubMed: 3312362]
- Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn. Reson. Med*. 1995; 34:537–541. [PubMed: 8524021]
- Bjork JM, Grant SJ, Hommer DW. Cross-sectional volumetric analysis of brain atrophy in alcohol dependence: effects of drinking history and comorbid substance use disorder. *Am. J. Psychiatry*. 2003; 160:2038–2045. [PubMed: 14594753]
- Blakemore SJ, Rees G, Frith CD. How do we predict the consequences of our actions? A functional imaging study. *Neuropsychologia*. 1998; 36:521–529. [PubMed: 9705062]
- Bora E, Fornito A, Pantelis C, Yucel M. Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. *J. Affect. Disord*. 2012; 138:9–18.
- Brady KT, Randall CL. Gender differences in substance use disorders. *Psychiatr. Clin. North Am*. 1999; 22:241–252. [PubMed: 10385931]
- Buhler M, Mann K. Alcohol and the human brain: a systematic review of different neuroimaging methods. *Alcohol. Clin. Exp. Res*. 2011; 35:1771–1793. [PubMed: 21777260]
- Chang L, Cloak C, Patterson K, Grob C, Miller EN, Ernst T. Enlarged striatum in abstinent methamphetamine abusers: a possible compensatory response. *Biol. Psychiatry*. 2005; 57:967–974. [PubMed: 15860336]

- Connolly CG, Bell RP, Foxe JJ, Garavan H. Dissociated grey matter changes with prolonged addiction and extended abstinence in cocaine users. *PloS One*. 2013; 8:e59645. [PubMed: 23527239]
- Crunelle CL, Veltman DJ, Booij J, Emmerik-van Oortmerssen K, van den Brink W. Substrates of neuropsychological functioning in stimulant dependence: a review of functional neuroimaging research. *Brain Behav*. 2012; 2:499–523. [PubMed: 22950052]
- DeYoung CG, Hirsh JB, Shane MS, Papademetris X, Rajeevan N, Gray JR. Testing predictions from personality neuroscience. Brain structure and the big five. *Psychol. Sci*. 2010; 21:820–828.
- Diamond ME, Ahissar E. When outgoing and incoming signals meet: new insights from the zona incerta. *Neuron*. 2007; 56:578–579. [PubMed: 18031676]
- Du MY, Wu QZ, Yue Q, Li J, Liao Y, Kuang WH, Huang XQ, Chan RC, Mechelli A, Gong QY. Voxelwise meta-analysis of gray matter reduction in major depressive disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry*. 2012; 36:11–16. [PubMed: 22001316]
- Ersche KD, Barnes A, Jones PS, Morein-Zamir S, Robbins TW, Bullmore ET. Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. *Brain*. 2011; 134:2013–2024. [PubMed: 21690575]
- Ersche KD, Jones PS, Williams GB, Turton AJ, Robbins TW, Bullmore ET. Abnormal brain structure implicated in stimulant drug addiction. *Science*. 2012; 335:601–604. [PubMed: 22301321]
