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In vivo analyses reveal hippocampal subfield volume reductions in adolescents with schizophrenia, but not with major depressive disorder

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ABSTRACT

Background: Adult studies have reported atypicalities in the hippocampus and subfields in patients with schizophrenia (SCZ) and major depressive disorder (MDD). Both affective and psychotic disorders typically onset in adolescence, when human brain develops rapidly and shows increased susceptibility to adverse environments. However, few in vivo studies have investigated whether hippocampus subfield abnormalities occur in adolescence and whether they differ between SCZ and MDD cases.

Methods: We recruited 150 adolescents (49 SCZ patients, 67 MDD patients, and 34 healthy controls) and obtained their structural images. We used FreeSurfer to automatically segment hippocampus into 12 subfields and analyzed subfield volumetric differences between groups by analysis of covariance, covarying for age, sex, and intracranial volume. Composite measures by summing subfield volumes were further compared across groups and analyzed in relation to clinical characteristic.

Results: SCZ adolescents showed significant volume reductions in subfields of CA1, molecular layer, subiculum, parasubiculum, dentate gyrus and CA4 than healthy controls, and almost significant reductions, as compared to the MDD group, in left molecular layer, dentate gyrus, CA2/3 and CA4. Composite analyses showed smaller volumes in SCZ group than in healthy controls in all bilateral composite measures, and reduced volumes in comparison to MDD group in all left composite measures only.

Conclusions: SCZ adolescents exhibited both hippocampal subfield and composite volumes reduction, and also showed greater magnitude of deviance than those diagnosed with MDD, particularly in core CA regions. These results indicate a hippocampal disease process, suggesting a potential intervention marker of early psychotic patients and risk youths.

1. Introduction

Both psychotic and affective disorders are prevalent types of mental disorders that have significant impact on daily life and increase the social burden (Masquelier et al., 2021). Extensive research has examined the mechanisms of pathophysiology for psychotic disorders, such as schizophrenia (SCZ), and affective disorders, such as major depressive disorder (MDD) (Gratton et al., 2020; Schmaal et al., 2020; Xia et al., 2019). Evidence suggests that core features of these psychiatric patients include memory deficits, reward and executive dysfunctions (Fox and Lobo, 2019; Yamashita et al., 2018; Zelazo, 2020). As a limbic structure, the hippocampus is likely to be involved in defects of memory, reward, and control processes as observed in mental disorders in general (Rolls et al., 2022) and in adult SCZ and MDD studies in particular (Haukvik et al., 2018; Roddy et al., 2019; Treadway et al., 2015).

Structural neuroimaging studies have consistently revealed smaller hippocampus volumes in SCZ patients (Roeske et al., 2021), but heterogeneous findings were found in patients with MDD (Ancelin et al.,

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2019; Brown et al., 2019; Ho et al., 2022; Shen et al., 2017). The hippocampus has been reported to be consisted of anatomically distinct and functionally specialized subfields that are diffusely connected with the cerebral cortex, thus forming "what," "where," and "reward" streams (Rolls et al., 2022). Various studies of SCZ patients have found reduced volumes in hippocampal subfields including CA1, CA2/3, CA4, which extended to other subfields, such as dentate gyrus and subiculum (Haukvik et al., 2015; Ho et al., 2017). These atypical volumes were systematically related to the cognitive and psychosis symptoms (Lang et al., 2022; Xiu et al., 2021). Other studies also reported severe hippocampal atrophy in individuals at high risk of SCZ (Choi et al., 2022).

For depression, some (but not all) neuroimaging studies have revealed hippocampal atypicalities in adult patients with MDD (Campbell et al., 2004; McKinnon et al., 2009). For example, the so far largest meta-analysis, based on cohorts from the ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) MDD Working Group, confirmed decreased hippocampal volumes in patients with MDD (Schmaal et al., 2016). However, opposite findings have also been reported (Shen et al., 2017). A recent 7T MRI study in MDD patients found no significant reductions in hippocampal volume, although these patients had an average 6.7-year episode (Brown et al., 2019). Overall, despite inconsistent findings, previous studies indicated that volumetric reductions in the hippocampal might be a biomarker for MDD and longer illness duration and increased numbers of episodes might aggravate hippocampal alterations (Schmaal et al., 2020).

Hippocampal in vivo studies revealed different kinds of damages in subfields in SCZ and MDD. SCZ has been found to impact the volume of almost all hippocampal subfields preferentially in CA regions, while MDD showed more alteration in the subiculum and dentate gyrus (Yeung and Brickman, 2020). Ota et al. (2017) directly compared the hippocampal volumes between SCZ and MDD and found that adults with SCZ exhibited significant volume reductions in the dentate gyrus, as compared to MDD patients and healthy controls. Although different degrees of severity of atypicalities in hippocampal subfields between in MDD and SCZ have been demonstrated, it remains unclear at what age these differences occur.

