



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

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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 (Haijma 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 otherwise-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 dcm2nii tool (<http://www.sph.sc.edu/comd/rorden/micron/>), 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

at $p < 0.05$. The statistical assumptions of ANCOVA were confirmed. Levene's test was used to check the homogeneity of variances while the homogeneity of regression slopes was confirmed by screening for significant interaction terms ($p < 0.05$) between psychosis group and the covariate of interest (in accordance with [Tabachnick and Fidell \(2007\)](#)). Visual inspection of residual plots was used to confirm the linearity of regression.

In an exploratory analysis, grey matter volumes were tested for associations with clinical indices. Associations between relative grey matter volumes (ROI/TBV) and clinical indices including total years of cocaine use, PANSS Positive Symptom subscale, PANSS Negative Symptom Subscale, and PANSS General Psychopathology subscale were tested with Spearman's rank correlation.

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.

3. Results

3.1. Demographic variables

All participants were clinically dependent on cocaine, a majority of which were crack cocaine users (86.4%). Typically, individuals were middle aged (46.1 ± 8.6 years) males (75%) with limited education (10.1 ± 2.2 years). The group of individuals with cocaine-associated psychosis had significantly higher ($p < 0.05$) PANSS subscales than the cocaine-dependent nonpsychotic group on Positive and General Psychopathology subscales, but not in the Negative subscale. The psychosis group had higher frequencies of current methamphetamine and marijuana dependency. No typical antipsychotics were prescribed in the total sample, while the atypical antipsychotic quetiapine was prescribed for 5.4% (4/74) of the CAP and 6.9% (2/29) of the CDN group. See [Table 1](#) for all demographic and substance use data.

3.2. Volumes of subcortical ROIs

The repeated measures ANCOVA showed a significant main effect of group in the thalamus ($F[1, 97] = 4.008, p = 0.048$), with no significant group \times side interaction ($F(1, 97) = 0.231, p = 0.632$). In the hippocampus, there was a significant effect of group ($F[1, 97] = 4.901, p = 0.029$) and a group \times side interaction ($F[1, 97] = 4.662, p = 0.033$), as shown in [Fig. 1](#). Since a significant group \times side interaction was

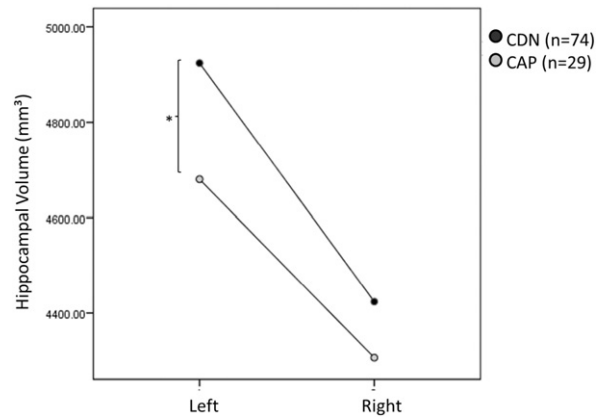


Fig. 1. Hemisphere \times group interaction in the hippocampus. Hippocampal volumes corrected for age, TBV, methamphetamine dependence, and marijuana dependence. *indicates a significant ($p < 0.05$) between group difference in the left, but not right, hemisphere.

found, post-hoc t-tests were performed separately for each hippocampal side. In these follow-up analyses, a significant effect of group was found for the left hippocampus ($F[1, 102] = 7.410, p = 0.008$), while the right hippocampus failed to achieve conventional significance ($F[1, 102] = 1.965, p = 0.164$). See [Table 2](#) for volumetric ANCOVA results. These results indicated that subjects with cocaine-associated psychosis had significantly smaller volumes of the thalamus and left hippocampus than cocaine dependent nonpsychotic individuals as shown in [Fig. 2](#). There were no significant interactions between drug dependency covariates and group. There was no effect of group on volume of the caudate ($F[1, 97] = 0.595, p = 0.442$).

3.3. Associations between clinical information and brain volumes

In exploratory analysis, no significant associations were found between clinical indices of symptom severity (PANSS positive, negative, general symptoms) or cocaine use (total years use) with bilateral thalamus, hippocampus, or caudate volumes when controlling for age, TBV, methamphetamine dependence and marijuana dependence.

Table 1
Demographic and substance use characteristics of population.

