



A comparison of regional brain volumes and white matter connectivity in subjects with stimulant induced psychosis versus schizophrenia

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Abstract

Rationale Schizophrenia and stimulant-induced psychosis (SIP) represent two different forms of psychotic disorder, with different etiologies. While many of the symptoms of psychosis are common to both disorders, there have been few direct comparisons between these conditions, especially when controlling for stimulant use in individuals with schizophrenia.

Objectives We directly compared both psychotic disorders with a comprehensive battery of clinical, neurocognitive and neuro-anatomical measures. This included one group with SIP (and concurrent stimulant dependence) and two groups with schizophrenia (either with or without concurrent stimulant dependence).

Methods Ninety-six participants were recruited from a marginalized urban population, which included 39 with SIP (and concurrent stimulant dependence), 18 with schizophrenia (*without* stimulant dependence), and 39 with schizophrenia (*with* concurrent stimulant dependence). All subjects had extensive clinical and neurocognitive evaluations, complemented with structural MRI including diffusion tensor imaging (DTI) sequences to determine regional brain volumes and white matter connectivity.

Results Both positive and negative symptoms were greater in the SZ-dependent group than the other two. Neurocognitive function was broadly similar. The structural brain imaging revealed lateralized changes to the left parietal/temporal lobe, in which regional volumes were smaller in the SZ-dependent than the SZ-non-dependent group. DTI analysis indicated extensive decreases in fractional anisotropy, with parallel increases in radial diffusivity, in the SIP group compared to the SZ-dependent group.

Conclusions These findings reveal both similarities and differences between SIP and schizophrenia. Furthermore, schizophrenia with concurrent stimulant dependence may be associated with a different clinical and neuroanatomical profile as compared to schizophrenia alone.

Keywords Cocaine · Dependence · Methamphetamine · Cognition · PANSS · Psychosis · Schizophrenia · Substance use · MRI · Diffusion tensor imaging

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Introduction

The psychotic disorders represent a cluster of severe psychiatric conditions associated with abnormal perception and thought, in which symptoms are generally typified by both positive (hallucinations, delusions, disorganized thought) and negative (blunted affect, social withdrawal, poor volition) features. Schizophrenia spectrum disorders and stimulant-induced psychosis (SIP) are two distinct forms of psychotic disorder that share many similar symptoms. Schizophrenia likely arises as a consequence of complex interactions between genetic diatheses and early environmental insults, resulting in altered neurodevelopment (Davis et al. 2016;

Lewis and Levitt 2002), whereas SIP occurs as a result of exposure in adulthood to high doses of psychostimulant drugs, such as methamphetamine or cocaine, which may interact with unknown preexisting vulnerabilities (Bramness et al. 2012; Gururajan et al. 2012).

Although SIP is defined by a more transient phenotype, both forms of disorder are associated with a high incidence and severity of positive psychotic symptoms (Panenka et al. 2013; Shelly et al. 2016). While the etiologies remain distinct, the positive symptoms of both disorders are believed to reflect, in part, dysregulation of the mesolimbic dopamine pathway (Laruelle 2000; Ujike 2002). This dopaminergic pathway exists as part of an extensive neural circuit which interacts with many other brain regions (Laviolette 2007), and alterations in numerous parts of this circuit throughout the brain could theoretically lead to downstream dysregulation of dopamine function (Di Forti et al. 2007). It is therefore important to compare different forms of psychosis and determine whether there is a shared, common set of neural pathways that are affected by all psychotic disorders, or whether each form of psychosis is associated with its own pattern of neuroanatomical change. In our recent studies where we compared cocaine-dependent subjects who exhibited SIP to cocaine users who did not experience psychosis, the psychotic group showed both subcortical gray matter alterations (Willi et al. 2016b) and regional decreases in white matter connectivity (Willi et al. 2017) that parallel those reported in schizophrenia, but a direct comparison to subjects with schizophrenia was not performed. Similar alterations have been observed in subjects with methamphetamine associated psychosis (Uhlmann et al. 2016; Vuletic et al. 2018).

A number of previous studies have conducted head-to-head comparisons between schizophrenia and SIP of the symptoms of psychosis, which have provided important information about the types and severity of such symptoms (McKetin et al. 2017; Medhus et al. 2013; Wang et al. 2016; Wilson et al. 2017). However, there is an almost complete absence of neuroimaging studies where these two disorders are directly compared within the same cohort, likely reflecting the challenges of finding subjects with these two distinct forms of psychosis in a shared environment. We are aware of only one study where MRI was used to directly compare these two different types of psychosis, whereby Zhang et al. (2018) compared 16 schizophrenia patients with 17 methamphetamine-induced psychosis patients in an fMRI task, observing differences in regional brain activity between the two groups (and controls).

The aim of the present study was therefore to directly compare subjects with schizophrenia to SIP in a comprehensive manner, using advanced neuroimaging techniques. This was made feasible through our ongoing longitudinal study of a marginalized urban cohort of individuals from Vancouver's Downtown Eastside (Honer et al. 2017; Jones et al. 2018;

Vila-Rodriguez et al. 2013). We compared a group of subjects with SIP to two groups of subjects with schizophrenia—individuals either *with* or *without* stimulant dependence. The schizophrenia group with stimulant dependence served to control for the independent effects of heavy stimulant use (seen in the SIP group) on the brain, which has well-established effects on brain measures (Panenka et al. 2013). All subjects had an extensive clinical and neurocognitive evaluation, which was complemented with structural MRI including diffusion tensor imaging (DTI) scans to determine regional brain volumes and white matter connectivity. Our working hypothesis was that while psychotic symptoms and neurocognition may be comparable between the groups, the neuroanatomical MRI measures would be more compromised in the schizophrenia groups (particularly those with stimulant dependence) as this is a lifelong condition associated with neurodevelopmental alterations.

Material and methods

Study population

All subjects were recruited as a part of an ongoing longitudinal observational cohort study in a marginalized population (Honer et al. 2017; Vila-Rodriguez et al. 2013). Participants were living in single room occupancy hotels in the Downtown East Side of Vancouver, Canada, which represents one of the poorest neighborhoods in the country and is a region associated with high rates of crime and substance use. From this cohort, inclusion criteria were a current diagnosis of schizophrenia *or* stimulant induced psychosis (with concurrent cocaine or methamphetamine dependence, or both). The schizophrenia group included both subjects with or without concurrent cocaine/methamphetamine dependence. Participants were required to be fluent in English, able to provide informed consent, and have completed both a PANSS assessment and brain MRI scan. Exclusion criteria included significant MRI artifacts and gross brain structure abnormalities. Consistent with the Canadian Tri-Council policy, the study was approved by the University of British Columbia Clinical Research Ethics Board. All subjects provided written informed consent and received a modest honorarium for their time.