Psychiatric disorders including SCZ and MDD typically emerge in adolescence, during which human brain develops rapidly and encompasses increased susceptibility to adverse environments (Foulkes and Blakemore, 2018). Focusing on the early signs of damage to the hippocampus during adolescence may thus help facilitate detection and treatment. As for adolescents, inconsistent findings about hippocampal reductions have also been reported. The ENIGMA MDD study (Ho et al., 2022) and another one on hippocampus subfield (Zhang et al., 2021) demonstrated smaller hippocampal and subfield volumes in patients with adolescent onset of MDD, which was in line with several previous studies (Barch et al., 2019; Kim et al., 2019; MacMaster et al., 2008). A longitudinal, risk-enriched community study suggested that volumetric changes and attenuated growth of the hippocampus were associated with the onset of MDD (Whittle et al., 2014). However, other studies found lower hippocampal volumes in adult patients only, but not adolescents (Shen et al., 2016). These inconsistent findings might be due to the heterogeneity of patients (Kiviruusu et al., 2020), as more than half of adolescent-onset patients had a recurrent episode of MDD (Schmaal et al., 2020). Another reason might be related to the differential neuroplasticity of the adolescent brain through learning, social support, and family economic status (Fandakova and Hartley, 2020). For adolescents with SCZ, there are unfortunately only few studies on structural atypicalities in the hippocampal subfields and only few in vivo studies have explored whether hippocampus atypicalities occur in adolescence and whether they differ between SCZ and MDD.

To sum up, the hippocampus is a critical brain structure that plays a crucial role in both SCZ and MDD. Given the insufficient availability of data regarding the hippocampal deficiencies in adolescent SCZ and MDD, we aimed to investigate the diagnostic efficacy of SCZ and MDD on the early development of the hippocampus and its subfields. To achieve this, we analyzed 3-T structural MRI data from adolescent patients with SCZ and MDD, using an advanced automated hippocampal segmentation technique (Iglesias et al., 2015). We expected to identify shared and distinct atypicalities in hippocampal subfields. We hypothesized that patients with SCZ would show significant hippocampal atrophy and such effects would be more prominently compared to patients with MDD. Additionally, we investigated the association between duration of episodes and hippocampal subfield volumes in patients with SCZ or MDD, hypothesizing that longer duration would be linked to more pronounced alterations in these subfields. More generally speaking, our study was supposed to serve two more general goals: to demonstrate the neuroprogressive nature of early or first-episode psychiatric disorder, if possible, and to identify neural biomarkers of these disorders—which both will be useful for the development of successful interventions in the future.

2. Methods

2.1. Participants

A total of 175 adolescents was recruited from the Department of Psychiatry of the First Affiliated Hospital of Chongqing Medical University, China. After excluding three participants who were either aged younger than 10 years or older than 20 years, and additional 22 participants who had poor quality MRI images, the current study finally included 150 participants (49 adolescents with SCZ, 67 adolescents with MDD, and 34 healthy controls, HC). These subjects were also reported in a previous study (Zhou et al., 2021). All adolescent patients were diagnosed with either SCZ or MDD using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P, Chinese version) administered by two clinical psychiatrists.

The inclusion criteria for SCZ patients were as follows: a) presence of two or more of DSM-IV psychotic symptoms (delusions, hallucinations, disorganized thinking, grossly disorganized or catatonic behavior, negative symptoms) for the majority of the same month; b) absence of major depressive, manic, or combined episodes. The inclusion criteria for MDD patients were as follows: a) occurrence of five or more DSM-IV depressive symptoms, with at least one of these symptoms being depressed state or lack of interest or pleasure, within the recent two-week period; b) symptoms causing clinically significant distress or functional impairment in social, work, or other important areas; and c) symptoms not attributed to substances (e.g., drugs) or general medical conditions. Exclusion criteria for all these patients included: a) comorbidity with another psychiatric disorder, such as substance use disorders or dissociative disorders; b) any neurological disease or morphologic atypicalities in the brain; c) any MRI contraindication, such as claustrophobia; d) current or prior history of psychotic symptoms (hallucination, delusion, etc) for adolescents with MDD. All HC subjects were recruited via public advertisements and had no diagnoses of current or historical psychiatric, neurological diseases.

This study was approved by the local ethics committees of both First Affiliated Hospital of Chongqing Medical University and Shandong Normal University. All participants and their legal guardians provided written informed consents.