	CDN (n = 74)		SIP (n = 29)		Test statistic ^a	p
	Mean (SD)	% (n/N)	Mean (SD)	% (n/N)		
Gender (F)		21.6% (16/74)		31% (9/29)	0.099 ^a	0.321
Age	46.1 (9.1)		46.0 (7.8)		0.050	0.961
Education	10.1 (2.4)		9.8 (1.4)		0.729	0.468
HIV positive		21.1% (15/71)		27.5% (8/29)	0.07 ^a	0.491
PANSS positive symptoms	12.5 (3.2)		16.4 (4.5)		−4.717	0.001
PANSS negative symptoms	15.4 (5.4)		16.9 (5.2)		−1.259	0.211
PANSS general psychopathology	33.9 (7.0)		37.2 (7.9)		−2.014	0.047
Total PANSS	61.9 (13.7)		70.5 (15.2)		−2.724	0.008
Cocaine inject		65.3% (47/72)		72.4% (21/29)	0.069 ^a	0.494
Cocaine powder dependence		38.4% (28/73)		44.8% (13/29)	0.06 ^a	0.552
Crack cocaine dependence		86.3% (63/73)		86.2% (25/29)	−0.001 ^a	0.99
Methamphetamine dependence		9.4% (7/74)		31% (9/29)	0.268 ^a	0.006
Marijuana dependence		21.6% (16/74)		41.4% (12/29)	0.2 ^a	0.043
Alcohol dependence		17.6% (13/74)		13.8% (4/29)	−0.046 ^a	0.646
Methadone dependence		56.8% (42/74)		65.5% (19/29)	0.08 ^a	0.421
Opioid dependence		48.6% (36/74)		67.8% (19/28)	0.172 ^a	0.084
Years cocaine use	13.8 (9.7)		13.3 (9.8)		0.236	0.814
Years Cannabis use	13.0 (13.0)		15.1 (11.9)		−0.743	0.459
Years opiate use	11.6 (11.4)		14.5 (11.4)		−1.082	0.282
Years alcohol use	12.4 (11.4)		12.7 (9.2)		−0.115	0.909

^a Test statistic either refers to a t-value, or a chi-square value.

Table 2
Sub-cortical regional brain volumes of population.

	CDN (n = 74)		CAP (n = 29)		Repeated measures ANCOVA Group		Repeated measures ANCOVA Side * Group		Post-hoc analysis	
	Mean (mm ³)	SD (mm ³)	Mean (mm ³)	SD (mm ³)	F	p	F	p	F	p
Thalamus	–	–	–	–	4.008	0.048	0.231	0.632	–	–
Left thalamus	8175.3	1152.6	7854.8	800.9	–	–	–	–	–	–
Right thalamus	7825.6	1068.6	7531.6	775.2	–	–	–	–	–	–
Hippocampus	–	–	–	–	4.901	0.029	4.662	0.033	–	–
Left hippocampus	4923.6	537.0	4681.5	463.8	–	–	–	–	7.410	0.008
Right hippocampus	4423.6	509.5	4307.0	389.2	–	–	–	–	1.965	0.164
Caudate	–	–	–	–	0.595	0.442	0.025	0.874	–	–
Left caudate	3844.6	1097.1	3630.0	833.8	–	–	–	–	–	–
Right caudate	3712.8	1082.8	3512.0	870.9	–	–	–	–	–	–

Grey matter volumes refer to raw volumes. Repeated Measures ANCOVA results refer to analysis controlling for age, TBV, methamphetamine dependence, and marijuana dependence. Post Hoc analysis performed when a significant Side*Group interaction was present.

4. Discussion

To our knowledge, the present study is the first to demonstrate grey matter volume reduction in the hippocampus and thalamus of cocaine dependent individuals with psychosis compared to those without psychosis. In the hippocampus, these findings were specific to the left hemisphere, a common laterality reported in the schizophrenia literature (Seidman et al., 2002). There was a higher prevalence of methamphetamine and marijuana dependence in those with psychosis, though controlling for these possible confounds did not eliminate the statistical findings observed in grey matter difference.

Grey matter structural abnormalities in SIP have been previously investigated, but only for the pharmacologically similar psychostimulant drug methamphetamine. Previous investigations of methamphetamine associated psychosis reported volumetric reductions in frontopolar

cortical areas (Aoki et al., 2013), bilateral hippocampus and bilateral amygdala (Orikabe et al., 2011). Here, we similarly report volumetric reductions in the hippocampus – though only on the left side. Structural abnormalities specific to left temporal lobe structures are commonly reported in psychosis, a pattern that has been proposed as a neurodevelopmental vulnerability for schizophrenia (Crow et al., 1989; Seidman et al., 2002; Shenton et al., 1992).