Measures

Information about demographic variables was collected, including gender, ethnicity, age, and education. Overall physical health was assessed using the Short Form 36 (SF-36) Health Survey, which is a self-administered questionnaire used in diverse patient populations (McHorney et al. 1994). Blood draws were conducted to test for the human immunodeficiency virus (HIV). Nicotine dependence was measured

using the Fagerström test (Fagerström 1978). For diagnosis of neuropsychiatric disorders, records of hospitalization for mental illness were obtained when possible, dating as far back as 50 years. The Mini-International Neuropsychiatric Interview was administered, and it was supplemented by a clinical interview and mental status examination carried out by an experienced psychiatrist (FVR and WGH). All of the clinical information gathered was included to determine psychiatric and substance dependence diagnoses, based on procedures from the Best Estimate Clinical Evaluation and Diagnosis form, adapted in this study to DSM-IV-TR criteria. Psychiatric health and substance use disorders were assessed according to DSM-IV-TR diagnostic criteria, as data collection for the study began before publication of the DSM-5. Drug and alcohol use was recorded by a trained research assistant using the Timeline Follow Back method (TLFB) to assess drug consumption for 7 days before the MRI acquisition (Sobell et al. 1996). We previously reported that this approach showed a strong correlation between self-report and results obtained from a urine drug screen for the major classes of drugs ($\kappa = 0.66\text{--}0.70$; Jones et al. 2013). Psychiatric medication use was recorded, including antipsychotics, antidepressants, mood stabilizers, and benzodiazepines. Psychosis symptom severity was measured using the full 30-item PANSS and analyzed using the five-factor model, as previously applied in marginalized populations (Alexander et al. 2017; Emsley et al. 2003; Willi et al. 2016a).

Neurocognition

To characterize cognition in the subjects, a battery of neuropsychological tests was administered by trained research assistants under the supervision of a registered neuropsychologist (AET), as per previous work (Gicas et al. 2017; Gicas et al. 2014). All neurocognitive tests were conducted within 1 month of the MRI scan, and most were completed on the same day. Tests assessed multiple neurocognitive domains, including verbal learning and memory using the total immediate and delayed recall scores, respectively, from the Hopkins Verbal Learning Test Revised (HVLTR) (Brandt and Benedict 2001); inhibition using the color-word subtest of the Stroop Color-Word Test; sustained attention using the A prime signal detection score from the Rapid Visual Information Processing (RVP) subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Fray et al. 1996); mental flexibility using the total adjusted errors score from the Intra-Extra Dimensional (IED) subtest of the CANTAB (Fray et al. 1996); and affective decision-making measured with the total net score from the Iowa Gambling Task (IGT) (Bechara et al. 1994). Additionally, a measure of acculturation was administered to determine English language fluency.

MRI acquisition

All scanning was performed on a 3 T MRI scanner (Philips Achieva) 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 \times 256 mm, acquisition matrix = 256 \times 250, reconstruction matrix = 256 \times 256, voxel spacing = 1.0 mm \times 1.0 mm \times 1.0 mm, 190 contiguous slices, slice thickness = 1 mm, gap = 0, SENSE = 1, scan duration 443 s.

Diffusion imaging was performed in the same session using the same MRI scanner with the following parameters: 70 continuous slices, 32 directions, acquisition matrix = 100 \times 100, reconstruction matrix = 112 \times 112, voxel spacing = 2.0 \times 2.0 mm, slice thickness = 2.2 mm TE = 60 ms, TR = 6594 ms, FOV = 224 \times 224 mm, flip angle = 90° , SENSE = 2.1, maximum number of gradient orientation = 33, $b = 700$ s/mm².

MRI processing

All T1-weighted images were visually inspected by qualified raters (DJL) for severe motion artifact/MRI abnormalities by a trained specialist. As previously (Panenka et al. 2007; Willi et al. 2016b), 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 resliced in coronal view. 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 gray matter, white matter, and CSF using the default configuration of SPM8 (Ashburner and Friston 2003). A brain mask was then created by collating the CSF, GM, and WM voxel data into shared digital space. Finally, scans underwent non-linear registration to the MNI 152 template by using the FSL FNIRT tool (Jenkinson et al. 2012). Once images were non-linearly coregistered to standard MNI 152 space, scans were batch uploaded for a standard FSL anatomic segmentation pipeline, which is distributed by the developers with the Harvard-Oxford scalable brain atlas (see <https://scalablebrainatlas.incf.org/human/HOA06>). This probabilistic atlas includes 48 cortical zones and 21 subcortical manually selected regions of interest extracted from high-resolution T1-weighted anatomic images from 37 healthy adults. For technical morphological atlas development notes, see Desikan et al. (2006)). Automated brain segmentation is based on the principles of mapping signal densities or intensities into a priori defined pre-labeled anatomic spaces. To create the pre-defined regions of interest, the atlas developers used their multiple normal MRI scans, which are each linearly transformed into stereotaxic space, and intensity-normalized and averaged the signals on a voxel-by-voxel basis. This results in an average-intensity MRI dataset (see Mazziotta et al. 2001) that is used as a normalized labeled template within a standardized anatomic

space of MRI-based brain anatomy. Signal intensity distributions from individual scans are then subjected to Fourier transformation and non-linear coregistration of local anatomic space into standardized labeled anatomic space to define the regions of interest in individuals. The volumes of all possible atlas-based regions of interest are automatically extracted by the software for both hemispheres. For the current study, gray matter areas in the fronto-temporal and fronto-parietal regions were probed, based on previous reports from psychotic populations (see (Iwashiro et al. 2012; Whitford et al. 2006)). We focused on segmented deep gray matter structures with direct relevance to psychosis that we have focused on previously, including the thalami, the hippocampi, and the basal ganglia (Barakauskas et al. 2010; Gicas et al. 2018; Willi et al. 2016b).

Similarly, all DTI images were reviewed for artifacts or abnormalities. The high-resolution DTI data were corrected for eddy current and head motion using affine regression of gradient volumes beginning with $b = 0$ volumes (<http://www.fmrilb.ox.ac.uk/fsl>). Slices that showed extreme intensities were re-estimated using the average of adjacent slices, followed by the averaging of the two slices. Using the Brain Extraction Tool with fractional intensity threshold of 0.3, a brain mask was created. To improve DTI tensor estimation, 3D Slicer was used for DTI fitting, implementing a non-linear least square technique with shifted negative eigenvalue option.