2.2. MRI data acquisition, preprocessing and segmentation of hippocampal subfields

All adolescent participants were scanned on a 3 T GE Signa Medical Systems scanner (Milwaukee, Wisconsin, USA) using a 12-channel head coil at the First Affiliated Hospital of Chongqing Medical University. We acquired 3D high-resolution anatomical T1-weighted images that covered the whole brain (TE = 3272 ms, TR = 8348 ms, flip angle = 12°, field of view = 240.128 × 240.128 mm^2, voxel size = 0.469 × 0.469 × 1.00 mm^3).

T1-weighted scans were preprocessed using the standard procedure

of FreeSurfer (version 6.0.0, http://surfer.nmr.harvard.edu) image analysis suite for volumetric and surface segmentation of the whole brain (Dale et al., 1999; Fischl and Dale, 2000). The original and processed brain images were visually inspected by two specialists for any anatomical or segmentation anomalies. Then, the advanced automated segmentation of the hippocampus was performed using Bayesian inference (Iglesias et al., 2015), resulting in the segmentation of both left and right hippocampus into 12 subfields. These subfields included the hippocampal tail, subiculum, CA1, fissure, presubiculum, parasubiculum, molecular layer, dentate gyrus, CA2/CA3, CA4, fimbria, and HATA (Fig. 1). Additionally, composite measures were computed by summing substructure volumes as suggested by a previous study (Roddy et al., 2019), which resulted in 7 composite measures for each hemisphere. These composite measures including Hippocampal Extended (HE, all computed hippocampal substructures except the fissure), Hippocampal Formation (HF, comprising of CA, dendate gyrus, subiculum and the tail components), Hippocampal Proper (HP, consisting of the all CA regions), combined dentate (CA4 and dentate gyrus), CA Only (CA1, CA2/3), Combined dentate/CA (dentate and CA regions), and CA2-CA4 (CA2/3 and CA4). The novel definition of hippocampal volumes could improve inter-subject inconsistencies and highlight the core of CA subfields in the process of disorder (Roddy et al., 2019).

2.3. Statistical analysis

Statistical analyses were performed using SPSS 26.0. Analyses of variance (ANOVA), two-sample *t*-test, and χ^2 test were performed to assess the groupwise differences in demographics and clinical characteristics among HC, MDD, and SCZ groups. Then, a mixed factorial ANOVA model was applied to assess the main effects and interactions of the diagnosis and hemisphere factors on the volume of hippocampal subfields. The 3 × 2 mixed ANOVA model included one dichotomous between-subjects variable (Diagnosis, 3 factors, HC, MDD and SCZ) and one dichotomous within-subjects variable (Hemisphere, 2 factors, left and right). Additional post-hoc analyses were performed to examine between-diagnosis differences (HC vs MDD vs SCZ, HC vs MDD, HC vs SCZ and MDD vs SCZ) in 12 hippocampal subfields. In these analyses, gender, age, and total intracranial volume (TIV) were included as covariates. False discovery rate (FDR) correction was applied for multiple comparisons to control type I error with R 4.1.1 (Genovese et al., 2002). Additionally, these models were applied to the composite measures of the hippocampus to demonstrate whether CA regions exhibited core effects. Finally, the associations between duration of episodes and hippocampus subfields and composite measures were examined by partial correlation analyses, separately for MDD and SCZ groups, covarying for gender, onset age, and TIV.

