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IMPACT OF SUBSTANCE USE DISORDER ON GRAY MATTER VOLUME IN SCHIZOPHRENIA

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Abstract

Substance use may confound the study of brain structure in schizophrenia. We used voxel-based morphometry (VBM) to examine whether differences in regional gray matter volumes exist between schizophrenia patients with (n=92) and without (n=66) clinically significant cannabis and/or alcohol use histories compared to 88 healthy control subjects. Relative to controls, patients with schizophrenia had reduced gray matter volume in the bilateral precentral gyrus, right medial frontal cortex, right visual cortex, right occipital pole, right thalamus, bilateral amygdala, and bilateral cerebellum regardless of substance use history. Within these regions, we found no volume differences between patients with schizophrenia and a history of cannabis and/or alcohol compared to patients with schizophrenia without a clinically significant substance use history. Our data support the idea that a clinically meaningful history of alcohol or cannabis use does not significantly compound the gray matter deficits associated with schizophrenia.

Keywords

voxel-based morphometry; psychosis; substance use disorders; alcohol; cannabis

1. Introduction

Comorbid substance use disorders are highly prevalent in individuals with schizophrenia spectrum psychotic disorders and are associated with increased mortality, decreased treatment compliance, and worse outcomes (Ascher-Svanum et al., 2006; Hjorthøj et al., 2015; Moore et al., 2012; Nesvåg et al., 2015; Volkow, 2009). It has been well documented that in schizophrenia there are gray matter deficits in multiple regions including the medial frontal gyrus, temporal cortex, insula, cingulate cortex, thalamus, hippocampus, and amygdala (Ellison-Wright and Bullmore, 2010; Shepherd et al., 2012; Van Erp et al., 2016). Substance use disorder comorbidity may be an important confound in investigations of the

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neurobiological basis of schizophrenia, since both illnesses are independently associated with changes in brain structure (Thoma and Daum, 2013; Van Haren et al., 2013; Weinberger and Radulescu, 2016).

Cannabis and alcohol are among the most frequently misused substances in schizophrenia (Nesvåg et al., 2015). Meta-analyses have revealed that many of the regions implicated in the pathophysiology of schizophrenia also show volume deficits in individuals with alcohol and cannabis use disorders who do not have psychosis. In non-psychotic individuals with alcohol use disorder, gray matter reductions have been identified in the dorsolateral prefrontal cortex, anterior cingulate cortex, temporal gyrus, insula, precentral gyrus, thalamus, hippocampus, and striatum (Xiao et al., 2015). Additionally, multiple previous studies have shown that greater atrophy in these regions is significantly associated with the severity of alcohol consumption (Yang et al., 2016). The effects of cannabis use on brain structure are more variable than those observed with alcohol use disorders, but increased severity of cannabis use is associated with greater structural changes in the hippocampus, prefrontal cortex, amygdala, insula, cerebellum, and striatum (Lorenzetti et al., 2016). Decreased hippocampal volume is the most consistently found structural alteration in cannabis users relative to non-users, with a medium effect size (Rocchetti et al., 2013). Current evidence suggests that alcohol and cannabis use disorders produce partially overlapping effects on the brain and the extent of changes in brain structure depends on the severity of use in non-psychotic individuals.

The extant literature comparing schizophrenia patients with and without a history of substance use has thus far not resolved whether substance use serves as a confound in studies of brain volume in schizophrenia. Some studies have found greater volume deficits due to substance use in both overall gray matter and specific brain regions, including the amygdala, hippocampus, cerebellum and cingulate cortex, while others have found no evidence for such differences (Malchow et al., 2013a; Thoma and Daum, 2013). Critically, only two previous studies have used whole brain, voxel based morphometry (VBM) to examine the effect of substance use on brain structure in schizophrenia. These studies are particularly relevant for examining the question of whether typical studies of brain volume in schizophrenia are confounded by the effects of comorbid substance use. Haller et al. (2013) reported no significant differences in gray matter volume between first episode psychotic disorder patients with and without comorbid cannabis use. In contrast, an earlier study by (Schiffer et al., 2010) found decreased gray matter volume in the anterior cingulate, frontopolar, and superior parietal cortices in a comparison of schizophrenia patients with and without a history of alcohol dependence. Most previous studies in this area have examined cortical thickness or used restricted region of interest analyses focused on determining whether specific brain structures are impacted by alcohol or cannabis use in schizophrenia (Supplementary Table 1).

