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ORIGINAL ARTICLE

Association Between Hippocampal Subfields and Clinical Symptoms of First-Episode and Drug Naive Schizophrenia Patients During 12 Weeks of Risperidone Treatment

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Abstract

Small hippocampal size may be implicated in the pathogenesis and psychopathology of schizophrenia (SCZ). However, does the volume of hippocampal subfields in SCZ patients affect response to antipsychotic treatment? In this study, we used risperidone to treat first-episode drug naïve (FEDN) SCZ patients for 12 weeks, and then explored the relationship between baseline hippocampal subfield volumes, as well as any changes in these hippocampal subfield volumes during treatment, and improvement in their psychopathological symptoms. By adopting a state-of the-art automated algorithm, the hippocampal subfields were segmented in 43 FEDN SCZ inpatients at baseline and after 12 weeks of risperidone monotherapy, as well as in 30 matched healthy controls. We adopted the Positive and Negative Syndrome Scale (PANSS) to assess psychopathological symptoms in patients at baseline and at post-treatment. Before treatment, SCZ patients had no significant differences in total or subfield hippocampal volumes compared with healthy volunteers. However, we found a significant correlation between a smaller left CA1 at baseline and a lower PANSS total score and general psychopathology sub-score at post-treatment (both $p < 0.05$). Furthermore, the left CA1 at baseline was significantly smaller in responders, who had >50% improvement in PANSS total score, than in non-responders ($p < 0.05$). Our results suggest that smaller left CA1 volume may be a predicator for improvement in psychotic symptoms of FEDN SCZ patients.

Keywords Schizophrenia · Hippocampus · First-episode · Risperidone · Treatment · Prediction

Introduction

Schizophrenia (SCZ) is one of the most common severe psychiatric disorders, with a prevalence rate around 1% worldwide [1]. Its core symptoms include positive symptoms, negative symptoms, and cognitive impairment. Although antipsychotic drugs can significantly improve the positive symptoms and some negative symptoms of patients, negative symptoms and cognitive impairment show limited responses [2, 3]. The incomplete response to antipsychotics in some SCZ patients is not readily predicted, but magnetic resonance imaging (MRI) technology can provide brain structure correlates for SCZ pharmacotherapy responses. In particular, many studies have demonstrated hippocampal volume reductions in SCZ patients' brains as the most distinguishing difference from healthy controls among both early and chronic patients [4–10]. Hippocampal abnormalities may be present before the first episode of psychosis [7, 11], and correlate with SCZ patients' clinical symptoms and cognitive impairment [9, 12–16].

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Anatomically, the formation of the hippocampus is not uniform, but consists of several subfields with distinct morphology and function, such as the cornu ammonis (CA) 1-4, dentate gyrus (DG), subiculum, and pre-subiculum or entorhinal cortex (EC) [17, 18]. In first-episode SCZ patients, one found lower CA1 and CA2 subfield volumes in the left hemisphere [19], while recent studies demonstrated that there was no difference in the volumes of hippocampal subfields between first-episode SCZ patients and healthy volunteers [9, 20]. In chronic medicated SCZ patients, several MRI studies identified hippocampal subfields with smaller volumes including the CA1, left CA2/3, and CA4/DG and subiculum [8, 9, 21]. Moreover, the positive symptoms especially hallucinations and delusions were inversely correlated with the bilateral CA1 and CA2/3 subfield volumes in chronic SCZ patients [22]. One study showed a significant association between smaller pre-subiculum volumes and negative symptoms [7]. Another study demonstrated reduced CA1 volume in early SCZ, with this focal atrophy in early illness extending to CA2/3 [9]. In contrast, one recent study showed significantly larger subfield volumes in bilateral CA4 and bilateral molecular and granular cell layers of DG in FEDN SCZ patients, but without differences from controls in total hippocampal volume [23]. Furthermore, several longitudinal studies have shown that antipsychotic treatment may affect hippocampal volumes [23, 24] with the dose of antipsychotic drugs being inversely associated with total hippocampal and subfield volumes [25, 26]. After 6-week antipsychotic treatment, patients displayed volume decreases in total hippocampus, as well as several subfields including those previously enlarged subfields at baseline, which were decreased to the levels of healthy controls [23]. One interpretation is that antipsychotic treatment may correlate with hippocampal brain tissue loss over time [23].