- Ersche KD, Williams GB, Robbins TW, Bullmore ET. Meta-analysis of structural brain abnormalities associated with stimulant drug dependence and neuroimaging of addiction vulnerability and resilience. *Curr. Opin. Neurobiol*. 2013; 23:615–624. [PubMed: 23523373]
- Fair DA, Schlaggar BL, Cohen AL, Miezin FM, Dosenbach NU, Wenger KK, Fox MD, Snyder AZ, Raichle ME, Petersen SE. A method for using blocked and event-related fMRI data to study "resting state" functional connectivity. *Neuroimage*. 2007; 35:396–405. [PubMed: 17239622]
- Falck RS, Wang J, Carlson RG, Eddy M, Siegal HA. The prevalence and correlates of depressive symptomatology among a community sample of crack-cocaine smokers. *J. Psychoactive drugs*. 2002; 34:281–288. [PubMed: 12422938]
- Farr OM, Hu S, Zhang S, Li CS. Decreased saliency processing as a neural measure of Barratt impulsivity in healthy adults. *Neuroimage*. 2012; 63:1070–1077. [PubMed: 22885245]
- Fein G, Di Sclafani V, Meyerhoff DJ. Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men. *Drug Alcohol Depend*. 2002; 68:87–93. [PubMed: 12167554]
- Filippini N, Nickerson LD, Beckmann CF, Ebmeier KP, Frisoni GB, Matthews PM, Smith SM, Mackay CE. Age-related adaptations of brain function during a memory task are also present at rest. *Neuroimage*. 2012; 59:3821–3828. [PubMed: 22155375]
- First, M.; Spitzer, R.; Williams, J.; Gibbon, M. Structured Clinical Interview for DSM-IV (SCID). American Psychiatric Association; Washington, DC: 1995.
- Fox HC, Hong KI, Siedlarz KM, Bergquist K, Anderson G, Kreek MJ, Sinha R. Sex-specific dissociations in autonomic and HPA responses to stress and cues in alcohol-dependent patients with cocaine abuse. *Alcohol Alcohol*. 2009; 44:575–585. [PubMed: 19793926]
- Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proc. Natl. Acad. Sci. U. S. A*. 2006a; 103:10046–10051. [PubMed: 16788060]
- Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat. Rev. Neurosci*. 2007; 8:700–711. [PubMed: 17704812]
- Fox MD, Snyder AZ, Zacks JM, Raichle ME. Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. *Nat. Neurosci*. 2006b; 9:23–25. [PubMed: 16341210]
- Franklin TR, Acton PD, Maldjian JA, Gray JD, Croft JR, Dackis CA, O'Brien CP, Childress AR. Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biol. Psychiatry*. 2002; 51:134–142. [PubMed: 11822992]
- Friston KJ, Ashburner J, Frith CD, Poline JB, Heather JD, Frackowiak RSJ. Spatial registration and normalization of images. *Hum. Brain Mapp*. 1995a; 3:165–189.
- Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. *Hum. Brain Mapp*. 1995b; 2:189–210.

