



Alcohol use disorders contribute to hippocampal and subcortical shape differences in schizophrenia[☆]

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ABSTRACT

Background: Alcohol abuse and dependence have been reported to exacerbate the clinical course of schizophrenia. However, the neurobiological basis of this co-morbid interaction is unknown. The aim of this study was to determine the relationship of co-morbid alcohol use disorder (AUD) with brain structure abnormalities in schizophrenia patients.

Methods: T1-weighted magnetic resonance images were collected from schizophrenia patients without a history of any substance use disorder (SCZ_0, n = 35), schizophrenia patients with a history of AUD only (SCZ_AUD, n = 16), and a healthy comparison group without a history of any substance use disorder (CON, n = 56). Large-deformation, high-dimensional brain mapping was used to quantify the surface shapes of the hippocampus, thalamus, striatum, and globus pallidus in these subject groups. Analysis of variance was used to test for differences in surface shape measures among the groups.

Results: SCZ_AUD demonstrated the greatest severity of shape abnormalities in the hippocampus, thalamus, striatum, and globus pallidus as compared to SCZ_0 and CON. SCZ_AUD demonstrated a combination of exaggerated shape differences in regions where SCZ_0 also showed shape differences, and unique shape differences that were not observed in SCZ_0 or CON.

Conclusions: Shape differences in schizophrenia were compounded by a history of co-morbid AUD. Future research is needed to determine whether these differences are simply additive or whether they are due to an interaction between the underlying neurobiology of schizophrenia and alcoholism. The consequences of such shape differences for the clinical course of schizophrenia are not yet understood.

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1. Introduction

Recent studies suggest that 20–50% of schizophrenia patients have a co-morbid alcohol use disorder (AUD) (Koskinen et al., 2009; Smith et al., 2008), and this comorbidity has been associated with greater severity in psychopathology (Margolese et al., 2004) and neurocognitive dysfunction (Manning et al., 2009). Co-morbid alcoholism in schizophrenia has also been associated with reduced medication

compliance and more frequent hospitalization (Drake et al., 1989). Although the literature suggests that alcoholism has a wide-reaching impact on the clinical course of schizophrenia, much less is known about how alcohol might be related to the underlying neurobiological substrates of the disorder.

Alcohol use has been associated with gray matter loss in subcortical brain structures in otherwise healthy subjects (Makris et al., 2008; Sullivan et al., 2005). Cellular processes implicated in the neurobiological effects of alcohol include overactivation of NMDA receptors, excitotoxicity, and inhibition of adult neurogenesis (Nixon, 2006; Sullivan and Pfefferbaum, 2005). Recently, experts have suggested that addiction and schizophrenia may have overlapping neurobiological substrates within the hippocampus and subcortical structures, which may place schizophrenia patients at increased risk for developing a substance use disorder (Chambers et al., 2001; Green et al., 2002). In turn, individuals at an elevated risk for schizophrenia have been suggested to be particularly vulnerable to the effects of alcohol on brain structure (Welch et al., in press).

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Furthermore, research suggests that reductions in gray matter were more prominent in schizophrenia patients with a co-morbid AUD than in schizophrenia patients without a co-morbid substance use disorder (Mathalon et al., 2003; Varnas et al., 2007). However, the literature examining the influence of alcohol on subcortical structures in schizophrenia has been inconsistent. One study did not find a difference in thalamic volume between schizophrenia patients with and without a co-morbid AUD (Sullivan et al., 2003), while another study suggested that the striatal volume of a comorbid group was intermediate between schizophrenia patients without an AUD and a comparison group with AUD (Deshmukh et al., 2005).

The results of structural neuroimaging studies suggest that volume loss within localized regions of the hippocampus (Tamminga et al., 2010) and subcortical structures, such as the thalamus (Byne et al., 2009), striatum and globus pallidus (Brandt and Bonelli, 2008), is characteristic of schizophrenia. In our prior studies of schizophrenia patients, we used high-resolution magnetic resonance (MR) imaging and computational algorithms for high-dimensional brain mapping to characterize neuroanatomical shapes as indicators of localized volume losses. The results of these studies suggest that schizophrenia patients have localized volume loss within the anterior and posterior extremes of the thalamus (Csernansky et al., 2004a; Harms et al., 2007), the anterior striatum and globus pallidus (Mamah et al., 2008; Mamah et al., 2007), and the anterior hippocampus (Csernansky et al., 2002).

In the present study, we used similar methods to compare the shapes of the hippocampus and subcortical structures between schizophrenia patients with a past history of an alcohol use disorder only (SCZ_AUD), and schizophrenia patients (SCZ_0) and healthy comparison subjects (CON) with no history of any substance use disorders. We hypothesized that volume loss and surface shape deformations in the hippocampus and subcortical structures present in SCZ_0 would be exaggerated in SCZ_AUD. In addition, we also sought to assess the relationship between a co-morbid AUD and psychopathology and neurocognitive dysfunction in schizophrenia. We hypothesized that SCZ_AUD would exhibit greater severity in positive, negative and disorganized symptoms, and greater impairment in neurocognition when compared to SCZ_0, and that this increased burden of psychopathology and neurocognitive deficit would be correlated with the exaggerated differences in neuroanatomical shapes.

2. Methods

2.1. Participants and inclusion criteria

Participants included 35 SCZ_0, 16 SCZ_AUD, and 56 CON who gave written informed consent after the study's risks and benefits were explained to them. They were selected from a longitudinal study of schizophrenia neuromorphometry; details of the selection and assessment for the main study are described in detail in previous publications (Brahmbhatt et al., 2006; Csernansky et al., 2004a). The institutional review boards at Northwestern University and Washington University in St. Louis approved the study protocol. In the current analysis, CON and SCZ_0 participants did not have a current or remote diagnosis of any substance use disorder, including alcohol, cannabis, cocaine, hallucinogens, sedatives, opiates, and stimulants. SCZ_AUD participants had a lifetime history of abuse or dependence for alcohol, but no other substance use disorders (Table 1). Participants were group-matched on age, gender, and parental socioeconomic status (Hollingshead, 1975).