Based on this consensus of reduced hippocampal CA1 volume in chronic and perhaps FEDN SCZ patients and a potential antipsychotic role in reducing hippocampal brain tissue with greater antipsychotic doses, we examined the correlations between hippocampal subfield volumes particularly CA1 and clinical symptoms in FEDN SCZ patients during risperidone treatment. In this study, we selected risperidone as an antipsychotic because a previous study showed that the antipsychotic mechanism of risperidone needed to reduce hippocampal activity and reduce feedback through the cortex-striatum-thalamic loop [28]. A subsequent study assessed the significance of the hippocampal volume differences and its relation with risperidone treatment in SCZ. The results demonstrated that the patients who responded well to risperidone treatment had significantly greater hippocampal volumes than the patients who did not respond properly, suggesting that hippocampal volume may be a predictor of the treatment response of SCZ patients to risperidone [29]. The present study had three purposes: (1) whether the FEDN SCZ patients at baseline differed from controls in their hippocampal subfield volumes particularly in CA1 and whether those volumes correlated with baseline PANSS scores, (2) whether baseline CA1 volumes would predict FEDN SCZ patients' responses to risperidone treatment, and (3) whether risperidone treatment would have a significant effect on the hippocampal subfields like CA1, and whether any changes in the hippocampal subfields would correlate with improvements in psychopathological symptoms.

Although antipsychotic treatment has shown effects on the hippocampus [23, 24], no study has reported a relationship between changes in hippocampal subfields with risperidone monotherapy and improvement in clinical symptoms in patients with FEDN SCZ. Our results examining the relationship between changes in hippocampal subfields and improvement in clinical symptoms before and after 12 weeks of risperidone treatment may provide valuable information about the role of hippocampal subfields in the psychopathology of SCZ patients and the pharmacological mechanisms underlying the effects of antipsychotic treatment on this brain structure.

Methods

Subjects

A total of 43 FEDN inpatients were enrolled from the Beijing Hui-Long-Guan Psychiatric Hospital. The inclusion criteria included (1) meeting DSM-IV criteria for a SCZ diagnosis, made by two independent psychiatrists using the Structured Clinical Interview for DSM-IV (SCID); (2) an acute episode; (3) age between 16 and 45 years, Han Chinese; (4) course of disease $\leq$ 5 years; (5) no previous psychotropic drug treatment; and (6) having no a diagnosis of schizoaffective disorder.

We posted advertisements in neighborhoods near Beijing Huilongguan Hospital and also distributed pamphlets recruiting healthy controls to local residents, explaining the purpose of this study and who was eligible to be a healthy participant. Among those who expressed interest, we randomly recruited 30 healthy controls between the ages of 16 and 45 years during the same period. Under the supervision of a research psychiatrist, trained researchers interviewed them. They did not have a personal history of Axis I disease, assessed by the researchers using SCID, and their first-degree relatives did not have any known history of mental illness.

All participants underwent physical examination and laboratory tests. Exclusion criteria for the participants were (1) having current physical diseases, (2) personal and family

history of any brain diseases, (3) lifetime alcohol or substance abuse/dependence history except for tobacco, and (4) refusal to provide written informed consent.

The Institutional Review Committee of Beijing Huilongguan Hospital approved the research protocol. We obtained the written informed consent of each participant.

Study Design and Assessments

Risperidone was used to treat 43 patients for 12 weeks. During the first week, the risperidone dose was titrated to 3~6 mg per day and remained at these levels throughout the study period. Also, lorazepam or chloral hydrate was used for insomnia, and benzhexol hydrochloride (as needed) for extrapyramidal side effects. There was no other prescribed drug during the study.