- Fusar-Poli P, Borgwardt S, Crescini A, Deste G, Kempton MJ, Lawrie S, Mc Guire P, Sacchetti E. Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis. *Neurosci. Biobehav. Rev.* 2011; 35:1175–1185. [PubMed: 21168439]
- Garavan H, Hester R. The role of cognitive control in cocaine dependence. *Neuropsychol. Rev.* 2007; 17:337–345. [PubMed: 17680368]
- Gu H, Salmeron BJ, Ross TJ, Geng X, Zhan W, Stein EA, Yang Y. Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity. *Neuroimage.* 2010; 53:593–601. [PubMed: 20603217]
- Haier RJ, Jung RE, Yeo RA, Head K, Alkire MT. Structural brain variation and general intelligence. *Neuroimage.* 2004; 23:425–433. [PubMed: 15325390]
- Hanlon CA, Dufault DL, Wesley MJ, Porrino LJ. Elevated gray and white matter densities in cocaine abstiners compared to current users. *Psychopharmacology.* 2011; 218:681–692. [PubMed: 21691942]
- Hayasaka S, Nichols TE. Validating cluster size inference: random field and permutation methods. *Neuroimage.* 2003; 20:2343–2356. [PubMed: 14683734]
- Hendrick OM, Ide JS, Luo X, Li CS. Dissociable processes of cognitive control during error and non-error conflicts: a study of the stop signal task. *PloS One.* 2010; 5:e13155. [PubMed: 20949134]
- Hu M, Crombag HS, Robinson TE, Becker JB. Biological basis of sex differences in the propensity to self-administer cocaine. *Neuropsychopharmacology.* 2004; 29:81–85. [PubMed: 12955098]
- Hu, S.; Chao, HA.; Zhang, S.; Ide, J.; Li, C-S. Changes in cerebral morphometry and amplitude of low-frequency fluctuations of BOLD signals during healthy aging: correlation with inhibitory control. 2013. *Brain Struct. Funct.* epub ahead of print
- Huselid RF, Cooper ML. Gender roles as mediators of sex differences in adolescent alcohol use and abuse. *J. Health Soc. Behav.* 1992; 33:348–362. [PubMed: 1464719]
- Ide JS, Li CS. A cerebellar thalamic cortical circuit for error-related cognitive control. *Neuroimage.* 2011; 54:455–464. [PubMed: 20656038]
- Ide, JS.; Zhang, S.; Hu, S.; Matuskey, D.; Bednarski, SR.; Erdman, E.; Farr, OM.; Li, CS. Gray matter volume correlates of global positive alcohol expectancy in non-dependent adult drinkers. 2013. *Addict. Biol.* epub ahead of print
- Jacobsen LK, Giedd JN, Gottschalk C, Kosten TR, Krystal JH. 2001; 158:486–489.
- Jones EG. Thalamic circuitry and thalamocortical synchrony. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 2002; 357:1659–1673. [PubMed: 12626002]
- Kanai R, Bahrami B, Rees G. Human parietal cortex structure predicts individual differences in perceptual rivalry. *Curr. Biol.* 2010; 20:1626–1630. [PubMed: 20727757]
- Karlsgodt KH, Lukas SE, Elman I. Psychosocial stress and the duration of cocaine use in non-treatment seeking individuals with cocaine dependence. *Am. J. Drug Alcohol Abuse.* 2003; 29:539–551. [PubMed: 14510039]
- Keller K, Menon V. Gender differences in the functional and structural neuroanatomy of mathematical cognition. *Neuroimage.* 2009; 47:342–352. [PubMed: 19376239]
- Konova AB, Moeller SJ, Tomasi D, Parvaz MA, Alia-Klein N, Volkow ND, Goldstein RZ. Structural and behavioral correlates of abnormal encoding of money value in the sensorimotor striatum in cocaine addiction. *Eur. J. Neurosci.* 2012; 36:2979–2988. [PubMed: 22775285]
- Lai CH. Gray matter volume in major depressive disorder: a meta-analysis of voxel-based morphometry studies. *Psychiatry Res.* 2013; 211:37–46. [PubMed: 23146253]
- Li CS, Chao HH, Lee TW. Neural correlates of speeded as compared with delayed responses in a stop signal task: an indirect analog of risk taking and association with an anxiety trait. *Cereb. Cortex.* 2009a; 19:839–848. [PubMed: 18678764]
- Li CS, Krystal JH, Mathalon DH. Fore-period effect and stop-signal reaction time. *Exp. Brain Res.* 2005; 167:305–309. [PubMed: 16160823]
- Li CS, Luo X, Sinha R, Rounsaville BJ, Carroll KM, Malison RT, Ding YS, Zhang S, Ide JS. Increased error-related thalamic activity during early compared to late cocaine abstinence. *Drug Alcohol Depend.* 2010; 109:181–189. [PubMed: 20163923]

