



Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Subcortical grey matter alterations in cocaine dependent individuals with substance-induced psychosis compared to non-psychotic cocaine users

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ARTICLE INFO

Article history:

Received 5 February 2016

Received in revised form 29 July 2016

Accepted 2 August 2016

Available online xxxx

Keywords:

Hippocampus

MRI

Thalamus

Methamphetamine

Psychostimulant

Addiction

ABSTRACT

After prolonged psychostimulant abuse, transient psychotic symptoms referred to as “substance-induced psychosis” (SIP) can develop – closely resembling symptoms observed in schizophrenia spectrum disorders. The comparability in psychotic presentation between SIP and schizophrénias suggests that similar underlying neural deficits may contribute to the expression of psychosis across these disorders. To date, neuroanatomical characterization of grey matter structural alterations in SIP has been limited to methamphetamine associated psychosis, with no studies controlling for potential neurotoxic effects of the psychostimulant that precipitates psychosis. To investigate grey matter subcortical alterations in SIP, a voxel-based analysis of magnetic resonance images (MRI) was performed between a group of 74 cocaine dependent nonpsychotic individuals and a group of 29 individuals with cocaine-associated psychosis. The cocaine-associated psychosis group had significantly smaller volumes of the thalamus and left hippocampus, controlling for age, total brain volume, current methamphetamine dependence, and current marijuana dependence. No differences were present in bilateral caudate structures. The findings of reduced thalamic and hippocampal volumes agree with previous reports in the schizophrenia literature, suggesting alterations of these structures are not specific to schizophrenia, but may be common to multiple forms of psychosis.

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1. Introduction

There are an estimated 14 to 21 million cocaine users worldwide, with particularly high rates of use in North America, Europe, and South America (World Drug Report, 2015). Approximately 50–75% of cocaine users experience acute psychotic symptoms during consumption, including paranoia, delusions, and vivid sensory hallucinations (Brady et al., 1991; Barr et al., 2006; Mooney et al., 2006; Satel and Edell, 1991; Smith et al., 2009; Vorspan et al., 2012). In a subset of 5–40% of cocaine dependent individuals, psychotic symptomatology can persist beyond intoxication and drug elimination as a syndrome referred to as “substance induced psychosis” (SIP) (Herrero et al., 2008; Roncero et al., 2014; Vergara-Moragues et al., 2012). SIP symptomatically resembles schizophrenia spectrum disorders, with the presentation of both positive (hallucinations, delusions, disorganized thinking) and

negative (flattened affect, emotional withdrawal, lack of spontaneity) symptoms. Clinical presentation of these psychotic symptoms, especially the positive symptoms, is frequently indistinguishable from those presented in idiopathic psychosis (Panenka et al., 2013; Shaner et al., 1998; Srisurapanont et al., 2003).

While genetic studies have provided preliminary evidence to suggest that genes associated with schizophrenia may be involved in the etiology of SIP (Grant et al., 2012), the neuroanatomical basis of SIP has been scarcely investigated. Only a small number of neuroimaging studies have addressed characterization of the structural abnormalities that may be associated with SIP. We previously reported white matter integrity deficits in cocaine-associated psychosis compared to cocaine-dependent nonpsychotic controls (Willi et al., 2016). In individuals with related methamphetamine-associated psychosis, grey matter volumetric reductions have been reported in frontal and temporal cortical areas (Aoki et al., 2013), as well as in the amygdala and hippocampus (Orikabe et al., 2011). However, these grey matter investigations compared patients with methamphetamine-associated psychosis to drug-

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naïve controls, making it difficult to determine which structural changes reflect the toxic effects of psychostimulant exposure, and which are unique to psychosis.

Chronic exposure to psychostimulants has been reported to cause structural alterations in the brains of users, with differences established in both active and long-term abstinent users (Mackey and Paulus, 2013); meta-analyses have highlighted both cortical and subcortical changes. The prefrontal cortex exhibits grey matter reductions (Ersche et al., 2013), while subcortically, basal ganglia enlargement (Churchwell et al., 2012; Ersche et al., 2011) and thalamic reduction (Ersche et al., 2013; Sim et al., 2007) have been observed with prolonged psychostimulant use. Volumetric studies investigating the hippocampus have produced conflicting evidence. Most studies report no difference in comparison to healthy controls (Bartzokis et al., 2002; Jacobsen et al., 2001; Jernigan et al., 2005), while a few studies report a decrease in hippocampal volume (Alia-Klein et al., 2011; Mackey and Paulus, 2013; Thompson et al., 2004).

Idiopathic psychoses, such as schizophrenia, have been associated with subtle-to-moderate sized regional alterations in brain volume, which may reflect effects of the illness and/or chronic antipsychotic medication (Shenton et al., 2001; van Erp et al., 2015). A recent meta-analysis of 35 studies comparing antipsychotic-naïve schizophrenia patients to controls found changes primarily in subcortical nuclei, with decreased volumes of the hippocampus, thalamus, and caudate (Hajima et al., 2013) – indicating that psychosis in the absence of antipsychotic drugs may be most strongly associated with subcortical changes. To date, the only grey matter subcortical structures that have specifically been investigated in SIP are the hippocampus and amygdala (Orikabe et al., 2011), and this study did not control for psychostimulant effects with a drug-taking, non-psychotic group.