Given that longer durations of illness could be related to progressive structural abnormalities (Wang et al., 2008), and that first and second generation antipsychotic (FGA, SGA; respectively) medications might have had distinct effects on brain structure (Corson et al., 1999; Staal et al., 2000), we examined whether there were significant differences between the relevant groups in duration of illness and type of

Table 1
Demographic, clinical, and pharmacological characteristics of study sample.

	CON (n = 56)	SCZ_0 (n = 35)	SCZ_AUD (n = 16)
Age, mean (SD), y	38.2 (12.1)	38.3 (13.1)	38.6 (14.7)
Duration of illness, mean (SD), y	–	14.3 (13.1)	17.0 (13.3)
Gender, no. (% male)	40 (71.4%)	24 (68.6%)	12 (75.0%)
SES, mean (SD)	3.2 (1.0)	3.6 (1.0)	3.4 (1.4)
Cigarettes smoked, mean (SD) (over past year) ^a	1465 (2871)	3201 (4605)	5243 (4853)
Substance use disorders			
Alcohol, no. (%)	0 (0.0%)	0 (0.0%)	16 (100%)
Cannabis, no. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cocaine, no. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hallucinogen, no. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sedatives, no. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Opioids, no. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stimulants, no. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Antipsychotic medication			
First-generation only, no. (%)	0 (0.0%)	4 (11.4%)	2 (12.5%)
Second-generation only, no. (%)	0 (0.0%)	15 (42.9%)	10 (62.5%)
Both, no. (%)	0 (0.0%)	11 (31.4%)	2 (12.5%)
Neither, no. (%)	131 (100%)	5 (14.3%)	2 (12.5%)

Abbreviations are as follows: healthy controls (CON); schizophrenia patients only (SCZ_0), and schizophrenia patients with a co-morbid alcohol use disorder (SCZ_AUD).

^a $F_{2,104} = 6.7$, $p = .002$; $CON_0 < SCZ_0$ ($p = .04$), SCZ_AUD ($p < .001$), $SCZ_0 < SCZ_AUD$ ($p = .08$).

drug treatment, but none were found (Table 1). We also examined cigarette consumption as a potential confound given that nicotine use has been related to reduced gray matter density (McClernon, 2009) and the vast majority of schizophrenia patients have nicotine dependence (Van Dongen, 1999). Although cigarette consumption differed between groups (Table 1), using this measure as a covariate did not affect the pattern of the results. Hence, cigarette consumption was not examined as a covariate in the final analysis.

2.2. Clinical measures

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 2002) was administered to determine the presence of a current diagnosis of schizophrenia and the presence of a past history (prior to the preceding 6 months) of a substance use disorder (SUD) for alcohol, cannabis, cocaine, hallucinogens, sedatives, opiates, and stimulants (participants diagnosed with a SUD during the 6 months preceding their SCID were excluded). SUDs were defined as meeting DSM-IV-TR criteria for abuse or dependence (present: yes = 1, no = 0). Self-report was used to assess duration of illness (operationalized as the number of years since first appearance of psychotic symptoms) and treatment with FGA and SGA medication. Cigarette consumption was estimated using self-report and a semi-structured interview adapted from Sullivan et al. (2000) and the Lifetime Alcohol Consumption Assessment Procedure (Skinner, 1982).

Participants completed a battery of neuropsychological tests that were sensitive to the neurocognitive deficits associated with schizophrenia. Based on prior research (Nuechterlein et al., 2004), we transformed raw scores from the neuropsychological tests into standardized scores (based on the current sample) for four domains: crystallized IQ, working memory, episodic memory, and executive functioning. Psychopathology (i.e., positive, negative, disorganization symptoms) was assessed using global ratings from the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1983b) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983a). A description of the specific neurocognitive and psychopathological tests and their scoring can be found in a prior publication (Smith et al., 2009).

2.3. Neuroimaging measures

Details of image acquisition, surface mapping and analysis can be found in previous published reports (Csernansky et al., 2004a; Mamah et al., 2007). MR scans were collected with a standard head coil on a Siemens Magnetom 1.5-Tesla (Erlangen, Germany) scanner using a turbo-FLASH sequence (repetition time = 20 ms, echo time = 5.4 ms, flip angle = 30°, 180 slices, FOV = 256 mm, matrix = 356 × 256, time = 13.5 min) that acquired 1 mm³ isotropic whole-head image (Venkatesan and Haacke, 1997). Total brain volume was estimated using an atlas scaling factor (ASF) (Buckner et al., 2004). The ASF is the reciprocal of the determinant of the alignment matrix to Talairach atlas space, and signifies the extent that brain volume contracts or expands during alignment. Although ASF showed a trend-level between-group difference ($F_{2,104} = 2.7, p = .07$), the addition of ASF as a covariate in statistical analyses did not change the pattern of results.

The surfaces of each structure were transferred from a template scan by applying Large-Deformation High-Dimensional Brain Mapping (HDBM-LD) (Csernansky et al., 2004b). The validity and reliability of HDBM-LD for mapping these structures has been reported previously (Csernansky et al., 2004a; Mamah et al., 2007). We consulted with an atlas of the human brain to associate deformation patterns to specific subcortical regions (Mai et al., 1997).

Structural volumes were calculated as the volume of the spaces enclosed within each surface. To assess structural shape, a principal components analysis on the surfaces was first used for dimensionality reduction, generating eigenvectors that represent variation in the shape of the left and right structures. In each structure, the first 10 eigenvectors accounted for more than 80% of total shape variance, and so average scores (L + R/2) for the first 10 eigenvectors from each hemisphere were used for statistical analysis.