TBSS processing

Using Tract-Based Spatial Statistics (TBSS) (Smith et al. 2006) and the randomize command in FSL version 5.0.11, the DTI metrics of fractional anisotropy (FA), axial diffusivity (AD), medial diffusivity (MD), and radial diffusivity (RD) were compared between SIP subjects, schizophrenia (SZ)-non-dependent, and SZ-dependent subjects, as previously with this cohort (Gicas et al. 2019). Individual FA images were first non-linearly registered onto the John Hopkins University International Consortium Brain Mapping (JHU-ICBM) FA $1 \times 1 \times 1$ mm standard space. An average FA image was then created from the individual FA images and skeletonized to form the mean FA skeleton, thresholded at a standard FA value of 0.25. AD, MD, and RD values were then projected onto the skeleton using the previous FA transformation. Voxel-wise statistics were then performed using the randomize command, covarying for age and sex. Randomize performed 5000 random permutations using a variance smoothing of 2 mm to improve estimation of the variance, and threshold-free cluster enhancement (TFCE) to control family-wise error and correct for multiple comparisons. Implicated neuroanatomical areas were identified using the John Hopkins University ICBM-DTI-81 white-matter atlas (Hua et al. 2008; Mori et al. 2008). The TBSS Fill command was used for ease of visualization of areas implicated in previous analyses.

Analysis

All data were analyzed using IBM SPSS Statistic software version 24 (SPSS Inc., IBM Corp., Armonk, USA). Group differences in clinical and demographic variables were compared using chi-square test, Fisher's exact test, and one-way analysis of variance (ANOVA). Continuous variables were measured for normal distribution using the Shapiro–Wilk test. Non-normal variables were analyzed using the non-parametric Kruskal–Wallis test.

For neurocognitive measures, a series of analyses of covariance (ANCOVAs) was used. The three subject groups were entered as the independent variable, with age and education included as covariates, and a domain-specific cognitive score was included as the dependent variable in each model. The assumptions of equality of variances and homogeneity of regression slopes were examined, and no violations were observed. Simple contrasts were used to examine group differences for a total of three pairwise comparisons for each model. The effect sizes (partial eta squared) for each group comparison are reported.

Group comparisons of brain volumes for regions of interest were analyzed using a one-way ANCOVA adjusted for age and intracranial volume (ICV), with the latter controlling for sex differences. The assumptions of ANCOVA were confirmed. Levene's test was used to check homogeneity of variances along with a screening for significant interaction terms between groups and covariates to assess homogeneity of regression slopes and an examination for outliers was done using Z scores set at ± 3.60 after using a Bonferroni correction based on sample size (Cousineau and Chartier 2010). A Bonferroni post hoc test was used to determine specific group differences. The alpha level was set at 0.05 for most analyses, apart from the regional brain volume analysis, where alpha level was decreased to 0.025 because of the number of multiple comparisons conducted. TBSS analysis was performed as described above (“TBSS processing” section).

Results

Demographics

The present study included a total of 96 participants who met inclusion criteria. Subjects were separated into three groups; 39 with stimulant induced psychosis (with concurrent stimulant dependence), 18 with schizophrenia (*without* stimulant dependence), and 39 with schizophrenia (*with* concurrent stimulant dependence). Demographics are described in Table 1. Participants were typically middle-aged (36.6 ± 1.1 years), with the SZ-non-dependent group being younger than the other two groups ($p < 0.05$). Females were more common in the SIP group than the

two schizophrenia groups ($p < 0.001$). The cohort's education was generally similar between groups, being non-significantly lower in the SIP group. Overall clinical health reported in the SF-36 health survey was good; there were no group differences in HIV infection or use of antiretroviral drugs. Antipsychotic drug use differed between groups ($p < 0.01$), with greater antipsychotic use in the SZ-dependent group than the SIP group ($p < 0.001$). The groups did not differ in use of other psychiatric medications, including antidepressants, mood stabilizers, and benzodiazepines.

Substance use

Polysubstance use was common in this cohort, consistent with previous studies of individuals in other marginalized inner-city populations (Kuramoto et al. 2011; Lecomte et al. 2013; O'Toole et al. 2004). Dependence on alcohol and cannabis was similar across all three groups (Table 1). There was a trend for a group difference in nicotine dependence, but this did not quite achieve significance. For heroin dependence, the SIP group had a significantly higher rate (55.3%) than the SZ-dependent group (17.9%) ($p < 0.05$), although there was no

Table 1 Sociodemographic, clinical, and substance use characteristics of the study population

	SZ-non-dependent ($n = 18$)		SZ-dependent ($n = 39$)		SIP ($n = 39$)		Test statistic ^a	<i>p</i> value
	Mean (SD)	Percent (n/N)	Mean (SD)	Percent (n/N)	Mean (SD)	Percent (n/N)		
Age	30.55 (11.47)		38.51 (10.46)		37.50 (9.80)		3.74	0.027
Gender (F)		22.2% (4/18)		7.7% (3/39)		43.6% (17/39)	13.65	0.001
Ethnicity								
White		77.8% (14/18)		69.2% (27/39)		48.7% (19/39)	7.20	0.117
First Nations		16.7% (3/18)		12.8% (5/39)		16.7% (13/39)		
Other		5.6% (1/18)		17.9% (7/39)		17.9% (7/39)		
Education (years)	11.17 (1.38)		10.77 (1.58)		10.00 (2.00)		5.16	0.076
HIV Positive		7.7% (1/13)		2.7% (1/37)		11.1% (4/36)	2.11	0.308
ARV therapy		5.6% (1/18)		0% (0/39)		7.6% (3/39)	2.99	0.224
FTND	2.29 (2.06)		4.58 (1.95)		4.22 (2.02)		5.94	0.051
SF-36	48.50 (7.68)		47.51 (9.92)		48.11 (9.33)		0.07	0.931
Antipsychotic		33.3% (6/18)		56.4% (22/39)		15.4% (6/39)	14.39	0.001
Antidepressant		5.5% (1/18)		12.8% (5/39)		10.3% (4/39)	0.70	0.705
Mood stabilizer		5.5% (1/18)		0% (0/39)		2.6% (1/39)	1.94	0.379
Benzodiazepine		11/1% (2/18)		10.3% (4/39)		2.6% (1/39)	2.19	0.335
Alcohol dependence		22.2% (4/18)		10.3% (4/39)		15.4% (6/39)	1.58	0.486
Cannabis dependence		61.1% (11/18)		46.2% (18/39)		30.8% (12/39)	4.90	0.100
Cocaine dependence		0.0% (0/18)		66.7% (26/39)		72.0% (28/39)	22.53	0.001
Methamphetamine dependence		0.0% (0/18)		61.2% (24/39)		53.8% (21/39)	15.74	0.001
Heroin dependence		27.8% (5/18)		17.9% (7/39)		55.3% (21/39)	12.07	0.002
Days used prior week								
Alcohol	0.63 (1.78)		0.24 (0.69)		0.86 (1.94)		2.18	0.337
Cannabis	3.63 (3.63)		3.06 (3.03)		1.14 (2.06)		11.82	0.003
Cocaine	0.0 (0.0)		1.21 (2.14)		2.39 (2.94)		13.29	0.001
Methamphetamine	0.13 (0.5)		1.62 (2.22)		1.50 (2.56)		7.46	0.024
Heroin	0.44 (0.964)		2.01 (2.26)		1.53 (2.77)		2.93	0.231
Number of subjects using drug in past week								
Alcohol		22.2% (4/18)		12.8% (5/39)		15.3% (6/39)	2.30	0.351
Cannabis		72.2% (13/18)		72.0% (28/39)		41.0% (16/39)	13.35	0.001
Cocaine		11.1% (2/18)		53.8% (21/39)		69.2% (27/39)	13.67	0.001
Methamphetamine		0.0% (0/18)		53.8% (21/39)		66.7% (26/39)	9.78	0.001
Heroin		22.2% (4/18)		20.5% (8/39)		48.7% (19/39)	6.99	0.03