The substances commonly misused by patients with schizophrenia can directly impact the very brain regions thought to be affected by disease processes in psychosis. Although current substance abuse or dependence may be an exclusionary criterion for many studies of brain structure in schizophrenia, a history of substance misuse often is not. VBM is a frequently used measure of identifying changes in brain structure in schizophrenia

(Shepherd et al., 2012). Yet, as outlined above, there is a paucity of studies directly examining how substance abuse or dependence affects gray matter volume as measured by VBM. Additionally, many of the studies that have examined volumetric changes related to substance use in schizophrenia have had small sample sizes (average total patient sample size N= 51, range = 17–165; Supplementary Table 1). The possibility exists that previous null findings were underpowered to detect a true effect or, alternatively, those studies with a positive finding were also underpowered but have overestimated the size of an effect (Button et al., 2013).

Here, we test the hypothesis that substance use significantly confounds the study of brain volume in schizophrenia using standard VBM analysis in a large sample of 158 schizophrenia patients well matched on all factors except history of alcohol and cannabis use. In this way, we hope to address the discrepancies in previous studies that were potentially due to low statistical power and variable analysis methods. We are interested in understanding whether the signature of changes in brain structure produced by psychosis are muddied by substance use, rather than asking how substance misuse impacts the brain in the same way with or without a comorbid psychotic disorder diagnosis. We first validate the established pattern of gray matter deficits in schizophrenia compared to healthy controls in multiple cortical and subcortical regions and show that volume deficits observed in our sample are consistent with prior literature. Critically, we then show that within these regions a history of substance use disorder comorbidity is not associated with greater deficits in gray matter volume.

2. Methods

2.1 Participants

Participants included 158 patients with a schizophrenia spectrum disorder (65 schizophrenia, 36 schizoaffective disorder, and 57 schizophreniform disorder) with and without clinically significant substance use histories, and 88 healthy control participants (Table 1) from an ongoing data repository at Vanderbilt University Medical Center, the Psychiatric Genotype/Phenotype Project (PGPP). Having a clinically significant substance use history was operationally defined as meeting criteria for a lifetime DSM-IV-TR diagnosis of alcohol or cannabis abuse or dependence. Patients in the repository with diagnoses of abuse or dependence of other substances were excluded from the present analysis. Of those who were included, 92 patients had significant substance use histories and 66 did not. None of the healthy control subjects had significant substance use histories.

Schizophrenia spectrum disorder patients were recruited from the inpatient unit and outpatient clinic of Centerstone and of Vanderbilt Psychiatric Hospital, and healthy control subjects were recruited through community advertisements, to contribute to the PGPP repository. The Vanderbilt University Institutional Review Board (Nashville, TN) approved the study protocol. All participants provided written informed consent to take part in the study and received monetary compensation for their time. Exclusion criteria for all participants included presence of significant head injury, major medical illnesses, pregnancy, pre-morbid IQ less than 75 as estimated by the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001), and current substance abuse or dependence within the past month at the

time of study enrollment. Inclusion criteria for patients required a diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder, assessed with the Structured Clinical Interview for DSM-IV, TR (SCID) (First et al., 1995). Additional inclusion criteria for healthy control subjects required a lack of past or present psychiatric diagnoses, as confirmed by the SCID. Participants were also assessed for clinical and cognitive functioning with the Global Assessment of Functioning (GAF) scale (DSM-IV, TR), the 17-item Hamilton Depression (HAM-D) rating scale (Hamilton, 1960), the Young Mania Rating Scale (YMRS) (Young et al., 1978), the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and the Screen for Cognitive Impairment in Psychiatry (SCIP) (Purdon, 2005). Additionally, patient medication status was assessed through structured interview and medical record review and chlorpromazine equivalents were calculated for all patients who were currently taking an antipsychotic (Gardner et al., 2010). Patients with a history of substance use disorder had higher mania symptoms and higher positive symptoms compared to patients without such history, but the patient groups were well matched on all other demographic, clinical, and cognitive factors measured (Table 1).