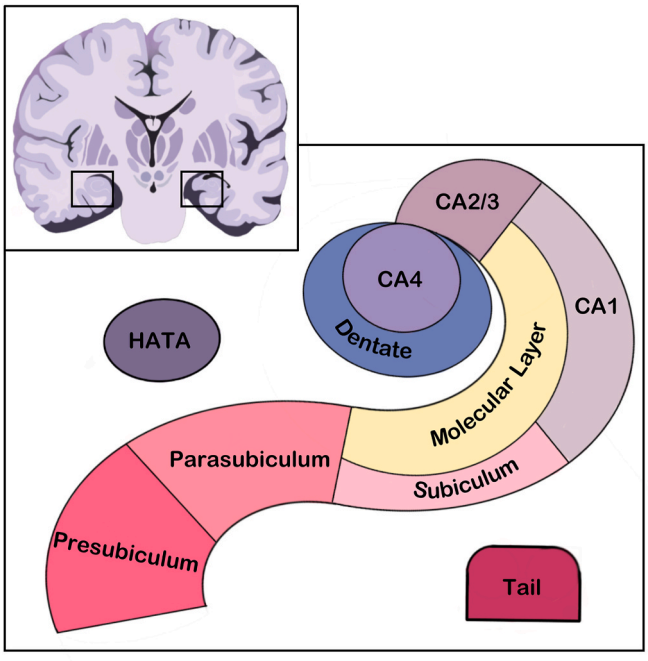

Fig. 1. Automated segmentation of hippocampal subfields using Freesurfer software. CA, cornu ammonis; HATA, hippocampal amygdalar transition area.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of all adolescent participants (HC, n = 34; MDD, n = 67; SCZ, n = 49) are presented in Table 1. Between group comparisons demonstrated no significant differences regarding gender ($\chi^2 = 0.60$, p = 0.742), age (F = 0.21, p = 0.810) and TIV (F = 0.82, p = 0.444) among all three groups.

With regard to clinical characteristics, no significant differences were found between the MDD and SCZ groups in terms of current episode duration (MDD: 7.88 ± 9.19; SCZ: 6.24 ± 12.29; t = 0.82, p = 0.412), number of participants with their first episode (MDD: n = 48; SCZ: n = 42; $\chi^2 = 3.22$, p = 0.073), and family history of mental disorders (MDD: n = 7; SCZ: n = 8; $\chi^2 = 0.87$, p = 0.352). As for treatment, a greater number of SCZ patients received medication (MDD: n = 34; SCZ: n = 42; $\chi^2 = 15.32$, p < 0.001) and physical therapy (MDD: n = 12; SCZ: n = 27; $\chi^2 = 17.54$, p < 0.001) than MDD patients, including transcranial magnetic stimulation and electric shock, which was consistent with the pathology of mental disorders (Kellner et al., 2020).

3.2. Volumetric measures of hippocampus subfields

For these 12 hippocampus subfields (descriptive values and their distribution were shown in Table S1 and Fig. 2), the mixed factorial ANOVA model yielded no significant interaction effects (Table S2) between diagnosis and hemisphere after FDR correction (all $p_s > 0.05$). However, significant main effects were observed for diagnosis in several subfields, including subiculum (F = 4.44,$\eta^2 = 0.03$, p = 0.022), CA1 (F = 12.47,$\eta^2 = 0.08$, p < 0.001), molecular layer (F = 10.49,$\eta^2 = 0.07$, p < 0.001), dentate gyrus (F = 5.88,$\eta^2 = 0.04$, p = 0.009), CA2/3 (F =

Table 1
Demographic and clinical characteristics of the adolescent sample.

Characteristics	HC (N = 34)	MDD (N = 67)	SCZ (N = 49)	*p*-value	F/t/χ^2
Gender (Male, %)	15 (44.12)	28 (41.79)	24 (48.98)	0.742	0.60
Age (year, Mean ± SD)	16.32 ± 2.99	16.22 ± 2.02	16.02 ± 1.80	0.810	0.21
TIV (year, Mean ± SD)	1484.68 ± 108.24	1459.73 ± 127.77	1448.33 ± 141.57	0.444	0.82
Current episode duration (month, Mean ± SD)	–	7.88 ± 9.19	6.24 ± 12.29	0.412	0.82
First episode (N, %)	–	48 (71.64)	42(85.71)	0.073	3.22
Treatment with medicine (N, %)	–	34 (50.75)	42 (85.71)	<0.001*	15.32
Physical intervention (N, %)	–	12 (17.91)	27(55.10)	<0.001*	17.54
Family history of mental disorders (N, %)	–	7 (10.45)	8(16.33)	0.352	0.87

HC, healthy control; MDD, major depressive disorder; SCZ, schizophrenia; TIV, total intracranial volume. *p* values with "*" indicated the significance with <0.05.