ARV antiretroviral, FTND Fagerström Test of Nicotine Dependence, SF-36 Short-Form 36

^a Test statistic either refers to F-ratio or chi-squared value; italicized entries represent $p < 0.05$

significant difference in number of days using heroin over the past week between the three groups ($p = 0.23$), based on the results of the TLFB. For other drugs measured by the TLFB, cocaine and methamphetamine use was notably more common in the two groups with stimulant dependence ($p < 0.05$), as would be expected. Cannabis use in the past week was more frequent in the two schizophrenia groups than the SIP group ($p < 0.005$). Number of subjects using the drug in the past week were consistent with the above results.

Psychosis symptom severity

PANSS data were analyzed using the five-factor model shown in Table 2 (Emsley et al. 2003). The positive subscale was non-normally distributed, therefore subject to non-parametric testing. The results indicated a significant group difference in the positive factor ($p < 0.001$), in which the SZ-dependent group's mean (23.18 ± 5.79) was significantly greater than both other groups ($p < 0.05$), and the SZ-non-dependent group's mean (19.89 ± 6.86) was higher than the SIP group (14.46 ± 3.58 ; $p < 0.001$). There was also a group difference ($p = 0.003$) in the negative factor, as the SZ-dependent group (21.68 ± 7.16) had higher mean scores than both the SIP (17.33 ± 5.78 , $p = 0.009$) and SZ-non-dependent (16.41 ± 5.01 , $p = 0.01$) groups. There was a non-significant trend ($p = 0.066$) for a group effect of the "excitement" factor, with scores highest in the SZ-dependent group followed by the SIP group.

Neurocognition

To compare neurocognitive functioning between subjects, scores were analyzed using a series of one-way ANCOVA adjusted for age and education (Table 3). Results of the omnibus test showed a non-significant trend and a medium effect size for the Stroop color-word subtest ($p = 0.072$, $\eta^2 = 0.058$), with the SZ-dependent group performing worse than the SZ-non-dependent group. There was also a non-significant trend with a medium effect size in the IED subtest ($p = 0.076$, $\eta^2 = 0.067$), as the SZ-dependent group performed worse than the SIP group. No other group differences in cognitive performance we observed ($p < 0.05$).

MRI regional brain volumes

The volumetric data were analyzed using a one-way ANCOVA to determine a statistically significant difference between the groups on ROI volumes (listed in Table 4), controlling for age and intracranial volume. As there were multiple group comparisons, a more conservative alpha level of 0.025 was included for significance. The ANCOVA indicated that there were group differences in the left planum temporale (PT) ($p = 0.021$) and the left parietal operculum (PO) ($p =$

0.009), in which the SZ-non-dependent group had a larger mean volume compared to the SZ-dependent group (PT $p = 0.039$; PO $p = 0.008$). There was also a trend for a group effect in the left anterior insula ($p = 0.049$), but this failed to meet the more stringent significance threshold. All other ROIs did not meet significance thresholds.

TBSS—whole brain

The SIP group had significantly ($p = 0.027$) lower FA compared to the SZ-dependent group in the following areas: body of the corpus callosum, splenium of corpus callosum, right cerebral peduncle, right anterior limb of internal capsule, right posterior limb of internal capsule, bilateral retrolenticular part of internal capsule, right anterior corona radiata, bilateral superior corona radiata, bilateral posterior corona radiata, bilateral posterior thalamic radiation, bilateral sagittal stratum, right external capsule, left cingulate gyrus, left hippocampus, bilateral superior longitudinal fasciculus, right uncinate fasciculus, and bilateral tapetum. A sample of TBSS for FA is available in Fig. 1.

The SIP group had higher RD compared to the SZ-dependent group ($p = 0.045$) in the following areas (Fig. 2): body of corpus callosum, splenium of corpus callosum, right retrolenticular part of internal capsule, right superior corona radiata, right posterior corona radiata, right posterior thalamic radiation, right sagittal striatum, right tapetum. A sample of the TBSS for RD is presented in Fig. 2. The SZ-non-dependent group did not differ from either of the two other groups with regard to FA or RD values. There were no differences present between groups in axial diffusivity, mean diffusivity, or white matter tract volume.

In exploratory analyses, the whole brain TBSS analyses for FA and RD values were reanalyzed using both heroin dependence and antipsychotic drug use as covariates, as the three groups differed significantly on these important variables. Addition of heroin dependence as a covariate did not affect results, as the FA values remained significantly greater in the SZ-dependent group than the SIP group, while RD values showed the opposite effect, consistent with the primary analysis. However, when antipsychotic drug use was included as a covariate (either with or without heroin dependence as a covariate) the difference between the two groups was no longer significant for either FA or RD values (both $p = 0.11$).

Correlations between neurocognition, psychosis, and brain measures

To determine if there were potential relationships between neurocognitive measures, scores on the PANSS, and the neuroanatomical indices provided by the structural and DTI scans, we correlated results from the key findings (Table 5). These included the cognitive measures of inhibition and

Table 2 Five-factor PANSS scores

	SZ-nondependent (<i>n</i> = 18) Mean (SD)	SZ-dependent (<i>n</i> = 39) Mean (SD)	SIP (<i>n</i> = 39) Mean (SD)	<i>F</i> value	<i>p</i> value
PANSS Positive	19.89 (6.86)	23.18 (5.79)	14.46 (3.58)	35.36	< 0.0005
PANSS Negative	16.41 (5.01)	21.68 (7.16)	17.33 (5.78)	6.31	0.003
PANSS Disorganized	13.38 (4.13)	17.26 (5.59)	16.76 (16.69)	0.76	0.472
PANSS Anxiety Depression	14.00 (4.61)	13.41 (4.01)	13.19 (4.18)	0.24	0.784
PANSS Excitement	7.22 (3.13)	9.41 (4.05)	8.10 (2.95)	2.81	0.066

Italicized entries represent $p < 0.05$

mental flexibility, the PANSS positive and negative subscales from the 5-factor model, individual FA values using the top 5 tracts from the whole-brain TBSS analysis that showed group differences in FA in at least 10% of the total tract volume, and finally the three brain regional volume from the T1 scan which showed group differences. Results are presented for each group individually and all groups combined.