2.4. Statistical analysis

To examine whether overall differences in the shapes of the structures existed across groups, we first conducted a multivariate analysis of variance (MANOVA) for each structure using the 10 averaged eigenvector scores as dependent variables with group (CON, SCZ_0, or SCZ_AUD) as a fixed effect. If a significant main effect of group was found for a particular structure, we then examined post-hoc pair-wise comparisons to determine which eigenvectors were significantly different between groups.

To visualize differences in the patterns of surface shape deformation between groups for each structure, we constructed average surfaces for the hippocampus, thalamus, striatum, and globus pallidus for each group. Between-group differences were computed as the difference between the average surfaces, and then visualized. One-way ANOVA examined between-group differences on the demographic and clinical and neurocognitive variables. A repeated measures ANOVA with group and hemisphere as fixed effects examined the total volume for each structure.

To correlate structural shape data with clinical and neurocognitive measures, a maximum likelihood estimate of the linear predictor (i.e., x_{beta}) was generated for each structure from a logistic regression

between SCZ_0 and SCZ_AUD based on the 10 averaged eigenvectors. This x_{beta} score provides a single 'measure' of neuroanatomical difference where a higher score reflected a more SCZ_0-like shape, while a lower score reflected a more SCZ_AUD-like shape.

3. Results

3.1. Surface shape analyses

3.1.1. Hippocampus

We found a significant main effect of group ($F_{2,101} = 2.6, p = .001$) on hippocampal shape. Posthoc between-group comparisons found that eigenvectors 5 ($p < .001$) and 10 ($p = .03$) discriminated SCZ_0 from CON; eigenvector 5 ($p < .001$) discriminated SCZ_AUD from CON; and eigenvector 10 ($p = .01$) discriminated SCZ_AUD from SCZ_0 (Table 2). See Fig. 1 for shape characteristics.

3.1.2. Thalamus

We found a significant main effect of group ($F_{2,99} = 2.3, p = .002$) on thalamic shape. Post hoc between-group comparisons found that eigenvectors 2 ($p = .009$), 4 ($p = .02$), and 10 ($p = .001$) discriminated SCZ_0 from CON; eigenvectors 2 ($p = .01$), 3 ($p = .03$), and 10 ($p = .08$) discriminated SCZ_AUD from CON; and eigenvector 3 ($p = .03$) discriminated SCZ_AUD from SCZ_0 (Table 2). See Fig. 2 for shape characteristics.

3.1.3. Striatum

We found a significant main effect of group ($F_{2,99} = 1.7, p = .04$) on striatal shape. Posthoc between-group comparisons found that eigenvector 2 ($p = .009$) discriminated SCZ_0 from CON; eigenvectors 1 ($p = .03$), 3 ($p = .001$), and 9 ($p = .02$) discriminated SCZ_AUD from CON; and eigenvector 3 ($p = .03$) discriminated SCZ_AUD from SCZ_0 (Table 2). See Fig. 3 for shape characteristics.

3.1.4. Globus pallidus

The main effect of group was significant on globus pallidus shape ($F_{2,99} = 1.7, p = .04$). Posthoc between-group comparisons found that eigenvector 1 ($p = .08$) discriminated SCZ_0 from CON; eigenvectors 1 ($p = .06$) and 3 ($p < .001$) discriminated SCZ_AUD from CON; and eigenvector 3 ($p = .001$) discriminated SCZ_AUD from SCZ_0 (Table 2). See Fig. 4 for shape characteristics.

Figs. 1–4 present visualizations of the estimated shape displacement for the thalamus and striatum. The flame scale in each figure reflects t -values with cooler colors ($t < 0$) indicating inward deformation and warmer colors ($t > 0$) reflecting outward deformation.

3.2. Volume analyses

We found a significant effect of group on the volume of the thalamus ($F_{2,99} = 5.2, p = .007$), with CON having greater volume than SCZ_0 and SCZ_AUD. SCZ_AUD had bilateral volume decreases in the thalamus (Left: -2.4% , Right: -2.5%) when compared to SCZ_0, however, these differences were not statistically different and were characterized by small effect sizes ($d = .20, d = .20$, respectively). We did not find a significant main effect of group on the remaining structures.

Table 2

Between-group comparisons for shape and significant eigenvectors in hippocampus and subcortical structures.

	MANOVA statistics $F_{df1,df2}, p$ -value	Post-hoc comparisons		
		SCZ_0 vs. CON	SCZ_AUD vs. CON	SCZ_AUD vs. SCZ_0
Hippocampus	$F_{2,101} = 2.6, p < .001$	Hi5***, Hi10*	Hi5***	Hi10*
Thalamus	$F_{2,99} = 2.3, p = .002$	Th2**, Th4*, Th10**	Th2*, Th3*, Th10+	Th3*
Striatum	$F_{2,99} = 1.7, p = .04$	St2**	St1*, St3***, St9*	St3*
Globus pallidus	$F_{2,99} = 1.7, p = .04$	Pl1+	Pl1+, Pl3***	Pl3***

+ $p < .08$, * $p < .05$, ** $p < .01$, *** $p < .001$.

