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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.

1. 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 GM volume in bilateral medial orbitofrontal cortex (OFC) in cocaine and amphetamine users, with the decrease associated with risk taking

☆ Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

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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; Speilberger et al., 1970) at admission. The average BDI (mean ± 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 = 2530 ms, TE = 3.66 ms, bandwidth = 181 Hz/pixel, flip angle = 7°, field of view = 256 × 256 mm, matrix = 256 × 256, 1 mm^3 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

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 life-time diagnosis of depression and PTSD (p's < 0.001, chi-square test).

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