Overall, correlations differed between groups, although there were some general trends. As a whole, within-domain correlations were higher, as PANSS positive and negative scores correlated quite strongly, while FA values correlated more strongly with each other than alternate measures, as did regional brain volumes. Both cognitive domains were notably more strongly correlated (negatively) with PANSS negative than PANSS positive scores. Group differences were evident in the associations between cognitive and psychosis scores, and FA values and regional brain volumes. The SZ-non-dependent group showed strong correlations between cognitive inhibition and FA values in all 5 tracts, and mental flexibility with 2 white matter tracts. Correlations were weaker between cognition and regional brain volumes, and there were few meaningful correlations between PANSS scores and brain measures. Interestingly, the SZ-dependent group did not exhibit the same strong correlations between cognition and FA values, and associations between PANSS scores and brain measures were also generally lower. The SIP exhibited

correlations for cognition/PANSS scores and brain measures approximately in between the two schizophrenia groups.

Discussion

In the present study, we directly compared two different types of psychotic disorder with a comprehensive battery of clinical, neurocognitive, and neuroanatomical measures. This included one group of subjects with SIP (and concurrent stimulant dependence) and two different groups with schizophrenia (either with or without concurrent stimulant dependence). As all groups were recruited from the same environment, they shared most of the same environmental variables (including high infection rates, poverty, homelessness, exposure to violence, limited formal education, other substances of abuse, etc.) that could represent major confounds otherwise. General physical health and infectious disease was comparable between the groups. Recent drug use also did not differ except for cannabis, which was more frequent in the two schizophrenia groups, and the psychostimulant drugs cocaine and methamphetamine, which were used much more often in the two groups with stimulant dependence. Interestingly, the groups differed significantly in the severity of their psychotic symptoms. Both positive and negative symptoms were notably greater in the

Table 3 Characterization of neurocognitive function

Test	SZ-non-dependent (<i>n</i> = 18) Mean (SD)	SZ-dependent (<i>n</i> = 39) Mean (SD)	SIP (<i>n</i> = 39) Mean (SD)	<i>F</i> value	<i>p</i> value	Partial eta-squared
Stroop color-word (inhibition)	42.12 (10.54)	33.13 (11.45)	36.79 (10.71)	2.707	0.072	0.058
HVLT-R immediate recall (verbal learning)	22.73 (8.25)	18.45 (6.03)	19.89 (5.55)	1.392	0.254	0.031
HVLT-R delayed recall (verbal memory)	7.60 (3.58)	6.11 (2.83)	6.24 (2.98)	0.363	0.679	0.009
IGT total net score (decision-making)	2.93 (24.33)	− 11.52 (31.56)	− 6.80 (39.71)	0.493	0.613	0.013
RVP (sustained attention)	0.872 (0.050)	0.864 (0.064)	0.857 (0.059)	0.022	0.978	0.001
IED (mental flexibility)	− 1.42 (0.377)	− 1.70 (0.361)	− 1.56 (0.326)	2.673	0.076	0.067

HVLT Hopkins Verbal Learning Test Revised, IGT Iowa Gambling Task, RVP Rapid Visual Information Processing, IED Intra-Extra Dimensional Set Shift

Table 4 Regional Brain volumes

Region of interest	Hemisphere	SZ-non-dependent (<i>n</i> = 18) Mean (SE) (mm ³)	SZ-dependent (<i>n</i> = 39) Mean (SE) (mm ³)	SIP (<i>n</i> = 39) Mean (SE) (mm ³)	<i>F</i>	<i>p</i> value
Inferior temporal gyrus	R	13,407.03 (264.13)	12,919.72 (174.97)	13,247.19 (176.33)	1.48	0.233
	L	12,657.26 (222.17)	12,188.99 (147.18)	12,487.96 (148.32)	1.86	0.161
Middle frontal gyrus	R	21,348.53 (523.16)	20,430.83 (346.57)	20,954.41 (349.27)	1.21	0.304
	L	21,714.59 (492.40)	20,479.25 (326.20)	21,247.09 (328.74)	2.59	0.080
Middle temporal gyrus	R	16,461.42 (344.26)	16,462.63 (228.13)	16,850.51 (229.90)	0.939	0.395
	L	15,225.68 (354.93)	15,727.56 (229.17)	15,860.79 (230.95)	1.15	0.321
Planum temporale	R	2319.87 (95.35)	2328.84 (63.17)	2292.43 (63.66)	0.084	0.919
	L	2565.14 (107.06)	2237.93 (70.92)	2454.61 (71.47)	4.02	<i>0.021</i>
Superior temporal gyrus	R	8259.07 (214.35)	8003.59 (142.00)	8262.05 (143.12)	0.959	0.387
	L	8271.41 (219.87)	7710.63 (145.66)	7981.88 (146.79)	2.38	0.098
Hippocampus	R	3780.31 (77.55)	3795.66 (51.37)	3854.46 (51.77)	0.446	0.642
	L	3659.45 (76.57)	3656.51 (50.72)	3680.54 (51.12)	0.060	0.942
Amygdala	R	1083.59 (22.32)	1085.40 (14.79)	1085.61 (14.90)	0.003	0.997
	L	1100.44 (21.77)	1081.76 (14.42)	1090.50 (14.53)	0.267	0.767
Parietal operculum	R	2564.32 (111.26)	2256.32 (73.71)	2401.71 (74.28)	2.78	0.067
	L	3255.47 (126.82)	2781.70 (84.01)	2981.01 (84.66)	4.93	<i>0.009</i>
Anterior insula	R	4598.34 (80.21)	4727.31 (53.14)	4807.77 (53.55)	2.30	0.106
	L	4711.20 (102.46)	4782.00 (67.88)	4979.47 (64.40)	3.11	0.049

Italicized entries represent $p < 0.05$

SZ-dependent group than the other two groups, and there was a non-significant trend for greater scores on the excitement factor in this group too. Neurocognitive function was broadly

similar between groups for most cognitive domains. However, there were notable group differences observed with both of the neuroimaging modalities. The structural brain imaging

Fig. 1 TBSS differences in fractional anisotropy between the SIP and SZ-dependent groups. A series of axial slices highlighting areas of significant decrease in FA between the SIP vs SZ-dependent groups. Images are in MRI space. Red indicates a minimum significant difference ($p = 0.05$) progressing to yellow indicating an increased difference ($p < 0.05$)

