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Altered functional connectivity and hyperactivity of the caudal hippocampus in schizophrenia compared with bipolar disorder: a resting state fMRI (functional magnetic resonance imaging) study

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Abstract

Background Schizophrenia patients frequently present with structural and functional abnormalities of the hippocampus (Hipp). Further, these abnormalities are often associated with specific symptom profiles.

Aim To determine whether schizophrenia patients show specific functional connectivity (FC) and activity abnormalities in each hippocampal subregion compared to the BD (bipolar disorder) and HC (healthy control) groups.

Methods Basal activation state and functional connectivity (FC) in four subregions of the bilateral Hipp were examined: left caudal (cHipp_L), right caudal (cHipp_R), left rostral (rHipp_L), and right rostral (rHipp_R). Resting-state functional magnetic resonance images were obtained from 62 schizophrenia patients, 57 bipolar disorder (BD) patients, and 45 healthy controls (HCs), and analyzed for fractional amplitude of low-frequency fluctuations (fALFF) as a measure of basal neural activity and for whole-brain FC based on the hippocampal subregions.

Results The schizophrenia group exhibited greater fALFF in bilateral cHipp (the caudal part of hippocampus) and rHipp (the rostral part of hippocampus) subregions compared to BD and HC groups as well as increased FC between the bilateral cHipp and multiple brain regions, including the thalamus, putamen, middle frontal gyrus, parietal cortex, and precuneus. Moreover, fALFF values of the bilateral cHipp were positively correlated with the severity of clinical symptoms as measured by the Positive and Negative Syndrome Scale.

Conclusions These findings confirm an important contribution of hippocampal dysfunction, especially of the cHipp, in schizophrenia. Further, hyper-connectivity and hyperactivity of the cHipp could serve as a biomarker for therapeutic development.

Keywords Schizophrenia, Resting state functional magnetic resonance, Caudal hippocampus

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Introduction

Schizophrenia is a severe psychiatric disorder that afflicts 1% of the global population, characterized by delusions, hallucinations, disorganized thinking, cognitive impairment, and negative symptoms [1]. A highly heritable disorder, schizophrenia may result from deficits in brain development and maturation, and symptoms frequently emerge between late adolescence and early adulthood [2]. While not directly fatal, the mental disease is associated with a 15-year reduction in life expectancy compared to the general population, in part due to a 5% to 10% lifetime risk of death by suicide [3]. The success of treatment for schizophrenia is variable, mainly because of an incomplete understanding of the pathophysiology underlying schizophrenia. Basic research into structural and functional impairments of key nodes in the brain is of great significance for the diagnosis and treatment of the disease.

Hippocampus is involved in multiple cognitive functions, such as emotion regulation, stress responses, visuospatial orientation and memory [4], also correlated with the formation of psychotic symptoms in schizophrenia or bipolar disorder [5, 6]. Moreover, a general reduction in hippocampal volume has been reported among asymptomatic individuals that eventually develop psychosis [7]. Functional magnetic resonance imaging (fMRI) have revealed dysconnectivity with other regions of the central nervous system [8, 9] potentially associated with dysregulation of synaptic development and synaptic protein expression [10, 11]. In addition, other functional imaging modalities have revealed higher resting metabolism and blood flow in the hippocampus of patients with schizophrenia [12].

Hippocampal dysfunction in schizophrenia is important to the impaired formation of habituation (an inability to modulate responses after repeated presentations of sensory stimuli), specific memory deficits, and dopaminergic system hyperactivity [13, 14]. Additionally, the magnitudes of structural and functional abnormalities of hippocampal correlated with clinical symptom severity and predict clinical progression from a prodromal to psychotic state [15]. There seemed to be a small alteration in hippocampal structure and function in BD [16]. Several studies have reported hippocampal subfield-level volume reductions and localized functional deficits in BD patients [16, 17]. Lithium treatment was associated with larger hippocampal volumes [18].