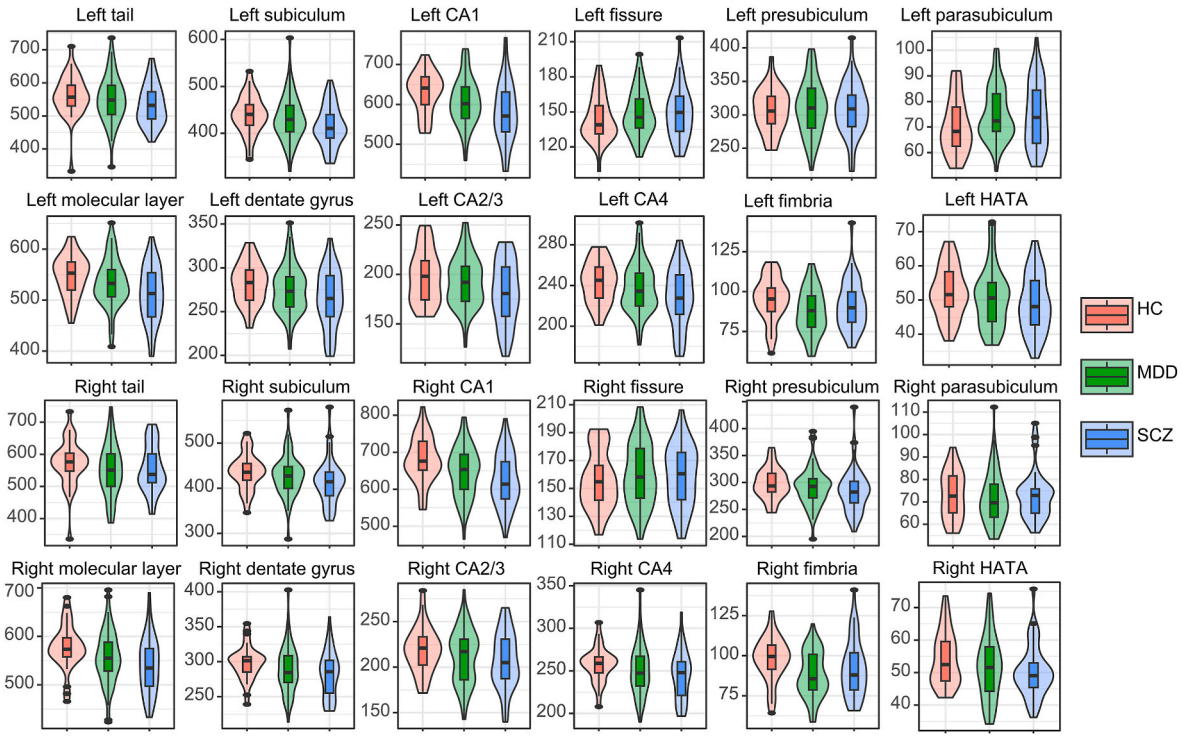

Fig. 2. Distribution of bilateral 12 hippocampal subfield volumes in HC, MDD and SCZ groups. Violin plots illustrating the data distributions (probability density), median and interquartile ranges. CA, cornu ammonis; HATA, hippocampal amygdalar transition area.

4.49,$\eta^2 = 0.03$, p = 0.022), CA4 (F = 5.20,$\eta^2 = 0.04$, p = 0.014) and fimbria (F = 7.31,$\eta^2 = 0.05$, p = 0.003). Main effects for hemisphere also revealed significances in subfields of CA1 (F = 41.53,$\eta^2 = 0.13$, p < 0.001), fissure (F = 20.99,$\eta^2 = 0.07$, p < 0.001), presubiculum (F = 21.38,$\eta^2 = 0.07$, p < 0.001), molecular layer (F = 28.59,$\eta^2 = 0.09$, p < 0.001), dentate gyrus (F = 27.78,$\eta^2 = 0.09$, p < 0.001), CA2/3 (F = 51.65,$\eta^2 = 0.15$, p < 0.001), and CA4 (F = 33.59,$\eta^2 = 0.10$, p < 0.001).

Further post-hoc analyses of covariance for each hippocampus

Table 2
Between group differences in volumetric substructures of hippocampus.

	HC vs. MDD vs.SCZ *p* Value	Effect Size, HC vs. MDD vs.SCZ, η^2	Pairwise Comparison HC vs. MDD *p* Value	Pairwise Comparison HC vs. SCZ, *p* Value	Pairwise Comparison MDD vs. SCZ p Value
Left Substructure					
Tail	0.261	0.022	0.715	0.155	0.182
Subiculum	0.134	0.033	0.750	0.076	0.135
CA1	0.020 *	0.082	0.275	0.021 *	0.066
Fissure	0.400	0.014	0.597	0.206	0.919
Presubiculum	0.617	0.007	0.597	0.444	0.919
Parasubiculum	0.067	0.047	0.107	0.075	0.919
Molecular layer	0.020 *	0.076	0.597	0.021 *	0.066
Dentate gyrus	0.067	0.046	0.597	0.076	0.089
CA2/3	0.067	0.046	0.597	0.100	0.066
CA4	0.067	0.048	0.597	0.076	0.066
Fimbria	0.083	0.041	0.107	0.376	0.182
HATA	0.272	0.020	0.597	0.155	0.294
Right Substructure					
Tail	0.642	0.008	0.487	0.472	0.832
Subiculum	0.318	0.027	0.694	0.156	0.399
CA1	0.032*	0.079	0.192	0.010 *	0.390
Fissure	0.642	0.007	0.487	0.464	0.832
Presubiculum	0.618	0.011	0.705	0.323	0.552
Parasubiculum	0.823	0.003	0.720	0.836	0.766
Molecular layer	0.059	0.062	0.382	0.018 *	0.390
Dentate gyrus	0.246	0.034	0.487	0.100	0.399
CA2/3	0.382	0.019	0.487	0.265	0.487
CA4	0.318	0.025	0.491	0.156	0.399
Fimbria	0.064	0.056	0.023*	0.273	0.399
HATA	0.359	0.021	0.487	0.156	0.585