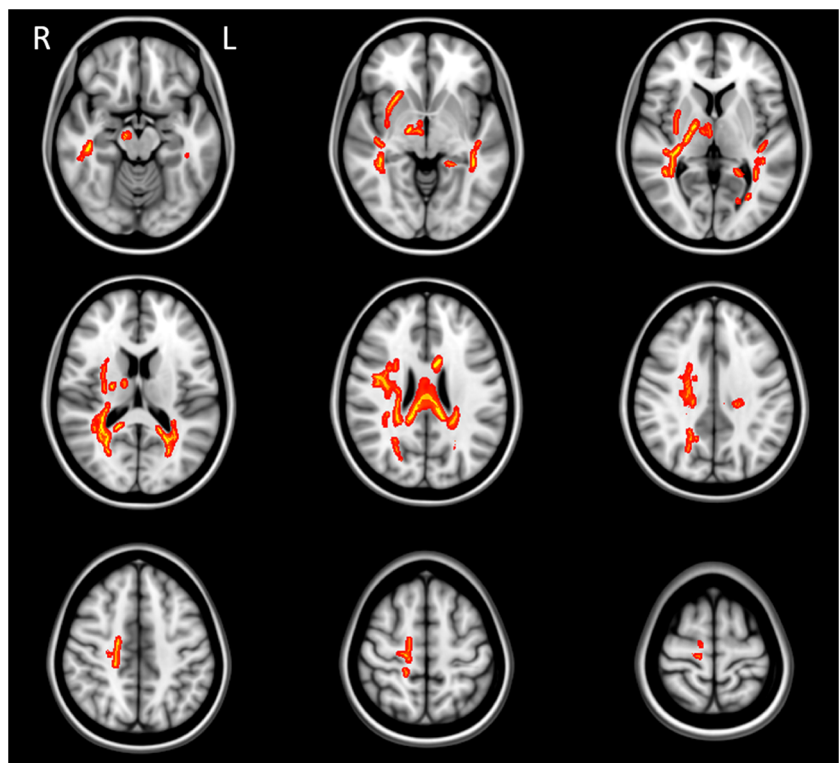
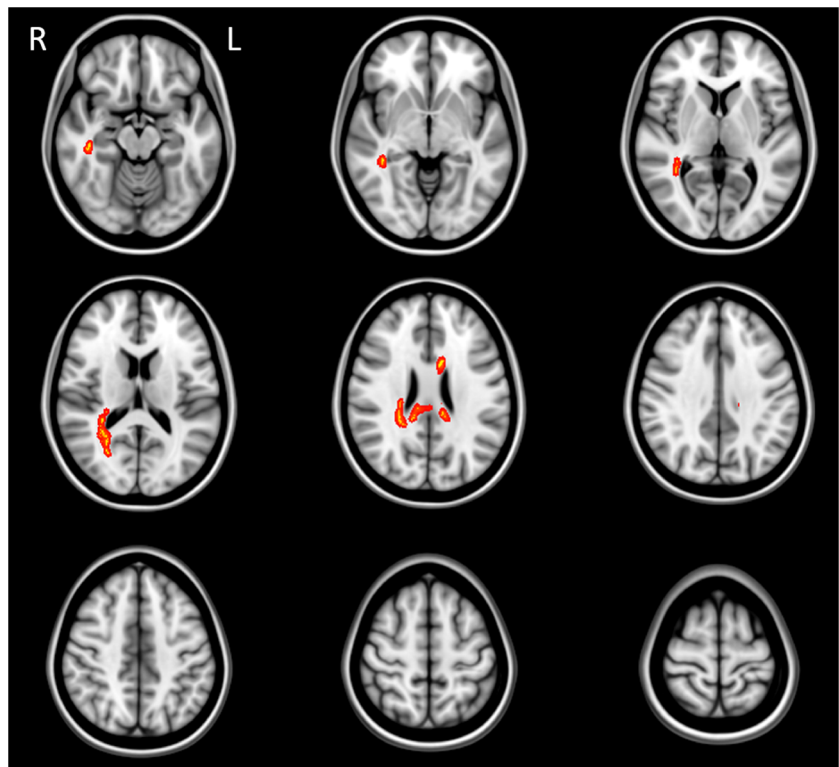


Fig. 2 TBSS differences in radial diffusivity between the SIP and SZ-dependent groups. A series of axial slices highlighting areas of significant decrease in RD between the SIP vs SZ-dependent groups. Images are in MRI space. Red indicates a minimum significant difference ($p = 0.05$) progressing to yellow indicating an increased difference ($p < 0.05$)



revealed lateralized changes to the left parietal/temporal lobe, in which regional volumes were smaller in the SZ-dependent than the SZ-non-dependent group. Diffusion tensor imaging analysis indicated extensive decreases in fractional anisotropy, with parallel increases in radial diffusivity, in the SIP group compared to the SZ-dependent group. An exploratory analysis of the correlations between cognition, PANSS scores and brain measures indicated both general trends across groups, as well as marked group differences. Correlations between cognitive measures of inhibition or mental flexibility and white matter FA values were high for multiple tracts for the SZ-non-dependent group, slightly less so for the SIP group, and least of all for the SZ-dependent group.

The current findings significantly extend our knowledge about the similarities and differences between these two forms of psychotic disorder, particularly with regard to individuals who live in marginalized conditions. To date, a number of studies have compared the symptoms of psychosis between SIP (or related conditions such as methamphetamine associated psychosis (MAP) (Alam Mehrjerdi et al. 2013)) and schizophrenia. Several of these studies have focused on qualitative differences in symptoms (McKetin et al. 2017), such as the presence of first rank symptoms (Shelly et al. 2016). This was beyond the scope of the present study, as our primary interest was in symptom severity. Of relevance, a Norwegian hospital inpatient study (Medhus et al. 2013) measured psychosis using the PANSS positive subscale, and observed no difference in

scores between psychotic methamphetamine users and schizophrenia patients who had not used methamphetamine, with PANSS positive group mean scores ranging between 22.8 and 23.5; negative symptoms were not measured. In our study, the SZ-dependent group exhibited greater PANSS positive scores (23.2 ± 6) than the other two groups, with a mean similar to those in the Norwegian study—indicating that their positive symptoms may be comparable in severity to inpatients who had recently been hospitalized for psychosis. The most likely explanation for the greater positive symptoms in the SZ-dependent than the non-dependent group is the additive effects of idiopathic psychosis combined with heavy psychostimulant use, each of which independently contributes to psychosis (McKetin et al. 2013; Sara et al. 2014). It is worth considering, though, that a recent study observed that methamphetamine use increased the positive, affective and psychomotor symptoms in subjects with a lifetime primary psychotic disorder, but did not increase negative symptoms (McKetin et al. 2016). In our study, negative symptoms were notably greater in the SZ-dependent than the SZ non-dependent group, suggesting that additional explanations should be considered. These include the possibility that the SZ-dependent group could be a more severely mentally ill group, independent of drug use, which would be consistent with the greatest use of antipsychotic drugs in this group. Additionally, it has been posited that individuals with schizophrenia who have more severe

Table 5 Correlations between cognition, PANSS scores, and brain measures in the three groups separately and all groups combined