Resting-state functional MRI (rs-fMRI) is widely used to measure blood oxygen level-dependent (BOLD) signal during rest to evaluate brain function. In recent years, Experts are concerned to achieve highly reliable measures of brain connectivity [19, 20]. Amplitude of low-frequency fluctuation (ALFF) was computed as the mean power spectrum in a specific low-frequency band (0.01–0.1 Hz) [21], and the fALFF was the ratio of the power spectrum in the low-frequency band (0.01–0.1 Hz) to the entire frequency range [22]. ALFF (fALFF) is an efficient index that quantifies local spontaneous neuronal activity, reflects the regional metabolic level of glucose and shows high test–retest reliability [23].The fractional ALFF (fALFF) is one of the most common metrics used to quantify these neural oscillations [22]; Functional connectivity (FC) is one of the most popular approaches to measure multi-regional cooperation within a special network, and it is capable of detecting the synchronization between regions. Both ALFF (fALFF) and the functional connectivity have been used to infer brain activity in psychiatric disorders [24–26]. Higher fALFF in the hippocampus were found in the individuals in the early stage of non-affective psychosis [27]. Furthermore, previous research reported spreading of hippocampal hyperactivity were proposed as a marker of illness progression [28].

So far, the role of the hippocampus in schizophrenia or bipolar disorder neuropathology is not fully understood. With substantial advances in magnetic resonance imaging (MRI) tools, new hippocampal segmentation algorithms have made it possible to label hippocampal subfields according to the Human Brainnetome Atlas identified by a connectivity-based parcellation framework [29]. Functional dissociations between rostral and caudal hippocampus have also been observed in humans and animals [30], including in the processing of novel versus repeated stimuli, emotional versus non-emotional stimuli, and encoding versus retrieval [31, 32].The posterior hippocampus has been implicated in the retrieval of memories associated with spatial context, while the anterior hippocampus mediates less context-dependent relational memory processes [33].

Basic behavioral and cognitive neuroscience studies have revealed important functional differences across the rostral-to-caudal axis of the hippocampus. However, it is unclear whether rostral and caudal subregions are differentially affected in schizophrenia or bipolar disorder. Therefore, additional studies are required to elucidate the precise relationships of axial subregions and the pathophysiology of schizophrenia to encourage more region-specific research.

In this study, we compared fractional amplitude of low-frequency fluctuations (fALFF) and FC of 4 subregions of the bilateral hippocampus among schizophrenia (SCH), bipolar disorder (BD) and healthy control (HC) groups. We hypothesized that the SCH group would show abnormal FC and activities in each hippocampal subregion compared to the other two groups. These findings could provide the dysfunction of key localized brain nodes

related to schizophrenia and new therapeutic targets for schizophrenia.

Materials and methods

Participants

Sixty-two patients with schizophrenia and 57 patients with BD (bipolar disorder) were recruited at the affiliated psychological hospital of Anhui Medical University; and 45 healthy control (HC) participants were recruited from the community through advertisement. The diagnosis of schizophrenia or bipolar disorder based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [34], criteria by certified psychiatrists. Exclusion criteria were: (1) younger than 18 or older than 50 years; (2) history or current neurological disorders or brain trauma; (3) electroconvulsive therapy within three months of the study; (4) contraindications for MRI scan (magnetic resonance imaging scan). Psychiatrist assessed symptom severity of patients by the Positive and Negative Syndrome Scale (PANSS) [35] and other scales (including Hamilton Depression Scale score, HAMD [36]; Young Manic Rating Scale score, YMRS [37].) on the day of MRI scan (magnetic resonance imaging scan) (Fig. 1).

The study protocol was approved by the Institutional Review Board of the Anhui Mental Health Centre. All participants or their legal guardians signed written informed consent after receiving a full explanation of the study.

MRI (magnetic resonance imaging) data acquisition

All participants were scanned in a General Electric (GE) 3-T scanner (Discovery GE750w) at the University of Science and Technology of China (USTC) or Anhui Mental Health Center. Participants were required to remain still with their eyes closed and stay awake during the scan. Earplugs and foam pads were used to reduce scanning noise and minimize head motion, respectively.

High spatial resolution T1-weighted anatomic images were obtained in the sagittal orientation with the settings as follows: repetition time [TR] = 8.16 ms; field of view = 256 × 256 mm^2; voxel size = 1 × 1 × 1 mm^3; flip angle = 12°; number of slices = 188; echo time = 3.18 ms and slice thickness = 1 mm. The resting-state functional images consisting of 217 echo-planar imaging volumes were collected with the parameters as follows: repetition time, 2400 ms; echo time, 30 ms; flip angle, 90°; matrix size, 64 × 64; field of view, 192 × 192 mm^2; slice thickness, 3 mm and 46 continuous axial slices covering the whole brain. (one voxel = 3 × 3 × 3 mm^3).

MRI (magnetic resonance imaging) processing

We processed fMRI (functional magnetic resonance imaging) images with the Data Processing Assistant for Resting-State Functional MR Imaging toolkit (DPARSF, http://rfmri.org/DPARSF) [38]. MRI data were preprocessed following as the pre-processing procedures in our previous work [39].