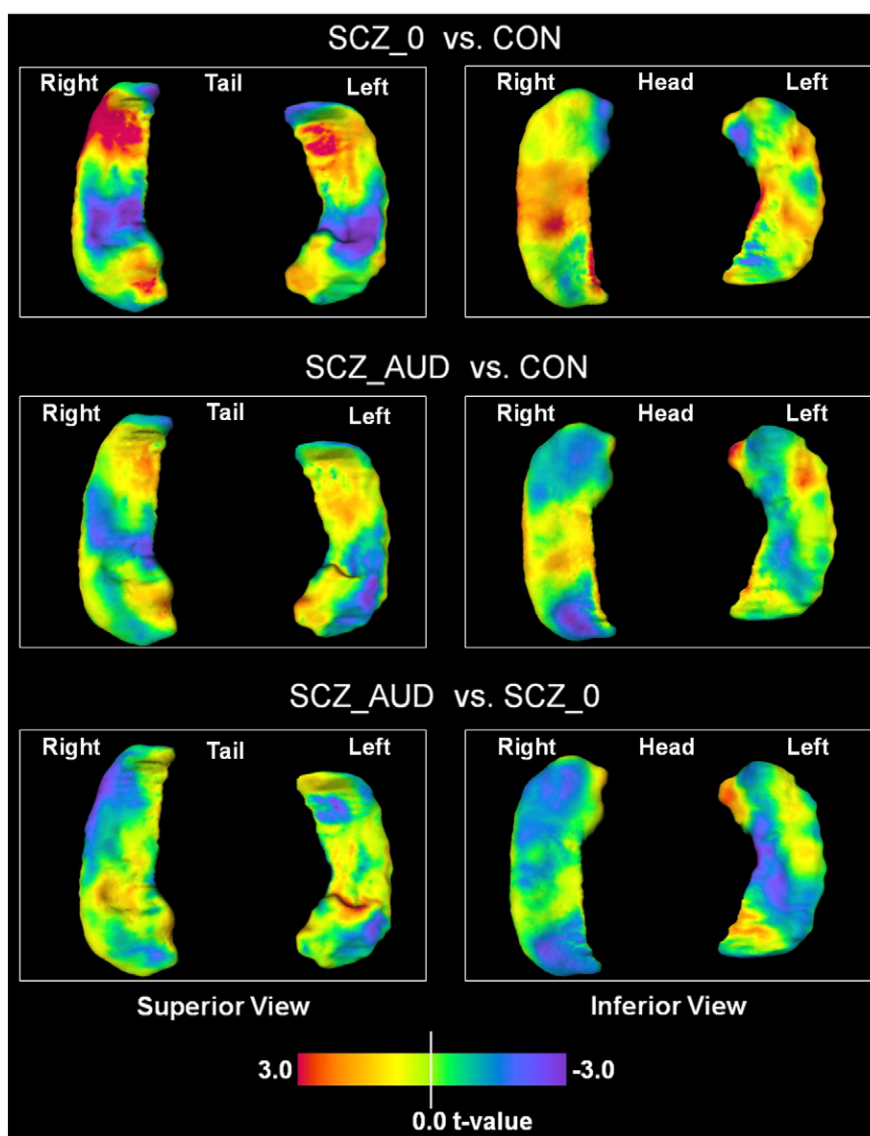


Fig. 1. Maps of hippocampus surface shape abnormalities. SCZ_0 were characterized by inward deformations in the mediadorsal regions with outward deformations near the dorsal head and tail. Ventral inward deformations were near the head with outward deformations in the medial regions. SCZ_AUD had similar patterns of dorsal abnormalities to SCZ_0, but to a lesser degree. Ventrally, SCZ_AUD had bilateral inward deformation in the head that extended more medially with additional inward deformation in the right tail.

Given that treatment with first-generation antipsychotic medication is related to enlarged basal ganglia volume (Gur et al., 1998), we examined volume difference in the striatum and globus pallidus between SCZ_0 and SCZ_AUD, while excluding CON. In this analysis, SCZ_AUD had bilateral volume decreases in the striatum (Left: -5.2% , Right: -5.9%) and globus pallidus (Left: -7.7% , Right: -5.3%) when compared to SCZ_0, which were characterized by medium sized effects in the striatum (Left: $d = .40$, Right: $d = .45$) and left globus pallidus (Left: $d = .51$, Right: $d = .36$). We found a significant main effect of hemisphere on the thalamus (Right > Left: $F = 8.5$, $p = .004$), striatum (Left > Right: $F = 52.7$, $p < .001$), and hippocampus (Right > Left: $F = 368.6$, $p < .001$), but not on the globus pallidus (Table 3). The group*hemisphere interactions failed to attain statistical significance for all four structures ($p > .10$).

3.3. Neurocognition and psychopathology

There was a significant main effect of group on crystallized IQ, working memory, episodic memory, and executive function. SCZ_0 and

SCZ_AUD scored significantly lower than CON (all $p < .05$) in all four neurocognitive domains (Table 4). Neurocognitive differences between SCZ_0 and SCZ_AUD did not achieve statistical significance (all $p \geq .10$) and were characterized by small effect sizes ($d < .40$) except for differences in episodic memory which had a medium effect size (SCZ_0 > SCZ_AUD: $d = .53$).

There was a significant main effect of group on positive, negative, and disorganization symptoms. As expected, for all three domains, SCZ_0 and SCZ_AUD scored significantly higher than CON (all $p < .01$) (Table 4). SCZ_AUD had higher scores on positive and negative symptoms than SCZ_0, but were non-significant ($p > .10$) and characterized by small effect sizes ($d < .40$). However, SCZ_AUD had greater disorganization symptoms than SCZ_0 ($p = .045$) which was characterized by a medium effect size ($d = .54$).