	1	2	3	4	5	6	7	8	9	10	11	12
Schizophrenia-non-dependent group (<i>n</i> = 18)												
1. Inhibition	1.000	0.440	−0.235	0.326	0.569*	0.562*	0.596*	0.546*	0.706*	0.207	0.345	0.368
2. Mental flexibility		1.000	−0.209	−0.213	−0.004	0.492 ^t	0.335	−0.004	−0.014	−0.220	0.212	0.057
3. PANSS negative			1.000	0.322	0.101	−0.094	0.179	0.442 ^t	0.070	−0.083	−0.286	0.247
4. PANSS positive				1.000	0.190	0.242	−0.096	0.278	0.240	0.288	−0.151	0.717*
5. Retrolenticular part of internal capsule (R)					1.000	0.400	0.666*	0.779**	0.921**	−0.189	−0.274	0.201
6. External capsule (R)						1.000	0.497 ^t	0.219	0.436 ^t	−0.236	−0.177	0.334
7. Tapetum (R)							1.000	0.548*	0.737*	−0.118	0.042	−0.106
8. Sagittal stratum (R)								1.000	0.768*	−0.356	−0.421	0.112
9. Posterior thalamic radiation (R)									1.000	−0.049	−0.088	0.148
10. Planum temporale (L) volume										1.000	0.717*	0.380
11. Parietal operculum (L) volume											1.000	−0.033
12. Anterior insula (L) volume												1.000
Schizophrenia-dependent group (<i>n</i> = 39)												
1. Inhibition	1.000	0.240	−0.330*	0.151	−0.222	0.125	−0.057	−0.196	−0.106	0.043	−0.111	0.053
2. Mental flexibility		1.000	−0.187	0.110	0.120	0.135	−0.050	0.004	−0.091	0.075	0.302 ^t	−0.040
3. PANSS negative			1.000	0.295 ^t	0.042	0.183	0.277	0.138	−0.123	−0.033	−0.057	−0.095
4. PANSS positive				1.000	−0.016	0.130	−0.192	−0.361*	−0.265	−0.111	−0.075	−0.102
5. Retrolenticular part of internal capsule (R) FA					1.000	0.210	−0.190	0.405*	0.665**	−0.177	−0.027	−0.167
6. External capsule (R) FA						1.000	0.277	0.076	−0.024	−0.064	−0.072	−0.097
7. Tapetum (R) FA							1.000	0.052	0.083	0.063	0.027	−0.151
8. Sagittal stratum (R) FA								1.000	0.338*	−0.191	−0.072	−0.112
9. Posterior thalamic radiation (R) FA									1.000	0.158	0.002	0.106
10. Planum temporale (L) volume										1.000	0.635**	0.469*
11. Parietal operculum (L) volume											1.000	0.352*
12. Anterior insula (L) volume												1.000
Stimulant-induced psychosis group (<i>n</i> = 39)												
1. Inhibition	1.000	0.278	−0.330*	−0.003	0.270	0.335 ^t	0.302 ^t	0.329 ^t	0.342*	0.027	−0.078	0.023
2. Mental flexibility		1.000	−0.242	0.138	0.064	−0.124	0.256	0.044	0.165	0.223	0.258	0.264
3. PANSS negative			1.000	0.335*	0.016	−0.050	−0.103	−0.178	−0.097	−0.021	−0.080	0.089
4. PANSS positive				1.000	0.146	0.243	0.349*	0.049	0.189	0.024	−0.102	0.180
5. Retrolenticular part of internal capsule (R) FA					1.000	0.664**	0.621**	0.705**	0.818**	0.258	0.278	0.238
6. External capsule (R) FA						1.000	0.509*	0.578**	0.513*	0.141	−0.027	0.148
7. Tapetum (R) FA							1.000	0.544*	0.726**	0.204	0.074	0.079
8. Sagittal stratum (R) FA								1.000	0.772**	0.013	−0.076	−0.099
9. Posterior thalamic radiation (R) FA									1.000	0.304 ^t	0.219	0.149
10. Planum temporale (L) volume										1.000	0.766**	0.457*
11. Parietal operculum (L) volume											1.000	0.272 ^t
12. Anterior insula (L) volume												1.000
Combined groups (<i>n</i> = 96)												
1. Inhibition	1.000	0.353*	−0.387**	0.033	0.101	0.182 ^t	0.163	0.101	0.207 ^t	0.133	0.075	0.082
2. Mental flexibility		1.000	−0.277*	−0.019	0.096	0.004	0.130	0.016	0.060	0.131	0.332*	0.094
3. PANSS negative			1.000	0.402**	0.066	0.151	0.144	0.090	−0.026	−0.114	−0.183 ^t	0.032
4. PANSS positive				1.000	0.241*	0.336*	0.189 ^t	0.135	0.200 ^t	−0.026	−0.122	0.143

Table 5 (continued)

	1	2	3	4	5	6	7	8	9	10	11	12
5. Retrolenticular part of internal capsule (R)					1.000	0.524**	0.437**	0.667**	0.813**	0.058	0.109	0.114
6. External capsule (R)						1.000	0.478**	0.444**	0.382**	−0.017	−0.098	0.079
7. Tapetum (R)							1.000	0.455**	0.575**	0.093	0.051	−0.008
8. Sagittal stratum (R)								1.000	0.677**	−0.107	−0.123	−0.035
9. Posterior thalamic radiation (R)									1.000	0.186 [†]	0.100	0.151
10. Planum temporale (L) volume										1.000	0.725**	0.423**
11. Parietal operculum (L) volume											1.000	0.223*
12. Anterior insula (L) volume												1.000

[†] $p < .10$; * $p < .05$; ** $p < .001$

negative symptoms are at a greater risk of substance use, reflecting an attempt to self-medicate with drugs (Potvin et al. 2006); further longitudinal study with this cohort will be needed to determine if this possibility may be true.

Cognitive performance between the three groups indicated relatively more subtle differences. Group effects in the omnibus tests did not achieve significance for any of the cognitive domains, with non-significant trends with medium effect sizes for inhibition and mental flexibility, which are both frontally mediated components of executive functioning, in which SZ-dependent group performed worse than the SZ-non-dependent and SIP groups respectively. In schizophrenia, neurocognitive impairment typically correlates more strongly with negative than other symptoms (Bowie and Harvey 2005), consistent with our findings in the present study too, where PANSS negative scores were correlated more strongly with cognitive measures than PANSS positive scores. As negative symptoms were greatest in the SZ-dependent group, this may explain why there was evidence for slightly worse cognition in two domains in this group. For the two schizophrenia groups, the present findings are largely consistent with the results of the CATIE study, which observed no major differences in cognition between schizophrenia subjects with substance abuse versus non-use for cannabis, cocaine, and methamphetamine (Bahorik et al. 2014). It is of interest that cognitive performance between the SIP and SZ-non-dependent groups did not differ significantly, given that cognitive impairment in schizophrenia is at the core of the disorder (Elvevag and Goldberg 2000). The limited number of studies that have directly compared neurocognitive function between schizophrenia and MAP have observed that both conditions are associated with equally severe impairments across a broad range of cognitive domains (Ezzatpanah et al. 2014; Jacobs et al. 2008). It has been suggested that this may reflect a shared dysfunction of both frontal and temporal lobes (Wearne and Cornish 2018), which are recruited in performing many standard neurocognitive tests. Our neurocognitive results are

therefore consistent with the literature, and add to current knowledge by noting that schizophrenia with concurrent stimulant dependence may not substantially exacerbate cognitive deficits further, in contrast to positive symptoms.