2.2 Sample selection

From the PGPP data repository, we selected all patients with a schizophrenia spectrum disorder diagnosis who had structural MRI data of appropriate quality for VBM analysis (n = 158). Next, out of all 158 healthy controls in the same repository, we selected 100 controls with structural MRI data who matched the race, sex, mean age, and mean parental education of our patient sample by removing 58 controls whose demographic characteristics of race, age, sex, and parental education differed from that of our patient sample. Of these 100 controls, 88 had MRI data of appropriate quality for VBM analysis, and made up our final healthy control group. The demographics of these 88 controls matched the average demographics of our patient sample (Table 1).

2.3 Structural MRI Data Acquisition and Analysis

Structural imaging data was acquired on a 3T Philips Intera Achieva scanner located at the Vanderbilt University Institute of Imaging Science (Philips Healthcare, Inc., Best, The Netherlands). We collected a 3D T1-weighted scan on each participant (voxel size = $1mm^3$; FOV = $256mm^2$; number of slices = 170; TE = 3.7ms; TR = 8.0ms).

T1-weighted structural brain images were visually inspected for motion and artifacts before VBM analysis and for segmentation errors prior to inclusion in the group analyses. Images that passed quality control were then preprocessed and segmented into gray matter, white matter and cerebrospinal fluid using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm) for SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and Matlab (The MathWorks, Inc., Natick, MA, USA). Following bias-correction and segmentation, the images underwent non-linear normalization to MNI space using the DARTEL algorithm (Ashburner, 2007). The images were modulated by non-linear warping only. Finally, the normalized gray matter images were smoothed with a 6mm kernel and used in the subsequent voxel-based statistical analyses. Between group comparisons were carried out in SPM8 using voxel-wise whole brain analysis of covariance (ANCOVA), with age included as a covariate. Analyses were

thresholded in SPM8 using a voxelwise p-value of .001 for the whole brain with a minimum cluster size of 418 voxels providing a cluster-wise false discovery rate of $\alpha = .05$.

2.4 Statistical analysis

We tested the hypothesis that schizophrenia spectrum disorder patients with and without a history of substance use disorder differ from each other in brain structure in two steps. First, we tested for a difference in gray matter volume between all patients and healthy control subjects by using a one-way independent samples ANCOVA. This was meant to identify gray matter volume deficits that can be attributed to schizophrenia, when controlled for the effect of age.

Second, we directly compared gray matter volumes between the schizophrenia spectrum disorder patients with and without a history of substance use disorder. We again used a voxelwise one-way independent samples ANCOVA masked by the results of our first analysis to compare the two patient groups in order to identify the potential impact of a history of substance use disorder on differences in brain structure initially attributed to schizophrenia.

3. Results

As expected, we identified reduced gray matter volume in schizophrenia in 14 clusters located in the bilateral precentral gyrus, right medial frontal cortex, right visual cortex, right occipital pole, right thalamus, bilateral amygdala and bilateral cerebellum (Table 2, Figure 1). These results were largely unchanged if we conducted the analysis as a 3-way ANCOVA considering schizophrenia patients with and without substance use history separately and identified psychosis related regions with a main effect of group (Supplementary Figure 1) or by including sex and race as covariates in the analysis.

When we compared in a voxelwise analysis within the 14 clusters identified in our initial analysis the 92 schizophrenia patients with a history of substance use disorder to the 66 schizophrenia patients without a history of substance use disorder, we did not find any significant differences. For illustrative purposes, the mean gray matter volume for each group was extracted from each of the 14 clusters and is shown in Figure 2. Across all brain regions, the difference between the age-adjusted mean gray matter volume values of healthy control subjects and either patient group was larger than any difference between the two patient groups.

The majority of patients in our schizophrenia and substance use disorder sample had a history of cannabis abuse or dependence, with or without alcohol abuse or dependence, while a minority had a history of only alcohol abuse or dependence (Table 1). When matched for age, gender, race, subject education, and parental education, the 16 schizophrenia patients with only alcohol abuse or dependence and 19 schizophrenia patients with only cannabis abuse or dependence did not differ in gray matter volume within regions that distinguished the schizophrenia patients from healthy control subjects.