By using the Positive and Negative Syndrome Scale (PANSS), two psychiatrists assessed the patient's psychopathological symptoms, while they were unaware of the patients' status. They both simultaneously received a training session in using PANSS before this study began. After training, they maintained an inter-rater correlation coefficient more than 0.8 for the PANSS total score during repeated assessments. They rated all patients at baseline and at the end of 12-week treatment. For each patient, the same investigator rated these scales at baseline and at 12 weeks.

Acquisition and Pretreatment of MRI Data

The structural T1-weighted scan of each subject was acquired on a GE 3 Tesla MRI scanner (GE Healthcare, Buckinghamshire, UK) using the spoiled gradient echo (SPGR) sequence with the following parameters: repetition time (TR) = 6.2 ms, echo time (TE) = 2.8 ms, flip angle = 8°, field of view (FOV) = 240 mm, slice thickness = 1.2 mm, matrix size = 256 × 256, and 142 slices.

Cortical reconstruction was performed with the FreeSurfer software (version 5.3.0; http://surfer.nmr.mgh.harvard.edu) [28]. The procedure included motion correction, intensity normalization, automated topology corrections, and automatic segmentations of cortical and subcortical regions. The cortex was segmented with Desikan-Killiany Atlas [29].

A novel automated algorithm from FreeSurfer was used to segment the hippocampal subfields. The subfield atlas was derived from high resolution (0.13 mm) ex vivo MRI data of postmortem medial temporal tissue from a 7-T scanner. This algorithm was proved to be more accurate than the previous method and was able to reliably identify granule cell layer (GCL) within the dentate gyrus (DG), and the molecular layer (ML) within the subiculum and the CA fields [13, 29]. The algorithm could also provide a better estimation of CA volumes. In the current study, we included eight hippocampal subfields: CA1, CA2 and CA3 (noted as CA3 due to the indistinguishable MR contrast between CA2 and CA3), CA4, GCL, ML, presubiculum (Presub), subiculum (Sub), and the hippocampal tail (Tail; the posterior end of the hippocampus) (Fig. 1) [13, 29].

We used a two-step quality control protocol, similar to the ENIGMA protocol (http://enigma.ini.usc.edu/) [13, 29]. To be brief, any outlier (five standard deviations) of any hippocampal subfield was excluded. Then, each segmented image, overlaid on the corresponding brain structural image, was visually inspected by two radiologists independently, in order to exclude segmentations with poor registration to the hippocampus location or with apparent wrong assignment of the subfields. We did not exclude any image because we did not find any outlier or bad segmentation of hippocampal subfields with the novel algorithm [29].

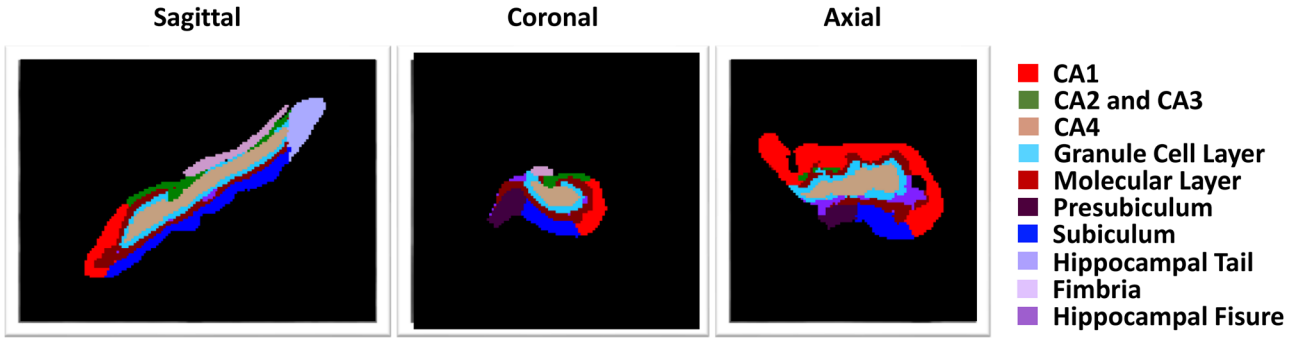

Fig. 1 Hippocampal subfield segmentation sample of a patient with schizophrenia. CA cornu ammonis