- Li CS, Sinha R. Inhibitory control and emotional stress regulation: neuroimaging evidence for frontal-limbic dysfunction in psycho-stimulant addiction. *Neurosci. Biobehav. Rev.* 2008; 32:581–597. [PubMed: 18164058]
- Li CS, Zhang S, Duann JR, Yan P, Sinha R, Mazure CM. Gender differences in cognitive control: an extended investigation of the Stop Signal Task. *Brain Imaging Behav.* 2009b; 3:262–276. [PubMed: 19701485]
- Lim KO, Wozniak JR, Mueller BA, Franc DT, Specker SM, Rodriguez CP, Silverman AB, Rotrosen JP. Brain macrostructural and microstructural abnormalities in cocaine dependence. *Drug Alcohol Depend.* 2008; 92:164–172. [PubMed: 17904770]
- Liu J, Lester BM, Neyzi N, Sheinkopf SJ, Gracia L, Kekatpure M, Kosofsky BE. Regional brain morphometry and impulsivity in adolescents following prenatal exposure to cocaine and tobacco. *JAMA Pediatr.* 2013; 167:348–354. [PubMed: 23400239]
- Lopez A, Becona E. Depression and cocaine dependence. *Psychol. Rep.* 2007; 100:520–524. [PubMed: 17564228]
- Lundqvist T. Imaging cognitive deficits in drug abuse. *Curr. Top. Behav. Neurosci.* 2010; 3:247–275. [PubMed: 21161756]
- Luo X, Zhang S, Hu S, Bednarski SR, Erdman E, Farr OM, Hong KI, Sinha R, Mazure CM, Li CS. Error processing and gender-shared and -specific neural predictors of relapse in cocaine dependence. *Brain.* 2013; 136:1231–1244. [PubMed: 23485852]
- Mackey S, Paulus M. Are there volumetric brain differences associated with the use of cocaine and amphetamine-type stimulants? *Neurosci. Biobehav. Rev.* 2013; 37:300–316.
- Maillet D, Rajah MN. Association between prefrontal activity and volume change in prefrontal and medial temporal lobes in aging and dementia: a review. *Ageing Res. Rev.* 2013; 12:479–489. [PubMed: 23183352]
- Makris N, Gasic GP, Kennedy DN, Hodge SM, Kaiser JR, Lee MJ, Kim BW, Blood AJ, Evins AE, Seidman LJ, Iosifescu DV, Lee S, Baxter C, Perlis RH, Smoller JW, Fava M, Breiter HC. Cortical thickness abnormalities in use and a pre-existing disposition to drug abuse? *Neuron.* 2008; 60:174–188. [PubMed: 18940597]
- Malik S, McGlone F, Dagher A. State of expectancy modulates the neural response to visual food stimuli in humans. *Appetite.* 2011; 56:302–309. [PubMed: 21232571]
- Manjon JV, Coupe P, Martí-Bonmati L, Collins DL, Robles M. Adaptive non-local means denoising of MR images with spatially varying noise levels. *J. Magn. Reson. Imaging.* 2010; 31:192–203. [PubMed: 20027588]
- Mann K, Ackermann K, Croissant B, Mundle G, Nakovics H, Diehl A. Neuroimaging of gender differences in alcohol dependence: are women more vulnerable? *Alcohol. Clin. Exp. Res.* 2005; 29:896–901.
- Margulies DS, Böttger J, Long X, Lv Y, Kelly C, Schafer A, Goldhahn D, Abbushi A, Milham MP, Lohmann G, Villringer A. Resting developments: a review of fMRI postprocessing methodologies for spontaneous brain activity. *MAGMA.* 2010; 23:289–307. [PubMed: 20972883]
- Matochik JA, London ED, Eldreth DA, Cadet JL, Bolla KI. Frontal cortical tissue composition in abstinent cocaine abusers: a magnetic resonance imaging study. *Neuroimage.* 2003; 19:1095–1102. [PubMed: 12880835]
- Mitchell AS, Browning PG, Baxter MG. Neurotoxic lesions of the medial mediodorsal nucleus of the thalamus disrupt reinforcer devaluation effects in rhesus monkeys. *J. Neurosci.* 2007; 27:11289–11295. [PubMed: 17942723]
- Moeller FG, Steinberg JL, Schmitz JM, Ma L, Liu S, Kjome KL, Rathnayaka N, Kramer LA, Narayana PA. Working memory fMRI activation in cocaine-dependent subjects: association with treatment response. *Psychiatr. Res.* 2010; 181:174–182.
- Monchi O, Petrides M, Petre V, Worsley K, Dagher A. Wisconsin Card Sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *J. Neurosci.* 2001; 21:7733–7741. [PubMed: 11567063]
- Moreno-Lopez L, Catena A, Fernandez-Serrano MJ, Delgado-Rico E, Stamatakis EA, Perez-Garcia M, Verdejo-Garcia A. Trait impulsivity and prefrontal gray matter reductions in cocaine dependent individuals. *Drug Alcohol Depend.* 2012; 125:208–214. [PubMed: 22391134]

