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Evidence for regional hippocampal damage in patients with schizophrenia

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Abstract

Purpose—Schizophrenia patients show cognitive and mood impairments, including memory loss and depression, suggesting damage in the brain regions. The hippocampus is a brain structure that is significantly involved in memory and mood function and shows impairment in schizophrenia. In the present study, we examined the regional hippocampal changes in schizophrenia patients using voxel-based morphometry (VBM), Freesurfer, and proton magnetic resonance spectroscopy (¹H MRS) procedures.

Methods—¹H MRS and high-resolution T1-weighted magnetic resonance imaging were collected in both healthy control subjects ($N=28$) and schizophrenia patients ($N=28$) using 3-Tesla whole body MRI system. Regional hippocampal volume was analyzed using VBM and Freesurfer procedures. The relative ratios of the neurometabolites were calculated using linear combination model (LCModel).

Results—Compared to controls, schizophrenia patients showed significantly decreased gray matter volume in the hippocampus. Schizophrenia patients also showed significantly reduced glutamate (Glu) and *myo*-inositol (mI) ratios in the hippocampus. Additionally, significant positive correlation between gray matter volume and Glu/tCr was also observed in the hippocampus in schizophrenia.

Conclusion—Our findings provide an evidence for a possible association between structural deficits and metabolic alterations in schizophrenia patients.

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Conflict of interest The authors declare that they have no conflict of interest.

Compliance with ethical standards

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Keywords

Proton magnetic resonance spectroscopy; Voxel-based morphometry; Schizophrenia; Hippocampus

Introduction

Schizophrenia is a severe mental disorder that involves a range of problems with thinking, perception, behavior, and social problems specially delusions, hallucinations, and disorganized speech [1]. Schizophrenia patients exhibit a wide range of cognitive and mood problems, including working memory and executive functions deficit, depression, and anxiety [2–5]. These characteristics indicate the presence of brain dysfunction and specifically to damage of the hippocampus, a brain structure integrally involved in such neurocognitive functions in schizophrenia [6–9].

Neuroimaging techniques provide evidences about the abnormality of the hippocampus in schizophrenia. Previous studies have shown structural abnormalities, including gray matter volume loss, in the hippocampus of schizophrenia patients [10–13]. Proton magnetic resonance spectroscopy (^1H MRS) has shown decreased *N*-acetyl-aspartate (NAA) level [14, 15] and increased [16] or no change [17, 18] in glutamate (Glu) levels in the hippocampus of patients affected with schizophrenia. There are few studies that have investigated the association between metabolic and structural measures in the hippocampus of schizophrenia patients [19, 20].

Our aim in this study was to examine regional hippocampal changes at structural and metabolite levels in schizophrenia patients, using VBM, Freesurfer, and ^1H MRS procedures. We hypothesized that schizophrenia patients would show structural and metabolic alterations in the hippocampus compared to healthy controls.

Methods

Subjects

Twenty-eight schizophrenia patients and 28 healthy controls were taken in the study. All schizophrenia patients were recruited from the Department of Psychiatry, Dr. Ram Manohar Lohia Hospital (RMLH), New Delhi, India. The diagnosis of the disorder was confirmed by interviewing the patients using the Hindi version of the Diagnostic Interview for Genetic Studies (DIGS) [21, 22]. All patients were on antipsychotic medications at the time of MRI acquisition.

All control subjects chosen for the study were recruited from the local community. Participants, both controls and patients, with a history of any clinical evidence of stroke, head injury, cardiovascular diseases, history of smoking, alcohol, or drug dependence were not included in the study.

The study was approved by the Institutional Ethics Committee of PGIMER, RMLH, New Delhi, India. Written informed consent was obtained from all the participants after complete description of the study to the participants.

Magnetic resonance imaging

Brain imaging was acquired using a 3.0-Tesla MR scanner (Magnetom Skyra, Siemens, Germany) with a 20-channel head and neck coil. The subject's head was immobilized using expandable ear cushions while subjects lay supine. High-resolution T1-weighted images were acquired using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence (TR = 1900 ms, TE = 2.07 ms, inversion time = 900 ms, matrix size = 256 × 256, FOV = 256 × 256 mm, slice thickness = 1 mm, number of slices = 160). For positioning the MRS voxel, anatomical images were acquired in all the three orthogonal planes. We also collected T2-weighted multislice images (TR = 5600 ms, TE = 100 ms, NEX = 1, 312 × 512 matrix, and FOV = 180 × 220 mm, 25 slices, slice thickness = 4.0 mm, distance factor = 1.2 mm) covering the entire brain to look for any neurological abnormalities.