Statistical Analyses

Initial analysis included all patients and healthy controls. Normality of the data was analyzed by the Kolmogorov-Smirnov test. Given that the symptoms measured by PANSS and all hippocampal subfield volumes were normally distributed, parametric testing was performed, as shown below. x^2 test and one-way analysis of variance were performed to compare group differences. Further, after controlling for covariates such as intracranial volume (ICV), age, sex, and education, one-way analysis of covariance (ANCOVA) was employed to compare each hippocampal subfield between patients and healthy volunteers. Then, using ICV, age, and gender as covariates, a partial correlation was performed between general clinical data, clinical symptoms on PANSS scores, and hippocampal subfield volumes. Further stepwise multiple regression analysis was conducted to confirm the relationship among clinical variables, clinical symptoms, and hippocampal subfields.

The effect of treatment was assessed using repeated measures multivariate analysis of variance (MANOVA) with the PANSS scores and the hippocampal subfield volumes as outcome measures. Then, we performed partial correlation analysis to explore the relationship between symptom improvement and hippocampal subfield volume changes, with ICV, sex, age, and age of onset as covariates. To protect from Type I Error, we employed a Bonferroni correction for multiple tests. The new *p*-value was the alpha-vale divided by the number of comparisons or correlation analyses. Finally, exploratory regression analyses were carried out to investigate whether there were associations between changes in volumes of hippocampal subfields and improvement in clinical symptoms.

In addition, we used the criteria of a 50% or more improvement in PANSS total score to define "responders" or "non-responders." We examined whether risperidone treatment for 12 weeks altered the hippocampal subfield volumes and whether differences in the hippocampal subfields occurred between responders and non-responders.

All statistical analyses were carried out using SPSS version 18.0 (SPSS Inc., Chicago, United States). In addition, the G*Power 3.1.9.2 program was used to perform a power calculation. The significance level was $p < 0.05$ (two-tailed).

Results

Baseline Comparisons Between SCZ Patients and Healthy Volunteers

All patients and healthy controls were right-handed. We did not find significant differences in sex, age, and education between SCZ patients and healthy volunteers (all $p > 0.05$). Also, we did not observe significant differences in any of hippocampal subfields between SCZ patients and healthy volunteers (all $p > 0.05$). According to the range of effect sizes of hippocampal subfield volumes between SCZ patients and healthy controls reported in previous study [27], these hippocampal subfield volume comparisons between SCZ patients and healthy controls in this study had insufficient statistical power and had a power of 0.28–0.45 across the whole right and left hippocampus level.

Relationships Between Psychopathology and the Subfield Volumes in SCZ at Baseline

Using multivariate regression analysis, larger volumes of the right molecular layer ($p = 0.003$), left CA1 ($p = 0.008$), left hippocampal tail ($p = 0.014$), and left pre-subiculum ($p = 0.019$) were significantly correlated with worse PANSS negative symptom score at baseline, accounting for 41% of its variance.

Changes in Clinical Symptoms and Subfield Volumes After Treatment

Of these 43 patients, 3 dropped out before 12-week treatment, which we did not include in the statistical analysis. The remaining 40 patients completed the full 12-week trial, and their demographics and clinical parameters are present in Table 1. After 12 weeks of risperidone treatment, all PANSS three subscale scores and total score were significantly reduced (all $p < 0.05$; Table 1). After the Bonferroni correction ($\alpha = 0.05/20 = 0.0025$), all these results remained significant (all Bonferroni corrected $p < 0.05$), except for negative symptom score (Bonferroni corrected p>0.05).