Defining axial subregions of the bilateral hippocampus

The bilateral hippocampus was segmented into four axial subregions according to the Human Brainnetome Atlas identified by a connectivity-based parcellation framework [29] (Fig. 2): the left rostral hippocampus, the left caudal hippocampus, the right rostral hippocampus, and the right caudal hippocampus. These subregions were then used as regions of interest (ROIs) for resting-state functional connectivity analyses.

Fractional amplitude of low-frequency fluctuations (fALFF) and functional connectivity analyses

As in our previous work [39], we first converted the filtered time series to a frequency domain power spectrum by fast Fourier transform. The fALFF of each subregion of bilateral hippocampus was calculated as the average of power in the range 0.01–0.1 Hz relative to the entire frequency spectrum. For standardization purposes, the value of fALFF for each voxel was z-normalized across the full brain for each subject. Then zfALFF values were

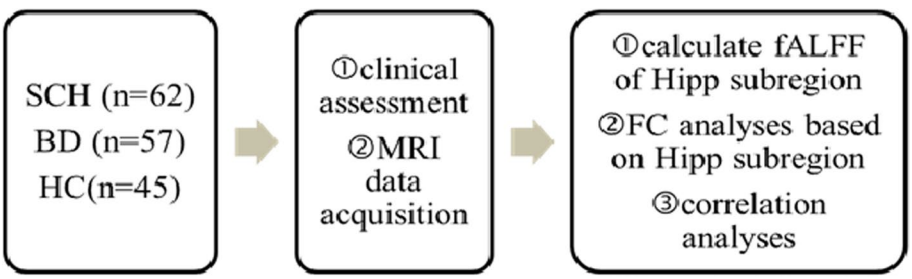

Fig. 1 The flowchart for the study. SCH: the schizophrenia group, BD: the bipolar disorder group, HC: the healthy control groups, MRI: magnetic resonance imaging HIPP: hippocampus, FC: functional connectivity

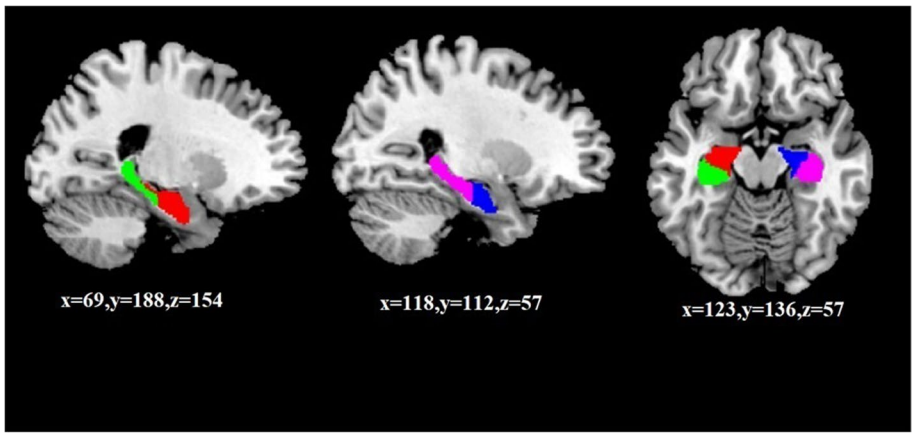

Fig. 2 The four subregions defined along the rostral-caudal axis of the bilateral hippocampus: left caudal hippocampus (green), right caudal hippocampus (purple), left rostral hippocampus (red), and right rostral hippocampus (blue). Regions are rendered on sagittal and ventral views

extracted from the rostral and caudal hippocampal regions of interest (ROIs) separately in each hemisphere and entered into statistical analyses as described below.

The mean time series of each hippocampal subregion was extracted. We then calculated the Pearson's correlation coefficients between the averaged time series for each hippocampal subregion and voxels in the whole brain regions. Subsequently, we applied Fisher's z transformation to normalize the correlation coefficients for further analysis.

Correlation analyses

We calculated the Pearson's correlation coefficients between the severity of clinical symptoms assessed and spontaneous neural activity of hippocampal subregions (zfALFF). Furthermore, Pearson's correlation coefficients between statistically significant FC values and PANSS scores were also calculated.

Pearson's correlation coefficients measures the linear relationship between two random variables. Pearson's correlation coefficients is defined as the quotient of the covariance and standard deviation product between two variables.