- Narayana PA, Datta S, Tao G, Steinberg JL, Moeller FG. Effect of cocaine on structural changes in brain: MRI volumetry using tensor-based morphometry. *Drug Alcohol Depend.* 2010; 111:191–199. [PubMed: 20570057]
- Nickl-Jockschat T, Habel U, Michel TM, Manning J, Laird AR, Fox PT, Schneider F, Eickhoff SB. Brain structure anomalies in autism spectrum disorder--a meta-analysis of VBM studies using anatomic likelihood estimation. *Hum. Brain Mapp.* 2012; 33:1470–1489. [PubMed: 21692142]
- O'Neill J, Cardenas VA, Meyerhoff DJ. Separate and interactive effects of cocaine and alcohol dependence on brain structures and metabolites: quantitative MRI and proton MR spectroscopic imaging. *Addict. Biol.* 2001; 6:347–361. [PubMed: 11900613]
- Pfefferbaum A, Desmond JE, Galloway C, Menon V, Glover GH, Sullivan EV. Reorganization of frontal systems used by alcoholics for spatial working memory: an fMRI study. *Neuroimage.* 2001; 14:7–20. [PubMed: 11525339]
- Poline JB, Worsley KJ, Evans AC, Friston KJ. Combining spatial extent and peak intensity to test for activations in functional imaging. *Neuroimage.* 1997; 5:83–96. [PubMed: 9345540]
- Rajapakse JC, Giedd JN, Rapoport JL. Statistical approach to segmentation of single-channel cerebral MR images. *IEEE Trans. Med. Imaging.* 1997; 16:176–186. [PubMed: 9101327]
- Rando K, Tuit K, Hannestad J, Guarnaccia J, Sinha R. Sex differences in decreased limbic and cortical grey matter volume in cocaine dependence: a voxel-based morphometric study. *Addict. Biol.* 2013; 18:147–160. [PubMed: 23167305]
- Raz E, Cercignani M, Sbardella E, Totaro P, Pozzilli C, Bozzali M, Pantano P. Gray- and white-matter changes 1 year after first clinical episode of multiple sclerosis: MR imaging. *Radiology.* 2010; 257:448–454. [PubMed: 20858849]
- Rosazza C, Minati L. Resting-state brain networks: literature review and clinical applications. *Neurolog. Sci.* 2011; 32:773–785.
- Roussotte F, Soderberg L, Sowell E. Structural, metabolic, and functional brain abnormalities as a result of prenatal exposure to drugs of abuse: evidence from neuroimaging. *Neuropsychol. Rev.* 2010; 20:376–397. [PubMed: 20978945]
- Rubin E, Aharonovich E, Bisaga A, Levin FR, Raby WN, Nunes EV. Early abstinence in cocaine dependence: influence of comorbid major depression. *Am. J. Addict.* 2007; 16:283–290. [PubMed: 17661196]
- Selvaraj S, Arnone D, Job D, Stanfield A, Farrow TF, Nugent AC, Scherk H, Gruber O, Chen X, Sachdev PS, Dickstein DP, Malhi GS, Ha TH, Ha K, Phillips ML, McIntosh AM. Grey matter differences in bipolar disorder: a meta-analysis of voxel-based morphometry studies. *Bipolar Disord.* 2012; 14:135–145. [PubMed: 22420589]
- Sim ME, Lyoo IK, Streeter CC, Covell J, Sarid-Segal O, Ciraulo DA, Kim MJ, Kaufman MJ, Yurgelun-Todd DA, Renshaw PF. Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects. *Neuropsychopharmacology.* 2007; 32:2229–2237. [PubMed: 17299505]
- Sommer MA, Wurtz RH. What the brain stem tells the frontal cortex. II. role of the SCMD-FEF pathway in corollary discharge. *J. Neurophysiol.* 2004; 91:1403–1423. [PubMed: 14573557]
- Speilberger, C.; Gorsuch, R.; Lushene, R. STAI manual. Consulting Psychologist Press; Palo Alto, CA: 1970.
- Spencer MD, Moorhead TW, Lymer GK, Job DE, Muir WJ, Hoare P, Owens DG, Lawrie SM, Johnstone EC. Structural correlates of intellectual impairment and autistic features in adolescents. *Neuroimage.* 2006; 33:1136–1144. [PubMed: 16996749]
- Stepniewska I, Preuss TM, Kaas JH. Thalamic connections of the dorsal and ventral premotor areas in New World owl monkeys. *Neuroscience.* 2007; 147:727–745. [PubMed: 17570597]
- Tanabe J, Tregellas JR, Dalwani M, Thompson L, Owens E, Crowley T, Banich M. Medial orbitofrontal cortex gray matter is reduced in abstinent substance-dependent individuals. *Biol. Psychiatry.* 2009; 65:160–164. [PubMed: 18801475]
- Thomas BS. The effectiveness of selected risk factors in mediating gender differences in drinking and its problems. *J. Adolesc. Health.* 1995; 17:91–98. [PubMed: 7495831]
- Tohka J, Zijdenbos A, Evans A. Fast and robust parameter estimation for statistical partial volume models in brain MRI. *Neuroimage.* 2004; 23:84–97. [PubMed: 15325355]