HC, health control; MDD, major depressive disorder; SCZ, schizophrenia. *p* values indicated the survived FDR correction. p values with "*" indicated significant differences (<0.05).

subfield of each hemisphere were conducted to investigate the diagnosis and hemisphere effects (Table 2), covarying for gender, age, and TIV. The results revealed that, compared to HCs, the SCZ group had significantly smaller volumes of bilateral CA1 (left, $F = 9.72, \eta^2 = 0.11$, $p = 0.021$; right, $F = 12.12, \eta^2 = 0.13$, $p = 0.010$), bilateral molecular layer (left, $F = 9.08, \eta^2 = 0.10$, $p = 0.021$; right, $F = 9.43, \eta^2 = 0.11$, $p = 0.018$), and a trend toward significance for left subiculum ($F = 4.68, \eta^2 = 0.06$, $p = 0.076$), parasubiculum ($F = 5.77, \eta^2 = 0.07$, $p = 0.075$), dentate gyrus ($F = 4.75, \eta^2 = 0.06$, $p = 0.076$) and CA4 ($F = 4.45, \eta^2 = 0.05$, $p = 0.076$) (Table 2 and Fig. 3). In addition, the MDD group had a significant smaller volumes of right fimbria ($F = 10.17, \eta^2 = 0.10$, $p = 0.023$) compared to the HC group. Results also revealed that SCZ group showed a trend toward significance of decreased volume in subfields of the left molecular layer ($F = 7.45, \eta^2 = 0.06$, $p = 0.066$), dentate gyrus ($F = 4.45, \eta^2 = 0.04$, $p = 0.089$), CA2/3 ($F = 5.65, \eta^2 = 0.05$, $p = 0.066$) and CA4 ($F = 5.40, \eta^2 = 0.05$, $p = 0.066$) compared to adolescents with MDD (Table 2 and Fig. 3). Finally, we added the medicine treatment and physical intervention as additional covariates for the SCZ vs. MDD analysis. The results showed no significant differences in any subfield volumes between the two groups (Table S3).

3.3. Composite measures of hippocampus

In the mixed factorial ANOVA analysis of composite measures, we did not find any significant interaction effects between diagnosis and hemisphere for the 7 composites examined (all $p_s > 0.05$, Table S4). However, we observed significant main effects of diagnosis (all $p_s < 0.005$) and hemisphere (all $p_s < 0.001$) (Table S4). We then performed post-hoc analysis of covariance for each hippocampus composite measure, also covarying for gender, age, and TIV. In both the left and right hippocampus, the SCZ group exhibited significantly smaller volumes than the HC group (Table 3) for all 7 composite measures (all $p_s < 0.05$), except for the right CA2-CA4 composite, which showed a marginal significance ($p = 0.083$). Additionally, SCZ group showed significantly smaller composite volumes than the MDD group for left hemispheric composite measures only (all $p_s < 0.05$, Table 3). Finally, for the SCZ and MDD comparison analysis, we included the medicine treatment and physical intervention as additional covariates. Results found that SCZ group still showed significantly smaller volumes than MDD groups for left composite measures (all $p_s = 0.06$, Table S5).

3.4. Associations with clinical symptom

In the MDD group, partial correlation analyses revealed a significant correlation between the duration of episodes and subfields of bilateral CA2/3, with negative correlations observed for both left ($r = -0.29$, $p = 0.022$) and right ($r = -0.28$, $p = 0.025$) hippocampus. However, no significant correlation was found between the duration of episodes and any composite measures in adolescents with MDD. On the other hand, in the SCZ group, no significant correlation was found between the duration of episodes and any hippocampus subfields or composite measures.

4. Discussion

The present study aimed to investigate possible differences in hippocampus subfield volumes between adolescents with MDD and SCZ. Using an adolescent MRI dataset and an automated hippocampal subfields segmentation algorithm, we found the following results of interest. Firstly, compared to healthy controls, adolescents with SCZ demonstrated significant hippocampal volume reduction, with the impaired area spreading outwards with CA regions as the core. Additionally, SCZ patients exhibited a reductive trend in the hippocampal subfields compared to those with MDD. Furthermore, increased duration of episodes was significantly associated with greater atypicality in bilateral CA2/3 for the MDD group.