3.4. Correlation analyses

The correlations between structure shape differences (i.e., between SCZ_0 and SCZ_AUD) were estimated only for episodic memory

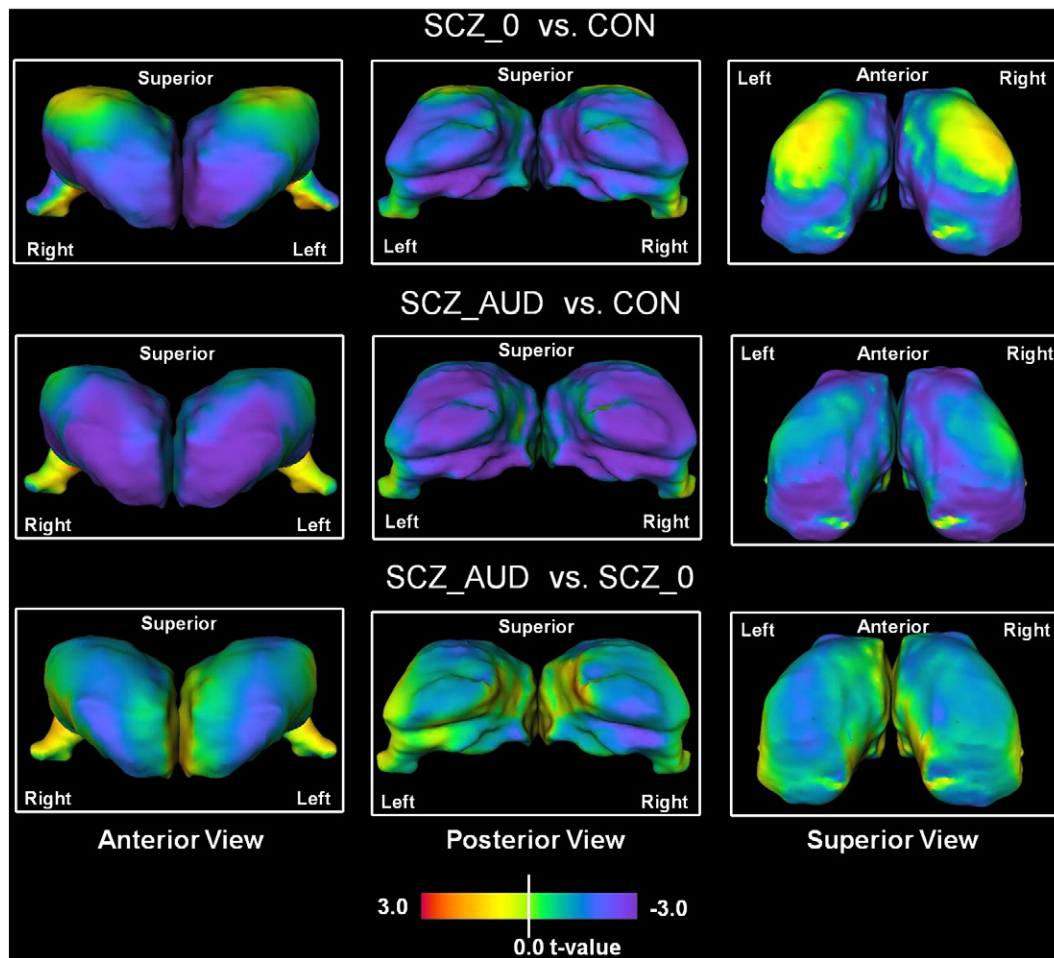


Fig. 2. Maps of thalamus surface shape deformations. SCZ_0 were characterized by inward deformations in the anterior and posterior regions of the thalamus, with additional inward deformations in the lateral posterior region. SCZ_AUD had inward deformations in similar regions to SCZ_0, however, the anterior and posterior inward deformations were exacerbated in SCZ_AUD. SCZ_AUD also had unique inward deformations in dorsal regions.

and disorganized symptoms, since the differences in these domains between SCZ_AUD and SCZ_0 were characterized by medium effect sizes. However, these shape differences between SCZ_AUD and SCZ_0 were not correlated with difference in severity of episodic memory or disorganized symptoms.

4. Discussion

Our results suggest that a remote history of AUD is related to deeper and more widespread inward shape deformations across the hippocampus and subcortical structures in schizophrenia patients. Further, the fact that histories of AUD in these patients were remote suggests that the differences associated with co-morbidity were long-lasting. Our findings were consistent with previous research suggesting that the effects of alcohol contribute to generalized gray matter volume across the brain (Fein et al., 2002; Pfefferbaum et al., 1998; Sullivan et al., 2005). Given the widespread localization of glutamate receptors and density of glutamatergic innervation throughout the brain (Fadda and Rossetti, 1998), our findings could be explained by excitotoxicity associated with hyperexcitable glutamate release during alcohol withdrawal (Tsai and Coyle, 1998).

Contrary to prior findings, we did not find significant between-group differences in the volumes of the hippocampus, thalamus, striatum, and globus pallidus (Deshmukh et al., 2005; Sullivan et al., 2003). The lack of statistical difference between SCZ_0 and SCZ_AUD in volume could be due to the localized nature of the neuroanatomical changes related to schizophrenia, alcohol use, or the combination of

the two disorders. The lack of difference in the striatum and globus pallidus could also be due to the sample sizes in this study since SCZ_AUD did show volume reductions characterized by medium effect sizes in each structure.

Schizophrenia patients without histories of any substance use disorder showed differences in neuroanatomical shapes that were generally consistent with our prior studies. For example, hippocampal shape differences in SCZ_0 were characterized by inward deformations of the anterior (head) region, with rostral movement of the hippocampal tail (Csernansky et al., 2002). SCZ_AUD had a similar pattern of hippocampal deformity, however, a more widespread pattern was present with inward deformation near the head and tail in the right hemisphere and inward deformations in the left head that extended more medially.

Thalamic shape differences in SCZ_0 were also consistent with prior work as they were characterized by inward deformations in regions corresponding to the anterior, mediodorsal, and pulvinar nuclei (Harms et al., 2007). While SCZ_AUD also showed deformations in these same regions, the inward deformations were deeper and more widespread, possibly involving thalamic regions beyond the anterior, mediodorsal and pulvinar nuclei. In addition, SCZ_AUD displayed inward deformations on the thalamic surface that were not observed in SCZ_0, particularly in the region of the dorsal thalamus.