Statistical analysis

We applied one-way analysis of covariance (ANCOVA) to calculate normally distributed demographic variables and compared the sex ratio among groups by chi-squared test. zfALFF values of each subregion of bilateral hippocampus were compared among groups by one-way ANCOVA followed by post hoc two-sample t-tests for comparisons, with sex, age, years of education and psychoactive medication dose as covariates.

By voxel-based one-way analysis of covariance (ANCOVA), We then compared functional connectivity maps (FCMs) based on each hippocampal subregion among groups with sex, age, years of education years of education and psychoactive medication dose as covariates.

Furthermore, we performed the Gaussian random field correction with a voxel-level threshold of $p<0.001$ and cluster-level threshold of $p<0.05$ to control for multiple comparisons. Post hoc two-sample t-tests were then applied to calculate differences in FC between groups within a mask showing group differences from the ANCOVA analysis.

Results

Demographic and clinical characteristics of the study population

There were no significant differences in age, sex ratio, or years of education among groups. Sixty-two patients with schizophrenia, 57 with bipolar disorder and 45 HCs were recruited. The details about demographic and clinical characteristics of the three groups were presented in Table 1. As expected, schizophrenia patients scored higher on the PANSS than HCs, while bipolar disorder patients scored higher on both the HAMD and YMRS compared to HCs.

Group differences in zfALFF within each subregion of the hippocampus

The values of zfALFF was higher in all four hippocampal subregions of the schizophrenia group compared to the other two groups (left caudal hippocampus [cHipp_L]: $(F(2,161)=52.47$, $p<0.001$, $\eta2=0.520$, statistical power$=0.789)$, right caudal hippocampus [cHipp_R]: $(F(2,161)=69.95$, $p<0.001$, $\eta2=0.568$, statistical power$=0.758)$, left rostral hippocampus [rHipp_L]: $(F(2,161)=35.57$, $p<0.001$, $\eta2=0.413$, statistical power$=0.634)$, and right rostral hippocampus

Table 1 Detailed demographics and clinical information of the study population

	SCH	BD	HC	statistic	*p* value
Age, mean (SD)	35.63(9.16)	32.40(8.73)	34.19(11.34)	F = 1.742	0.179
Sex				$\chi 2 = 2.997$	0,223
Male	16	19	15		
Female sex, No	46	38	20		
education years, mean(SD)	11.08(3.47)	11.79(3.38)	11.76(4.19)	F = 0.686	0.505
duration of disease, mean(SD)	9.50(3.70)	8.98(4.3)		t = 0.711	0.478
Clinical characteristics					
PANSS_totel, mean(SD)	52.60(12.5)	32.03(1.63)	31.58(1.42)	F = 109.97	< 0.001
PANSS_P	13.81(4.49)	7.79(0.67)	7.77(0.71)	F = 71.62	< 0.001
PANSS_N	15.35(7.19)	7.81(0.69)	7.69(0.62)	F = 45.35	< 0.001
PANSS_G	23.44(5.06)	18.53(1.52)	18.42(1.47)	F = 33.83	< 0.001

Abbreviations: SCH schizophrenia, *BD* bipolar disorder, *HC* health control, *SD* Standard Deviation, *PANSS* positive and negative syndrome scale, *PANSS_P* the positive scale of PANSS, *PANSS_N* the negative scale of PANSS, *PANSS_G* the general psychopathology scale of PANSS

[rHipp_R]: ($F(2,161) = 29.11$, $p < 0.001$, $\eta 2 = 0.356$, statistical power = 0.685), but did not differ between BP and HC groups (all $p > 0.05$) (Fig. 3).

Functional connectivity differences with each hippocampal subregion among groups

We found the significantly stronger connections of the left caudal hippocampus (Fig. 4) and right caudal hippocampus (Fig. 5) with the thalamus, putamen, frontal cortex, and parietal cortex in the schizophrenia patients. In contrast, FC values of bilateral caudal hippocampal subregions and the frontal cortex were lower in the BD group compared to schizophrenia and HC groups. No significant differences in FC between bilateral rostral hippocampus and other regions among the three groups were found. The locations and sizes of voxel clusters with significant FC differences based on the subregion of bilateral hippocampus are listed in Tables 2 and 3.

Correlation analyses

We found a positive association between PANSS scores and zfALFF values in bilateral cHipp subregions (left: $r = 0.550$, $p < 0.001$; right: $r = 0.457$, $p < 0.001$) (Fig. 5) but not in bilateral rHipp subregions among schizophrenia patients after multiple comparisons correction. There were no significant correlations between FC and PANSS scores after multiple comparisons correction in any group (Fig. 6).