Table 1 Clinical symptoms at pre-and post-treatment in first-episode schizophrenia patients treated with risperidone for 12 weeks

	Pre-treatment ($n = 43$)	Post-treatment ($n = 40$)	F	p-value
PANSS				
Positive subscale	25.2 ± 6.8	15.6 ± 7.4	57.9	<0.001
Negative subscale	21.2 ± 9.4	17.7 ± 8.0		0.014
General psychopathology	43.8 ± 14.0	29.8 ± 12.1	6.7	<0.001
Total score	90.6 ± 24.8	63.1 ± 24.8	55.2	<0.001

Relationship Between Changes in Clinical Outcome and Subfields Before and After Treatment

After 12 weeks of treatment, we obtained the hippocampal subfield data of 26 patients, because 10 patients refused to receive the second MRI scan and 4 patients were unable to obtain an MRI scanner. Because a large proportion of the sample did not agree to be scanned after 12 weeks of treatment, we compared those who did not complete the follow-up scan with those who did complete the follow-up scan in terms of age, gender, education, PANSS scores at baseline or post-treatment, and change in PANSS scores during treatment. However, there were no significant differences in any of the variables between the completion and non-completion groups (all $p > 0.05$).

After 12 weeks of risperidone treatment, we did not observe any significant changes in all hippocampal total and subfield volumes (all $p > 0.05$; Table 2). According to the range of effect sizes of hippocampal subfield volumes before and after antipsychotic treatment reported in previous study [27], these hippocampal subfield volume changes before and after risperidone treatment in this study had insufficient statistical power and had a power of 0.57–0.73 across the whole right and left hippocampus level.

We used the criteria of a 50% or more improvement in PANSS total score to define "responders" or "non-responders." Compared to the non-responder group (623.3 ± 56.8; n = 19), the responder group (582.6 ± 42.3; n = 21) showed significantly lower left CA1 volume at baseline ($F = 4.25$, df = 1, 39, $p < 0.05$). After controlling for the confounding factors, ANCOVA analysis still showed significant difference in left CA1 at baseline ($F = 3.88$, df = 6, 33, $p < 0.05$). However, this significance did not pass Bonferroni correction ($\alpha = 0.05/16 = 0.003$;Bonferroni corrected $p > 0.05$).

Further, we found a significant correlation between a larger left CA1 at baseline and a worse PANSS total score ($r = 0.35$, df = 40, $p < 0.05$) and general psychopathology sub-score at post-treatment ($r = 0.33$, df = 40, $p < 0.05$) (Fig. 2), which confirmed the above result dichotomizing the patients into "responders" and "non-responders." After controlling for ICV, sex, age, age of onset, and baseline PANSS total score as covariates, these correlations remained significant (both $p < 0.05$). However, these significances did not pass Bonferroni correction ($\alpha = 0.05 / 4 \times 16 = 0.0008$; both Bonferroni corrected $p > 0.05$). In addition, there were no significant correlations between the reduction of PANSS scores and changes in any hippocampal subfield volumes (all $p > 0.05$).

Table 2 Hippocampal subfield volumes in first-episode schizophrenia patients at pre- and post-treatment with 12 weeks of risperidone treatment

	Pre-treatment	Post-treatment		
	($N = 43$)	($n = 26$)	F	p
Left hippocampus	3342.7 ± 283.0	3343.6 ± 262.0	0.001	0.99
CA1	604.7 ± 60.5	602.9 ± 53.2	0.03	0.86
CA3	196.3 ± 18.6	196.7 ± 16.1	0.02	0.90
CA4	251.2 ± 24.9	252.6 ± 23.8	0.10	0.76
GCL	297.4 ± 29.2	297.7 ± 27.5	0.002	0.97
Presubiculum	300.0 ± 32.2	299.6 ± 28.6	0.01	0.93
Subiculum	400.0 ± 39.1	400.1 ± 38.1	0.05	0.83
Hippocampal tail	526.9 ± 72.9	525.1 ± 61.3	0.04	0.85
Molecular layer	543.6 ± 48.8	545.6 ± 46.9	0.06	0.82
Right hippocampus	3357.8 ± 275.0	3357.6 ± 222.4	0.000	1.00
CA1	624.0 ± 54.6	624.8 ± 45.6	0.011	0.92
CA3	208.0 ± 22.1	207.4 ± 19.7	0.01	0.94
CA4	255.8 ± 23.3	257.5 ± 21.9	0.14	0.71
GCL	301.0 ± 26.8	302.5 ± 24.6	0.09	0.74
Presubiculum	282.4 ± 36.1	280.9 ± 32.0	0.12	0.73
Subiculum	401.2 ± 38.8	399.0 ± 32.0	0.25	0.62
Hippocampal tail	519.7 ± 82.9	519.2 ± 66.6	0.003	0.96
Molecular layer	557.4 ± 45.8	557.0 ± 38.9	0.002	0.97