Striatal shape differences in SCZ_0 were characterized by inward deformations in regions corresponding to the anterior caudate nucleus and putamen. This shape difference is consistent with prior work (Mamah et al., 2007). Again, inward deformation patterns of the

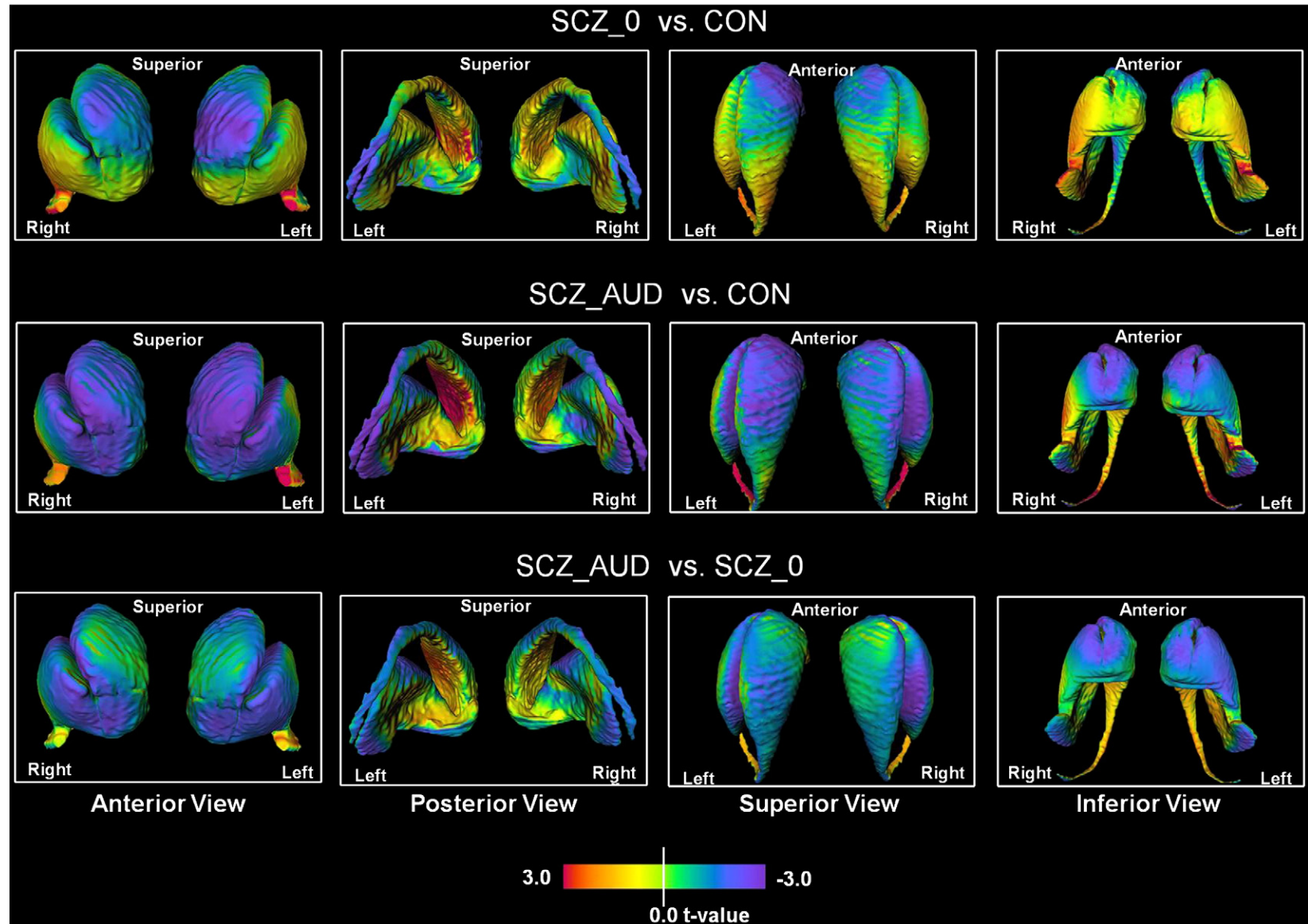


Fig. 3. Maps of striatum surface shape deformations. SCZ_0 was characterized by inward deformation in the dorsal anterior striatum with inward deformations in the posterior striatum. The anterior surfaces of the posterior caudate and putamen display a forward shift that may be secondary to the posterior inward deformations. SCZ_AUD had inward deformations in similar regions to SCZ_0, however, they were more exaggerated and extended dorsally from the anterior to posterior regions. Striatal shape differences distinct to SCZ_AUD were localized to inward deformations in the ventral striatum.