- Tomasi D, Goldstein RZ, Telang F, Maloney T, Alia-Klein N, Caparelli EC, Volkow ND. Thalamo-cortical dysfunction in cocaine abusers: implications in attention and perception. *Psychiatry Res.* 2007; 155:189–201. [PubMed: 17582746]
- Urbain N, Deschênes M. Motor cortex gates vibrissal responses in a thalamocortical projection pathway. *Neuron.* 2007; 56:714–725. [PubMed: 18031687]
- van Gaal S, Scholte HS, Lamme VA, Fahrenfort JJ, Ridderinkhof KR. Pre-SMA graymatter density predicts individual differences in action selection in the face of conscious and unconscious response conflict. *J. Cogn. Neurosci.* 2011; 23:382–390. [PubMed: 20175674]
- Volkow ND, Tomasi D, Wang GJ, Fowler JS, Telang F, Goldstein RZ, Alia-Klein N, Wong C. Reduced metabolism in brain "control networks" following cocaine-cues exposure in female cocaine abusers. *PloS One.* 2011; 6:e16573. [PubMed: 21373180]
- Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C. Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J. Neurosci.* 2006; 26:6583–6588. [PubMed: 16775146]
- Wagner G, Koch K, Reichenbach JR, Sauer H, Schlosser RG. The special involvement of the rostromedial prefrontal cortex in planning abilities: an event-related fMRI study with the Tower of London paradigm. *Neuropsychologia.* 2006; 44:2337–2347. [PubMed: 16806311]
- Wagner G, Koch K, Schachtzabel C, Reichenbach JR, Sauer H, Schlosser Md RG. Enhanced rostral anterior cingulate cortex activation during cognitive control is related to orbitofrontal volume reduction in unipolar depression. *J. Psychiatr. Neurosci.* 2008; 33:199–208.
- Weller RE, Stoeckel LE, Milby JB, Bolding M, Twieg DB, Knowlton RC, Avison MJ, Ding Z. Smaller regional gray matter volume in homeless african american cocaine-dependent men: a preliminary report. *Open neuroimag. J.* 2011; 5:57–64. [PubMed: 22135719]
- Wheeler AL, Lerch JP, Chakravarty MM, Friedel M, Sled JG, Fletcher PJ, Josselyn SA, Frankland PW. Adolescent cocaine exposure causes enduring macroscale changes in mouse brain structure. *J. Neurosci.* 2013; 33:1797–1803a. [PubMed: 23365219]
- Winkler AD, Hu S, Li CS. The influence of risky and conservative mental sets on cerebral activations of cognitive control. *Intl. J. Psychophysiol.* 2012; 87:254–261.
- Yamamoto T, Yoshida K, Yoshikawa H, Kishimoto Y, Oka H. The medial dorsal nucleus is one of the thalamic relays of the cerebellocerebral responses to the frontal association cortex in the monkey: horseradish peroxidase and fluorescent dye double staining study. *Brain Res.* 1992; 579:315–320. [PubMed: 1378349]
- Yan X, Zhang J, Shi J, Gong Q, Weng X. Cerebral and functional adaptation with chronic hypoxia exposure: a multi-modal MRI study. *Brain Res.* 2010; 1348:21–29. [PubMed: 20599837]
- Zang YF, He Y, Zhu CZ, Cao QJ, Sui MQ, Liang M, Tian LX, Jiang TZ, Wang YF. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev.* 2007; 29:83–91. [PubMed: 16919409]
- Zar, JH. *Biostatistical Analysis.* Prentice-Hall, Inc.; New Jersey: 1999.
- Zhang S, Li CS. A neural measure of behavioral engagement: task-residual low-frequency blood oxygenation level-dependent activity in the precuneus. *Neuroimage.* 2010; 49:1911–1918. [PubMed: 19761851]
- Zou QH, Zhu CZ, Yang Y, Zuo XN, Long XY, Cao QJ, Wang YF, Zang YF. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *Journal of neuroscience methods.* 2008; 172:137–141. [PubMed: 18501969]