We collected MRS data from the right hippocampus of voxel of 25 × 10 × 10 mm³ (Fig. 1a). The voxel was carefully placed in the right hippocampus so as to maximize the amount of gray matter (GM) while avoiding adjoining major vessels and cerebrospinal fluid (CSF). Automated global and localized shimming were performed to minimize the B₀ inhomogeneities and to optimize field homogeneity across the voxel of interest. Water-suppressed spectra were acquired using single-volume point-resolved spectroscopy sequence (PRESS) with the following acquisition parameters: TR/TE = 2000/33 ms, 2048 spectral points, 1200-Hz spectral bandwidth, and 196 averages. We used chemically selective suppression (CHESS) pulse sequence for water suppression.

Data processing

Structural data analysis

Voxel-based morphometry analysis: We used the statistical parametric mapping package SPM12 (Wellcome Department of Cognitive Neurology, UK; <http://www.fil.ion.ucl.ac.uk/spm/>) and MATLAB-based (The MathWorks Inc., Natick, MA) custom software to process images. All the steps for structural data processing were followed as described in detail [23]. We used Diffeomorphic Anatomic Registration Through Exponentiated Lie Algebra (DARTEL) algorithm toolbox in order to improve the registration of the MRI images. Firstly, the anatomical images were segmented into GM and white matter (WM) probability maps using the “new segment” option of SPM 12. Then, the flow fields and a series of template images were generated by running “DARTEL (create templates)” option. Finally, the anatomical images were smoothed (10-mm full width at half maximum), modulated, and spatially normalized into MNI space by using the flow fields and final template generated in the previous step.

FreeSurfer analysis: FreeSurfer software (v 6.0.0) (<http://surfer.nmr.mgh.harvard.edu/>) was used to obtain hippocampus volumes for all subjects. The methods of the automated volumetric approach have been described in detail previously [24]. FreeSurfer analyses were performed on Ubuntu 16.04.3 LTS, which allowed the FreeSurfer “recon-all” function for

cortical reconstruction and brain segmentation (<http://surfer.nmr.mgh.harvard.edu/fswiki/recon-all>) to complete 56 participants in less than 30 h. After the “recon-all” function, the neuroanatomical labels were inspected for accuracy in all patients and controls. All subjects’ processed data were manually evaluated by an investigator to ensure no brain areas were excluded. No errors in the automatic labelling were observed for any subject, and so all data obtained from FreeSurfer analyses were 100% automated and not influenced by manual intervention.

Magnetic resonance spectroscopy data analysis—The spectra were processed using linear combination model (LCModel) software [25, 26]. Spectral peaks were assigned with reference to the water peak (4.7 ppm). Only those metabolites are included which show Cramer-Rao lower bound (CRLB) less than or equal to 20% for quantitative reliability [27]. In our study, we used metabolite ratios to reduce the variability in absolute values for different metabolites as observed in subjects. We used total creatine (tCr) values as the internal reference for relative quantification [26].

Statistical analyses

We used statistical package for social sciences (SPSS v22) for assessment of demographic data. The demographic data of schizophrenia patients and controls were compared using independent samples *t* test. Statistical threshold values of $p < 0.05$ were considered a significant difference.

For regional GM volume differences between groups, the smoothed whole-brain GM maps of schizophrenia patients and controls were compared using analysis of covariance (ANCOVA), with age and gender as covariates. A whole-brain analysis was performed, with a significance level of $p < 0.001$, uncorrected for multiple comparisons. The statistical parametric maps showing gray matter volume difference were set at threshold of $p < 0.001$ for each voxel and a minimum cluster size of 1056 voxels, which give a corrected threshold of $p < 0.05$ by using AlphaSim in REST software.

Regional hippocampal volumes were examined for significant differences between schizophrenia and controls using ANCOVA, with age and gender included as covariates. We considered a $p < 0.05$ value statistically significant.

Differences in metabolite ratios were compared with multivariate analysis of covariance (MANCOVA) using general linear model (GLM). To control the effect of age and sex between the two groups, age and sex were taken as covariates of no interest. In schizophrenia patients as well as healthy controls, Pearson’s correlation coefficient was also computed to study the relationship between metabolite ratios and gray matter volumes from the hippocampus region. The level of significance was set at $p = 0.05$.