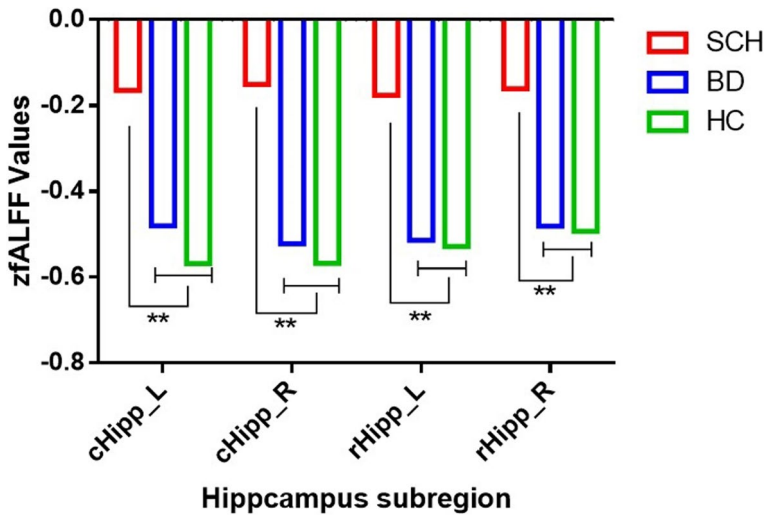

Fig. 3 Higher zfALFF values in both rostral and caudal subregions of the bilateral hippocampus among schizophrenia patients (SCH group) compared to bipolar disorder patients (BD group) and healthy matched controls (HC group). cHipp_L: left caudal hippocampus, cHipp_R: right caudal hippocampus, rHipp_L: left rostral hippocampus, rHipp_R: right rostral hippocampus. zfALFF: z-normalized fractional amplitude of low-frequency fluctuations. *$p < 0.05$ and **$p < 0.01$

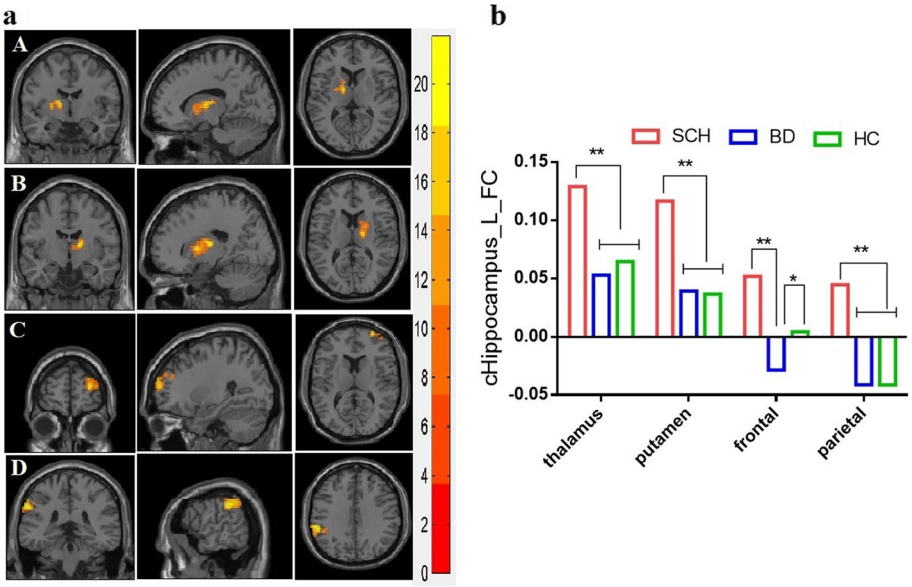

Fig. 4 Functional connectivity to the left caudal hippocampus (cHipp_L) in schizophrenia (SCH), bipolar disorder (BD), and healthy control (HC) groups. **a** Voxel clusters with significant FC are color-coded. A–D show selected slices in the sagittal plane (left column), coronal plane (middle column), and axial plane (right column). **b** Bar plot of average FC values with the cHipp_L for the three groups. cHippocampus_L_FC: functional connectivity values based on the left caudal hippocampus