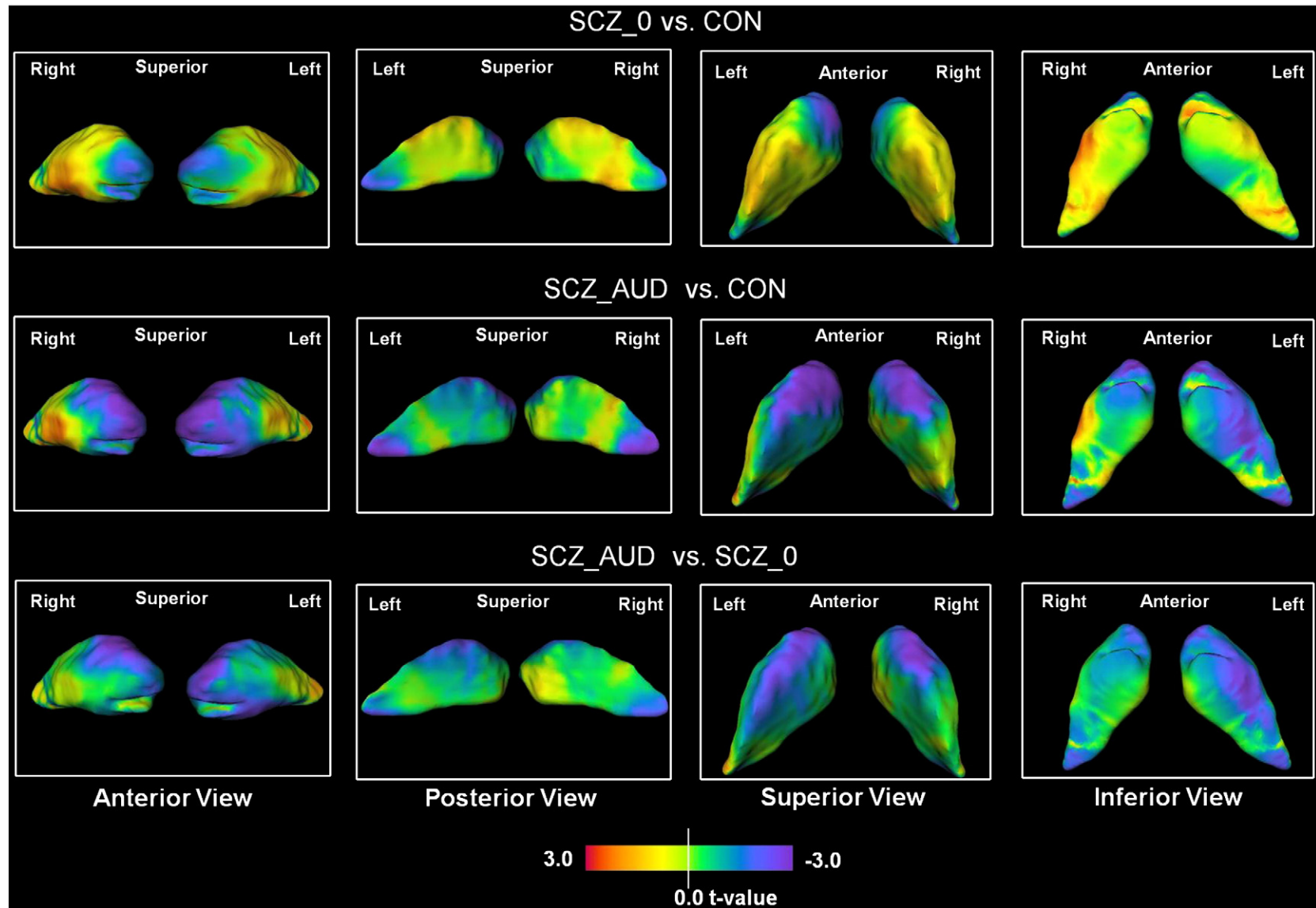


Fig. 4. Maps of globus pallidus surface shape deformations. SCZ_0 were characterized by inward deformations in the anterior and posterior regions of the globus pallidus. SCZ_AUD had exacerbated deformations in similar regions with additional inward deformations in the anterior regions that extended more dorsally. SCZ_AUD were also characterized by inward deformations in the ventral regions that extended from anterior to posterior.

Table 3
Estimated mean (SD) volumes of hippocampus and subcortical structures (mm³).

Structures	ANOVA statistics				Hemisphere	CON (n = 56)		SCZ_0 (n = 35)		SCZ_AUD (n = 16)	
	Group		Hemisphere			Mean	SD	Mean	SD	Mean	SD
	F-value	df	F-value	df							
Hippocampus	0.6	2,101	368.6 ^{***}	1,101	Left	2331	(367)	2377	(328)	2310	(345)
					Right	2749	(413)	2850	(417)	2707	(403)
Thalamus	5.3 ^{**} , ^a	2,99	8.5 ^{**}	1,99	Left	7770	(721)	7357	(861)	7180	(916)
					Right	7934	(746)	7461	(892)	7277	(982)
Striatum	1.2	2,99	52.7 ^{***}	1,99	Left	8860	(988)	8982	(1099)	8519	(1232)
					Right	8628	(966)	8802	(1069)	8286	(1235)
Globus pallidus	1.5	2,99	1.7	1,99	Left	1669	(174)	1681	(271)	1552	(237)
					Right	1662	(181)	1688	(261)	1598	(234)

Abbreviations are as follows: healthy controls (CON); schizophrenia patients only (SCZ_0), and schizophrenia patients with a co-morbid alcohol use disorder (SCZ_AUD).

*** p < .001.

** p < .01.

^a CON > SCZ_0 (p = .013), SCZ_AUD (p = .008), SCZ_0 > SCZ_AUD (p = .46).

anterior striatum were also found in SCZ_AUD, but in SCZ_AUD these alterations were again deeper and more widespread. Furthermore, SCZ_AUD had distinct inward deformations of the anterior-ventral region of the striatum surface, in a region corresponding to the nucleus accumbens.

Neuroanatomical abnormalities of the globus pallidus have not been frequently associated with schizophrenia, and only achieved statistical significance at the trend level in our prior work (Mamah et al., 2007). Although the current analysis found that a main effect of group on globus pallidus shape attained statistical significance, the post-hoc comparison between SCZ_0 and CON was again characterized by a trend level difference. However, the difference between SCZ_AUD and SCZ_0 was more robust with SCZ_AUD characterized by deeper inward deformations in the anterior regions that extend more dorsally.