Results

Demographic and clinical characteristics

Demographic and clinical variables of schizophrenia patients and control subjects are summarized in Table 1. No significant differences in age ($p = 0.238$) and gender ($p = 0.794$) appeared between groups.

Regional hippocampus volume differences

Schizophrenia patients showed significantly reduced gray matter volume in the multiple brain regions including the right hippocampus, right parahippocampal gyrus, right inferior temporal gyrus, left precentral gyrus, and right insula lobe, compared to healthy controls (Fig. 2 and Table 2). After controlling for age and gender, schizophrenia patients showed significantly reduced hippocampal volumes compared to healthy controls (Table 1.)

Magnetic resonance spectroscopy results

Our results showed a significantly reduced Glu/tCr and mI/tCr ratios in the hippocampus of schizophrenia patients compared to controls ($p = 0.032$ for Glu/tCr and $p = 0.009$ for mI/tCr). No significant differences were observed in NAA/tCr, tCho/tCr, NAA + NAAG/tCr, and Glx/tCr. The metabolite ratios with reference to tCr from the right hippocampus region of schizophrenia patients ($N = 28$) and healthy controls ($N = 28$) were provided in Table 3. The representative spectra acquired from the right hippocampus region of a control subject are shown in Fig. 1b.

Correlation between hippocampal volume and neurometabolites

Only Glu/tCr showed significant positive correlation with reduced hippocampus volume in schizophrenia patients ($r = 0.385$, $p = 0.05$) (Fig. 3). In healthy controls, no significant correlation was observed between metabolite ratios and hippocampus volume ($r = 0.081$, $p = 0.694$) (Fig. 3).

Discussion

In the present study, regional gray matter volume loss was observed in the hippocampus of schizophrenia patients compared to healthy controls. Schizophrenia patients showed decreased metabolite ratios, i.e., Glu/tCr and mI/tCr ratios in the right hippocampus compared with healthy controls. Also, Gu/ tCr ratio showed positive correlation with reduced hippocampus volume in the hippocampus in schizophrenia patients.

Reduced regional hippocampal volume in schizophrenia

Schizophrenia patients showed regional gray matter volume loss in the hippocampus compared to healthy controls. The pattern of the localized volume loss in the hippocampus may indicate specific mechanisms of damage in schizophrenia. The hippocampal volume loss may also impact other brain structures that receive input from the hippocampus. In our study, VBM showed reduced gray matter volume in the parahippocampal gyrus, inferior temporal gyrus, and insular cortex, brain regions that communicates directly or indirectly with the hippocampus. Previous meta-analyses and reviews have shown gray matter volume

loss in the hippocampus in schizophrenia [10–13]. Therefore, the gray matter volume loss in the hippocampus along with other brain regions may also explain clinical manifestations such as memory and mood impairments in schizophrenia patients.

Neurometabolite alterations in schizophrenia

¹H MRS showed a significantly reduced Glu/tCr and mI/tCr ratios in the hippocampus in schizophrenia patients compared to healthy controls. The reduced Glu/tCr and mI/tCr ratios likely result, in part, from decreased glutamate activity or abnormal Glu-Gln cycle [28] and decreased glial content or dysfunctional glia which might result from glutamate-mediated toxicity [29], which is consistent with the tissue damage in the right hippocampus observed in our study. Most studies showed no difference in glutamate levels in medicated schizophrenia patients and healthy controls [17, 18]. Few studies have shown elevated Glu level in unmedicated schizophrenia patients and suggested the possible normalization of Glu levels with antipsychotic medication in other brain regions [30–32]. In our study, we did not find any correlation between metabolite ratios and chlorpromazine (CPZ) antipsychotic dose in schizophrenia.

Positive correlation between metabolite ratios and regional hippocampal volume

Schizophrenia patients showed positive correlation between Glu/tCr ratio and hippocampal volume in the hippocampus. Few studies have shown the correlation of metabolic and structural measures in the hippocampus of schizophrenia patients [19, 33]. Kragulic et al. have shown negative correlation between hippocampal VBM measure and Glx/tCr in unmedicated schizophrenia patients but not in healthy controls [19]. Nenadic et al. provided evidence of a structural impact on different brain regions in relation to hippocampal Glu and NAA levels and demonstrates that these associations are different between ultra-high risk and first-episode schizophrenia [33]. In line with these studies, our findings suggest an association between structural deficits and metabolic alterations in the hippocampus in patients with schizophrenia.