There were no significant differences in hippocampal subfields between schizophrenia patients and healthy controls (all $p > 0.05$)

CA cornu ammonis, *GCL* granule cell layer

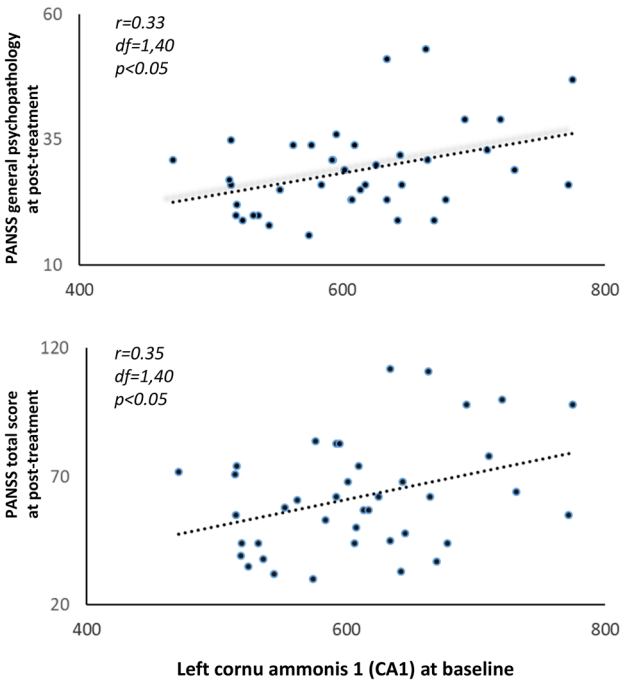

Fig. 2 After controlling for sex, age, education, age of onset, and intracranial volume (ICV), the partial correlation analysis showed that the volumes of left cornu ammonis 1 (CA1) at baseline was associated PANSS total score and general psychopathology (both $p <$ 0.05) at the end of 12 weeks of risperidone treatment in first-episode patients with schizophrenia

Discussion

This study found no significant hippocampal subfield volume deficits in FEDN SCZ patients compared to healthy controls, but small volumes of some subfields at baseline were associated with greater negative symptoms. However, this significance failed multiple testing corrections. In addition, no hippocampal subfield volumes showed significant volume changes after treatment. Taken together, these findings of this study predominantly indicate negative results. To our knowledge, this study provides the first evidence on longitudinal changes in specific hippocampal subfields and improvement in psychopathological symptoms in patients with FEDN SCZ after risperidone monotherapy. The finding of a significant association between baseline hippocampal subfield and response to risperidone treatment may provide a new way to understand the role of hippocampal subfields in predicting the effects of antipsychotic treatment.

Hippocampal Subfields in FEDN SCZ Patients at Baseline

Although many studies showed smaller volumes of the whole hippocampus or its subfields in SCZ [4, 6, 7, 9], we did not observe any hippocampal subfield volume deficits in the patients with FEDN SCZ, which is consistent with a previous study in patients with first-episode SCZ, showing no significantly abnormal hippocampal subfields [8]. Some studies have indicated that a longer course of disease and prior antipsychotic treatment may contribute to volume reductions of hippocampal subfields in SCZ patients [23, 24, 26]. One recent study indicated that longer untreated psychosis duration was also correlated with smaller whole hippocampal and some of subfield volumes [30]. Another study demonstrated that the CA1 volume was selectively decreased in patients in the early to mid-course of schizophrenia. Moreover, their longitudinal analysis demonstrated that the focal atrophy correlated with early disease extended beyond CA1 over time and involved other subfields, including CA2/3 and GCL [9]. Another longitudinal study showed that after 12-week antipsychotic treatment for patients with first-episode psychosis, DG and CA4 volumes were significantly reduced [31]. Another recent study showed significantly greater volumes of hippocampal subfields in FEDN SCZ patients at baseline, and after only 6-week treatment with antipsychotics, these patients exhibited volume reductions in total hippocampus and several subfields [27]. Our results suggest that acute or mid-term antipsychotic treatment may not impact hippocampal structural volume, although reduced hippocampal subfield volumes seem characteristic of chronic SCZ patients. Different antipsychotic drugs may also have different effects on hippocampal volumes, since our study used a monotherapy with risperidone at a relatively low to moderate dose of 3~6 mg/day, while the patients in other studies took various types of antipsychotic drugs [9, 27, 31]. A previous animal study reflected such medication specific effects such that olanzapine administration caused significant reduction in total hippocampus, CA1, and DG molecular layer volumes [32]. Thus, these results show reduced volumes of hippocampal subfields in chronically treated SCZ patients, but the results are mixed for FEDN patients,