4. Discussion

Critics of neuroimaging in psychotic disorders have suggested that substance use disorder confounds the study of the neural basis of schizophrenia (Thoma and Daum, 2013; Van Haren et al., 2013; Weinberger and Radulescu, 2016). Previous meta-analyses of VBM studies in schizophrenia have found consistent gray matter deficits in the frontal, temporal, cingulate and insular cortices and the thalamus when compared to healthy control subjects (Ellison-Wright and Bullmore, 2010; Shepherd et al., 2012). While we did not find significant deficits in the cingulate and insula in our analysis of all schizophrenia spectrum disorder patients compared to controls, we observed gray matter volume deficits in all other expected regions, validating our findings as representative of the volume deficits typically observed in VBM studies of schizophrenia. Here we were able to show that significant differences in gray matter volume attributed to the diagnosis of schizophrenia are not significantly compounded by a history of cannabis and alcohol use disorders. This finding held even when we considered separately those patients who had abuse or dependence of cannabis alone or alcohol alone.

Our results bridge a critical gap in the existing literature on the impact of substance use disorders on brain volume changes observed in schizophrenia. The majority of studies in this area have used region of interest analysis to examine whether changes in brain volume in schizophrenia are affected by substance use. Of the two studies using a whole brain VBM analysis to investigate this question, our findings are in agreement with the study by Haller et al. (2013), who did not find differences in gray matter volume between first episode psychotic disorder patients with and without comorbid cannabis use. The other whole brain study by Schiffer et al. (2010) found decreased gray matter volume in the anterior cingulate, frontopolar, and superior parietal cortices in a small sample of schizophrenia patients with a history of alcohol dependence compared with schizophrenia patients without such a history. A key difference between these results and our findings is that the regions found by Schiffer et al. did not overlap with the regions they identified as having decreased gray matter volume in schizophrenia patients without alcohol dependence compared to healthy controls in the same study. Taken together with these previous studies, our results suggest that psychosis related changes in brain volume found with VBM do not reflect changes due to misuse of cannabis or alcohol.

It is possible that a region of interest analysis may be more sensitive for detecting substance induced volumetric changes in brain regions affected by psychosis. This may be particularly relevant for cannabis users in those areas with high concentrations of cannabinoid receptors (Lorenzetti et al., 2016). Of the studies that have used a region of interest analysis to test how substance use affects brain volume in psychosis, findings are mixed (Supplementary Table 1). Cannabis use in psychosis patients has been associated with decreased volume in the cingulate cortex (Bangalore et al., 2008; Rapp et al., 2013; Szeszko et al., 2007) and hippocampus (Ebdrup et al., 2010), increased putamen volume (Koenders et al., 2015) or no differences in cannabis users compared to non-users (Cahn et al., 2004; Haller et al., 2013; Malchow et al., 2013b; Solowij et al., 2013; Wobrock et al., 2009). Two early studies examining alcohol use found decreased prefrontal cortex (Mathalon et al., 2003) and cerebellar vermis (Joyal et al., 2004) volume in chronic schizophrenia patients with and

without alcohol use disorder, but the majority of studies have found no differences in regional brain volume related to alcohol misuse above and beyond the volume deficits observed in psychosis patients who are non-users (Deshmukh et al., 2005; Gizewski et al., 2013; Lange et al., 2017; Nesvåg et al., 2007; Sullivan et al., 2000; Sullivan et al., 2003; Varnäs et al., 2007). Some of the heterogeneity in region of interest findings can be explained by small sample sizes, differing clinical and demographic characteristics of patient samples, use of alcohol and/or cannabis, severity of substance use, and methods used for volume analysis (VBM vs. automated segmentation vs. manual segmentation). Overall, even using a targeted region of interest approach, there is only weak evidence that volumetric changes attributed to psychosis are confounded by substance use.

Additionally, the combination of different sample sizes, statistical thresholds, and smoothing kernels used in past VBM analyses are likely to be key factors in the lack of agreement across studies. The use of a larger smoothing kernel increases the size of a cluster that will be identified in a VBM analysis (Henley et al., 2010) and combined with the generally small sample sizes under consideration this can greatly impact the reproducibility, sensitivity, and specificity of the analysis (Button et al., 2013; Ioannidis, 2011; Shen and Sterr, 2013). Recent reviews of the literature on substance use and other measures of brain structure in schizophrenia, including manual volumetry, cortical thickness, and shape analysis, have similarly identified a pattern of inconclusive or largely negative results (Malchow et al., 2013a; Thoma and Daum, 2013).