In summary, the results of our analysis of neuroanatomical shapes in schizophrenia patients with and without a history of AUD is consistent with the hypothesis that alcohol use may have contributed to a neurodegenerative process, as has been described in subjects without schizophrenia (Mechtcheriakov et al., 2007). However, the similarity of shape deformation patterns in our participants with schizophrenia and without AUD suggested that alcohol is exacerbating an existing neurobiological alteration associated with schizophrenia (see Figs. 1–4). However, alcohol use may be contributing to volume losses in other distinct regions, since SCZ_AUD showed some patterns of deformation that were not seen in SCZ_0. The cellular basis

of the interaction between schizophrenia and alcohol use cannot be inferred from the results of our study. Rather, studies in animal models of schizophrenia-related neuroanatomical defect, where the dose and timing of alcohol exposure can be controlled, and the effects of the co-morbid interaction can be assessed at the tissue level, are needed to address this question.

We were surprised that no correlations were found between the observed differences in neuroanatomical shapes and measures of psychopathology and neurocognition. Although prior research suggests that co-morbid AUD can contribute to the severity of neurocognitive deficits in schizophrenia (Manning et al., 2009), we failed to find statistically significant between-group differences when comparing SCZ_AUD to SCZ_0 on measures of neurocognition. However, a medium effect size distinguished SCZ_AUD as having greater impairments in episodic memory when compared to SCZ_0. Previous work also indicated that co-morbid substance use disorders were associated with more severe psychopathology (Margolese et al., 2004). Our findings suggested a similar pattern for each symptom type, however, the difference between SCZ_AUD and SCZ_0 was only statistically significant for disorganization symptoms.

There were several limitations to the study. Although our findings suggest that a co-morbid AUD can have significant lasting effects on brain morphometry of schizophrenia patients, the cross-sectional nature of this study does not establish causality. Future research would need to replicate our findings in a longitudinal analysis. Although the small sample size for SCZ_AUD may have limited the

Table 4
Standardized mean (SD) for neurocognition and psychopathology.^a

	ANOVA statistics	CON (n = 56)	SCZ_0 (n = 35)	SCZ_AUD (n = 16)
Neurocognition				
Crystallized IQ ^b	F _{2,98} = 8.7, p < .001	.57 (.87)	-.26 (.97)	.00 (1.0)
Working memory ^c	F _{2,98} = 18.9, p < .001	.51 (.71)	-.34 (.77)	-.44 (.68)
Episodic memory ^d	F _{2,98} = 40.9, p < .001	.69 (.71)	-.42 (.66)	-.78 (.70)
Executive functioning ^e	F _{2,98} = 28.0, p < .001	.48 (.56)	-.57 (.80)	-.46 (.84)
Psychopathology				
Positive symptoms ^f	F _{2,57} = 6.2, p < .001	-.77 (.00)	.10 (.88)	.43 (.90)
Negative symptoms ^g	F _{2,57} = 12.8, p < .001	-.88 (.14)	.38 (.80)	.48 (.65)
Disorganized symptoms ^h	F _{2,57} = 12.1, p < .001	-.70 (.08)	.04 (.51)	.35 (.64)

Abbreviations are as follows: healthy controls (CON); schizophrenia patients only (SCZ_0), and schizophrenia patients with a co-morbid alcohol use disorder (SCZ_AUD).

^a Ns for cognition: CON = 55, SCZ_0 = 31, SCZ_AUD = 15 and Ns for psychopathology: CON = 9, SCZ_0 = 35, SCZ_AUD = 15.

^b CON > SCZ_0 (p < .001) and SCZ_AUD (p = .03), SCZ_0 < SCZ_AUD (p = .37).

^c CON > SCZ_0 (p < .001) and SCZ_AUD (p < .001), SCZ_0 > SCZ_AUD (p = .68).

^d CON > SCZ_0 (p < .001) and SCZ_AUD (p < .001), SCZ_0 > SCZ_AUD (p = .10).

^e CON > SCZ_0 (p < .001) and SCZ_AUD (p < .001), SCZ_0 < SCZ_AUD (p = .61).

^f SCZ_0 and SCZ_AUD > CON (p = .006, p = .001) and SCZ_AUD > SCZ_0 (p = .19).

^g SCZ_0 and SCZ_AUD > CON (p < .001, p < .001) and SCZ_AUD > SCZ_0 (p = .63).

^h SCZ_0 and SCZ_AUD > CON (p < .001, p < .001) and SCZ_AUD > SCZ_0 (p = .045).

detection of weaker relationships in volume, we found clear between-group differences with respect to shape abnormalities. Also, we did not assess whether participants were currently receiving pharmacological treatment for substance use, nor did we assess current or remote patterns of substance use. Thus, future research is needed to examine the effects and patterns of current substance use and abstinence on brain structure in schizophrenia. Lastly, future research would also benefit from the addition of a comparison group with a remote alcohol use disorder and no other co-morbidities. The analysis of this group might enable research to more clearly characterize whether shape differences were specific to alcohol or an interaction between alcohol and schizophrenia.

In conclusion, our findings suggest that a co-morbid AUD can exaggerate structural differences in the shape of the hippocampus and subcortical structures previously reported in schizophrenia patients. A co-morbid AUD was also found to be related to deformations distinct from the pattern found in SCZ_0. Further research is needed to identify whether deformations are related to the direct effects of alcohol on the structure or related to an interaction between alcohol and schizophrenia.

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Contributors

All authors have made significant scientific contributions to this manuscript. Matthew J. Smith contributed to the conceptualization of the study, conducted the statistical analyses, and wrote the first draft of the manuscript. Drs. Csernansky and Barch contributed to the conceptualization and implementation of the study, secured funding, and assisted with the editing of the final manuscript. Dr. Wang contributed to the study conceptualization, finalizing the methods, and editing the manuscript. Drs. Cronenwett, Goldman, and Mamah contributed to the conceptualization of the study and to the editing of the manuscript. All authors approved the final manuscript.

Conflict of interest

There are no conflicts of interest between the authors and the reported research.

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