Figure 1.

Voxel based morphometry: analysis of covariance comparing cocaine dependent (CD) and healthy control (HC) participants, with age and years of alcohol use as covariates. (A) The results were examined at voxel $p < 0.05$, corrected for family-wise error (FWE) of multiple comparisons. Compared to HC, CD showed gray matter (GM) volume loss in multiple cortical regions, including the temporal cortex, middle and posterior cingulate cortex, superior frontal cortices, and the cerebellum. Conversely, no brain regions showed greater GM volume in CD, as compared to HC, at this threshold. (B) The same contrast examined at voxel $p < 0.0001$, and cluster $p < 0.05$, FWE corrected. In addition to decreased GM volume in the cortical regions and cerebellum, CD also showed increased GM volume in the right

ventral putamen, compared to HC (**Table 2A**). Color bars represent voxel T value. Neurological orientation: R=right.

Figure 2. Gender difference in the correlation of GM volume with years of cocaine use in the cocaine dependent group, for the three regions of interest. Compared to men, women showed a steeper decline in GM volume of the right superior frontal gyrus with the duration of use ($p < 0.016$, test of difference in slope; Zar, 1999).

Figure 3.

Differences in fractional amplitude of low frequency fluctuation (fALFF) of BOLD signals between CD and HC participants. (A) At voxel $p < 0.05$, corrected for family-wise error (FWE) of multiple comparisons, a single cluster in the thalamus showed decreased fALFF in CD, as compared to HC. (B) The same contrast examined at voxel $p < 0.0001$ and cluster $p < 0.05$, FWE corrected, identified additional differences (Table 2B). Color bars represent voxel T value. Neurological orientation: R=right.