While a recent study reported higher hippocampal subfield volumes in patients with first-episode antipsychotic naïve SCZ [27], another more recent study found more hippocampal subfield deficits (particularly right hippocampus) in never-treated than treated SCZ patients, suggesting that antipsychotic treatment may reduce shrinkage of hippocampal structures in SCZ [26]. These discrepancies may reflect different methods of acquiring the neuroimaging data or segmenting the hippocampal subfields, different course of disease, exposure to antipsychotic treatment, or even different ethnicities. We speculate that the hippocampus and its subfields may be unimpaired at the onset of SCZ, but the hippocampus gradually becomes damaged and shrinks with the development of illness. Contributing factors may be long-term exposure to chronic duration of disease, antipsychotic treatment, smoking, antipsychotic-induced side effects, or comorbid diseases.

We found that multiple hippocampal subfields including left CA1, right molecular layer, left pre-subiculum, and left hippocampal tail were significantly correlated with PANSS negative symptoms, but few other studies have explored the relationship between clinical symptoms and hippocampal subfields of SCZ patients. A previous study showed that the posterior CA1 and left anterior subfield volume deficits were correlated with positive symptoms, especially hallucinations and delusions [33]. A subsequent study found that CA1 and CA2/3 subfield volumes were negatively associated with PANSS [19]. Another study showed that smaller subiculum volumes were associated with negative symptoms [7]. Taken together with our findings, we propose that structural damage to the hippocampus is not evident at SCZ onset across all patients, but patients with smaller hippocampal subfields may have more severe negative symptoms, possibly due to abnormal functional activity in these subfields such as left CA1. Interestingly, a previous study reported that the right hippocampus of patients with first-episode SCZ had greater resting state activity, which was associated with more negative symptoms [34], as we found in the current study. Moreover, they found that negative symptoms were inversely related to cognitive functioning in relation

to hippocampal activation [34]. However, the mechanisms involved this association between some hippocampal subregions and negative but not positive symptoms at this stage of illness progression are not clear. Given that negative symptoms, cognitive impairment, and hippocampal dysfunction often occur in the prodromal phase of SCZ patients [7], it can be hypothesized that these phenotypes may include core features of the disease and may more accurately reflect the neuropathological state than positive symptoms.

It is worth mentioning that the hippocampus is a highly heterogeneous structure consisting of multiple subregions with different afferent and efferent projections [35], associated with the pathophysiology of schizophrenia [12, 36]. These abnormalities are also seen in relatives of schizophrenia patients, implying that genetic factors may play a role [37]. Various changes in hippocampal morphology, perfusion, and activation have been described in schizophrenia [12], for example, hippocampal hyperactivity, reduced hippocampal size, and, in particular, reduced populations of inhibitory neurons [38]. Several models of abnormal hippocampal formation circuits in schizophrenia have been developed [36]. Some symptoms of schizophrenia may be caused by malfunctions in hippocampal formation circuits. For example, increased excitability of CA3 may cause hallucinations [39]. According to the model of Tamminga et al., there is primary damage to the DG and reduced input to CA3, which is necessary for the production and retrieval of declarative memories and may lead to psychotic symptoms such as hallucinations and delusions [12]. These findings support the hypothesis of schizophrenia based on hippocampal formation circuits [36]. Although these first findings should be viewed with caution, we anticipate that better localization of abnormalities in hippocampal subregions in schizophrenia will help to understand the underlying pathophysiological mechanisms.