Our study found that the influence of SCZ on the hippocampus were preferentially reflected in CA1 and molecular layers, and with a trend towards regions of subiculum, parasubiculum, dentate gyrus, and CA4. As the intergral part of hippocampal circuitry, CA1 contains pyramidal neurons that generate much of output to subiclum and other regions (Tannous et al., 2018). The molecular layer includes interneurons that connects the subiclum and other CA regions. Subiculum and parasubiculum make up the outflow parts of hippocampal circuitry and receive the signal from the hippocampal intergral part. Prior studies also found that CA1 was involved in self-awareness (Danjo et al., 2018), contextual memory retrieval (Dimsdale-Zucker et al., 2018), and autobiographical memory (Bartsch et al., 2011), and was particularly vulnerable to a variety of cytotoxic and metabolic challenges (Bartsch

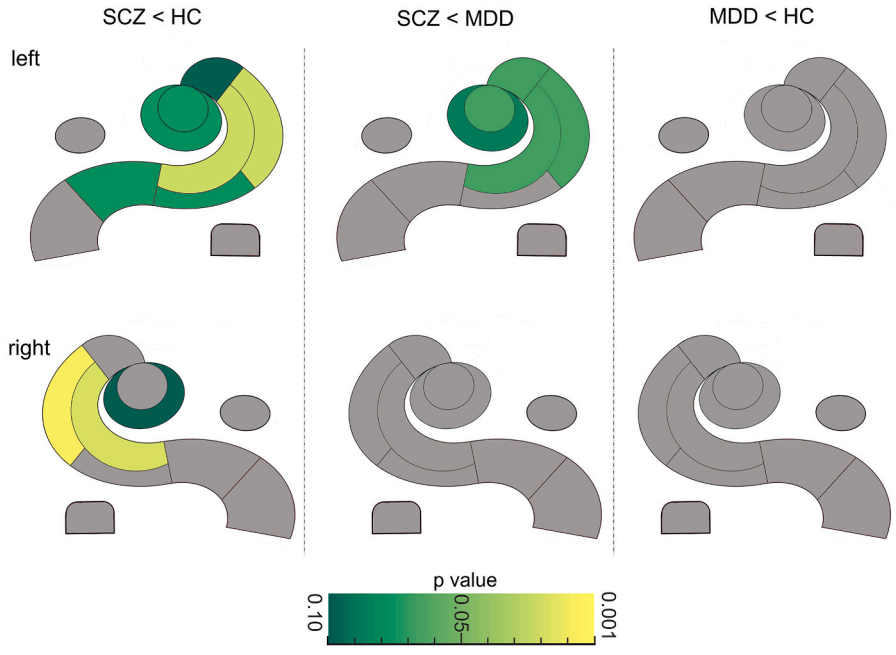

Fig. 3. Group comparisons of hippocampal subfield volumes. (a) Differences in hippocampal subfield volumes between adolescents with SCZ and HC; (b) differences in hippocampal subfield volumes between adolescents with SCZ and MDD; (c) differences in hippocampal subfield volumes between adolescents with MDD and HC.

Table 3
Between group differences in volumetric composite measures of hippocampus.

	HC vs. MDD vs.SCZ *p* Value	Effect Size, HC vs. MDD vs.SCZ, η^2	Pairwise Comparison HC vs. MDD *p* Value	Pairwise Comparison HC vs. SCZ, *p* Value	Pairwise Comparison MDD vs. SCZ p Value
Left Hippocampal Composite					
Hippocampal Extended	0.017 *	0.059	0.472	0.013 *	0.021 *
Hippocampal Formation	0.009 *	0.077	0.450	0.013 *	0.021 *
Hippocampal Proper	0.009 *	0.075	0.417	0.013 *	0.021 *
Left Anatomical Composite					
Combined Dentate	0.031 *	0.047	0.472	0.040 *	0.029 *
CA Only	0.009 *	0.079	0.417	0.013 *	0.021 *
Combined Dentate/ CA	0.009 *	0.070	0.417	0.013 *	0.021 *
CA2-4	0.026 *	0.051	0.472	0.040 *	0.021*
Right Hippocampal Composite					
Hippocampal Extended	0.037 *	0.051	0.135	0.014 *	0.211
Hippocampal Formation	0.037 *	0.049	0.135	0.015 *	0.211
Hippocampal Proper	0.037 *	0.058	0.135	0.014 *	0.211
Right Anatomical Composite					
Combined Dentate	0.130	0.030	0.318	0.043 *	0.211
CA Only	0.037 *	0.065	0.135	0.014*	0.211
Combined Dentate/ CA	0.037 *	0.054	0.135	0.014 *	0.211
CA2-4	0.172	0.024	0.318	0.083	0.217