A significant strength of our study is the large sample of well characterized and well-matched schizophrenia patients, with only 2 recent studies reaching sample sizes similar to our study (Koenders et al., 2015; Lange et al., 2017). Although the article by Koenders et al. is better positioned to address questions regarding the effect of alcohol use on the brain regardless of psychotic disorder diagnosis, our study extends their findings to a large group of individuals with schizophrenia and comorbid alcohol and/or cannabis abuse or dependence. In the study by Lange et al., only a small portion of the schizophrenia patient sample met criteria for Alcohol Use Disorder (n=13) or other Substance Use Disorder (n=32). Koenders et al. examined brain structure in a large group of male early stage schizophrenia patients with (n=80) or without (n=33) cannabis use disorder. Our study expands on their finding by including both male and female patients.

Our study also has several limitations. First, we relied on patient report to determine the history of substance use disorders, similar to previous studies. Second, we used categorical diagnoses, not dimensional assessments, to group patients into cohorts with and without substance use disorders. However, this is common practice (Supplementary Table 1), and the one previous study that used a continuous assessment of substance use did not yield different results (Lange et al., 2017). Third, we used DSM-IV-TR rather than DSM-5 diagnoses. While this sets us apart from future studies that will use DSM-5 criteria, this allowed for better comparison with previous studies. Fourth, patients were excluded from the study if they met criteria for substance abuse or dependence in the past month. While this is standard for schizophrenia studies, it could have led to the exclusion of more severely ill substance use disorder patients. Conversely, we did not have a biological measure of substance use such as blood or urine screening at the time of the scan so we cannot conclusively state that

participants were not using substances at the time of the scan. Importantly, although we have a large sample size compared to many previous investigations, we cannot rule out the possibility that substance use does alter brain structure in regions affected by psychosis and that a larger study could detect such an effect. Finally, we employed only one commonly used measure of brain structure.

We find that a clinically meaningful history of alcohol or cannabis use does not significantly compound the gray matter deficits associated with schizophrenia. Longitudinal studies examining the effects of alcohol and cannabis will be especially informative in elucidating the impact of substance use on brain health in psychotic disorders. For example, two studies have shown that cannabis use relates to changes in cortical thickness over time and may accelerate thinning in several regions of the cerebral cortex (Hartberg et al., 2018; Rais et al., 2010). Future large scale longitudinal studies of additional measures of brain structure and function, such as cortical thickness, diffusion tensor imaging, and resting state connectivity, are needed to better understand the clinical and neural trajectories of schizophrenia patients with a history of substance use disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Substance use may confound the study of brain structure in schizophrenia.
- We compared schizophrenia patients with and without substance use histories.
- We replicated gray matter volume deficits known to occur in schizophrenia.
- These did not significantly differ in patients with and without substance use.
- A substance use history does not compound gray matter deficits in schizophrenia.

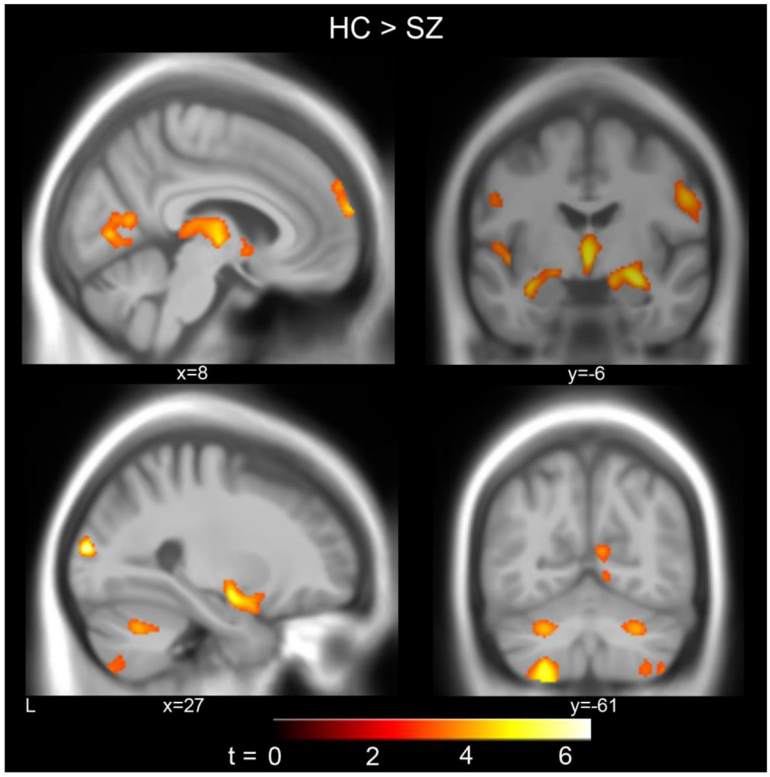

Fig. 1.