Limitations

There are certain limitations in the present study. The first limitation is the measurement of metabolites is in ratios, not in absolute concentrations. Secondly, all the patients in this study were on medication. But we did not find any correlations between metabolite ratios and gray matter volumes and CPZ antipsychotic dose in schizophrenia patients. It would have been beneficial if a third group consisting of first-episode patients without treatment can be included to determine the potential effect of pharmacological treatment.

Conclusion

The overall findings of this study provide an evidence for a possible association between structural deficits and metabolic alterations in schizophrenia patients as compared to controls. These findings also suggest regional hippocampal damage in schizophrenia.

Acknowledgments

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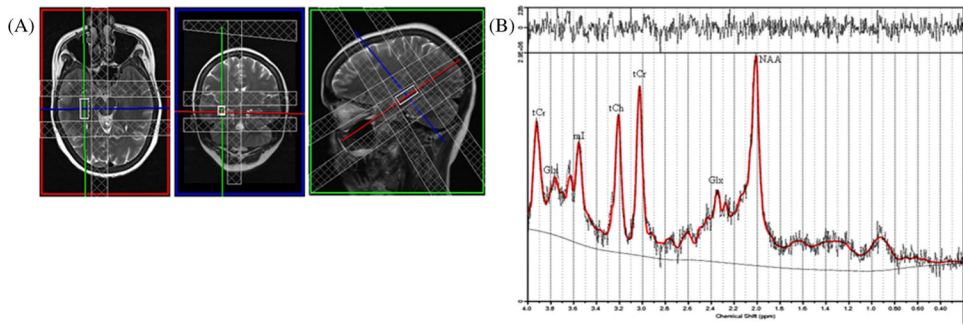


Fig. 1.
a Location of 2.5 cm³ voxel and **b** its representative 1H MRS spectrum acquired from the right hippocampus as analyzed by LCModel of a control subject

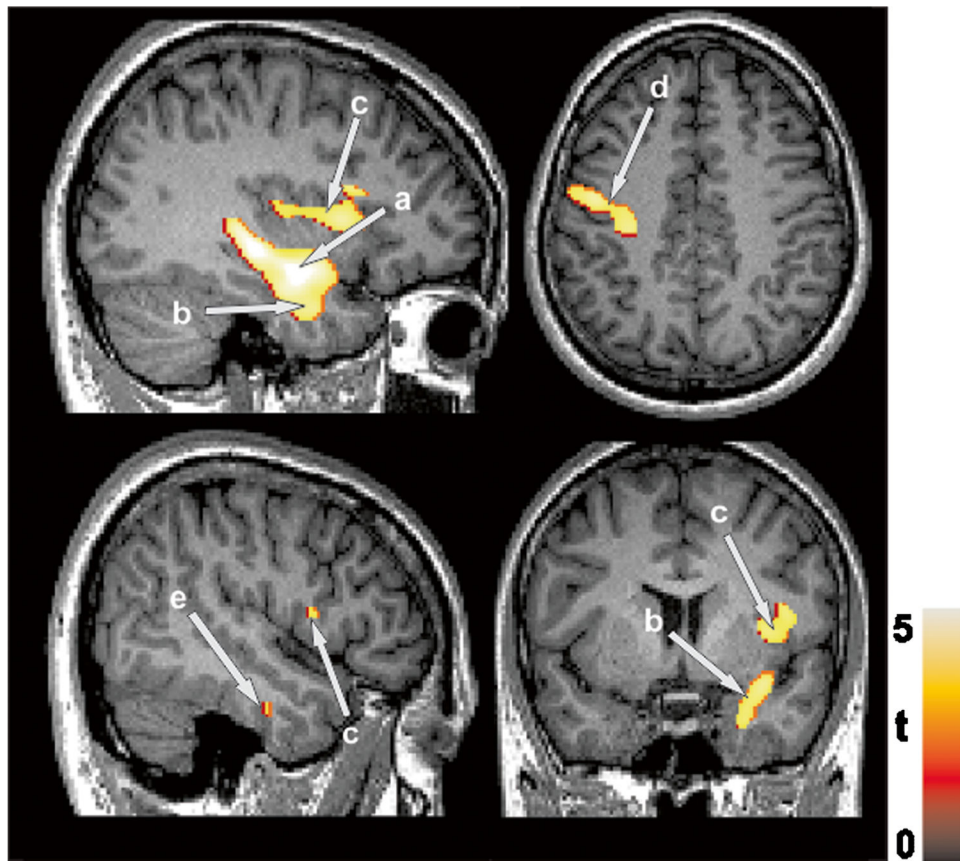


Fig. 2. Gray matter volume loss in brain areas including the **a** right hippocampus, **b** right parahippocampal gyrus, **c** right insula lobe, **d** left precentral gyrus, and **e** right inferior temporal gyrus, in schizophrenia patients compared to healthy controls