Hippocampal volumetric reduction has been consistently observed in meta-analyses of schizophrenia (Hajima et al., 2013; Shenton et al., 2001; van Erp et al., 2015). Additionally, smaller hippocampal volumes have been reported in groups with a high risk, either clinically (Pantelis et al., 2003) or genetically (Keshavan et al., 2002), for developing schizophrenia. Similarly, thalamic volume reduction has been reported in subjects with chronic schizophrenia and first episode psychosis (Adriano et al., 2010; Hajima et al., 2013), as well as in those at high

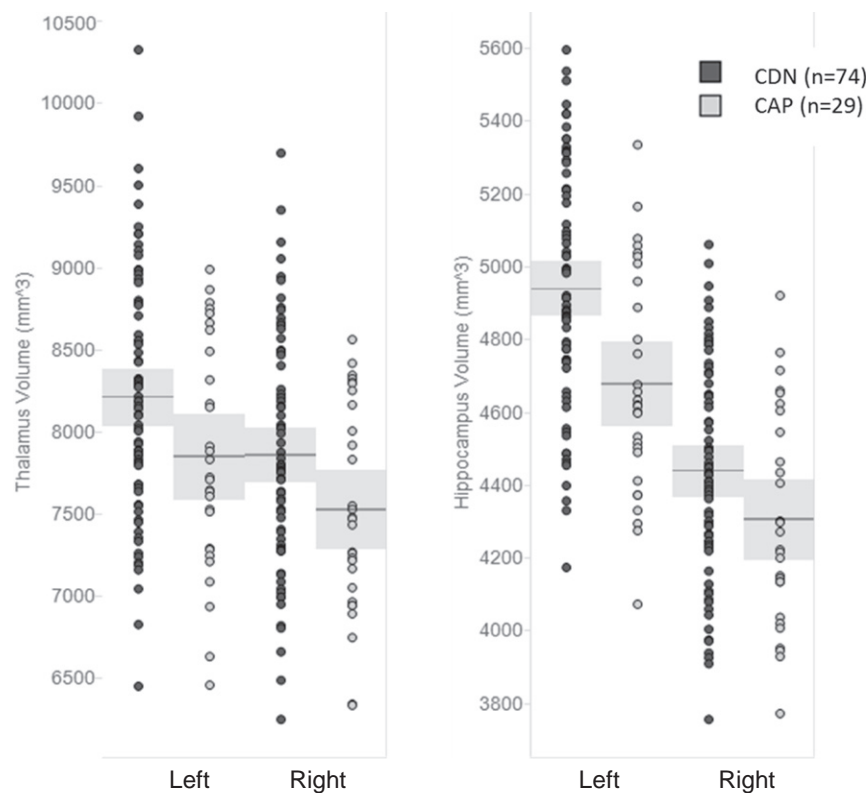


Fig. 2. Plots of grey matter volume corrected for age, TBV, methamphetamine dependence, and marijuana dependence. Scatter plots show mean volumes and 95% confidence intervals for each structure in cocaine dependent nonpsychotic (CDN, n = 74) and cocaine associated psychosis (CAP, n = 29) groups.

risk for developing schizophrenia (Lawrie et al., 2001). Combined with our findings presented here, this suggests that hippocampal and thalamic abnormalities are associated with psychosis. A combined hippocampal/thalamic deficit is consistent with the *N*-methyl-D-aspartate receptor (NMDAR) hypofunction model of schizophrenia (Lisman et al., 2010), which posits that inhibition of NMDA receptors of the thalamus can lead to a positive feedback loop circulating from thalamus to hippocampus to activation of the dopaminergic system, thereby leading to increased dopamine release in the thalamus. Whether the structural reductions seen in the thalamus and hippocampus result from a neurodevelopmental vulnerability or as a result of a heightened susceptibility to the toxic effects of psychostimulants remains unknown.