Reduced gray matter volume in schizophrenia spectrum patients compared to healthy controls. Statistical results thresholded at voxelwise $p < 0.001$, cluster size $k = 418$ for cluster FDR < 0.05. Slice labels indicate MNI coordinates.

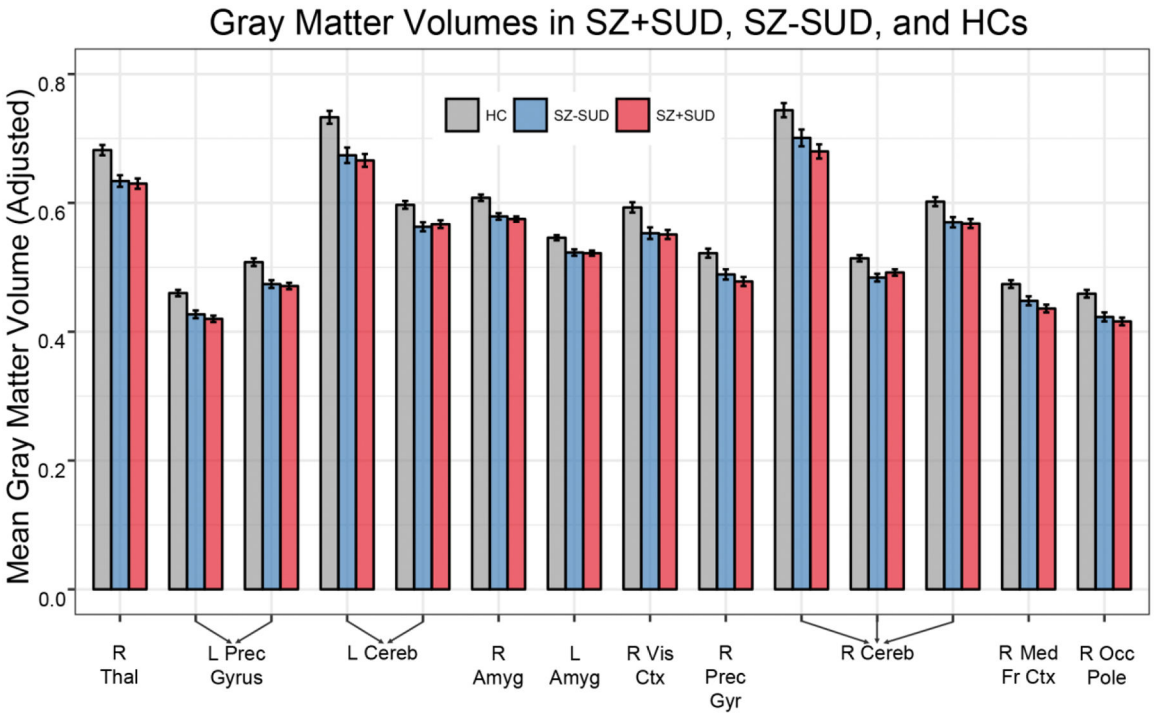

Fig. 2.

In a voxelwise analysis within the regions previously identified to differ between healthy controls (HC) and all schizophrenia spectrum patients, no significant differences in mean gray matter volume were found between schizophrenia spectrum patients with (SZ+SUD) and without (SZ-SUD) substance use histories ($p > 0.05$). For display purposes, bars represent age-adjusted mean gray matter volumes extracted from 14 clusters identified in the first analysis of all schizophrenia patients compared to healthy controls. Error bars indicate standard error of the mean.

Table 1.

Demographics and clinical characteristics.