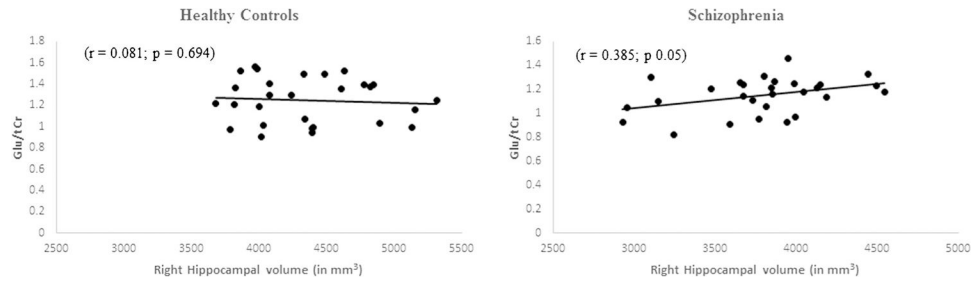


Fig. 3. Scatter plot showing correlation between hippocampus volume and Glu/tCr ratio quantified from the right hippocampus region in controls and schizophrenia patients

Table 1

Demographic and clinical characteristics of subjects

	Schizophrenic patients (N = 28) (mean ± SD)	Healthy controls (N = 28) (mean ± SD)	p value
Age (years)	33.89 ± 9.34	31.44 ± 7.36	0.238
Gender (male/female)	12/16	14/14	0.794
Years of education	9.64 ± 3.43	12.3 ± 3.4	
Duration of illness (in weeks)	479.65 ± 323.65	NA	
SANS total score	11.8 ± 5.9		
SAPS total score	8.1 ± 4.4		
Antipsychotic equivalent dosage of CPZ, mg/day	488.14 ± 328.94		
Duration of antipsychotic drug taken (in weeks)	451.47 ± 318.13		
Hippocampal volumes (in mm ³)			
Right hippocampus	3786.8 ± 426.2	4354.4 ± 457.6	< 0.001
Left hippocampus	3610.7 ± 402.7	4089.2 ± 444.5	< 0.001

SANS Scale for the Assessment of Negative Symptoms, SAPS Scale for the Assessment of Positive Symptoms, CPZ chlorpromazine

Regions of gray matter volume loss in schizophrenia patients compared to healthy controls

Table 2

Brain regions	MNI coordinates	z-score	t value	p FWE-corr	Cluster size (voxels)
R hippocampus	36 - 9 - 17	4.64	5.19	0.019	
R parahippocampal gyrus	33 - 8 - 29	4.26	4.68	0.025	3815
R inferior temporal gyrus	48 - 12 - 29	4.12	4.22	0.031	
L precentral gyrus	-42 - 18 65	4.28	4.71	0.032	1617
R insula lobe	36 9 5	4.40	4.59	0.012	1080
R rolandic operculum	44 8 12	4.38	4.48	0.042	

MNI/Montreal Neurological Institute, L:left, R:right

LCModel analysis of metabolite ratios normalized to tCr (Cr + PCr) resonance calculated from the spectra obtained from the right hippocampus of both controls and schizophrenia patients ($N = 28$)

Table 3

Metabolite ratios	Healthy controls mean \pm SD	Schizophrenia mean \pm SD	<i>p</i> value
Glu/tCr	1.24 \pm 0.21	1.15 \pm 0.16	0.032 *
mI/tCr	0.98 \pm 0.22	0.85 \pm 0.19	0.009 *
NAA/tCr	0.94 \pm 0.18	0.94 \pm 0.12	0.978
GPC + PCh/tCr	0.30 \pm 0.03	0.31 \pm 0.05	0.225
NAA + NAAg/tCr	1.09 \pm 0.12	1.04 \pm 0.13	0.148
Glx/tCr	2.07 \pm 0.40	1.97 \pm 0.43	0.213

Asterisk indicates significant difference between groups (* $p < 0.05$)