HC, health control; MDD, major depressive disorder; SCZ, schizophrenia. *p* values indicated the survived FDR correction. p values with "*" indicated significant differences (<0.05).

et al., 2015). The decreased volumes in these subfields found in adolescents with SCZ suggested that disruption of hippocampal circuitry occurred through the internal to output way. Taken together, these findings may explain why patients with SCZ show severe cognitive deficits besides the positive symptoms. Moreover, our findings are in line with previous studies of adult SCZ patients (Ho et al., 2017), indicating that the age of onset for psychotic disorder does predict differential damages to the hippocampus.

Compared to affective disorders, the structural atypicalities of the hippocampus might be more extensive in patients with psychotic disorders. The main symptoms of SCZ include hallucinations, delusions, disorganized speech, lack of motivation, trouble with thinking and other cognitive functions, such as memory (Aleman et al., 1999), attention (Carter et al., 2010)—all of which are relate to the hippocampus (Tyng et al., 2017). In affective disorders, there are considerable individual differences across patients with MDD. Although the majority of depressed patients show long-term mood atypicalities, there seems no significant impairment of orientation and spatial memory in some patients with MDD. For example, Tannous et al. (2018) found significantly smaller volumes in the hippocampal subfields, including right CA1, bilateral molecular layer, in adolescents with bipolar disorder, but no significant differences in hippocampus in adolescents with MDD, compared to both bipolar disorder and healthy controls. Overall, existing evidence suggests that symptom severity might be critical for the greater significances of hippocampal atypicalities in psychotic disorders.

This study focused on adolescents, and the results may provide some insights into future interventions in adolescent mental disorders. Currently, the treatment of severe cases of SCZ and MDD has mainly focused on drug intervention, such as escitalopram and aripiprazole treatment (Islam et al., 2022), and physical intervention, including electroconvulsive therapy (Jiang et al., 2022). The significant volumetric reduction of the hippocampus in adolescents with SCZ and associations between the duration of episode and atypicality of subfields in MDD suggested that cognitive intervention and non-invasive brain stimulation targeting the hippocampus might be useful in reducing the severity of symptoms. In addition, as a treatment without side effects, these non-invasive interventions might effectively prevent the transition from MDD to SCZ and stop the deterioration of depressive symptoms. In conclusion, non-invasive stimulation and cognitive training targeting the hippocampus might be useful for early prevention and interventions in individuals with mental disorders.

There are several limitations in this study that should be acknowledged. First, the sample size of this study is relatively small, which might reduce the statistical power and limit the generalizability of the findings to larger populations. Future studies with larger sample sizes of adolescents are needed to replicate these results. Second, as the hippocampus is a subcortical structure, its imaging is more susceptible to the artifacts and technical limitations that could decrease the segmentation performance. We scanned the hippocampus with 3T MRI and a 12-channel head coil, which might increase the artifacts and lower the microstructural detection. Together with the novel segmentation method used in this study, the use of ultra-high field MRI, such as 7T or higher (Brown et al., 2019), and auxiliary imaging data, such as T2-weighted structural images (Roddy et al., 2019), could potentially improve the accuracy of hippocampal segmentation in future studies. Third, the participants of the current study were not assessed for memory or other cognition-related functions, which precluded the investigation on potential associations between hippocampal volume and cognitive impairments. Future studies that include comprehensive cognitive assessments would provide a more complete understanding of the role of hippocampus in cognitive functioning in adolescents with mental disorders.

5. Conclusions

In summary, our study included an adolescent MRI dataset and adopted a hippocampal segmentation algorithm and revealed that psychotic disorders in adolescence were strongly associated with hippocampal CA regions, the core subfields of the hippocampus, and the outflow parts of hippocampal circuitry. Additional subfield and composite analyses suggested that adolescents with SCZ showed greater volume reduction than MDD patients in core CA regions of the hippocampus. These findings indicated a hippocampal disease process and suggested a potential invention marker in early psychotic patients and at-risk youths.

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Authors' contributions

Kangcheng Wang: conceptualization, methodology, software, formal analysis, and writing. **Xingyan Li**: conceptualization, methodology, software, and formal analysis. **Xiaotong Wang**: figure drawing by hands. **Bernhard Hommel**: writing. **Xiaodi Xia**: data collection. **Jiang Qiu**: data collection, and writing. **Yixiao Fu**: data collection, and writing. **Zheyi Zhou**: conceptualization, methodology, software, formal analysis, and writing.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2023.07.012.

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