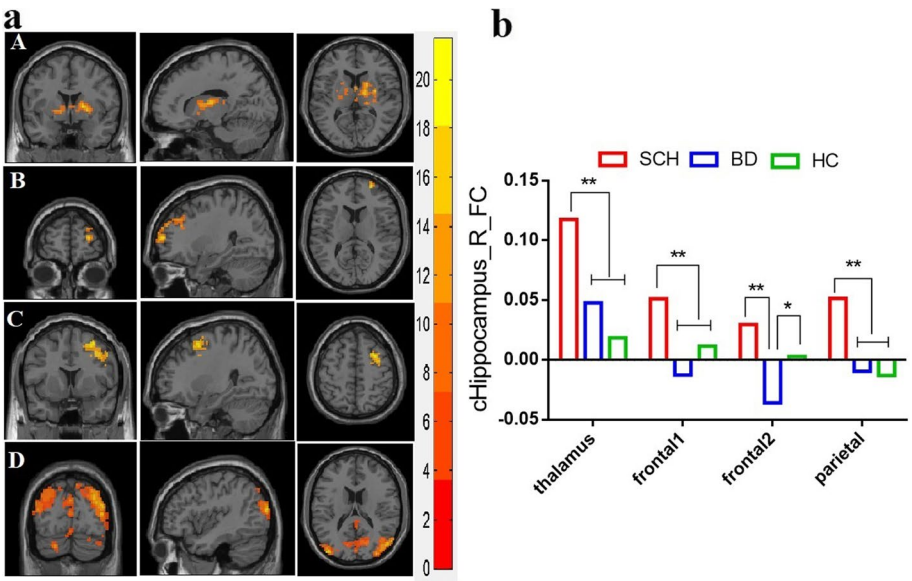

Fig. 5 Functional connectivity to the right caudal hippocampus (cHipp_R) in schizophrenia (SCH), bipolar disorder (BD), and healthy control (HC) groups. **a** Voxel clusters with significant FC are color-coded. A–D show selected slices in the sagittal plane (left column), coronal plane (middle column), and axial plane (right column). **b** Bar plot of average FC values with the cHipp_R for the three groups. cHippocampus_R_FC: functional connectivity values based on the right caudal hippocampus

Discussion

The schizophrenia group exhibited higher fALFF values in both the caudal and rostral regions of the bilateral hippocampus compared to bipolar disorder patients and healthy matched controls. In addition, schizophrenia patients demonstrated stronger FC from bilateral caudal hippocampus to the thalamus, putamen, middle frontal gyrus, parietal cortex, and precuneus. Moreover, the zfALFF values of the bilateral cHipp were positively correlated with the severity of clinical symptoms (higher

Table 2 Brain regions showing significant differences in the three-group analysis of FC based on cHipp_L

Significant region	Cluster size	Peak MINI coordinate			F value	*p* value
		X	Y	Z		
A.thalamus caudate	80	−15	−6	9	21.59	< 0.001
B.putamen thalamus pallidum	149	18	−9	12	25.41	< 0.001
C.frontal frontal_Mid_R middle frontal gyrus	145	27	60	12	19.47	< 0.001
D.parietal supramarginal_R inferior parietal lobule	156	57	−36	30	20.62	< 0.001

MNI montreal neurological institute, X, Y, and Z are MNI coordinates referring to the center of gravity of the cluster

Table 3 Brain regions showing significant differences in the three-group analysis of FC based on cHipp_R

Significant region	Cluster size	Peak MINI coordinate			F value	*p* value
		X	Y	Z		
A.putamen thalamus pallidum	458	-21	-18	15	24.66	< 0.001
B.frontal cortex1 superior frontal gyrus middle frontal gyrus	126	27	60	12	12.49	< 0.001
C.frontal cortex2 middle frontal gyrus inferior frontal gyrus	216	27	9	54	14.21	< 0.001
D.parietal precuneus	3933	-42	-81	18	10.17	< 0.001

PANSS scores) in the schizophrenia group. Consistent with our hypothesis, these findings suggest that functionally dissociated regions of the hippocampus along the rostral–caudal axis are differentially disturbed in schizophrenia and that these disturbances related to schizophrenia symptoms.

Higher zfALFF values of each subregion of bilateral hippocampus in the schizophrenia group

We observed higher zfALFF values in both rostral and caudal subregions of bilateral hippocampus in the schizophrenia group compared to BD and HC groups, suggesting hyperactivity of hippocampal neurons in schizophrenia. Study in rodent models have presented that hippocampal hyperactivity, may indirectly elicit excessive dopamine release from the ventral tegmental area by disinhibiting effects of parvalbumin interneuron [40], which may contribute to the psychotic features of schizophrenia. A hyperdopaminergic state in turn can further enhance hippocampal activity via reciprocal connections between the hippocampal formation and midbrain dopamine neurons [41]. A longitudinal study of clinical high-risk patients exhibited specific hippocampal dysfunction that progresses as individuals transited to psychosis [28]. The severity of delusions in schizophrenia was found to be strongly associated with greater blood volume in the hippocampus [15]. Schizophrenia patients had decreased regional volumes of hippocampus, maybe related to their poorer cognitive function, than those with mood disorders [42]. Treatment-resistant schizophrenia patients experience symptom improvement after adjunct exercise, accompanied by hippocampal plasticity progression [43]. The growing evidence suggested that hippocampal dysfunction is a feature of schizophrenia.