Typical antipsychotic drugs have been confirmed to cause volumetric enlargements in the basal ganglia (Chakos et al., 1995). However, meta-analysis of antipsychotic naïve patients with schizophrenia has recently reported that psychosis is associated with a volumetric reduction of the caudate (Haijma et al., 2013). Contrary to this effect of psychosis in an antipsychotic-naïve population, chronic cocaine use can cause volumetric increases of the caudate (Ersche et al., 2011). As these two factors have seemingly opposing effects, the volumetric result of the combination of exposures is of interest. Data are limited, but comparison between schizophrenia subjects with or without a concurrent substance use disorder (mostly alcohol and cannabis) found increased grey matter volumes in the basal ganglia of the dual diagnosis group (Koenders et al., 2015; Potvin et al., 2007), suggesting that exposure to non-psychostimulant substance abuse results in a measurable difference in basal ganglia volume. Our present study, with no participants treated with typical antipsychotic drugs, noted no differences in caudate volume between cocaine users with or without concurrent psychosis. This may indicate that the caudate is not affected in SIP, or that smaller basal ganglia volumes in the SIP group were reversed by chronic cocaine exposure; the answer to this issue is beyond the scope of the present study, and will need to be addressed in future longitudinal studies.

Though the findings of reduced thalamic and hippocampal volumes are consistent with reports in the schizophrenia literature (Adriano et al., 2010; Haijma et al., 2013; Shenton et al., 2001), the relationship between psychostimulant use, grey matter volume and psychosis remains a complex issue. The grey matter volume reductions reported here could represent neurodevelopmental substrates for psychosis that exist prior to drug use, akin to the neurodevelopmental hypothesis of schizophrenia (Weinberger et al., 1986). Alternatively, volumetric reductions could reflect a heightened susceptibility to the neurotoxic effects of chronic psychostimulant exposure, in line with the neurotoxicity model (Hsieh et al., 2014; Robinson and Becker, 1986). The notion that some degree of drug-induced damage is necessary to precipitate an episode of SIP is supported by an average latency from first use of methamphetamine to onset of psychosis as 3–5 years (Ujike and Sato, 2004). Additionally, psychosis relapse has been shown to follow subsequent stressors such as continued usage of methamphetamine or insomnia, suggesting an underlying neurological change has occurred between pre and post SIP (Sato et al., 1992; Ujike and Sato, 2004). Additional longitudinal studies will be required to address this issue – especially in the context of sustained abstinence.

A limitation of this study is the absence of a cocaine-naïve control group. Though this would not change the observation that SIP is associated with decreased hippocampal and thalamic volumes compared to non-psychotic cocaine users, it would provide insight into the nature of potential additive deficits of comorbid psychosis and substance abuse. However, a cocaine-naïve control group would likely not be matched on the multitude of other environmental factors inherent to being part of a marginalized population (high infection rates, homelessness, limited formal education, other substances of abuse, etc.), and thus separation of drug versus other environmental effects on the brain would not be feasible. Additionally, acute substance use (previous 48 h) was not controlled for, as the urine drug screen did not occur on the date of the MRI scan for most subjects. However, the authors are

not aware of a literature suggesting subcortical grey matter volumes are susceptible to acute drug exposure. We were also not able to assess first age of use specifically of the drug methamphetamine.

5. Conclusions

This is the first study to investigate grey matter structural differences associated with psychosis in cocaine dependent individuals, and the first grey matter investigation of SIP to control for the effects of the substance precipitating psychosis. Akin to reports in schizophrenia, we report grey matter volumetric reductions in the thalamus and left hippocampus in individuals with cocaine associated psychosis compared to cocaine dependent nonpsychotic individuals. Though care must be taken in interpreting our findings as we did not compare our sample to that of a schizophrenia sample, the present study provides intriguing evidence that grey matter volume reductions in specific subcortical nuclei may be common to multiple forms of psychosis.

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Contributors

TSW and AMB drafted the manuscript. Authors WGH, AET, AMB, RMP were involved in the design of the study. Authors WJP, WGH, FVR, OL, GWM undertook clinical data collection. TSW, GNS, DJL undertook statistical analysis. WS, ATV, and AR were involved in scan acquisition and quality control. All authors contributed to the final version of the manuscript.

Conflict of interest

Drs. Lang, Vila-Rodríguez, Thornton, Leonova, Rauscher, MacEwan, Vertinsky, Smith and Panenka report no competing interests. Mr(s). Willi and Su report no competing interests.

Dr. Honer has received consulting fees or sat on paid advisory boards for: In Silico, Otsuka/Lundbeck, Roche and Eli Lilly; received honoraria from Rush University, University of Ottawa, University of Calgary, University of Hong Kong, British Columbia Health Authorities, the British Association for Psychopharmacology, and the Canadian Psychiatric Association; and received grants from the Canadian Institutes of Health Research (CIHR).

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