		Psychosis Patients						
	Healthy Controls	All Patients	SZ+SUD	SZ-SUD	HC > All Patients		SZ+SUD > SZ-SUD	
	n=88 Mean (SD)	n=158 Mean (SD)	n=92 Mean (SD)	n=66 Mean (SD)	Statistic	p	Statistic	p
Age	29.51 (10.36)	29.58 (11.81)	29.75 (11.85)	29.33 (11.85)	t=−0.04	0.97	t=0.22	0.83
Sex (M/F)	60/28	112/46	70/22	42/24	χ^2=0.20	0.66	χ^2=2.89	0.09
Race (C/AA/O)	58/28/2	97/54/7	60/26/6	37/28/1	χ^2=1.96	0.74	χ^2=5.19	0.27
Participant Education[a]	15.43 (1.90)	13.17 (2.25)	13.18 (2.00)	13.17 (2.56)	t=7.87	<0.001	t=0.02	0.99
Parental Education[b]	14.14 (2.15)	14.29 (2.89)	14.23 (2.92)	14.37 (2.86)	t=−0.44	0.66	t=−0.27	0.79
Smokers/Non-smokers	18/69	91/67	74/18	17/49	χ^2=32.58	<0.001	χ^2=47.74	<0.001
Diagnosis								
Schizophrenia		65	38	27				
Schizoaffective		36	26	10			χ^2=4.84	0.09
Schizophreniform		57	28	29				
Duration of Illness (years)		9.01 (11.98)	9.77 (12.10)	7.95 (11.83)			t=−0.94	0.35
GAF	93.28 (8.50)	46.71 (14.68)	45.32 (14.26)	48.73 (15.16)	t=−31.05	<0.001	t=−1.42	0.16
WTAR	110.31 (12.22)	97.66 (16.22)	98.58 (15.3)	96.35 (17.49)	t=−6.89	<0.001	t=0.85	0.40
SCIP	−0.01 (0.66)	−1.19 (0.98)	−1.22 (0.98)	−1.15 (1.00)	t=−11.18	<0.001	t=−0.45	0.65
PANSS		67.87	69.42	65.74			t=1.26	0.21
Positive		18.78	19.98	17.14			t=2.55	0.01
Negative		16.54	15.95				t=−1.13	0.26
General		32.61	33.60	31.26			t=1.72	0.09
YMRS		4.66 (5.74)	5.90 (6.23)	3.00 (4.55)			t=3.27	0.002
HAMD		8.72 (6.26)	8.74 (6.33)	8.68 (6.21)			t=0.62	0.95
Medication Status (Medicated/Unmedicated)		138/20	81/11	57/9			χ^2=0.10	0.75
CPZ Equivalents		439.89 (286.31)	447.01 (249.34)	429.78 (334.00)			t=0.35	0.73
Substance Abuse or Dependence								
Cannabis only			44					
Alcohol only			16					
Cannabis and Alcohol			32					

[a] Participant education available for 147 patients (85 SZ+SUD, 62 SZ-SUD) and all controls.

[b] Parental education available for 138 patients (83 SZ+SUD, 55 SZ-SUD) and all controls.

Table 2.

Brain regions showing significantly lower gray matter volume in schizophrenia spectrum disorder patients compared to controls.

	Peak coordinates (MNI)					
Region	**x**	**y**	**z**	**Cluster size**	**Cluster p(FDR)**	**Peak t-statistic**
1. Right Thalamus	2	−14	−5	2592	<0.001	6.66
2. Left Precentral Gyrus	−47	−15	41	1649	<0.001	5.19
	−54	2	1	785	0.006	4.45
3. Left Cerebellum	−26	−65	−56	1368	<0.001	5.49
	−24	−65	−33	990	0.002	4.34
4. Right Amygdala	27	−6	−15	1184	0.001	5.35
5. Left Amygdala	−32	−7	−18	636	0.014	4.64
6. Right Primary Visual Cortex	8	−75	3	592	0.017	4.44
7. Right Precentral Gyrus	56	−4	29	538	0.022	4.44
8. Right Cerebellum	36	−56	−56	531	0.022	3.86
	18	−54	−29	425	0.037	3.85
	29	−60	−33	418	0.037	4.17
9. Right Medial Frontal Cortex	11	65	18	516	0.022	4.73
10. Right Occipital Pole	27	−90	14	450	0.034	6.33