The goal of the current study was to investigate subcortical grey matter volumes in cocaine users with SIP, as both of these exposures have been independently associated with subcortical changes, but their combined effect is unknown. A voxel-based analysis was performed between a group of cocaine-dependent nonpsychotic subjects and a group with cocaine-associated psychosis, where antipsychotic medication was not common. Based on the previous literature on the effects of psychosis and psychostimulant use, three hypotheses were made. First, because smaller hippocampi are frequently reported in psychosis, but rarely in psychostimulant use, we hypothesized smaller hippocampal volumes in cocaine associated psychosis (CAP) than in nonpsychotic cocaine users. Second, because smaller thalami are reported in both psychosis and psychostimulant use, we hypothesized the CAP group would have modestly smaller thalami as a result of additive exposures. Lastly, as psychosis has been associated with reduced basal ganglia volumes, we hypothesized smaller caudate volumes in CAP.

2. Materials and methods

2.1. Participants

Participants were recruited as part of a larger study of 370 subjects living in single room occupancy hotels with a history of mental illness and/or substance abuse in the Downtown Eastside of Vancouver, B.C. (Vila-Rodriguez et al., 2013). Subjects were evaluated by a qualified psychiatrist and received a brain MRI as part of the study. For the current investigation, exclusionary criteria were a history of a DSM-IV-TR diagnosis of schizophrenia, schizoaffective disorder, psychosis not-other-wise-specified, or bipolar disorder. Additional exclusionary criteria included past stroke/hemorrhage, significant MRI artifacts (motion, major distortion) and other gross morphometric brain abnormalities (i.e. encephalomalacia, chronic trauma). Of the remaining 138 participants, only participants meeting DSM-IV criteria for current cocaine dependence were retained (confirmed by positive cocaine urine drug screen within 2 weeks of scan) yielding 103 total subjects to be included in this analysis. Subjects were divided into two groups: 1) 29 cocaine-

associated psychosis subjects (CAP), and, 2) 74 cocaine-dependent non-psychotic subjects (CDN). In accordance to Tri-Council policy, the study was approved by the University of British Columbia Clinical Research Ethics Board. All participants provided written informed consent.

2.2. Demographics

Demographic data including age, gender, and education were collected. The Mini-International Neuropsychiatric Interview was administered, and was supplemented by a clinical interview and mental status examination. Diagnoses of psychiatric disorders and substance dependency were made according to the DSM-IV TR by an experienced psychiatrist (WGH, OL or FV-R) through consensus evaluation with the Best Estimate Clinical Evaluation and Diagnosis (BECED; (Endicott, 1988)). Years of regular substance use and age of first use were provided by self-report for cocaine, marijuana, opioids, and alcohol. Psychosis severity at the time of MRI scan was assessed with the Positive and Negative Symptom Scale (PANSS, (Kay et al., 1987)).

2.3. MRI acquisition

All scanning was performed on a 3 T MRI Scanner (Philips Achieva) at the University of British Columbia MRI Research Centre between 2008 and 2014 utilizing an 8-channel SENSE head coil. High resolution 3D T1-weighted FFE sagittal images were acquired with the following parameters: TE = 3.7 ms, TR = 8.1 ms, flip angle = 8°, FOV = 256 mm × 256 mm, acquisition matrix = 256 × 250, reconstruction matrix = 256 × 256, voxel size = 1.0 × 1.0 × 1.0 mm³, 190 contiguous slices, gap = 0, scan duration = 443 s, no partial parallel imaging acceleration.

2.4. Image processing

All images were visually screened for severe motion artifact/MRI abnormalities by a trained specialist (DL, WS). The high resolution T1-weighted images were converted to NIFTI format by using the dcm2ni tool (<http://www.sph.sc.edu/comd/rorden/mricron/>), and reoriented to the axial plane. Intensity bias correction was used to adjust for non-uniformity using the MINC N3 tool (Sled et al., 1998). The bias-corrected image was then segmented into grey matter, white matter, and cerebrospinal fluid using the default configuration of SPM8 (Ashburner and Friston, 2003). A brain mask was then created by merging cerebrospinal fluid (CSF), grey matter (GM), and white matter (WM) voxels, followed by morphological operations. Finally, scans underwent nonlinear registration to the MNI 152 template by using the FSL FNIRT tool (Andersson et al., 2007). Segmentation into deep grey matter structures of interest was performed with the Harvard-Oxford subcortical atlas.

2.5. Statistical analysis

Clinical and demographic differences between groups were analyzed by either a chi-square test or independent t-tests. The Shapiro-Wilk's test of normality was used to assess the normality of the distribution of subcortical grey matter volumes of interest. When outliers (>3.3 SD from the mean) were present in grey matter volumes of interest (hippocampus, thalamus and caudate), the raw score was adjusted to the most inlying extreme score as recommended by Tabachnick and Fidell (2007).

For group comparison of region of interest (ROI; hippocampus, thalamus, caudate) volumes, we employed a repeated measures ANCOVA with 1 between-subject factor (group: CAP/CDN) and 1 within-subject factor (hemisphere: left/right). Volumes of the ROIs were used as the dependent variable with total brain volume, age, methamphetamine dependence, and marijuana dependence as covariates. In the case of a significant group-by-hemisphere interaction, post-hoc t-tests were performed separately for each hemisphere. Statistical significance was set

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