Table 1

Demographics and clinical characteristics of participants

	Cocaine Dependent (CD)			Healthy Control (HC)		
	All (84)	Women (29)	Men (55)	All (86)	Women (39)	Men (47)
Age (years)	39.8±7.6	39.6±7.9	40.0±7.5	38.1±11.0	37.9±10.6	39.4±11.3
Race (EA/AA/Others)	23/55/6	12/15/2	11/40/4	37/38/11	15/19/5	22/19/6
Education (years)	12.1±1.5	12.2±1.1	12.0±1.6	14.1±1.9	14.1±1.8	14.2±2.1
Cigarette smokers (n, %)	66 (79%)	19 (66%)	47 (85%)	27 (31%)	15 (38%)	12 (26%)
Years of cocaine use	18.0±8.2	17.9±8.0	18.0±8.4	0	0	0
Years of alcohol use	16.5±9.1	14.1±8.2	17.8±9.4	15.6±13.0	14.1±11.7	16.8±13.9
Years of cannabis use	9.3±7.3	8.7±6.3	9.7±8.3	0.06±0.28	0	0.11±0.37
Life time depression (n, %)	22 (26%)	8 (28%)	14 (25%)	0	0	0
Life time PTSD (n, %)	19 (23%)	10 (34%)	9 (16%)	0	0	0

Note: CD and HC did not differ in age ($p=0.458$; two-tailed two-sample t test), gender composition ($p=0.199$, chi-square test), or years of alcohol use ($p=0.570$, t test). However, CD and HC are significantly different in race composition ($p<0.05$, chi-square test), years of education ($p<0.001$, t test), rate of cigarette smoking ($p<0.001$, chi-square test), use of marijuana ($p<0.001$, t -test), and lifetime diagnosis of depression and PTSD ($p's<0.001$, chi-square test).

Table 2

Differences in gray matter (GM) volume and fractional amplitude of low-frequency fluctuations (fALFF) between cocaine dependent (CD) and healthy control (HC) participants (p voxel $p < 0.0001$ and cluster $p < 0.05$, FWE corrected).

A) GM volume

Cluster size (# of voxels)	p-value corr. (cluster level)	Z-value	MNI coordinate (mm)			Identified brain region
			x	y	z	
CD > HC						
447	0.0057	4.47	24	16	-11	R putamen
HC > CD						
9,540	0.0000	6.30*	37	0	-37	R inferior temporal C
2,561	0.0000	6.14*	-2	-24	44	L middle/post cingulate C
1,010	0.0001	6.11*	21	-60	-34	R cerebellum
1,807	0.0000	6.07*	-27	9	62	L superior frontal G
		4.57	-35	-23	61	L precentral G
1,020	0.0001	5.35*	-36	7	-43	L temporal pole
701	0.0009	5.32*	28	3	62	R superior frontal G
1,937	0.0000	5.12*	9	-65	29	R precuneus
		4.65	7	-63	7	R lingual G
		4.29	-5	-68	26	L cuneus
585	0.0020	5.12*	12	-6	71	R superior frontal G
459	0.0051	5.05*	49	-2	10	R insula/mid temporal C
414	0.0074	4.79	-33	25	-26	L posterior orbital G
187	0.0202	4.79	-29	-50	53	L postcentral S
209	0.0461	4.75	-54	-11	41	L postcentral G
188	0.0272	4.72	-14	21	64	L superior frontal G
365	0.0111	4.68	46	-77	10	R middle temporal G
283	0.0227	4.62	-39	-39	-35	L cerebellum
215	0.0434	4.40	25	-44	58	R postcentral G

B) fALFF

Cluster size (# of voxels)	p-value corr. (cluster level)	Z-value	MNI coordinate (mm)			Identified brain region
			x	y	z	
CD > HC						
3,753	0.0001	5.82*	0	−13	10	thalamus
1,512	0.0001	4.75	0	−10	55	supplementary motor area
1,026	0.0020	4.60	27	−7	13	R pallidum
HC > CD						

Cluster size (# of voxels)	p-value corr. (cluster level)	Z-value	MNI coordinate (mm)			Identified brain region
			x	y	z	
1,431	0.0001	4.70	9	53	25	R middle frontal G
621	0.0170	4.56	-30	-70	40	L middle occipital G
756	0.0090	4.50	36	-61	34	R angular G

Note: All voxel peaks that are 8mm apart are identified in the same cluster.

* indicates clusters that also contain voxels that are significant at voxel threshold $p < 0.05$, FWE corrected. R: right; L: left; C: cortex; G: gyrus; S: sulcus; mid: middle; post: posterior.