The Left CA1 Volumes at Baseline May Predict the Response to Risperidone Treatment for General Psychopathological Symptoms

We found no significant hippocampal subfield deficits in FEDN SCZ patients compared to healthy controls, but smaller baseline hippocampal subfield volumes, especially of CA1, may predict improvement with risperidone treatment, specifically in general psychopathological symptoms. A recent report revealed that baseline right CA3 volume was positively correlated with improvement in Global Assessment of Functioning (GAF) after 6 weeks of antipsychotic treatment [27], which is consistent with our current study when contrasting right to left sided hippocampal volumes (left relatively smaller). A previous study also showed that over a 6-year follow-up, a subgroup of SCZ patients exhibited an increase in bilateral hippocampal volumes, who had better results in clinical, cognitive and functional domains [40]. These findings indicate that the hippocampal volume at baseline may be a potential biomarker for antipsychotic treatment response in schizophrenia. However, hippocampal laterality may be important for the optimal use of this non-invasive biomarker to predict treatment response in early schizophrenia.

In this study, there are several limitations that need to be mentioned. First, the power for the current study was insufficient, ranging from 0.28 to 0.45 for the hippocampal subfield volume comparisons between SCZ patients and healthy controls, and from 0.57 to 0.73 for the hippocampal subfield volume changes before and after risperidone treatment. Considering that this was difficult to recruit FEDN SCZ patients. Although considering that this was difficult to recruit FEDN SCZ patients, our sample size in this study was still relatively small. Hence, results are worthwhile as preliminary and replicated research samples from different races will be important to confirm our results. In addition, studies with low statistical power increase the likelihood that a statistically significant finding represents a false positive result. Also, studies with low statistical power reduce the likelihood that a statistically significant result reflects a true effect [41, 42]. Currently, it appears that studies with low statistical power appear to be common in the biomedical sciences, especially in the neurosciences, which may depend on research methodology. Therefore, improving reproducibility and interpretability is very important and requires attention to well-established methodological principles [41, 42]. Second, in our current study, only a single antipsychotic drug risperidone at a relatively stable dose was used. Therefore, the dose correlation must be carefully considered, and whether the results of this study can be generalized to other antipsychotics and other higher doses requires further research. Third, the treatment duration of this study in FEDN schizophrenia is relatively short, and the effect of long-term antipsychotic treatment on the hippocampal subfields needs to be explored in the future. Finally, approximately one-third of patients did not have a scan after 12 weeks of risperidone treatment. Although we did not find significant differences in any of the variables between completers and non-completers, it was still possible that those who did not complete the follow-up scans differed from completers, which may have impacted observed results. This limitation should be compensated for in future studies.

In summary, we did not observe obvious baseline hippocampal subfield deficits in patients with FEDN SCZ; however, patients with larger hippocampal subfields may have more severe negative symptoms. We found that the baseline smaller left CA1 was significantly associated with the post-treatment PANSS general psychopathology and total scores after 12 weeks of risperidone treatment, suggesting that the smaller baseline left CA1 may predict the response to risperidone treatment. However, we found no significant

association between changes in hippocampal subfield volumes and improvement in clinical symptoms of SCZ patients after 12 weeks of treatment. Overall, due to the relatively limited sample size, using a single antipsychotic risperidone at a relatively modest and stable dose, and a relatively short treatment duration, replicated research samples from different ethnicities using different antipsychotic treatments for a long time will be optimal for supporting the use of this biomarker with antipsychotic treatment and prognosis.

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Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

Author Contribution XL and XZ made substantial contributions to the design of this study, and performed analysis, made interpretation of data, and drafted the manuscript. DC and MX were responsible for the acquisition of clinical and MRI data for this study. DW, HZ, and LW helped draft the work and revise it critically. BC helped to carry out the analysis of MRI data and interpret the results. All authors have made significant contributions to the paper for important intellectual content, and they have read and approved the final version of the paper to be published.

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Declarations

Conflict of Interest The authors declare no competing interests.

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