The structural neuroimaging data revealed several differences between the SZ-dependent and SZ-non-dependent groups. Both the left planum temporale and left parietal operculum were smaller in the SZ-dependent group. As noted above, this could potentially reflect the effects of greater drug use in the SZ-dependent group, or the possibility that these subjects have a more severe primary psychotic disorder than the non-dependent group, based on greater negative symptoms. While psychostimulant drugs have well-characterized effects on regional brain volumes (Barr et al. 2006; Berman et al. 2008), we are not aware of any studies where these two regions were uniquely affected, as anatomical changes are typically more diffuse, and often prominent in regions that receive a dense dopaminergic input (Panenka et al. 2013), which the planum temporale and parietal operculum do not. By contrast, both brain regions exhibit a decreased volume in schizophrenia (Csemansky et al. 2008; Douaud et al. 2007; Ohi et al. 2016), with the left planum temporale being specifically affected (Ratnanather et al. 2014; Vita et al. 2012), indicating the reasonable possibility that group differences may be related to their primary psychotic disorder. Given that the current regional differences were both defined and lateralized, it will be important to determine in future studies, where schizophrenia stimulant users are compared to non-users, whether such changes reflect neurodevelopmental or neurotoxic effects.

The most striking neuroanatomical finding was with the DTI sequence, in which the SIP group unexpectedly exhibited an extensive global decrease in FA values, with a corresponding increase in RD, compared to the SZ-dependent group. White matter microstructural organization can be estimated using DTI, which measures the directionality of water diffusion within tissue to infer structural characteristics (Ellison-Wright and Bullmore 2009). In white matter, water diffuses

more easily along—rather than across—the fiber tract axis, resulting in anisotropic diffusion. The most common index for quantifying anisotropy is with FA, while RD reflects the total diffusion perpendicular to the main fiber axis, and is thought to be sensitive to membrane permeability, with increases in RD reflecting deficits in myelin integrity (Song et al. 2003). The decreases in FA and increases in RD in the SIP group are therefore consistent with a reduction in white matter integrity, compared to the SZ-dependent group. Changes in FA and RD have been reported in previous studies of both stimulant abuse (Tang et al. 2015; Tobias et al. 2010; van Son et al. 2016) and schizophrenia (Kubicki and Shenton 2014), although we are not aware of any studies that have compared the two directly. Given that idiopathic psychosis and heavy stimulant use would appear to represent independent risk factors for decreased FA and increased RD, it was unexpected that the SIP group exhibited significantly greater white matter deficits than the SZ-dependent group. One possible explanation may be related to greater heroin dependence in the SIP group. While the two groups were generally evenly matched on substance use, the SIP group had a higher rate of heroin dependence (even though use did not differ over the last month), and lifetime heroin use has been associated with lower FA values (Wollman et al. 2015). Alternately, antipsychotic drug treatment was much more common in the SZ-dependent than the SIP group. A recent study in schizophrenia noted that FA values were lower in subjects who had never received antipsychotic drug treatment compared to those who had (Xiao et al. 2018), while another study noted an increase in FA values in previously antipsychotic-naïve schizophrenia patients after antipsychotic treatment and alleviation of psychosis (Serpa et al. 2017), suggesting that antipsychotics may have neuroprotective effects on white matter pathways in psychosis. In our exploratory analyses, when both heroin dependence and antipsychotic drug use were included as covariates in the whole brain TBSS analysis, heroin dependence did not affect group differences in FA or RD values, consistent with a recent study (Uhlmann et al. 2016). However, covarying for antipsychotic drug use resulted in the loss of significance between the SIP and SZ-dependent groups for both FA and RD values, indicating that antipsychotics may be affecting white matter integrity. While the effects of antipsychotic drug treatment on stimulant-induced decreases in white matter FA remain unknown, the present study provides indirect but tantalizing evidence that antipsychotics might be neuroprotective in subjects with SIP, and treatment with such agents could help maintain the health of white matter pathways in the brain. Clearly, further study is required to address this potentially important possibility.

A limitation of this study is that we did not include a stimulant-naïve control group without a primary psychotic disorder, as such individuals are almost non-existent in this cohort. While the absence of such a control group would not

change the observed group differences, it would be of interest to determine the magnitude of deficits compared to the normal population. However, a stimulant-naïve non-psychotic control group would likely not be matched on the multitude of other environmental factors inherent to being part of a marginalized population, and thus make separation of the effects of stimulant drugs and/or idiopathic psychosis from other environmental effects on the brain not feasible. Indeed, many of these variables are more common among people with mental illness, and so the current groups are well matched to avoid potential compounds that can occur when comparing to the general population (Wilson et al. 2016). However, the present study could have benefitted from including a group with stimulant dependence who were not psychotic. This would have controlled for both drug exposure and many of the other environmental variables for the two groups (SIP and SZ-dependent) with stimulant dependence, in a manner similar to our previous studies comparing cocaine users with psychosis to non-psychotic cocaine users (Willi et al. 2017). It would not, though, be as informative a comparison group for the schizophrenia group without stimulant dependence. A second limitation is that not all subjects with dependence had used psychostimulant drugs in the past week, and previous studies have shown that altered brain network connectivity is related to recency of drug use in methamphetamine psychosis (Ipser et al. 2018). Future studies should address this issue if possible.

In conclusion, the present study is the first to directly compare SIP to two groups with schizophrenia, including those with or without stimulant dependence, to control for heavy drug use. The SZ-dependent group showed more severe positive and negative symptoms, and smaller volumes versus the SZ-nondependent group in two brain regions. The SIP group exhibited the least severe psychotic symptoms, yet had the lowest FA values, with a clear decrease in white matter integrity compared to the SZ-dependent group. Overall, these findings indicate that while the neurocognitive phenotypes do not appear to differ substantially between both forms of psychosis, symptom severity and brain neuroanatomy do, and that concurrent stimulant use in schizophrenia may be an important modifier to consider in future studies.

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Compliance with ethical standards

Conflict of interest Drs. Gicas, Lang, Panenka, Rauscher, Vila-Rodriguez, and Barr report no competing interests. Mr. Alexander and Ms. Wong, Chan and Jones 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

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