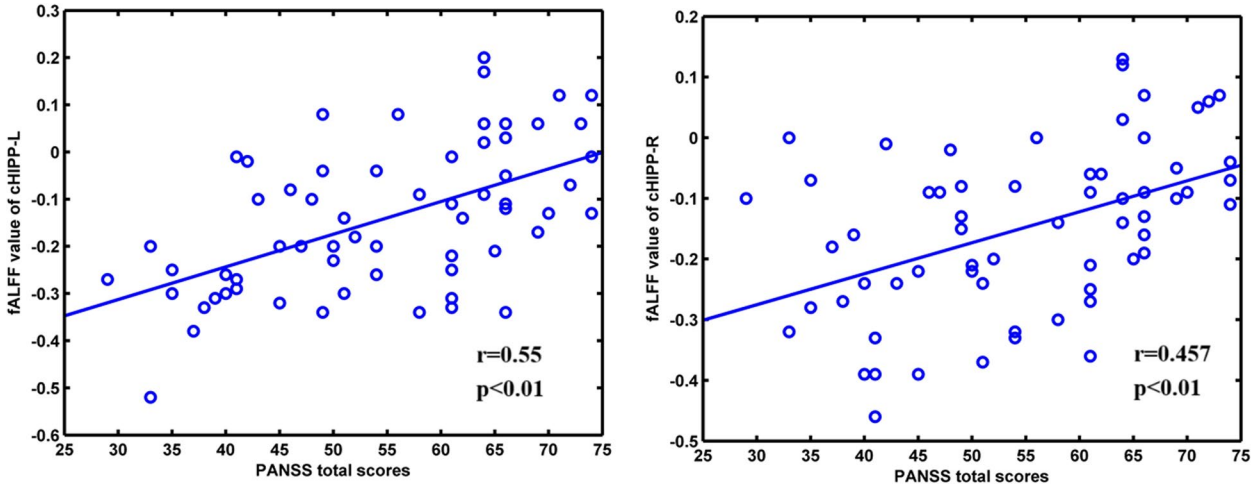

Fig. 6 Association between schizophrenia symptom severity as measured by PANSS score and fALFF in the bilateral caudal hippocampus in SCH group. cHipp_L: the left caudal hippocampus, cHipp_R: the right caudal hippocampus. PANSS: Positive and Negative Syndrome Scale. SCH group: schizophrenia group. zfALFF: z-normalized fractional amplitude of low-frequency fluctuations

Indeed, several studies have reported hippocampal hyperactivity in schizophrenia patients that correlated with psychosis. Likewise, we found the zfALFF values in the caudal hippocampus of schizophrenia patients were positively correlated with severity of clinical symptoms as measured by PANSS scores [44, 45]. Post-mortem studies have also suggested the caudal hippocampus may be particularly vulnerable to the pathophysiology of schizophrenia [46].

Abnormal functional connectivity based on caudal hippocampus in patients' group

In addition to hyperactivity within the caudal hippocampus, we found increased FC between the bilateral cHipp and multiple brain regions, including the thalamus, putamen, middle frontal gyrus, parietal cortex, and precuneus, suggesting wide dissemination of this hyperactive state.

The thalamus has long been implicated in schizophrenia pathophysiology, mainly due to its strong reciprocal FC with the hippocampus and prefrontal cortex [47]. Abnormal resting-state FC between the thalamus and hippocampus has been reported in both schizophrenia patients and individuals at-risk for schizophrenia, and further may predict conversion to psychosis among at-risk individuals [48, 49]. Some studies suggested that the thalamus may serve as a key node for wide network dysfunction in schizophrenia [50].

Cortical–basal ganglia–thalamocortical circuits responsible for multiple aspects of executive/associative, motor, and emotional/motivational function [51]. The putamen receives extensive dopaminergic input from various cortical areas, and sends output to the cortical regions via the thalamus [52]. Dysfunction of the putamen may be associated with the inappropriate and excessive dopamine signaling implicated in the neural mechanisms of schizophrenia [53].

The hippocampus is a brain area considered a major player in supporting memory and global cognition. In this study, we found abnormal neural activity within subregions of bilateral hippcampus and increased FC of the caudal hippcampus in SCH patients. Functionally, the rostral and caudal hippocampus appeared to be involved in different forms of learning and memory. This research suggested that abnormal key nodes within a global framework contribute to the diverse clinical manifestations of SCH disorder, which may be the future clinical intervention target.

The middle frontal gyrus is a hub of mesocorticolimbic dopaminergic pathway that functions in reward-dependent actions, and reward mechanisms have suggested impaired in schizophrenia [53]. The middle frontal gyrus itself is responsible for the appreciation phase of humor and language processing [54]. We found increased FC between the bilateral cHipp and the middle frontal gyrus, and suggested that this impairment might contribute to the intrinsic motivation abnormalities frequently observed in schizophrenia. In contrast, the bipolar disorder group showed decreased FC between bilateral caudal hippocampus and frontal cortex compared to both the schizophrenia and HC groups. These distinct FC abnormalities may explain the difference in behavioral motivation between BD and schizophrenia patients.

The precuneus and parietal cortex are the functional core of the default mode network (DMN), which implicated in a wide range of higher-order functions including self-referential cognition, reflective activity and

memory-based problem solving etc. [55, 56]. Previous study reported increased FC within the DMN in schizophrenia, which was related to the progressive symptoms [57]. Thus, the increased FC of the key nodes within the DMN contribute to the clinical symptoms and cognitive deficits observed in schizophrenia.

Interestingly, we found FC between bilateral caudal hippocampal subregions and the frontal cortex were decreased in the BD group compared to schizophrenia and HC groups. Bipolar disorder (BD) is a severe psychiatric disorder characterized by mood fluctuations and cognitive impairments, related to hyperactivations in subcortical regions (including amygdala and hippocampal) and hypoactivation frontal [58, 59], whereas frontal regions are involved in the evaluation and regulation of emotional responses [60]. Decreased FC between bilateral caudal hippocampal subregions and the frontal cortex might suggest that impaired frontal inhibitory control to the hyperactive limbic system leading to impulsive behavior and emotion in the BD group [61].

This study has several limitations. First, the sample size was moderate, so significant effects must be further verified in a larger cohort. Second, this was a cross-sectional study, longitudinal follow-up was needed. Third, medication status may have been a major confound difficult to control for given that most all patients take medication. However, this was unreasonable keeping patients medication-free on the ethical considerations. Fourth, some of our results are inconsistent with previous researches, possibly because of participants heterogeneity, such as first-episode, chronic, or acute episode patients [62]. Lastly, our results should be compared with caution to other studies, due to the biased gender differences or age distribution of the recruited sample, which affects the generalization of the study results.

This may be due to the selection bias of the age and sex of the enrolled sample, which affects the generalization of the study results.

Conclusion

Patients with schizophrenia show neural hyperactivity within the bilateral hippocampus and hyperconnectivity of the bilateral caudal hippocampus with the thalamus, putamen, middle frontal gyrus, parietal cortex, and precuneus. Increased activity in the bilateral cHipp was positively correlated clinical symptom severity. Collectively, these findings strongly implicate hippocampal dysfunction in the pathophysiology of schizophrenia, especially the caudal hippocampus. These abnormalities may be key biomarkers for disease progression or serve as therapeutic targets. Additional studies are required to elucidate the longitudinal relationship between regional hippocampal abnormalities and disease trajectory.

Authors' contributions

Li Zhang: data acquisition, data analysis and the manuscript writing Wenli Wang: clinical evaluation and data acquisition Zhiyong Li: data analysis and data interpretation Ruan Yuan: clinical evaluation and data acquisition Le Sun: data analysis and clinical evaluation Gong_jun Ji: data analysis and data interpretation Kai Wang: study design and critical revision of the article. Yanghua Tian: study design and critical revision of the article. all authors have read the final version of the manuscript and approved the final article were true.

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Data availability

If required, we can provide research data with the consent of the corresponding authors.

Declarations

Ethics approval and consent to participate

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration. All procedures involving human subjects/patients were approved by Anhui Mental Health Centre Ethics Committee. All subjects or their guardians volunteered to participate in the study and signed a written informed consent form after receiving a full written and verbal explanation of the study. They received information on the rationale of the research and were informed that they are free to withdraw from the study at any time. Clinical trial number: not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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