Section: Psychiatry

Original Research Article

# SERUM NCAM LEVELS & GLUTAMATE LEVELS IN HIPPOCAMPUS ON MR SPECTROSCOPY IN PATIENTS OF FIRST EPISODE AND CHRONIC SCHIZOPHRENIA: A COMPARATIVE STUDY

***Satwinder Kaur[1], Gurpreet Kaur[2], Sarvpreet Singh Malhi[3]***

*[1]Junior Resident, Department of Psychiatry, CIP Ranchi, India.*
*[2]Senior Resident, Department of Psychiatry, Government Medical College, Patiala, India.*
*[3]Medical Officer Specialist, CHC, Ludhiana, India.*

***Received*** *: 11/03/2025*
***Received in revised form*** *: 09/05/2025*
***Accepted*** *: 28/05/2025*

**Corresponding Author:**
**Dr. Gurpreet Kaur,**
Senior Resident, Department of Psychiatry, Government Medical College, Patiala, India.
Email: gurpreet.randhawa10@gmail.com

**DOI:** 10.70034/ijmedph.2025.2.335

**Source of Support:** Nil,
**Conflict of Interest:** None declared

**Int J Med Pub Health**
2025; 15 (2); 1879-1887

ABSTRACT

**Background: Aim:** The aim of the present study was to assess serum NCAM level and glutamate level in the hippocampus on MR spectroscopy in patients with first-episode schizophrenia, and chronic schizophrenia and to compare it with healthy controls.

**Materials and Methods:** The cross-sectional study was conducted at the Central Institute of Psychiatry, Ranchi. The sample size consisted of 20 patients with first-episode schizophrenia, 20 patients with chronic schizophrenia, and 20 matched healthy controls.

**Results:** There were significant differences in the employment status and socio-economic status between the three groups as 65% patients with first episode schizophrenia were found to be unemployed (p=0.031) and 95% belonged to lower socio-economic status (p=0.001). The mean duration of illness was comparatively higher in patients with chronic schizophrenia (77.50 months) as compared to patients with first episode schizophrenia (4.90 months). In the study, gender distribution showed a higher percentage of males across all groups (CH: 95%, CN: 80%, FE: 90%) with no significant difference ($\chi^2 = 1.48$, $p = 0.32$). The PANSS scores reveal significantly higher symptom severity in the FE group (mean = 71.25, SD = 7.72) compared to the CH group (mean = 60.60, SD = 6.5; $p < 0.01$). No significant intergroup variations were observed among the three groups in the mean serum NCAM levels Kruskal-Wallis non-parametric one-way ANOVA was conducted to compare NCAM levels across three groups: FE Group, CH Group, and CN Group, each with 20 participants. A significant negative correlation was found between duration of illness and NCAM (r=-0.49, p=0.027).

**Conclusion:** Our findings showed no statistically significant differences in NCAM levels or hippocampal glutamate concentrations across the FE, CH, and CN groups, suggesting these biomarkers may not differentiate between the stages of schizophrenia or from healthy individuals in a cross- sectional analysis. However, a significant correlation was observed between NCAM levels and age within the FE group, implying a possible age-related alteration in NCAM among first-episode patients.

**Keywords:** Serum NCAM level, glutamate level, hippocampus, MR spectroscopy, schizophrenia.

## INTRODUCTION

Schizophrenia is a complex mental illness shaped by genetic, environmental, and developmental factors. Abnormal brain maturation, notably through excessive synaptic pruning, leads to reduced cortical dendrite density, contributing to brain volume reduction and connectivity deficits.[1] Neuroimaging

studies reveal structural abnormalities in the prefrontal cortex and hippocampus, along with disruptions in dopamine and glutamate neurotransmission systems.[2] In schizophrenia, hippocampal pyramidal layers, primarily consisting of glutamatergic neurons (about 90%), exhibit significant alterations.[3] These changes are not only seen in patients but also in their relatives and individuals at risk for the disorder.[4,5] Dysfunctions in the hippocampus, especially involving glutamatergic signaling, are thought to be central to the disorder's pathology.[6]

The glutamate hypothesis proposes that hypofunction of NMDA receptors is a crucial factor in schizophrenia's development.[7,8] While initial research suggested reduced glutamate levels (Kim et al., 1980), more recent studies indicate an excessive involvement of glutamate in the disorder.[10] Elevated hippocampal glutamate levels observed through proton magnetic resonance spectroscopy (1H-MRS) in schizophrenia are associated with hypermetabolism and tissue atrophy.[11,12] Glutamate dysregulation is linked to increased symptom severity and cognitive impairments in affected individuals.[13]

Schizophrenia (SZ) is both a neurodevelopmental and neurodegenerative disorder, characterized by impairments in long-range and synaptic connectivity. Disruptions in the polySia-NCAM system have been associated with SZ, with changes in polySia-NCAM immunoreactivity found in critical brain areas like the hippocampus and dorsolateral prefrontal cortex, which are key to cognition and SZ pathophysiology.[14,15]

Studies have also observed abnormal levels of NCAM isoforms and soluble fragments in the cerebrospinal fluid and various brain regions in SZ patients. Genetic studies highlight NCAM and the polySia-synthesizing enzyme ST8SIA2 as potential susceptibility genes for SZ, although findings remain varied.[16,17] These findings suggest that polySia-NCAM dysfunction might play a role in the development of SZ. The neural cell adhesion molecule (NCAM), also known as CD56, belongs to the immunoglobulin superfamily and is expressed in neurons and glial cells. NCAM is crucial for cell adhesion, neural migration, neurite growth, synaptic plasticity, and brain development, all of which support learning and memory processes.[18-20]

The aim of the present study was to assess serum NCAM level and glutamate level in the hippocampus on MR spectroscopy in patients with first-episode schizophrenia, and chronic schizophrenia and to compare it with healthy controls.

## MATERIALS AND METHODS

The cross-sectional study was conducted at the Central Institute of Psychiatry, Ranchi. The sample size consisted of 20 patients with first-episode schizophrenia, 20 patients with chronic schizophrenia, and 20 matched healthy controls.

The study included 60 participants (N = 60). They were divided into three groups of 20 participants each:

Group FE – First episode of schizophrenia
Group CH – chronic schizophrenia
Group CN – control group/Healthy individuals.

| Group | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| First Episode Schizophrenia (FE Group) | 1. Diagnosis of Schizophrenia according to Diagnostic Criteria for Research of ICD-10 DCR (WHO, 1993).<br>2. First episode schizophrenia – duration of illness 6 months or less.<br>3. Age group between 18-50 years of age of either sex.<br>4. Patients giving written informed consent | 5. Current neurological or any comorbid major psychiatric disorders except nicotine or caffeine dependence.<br>6. Received ECT in the last 6 months.<br>7. History of substantial brain damage or any neurological procedures.<br>8. Presence of any metallic implants in the body.<br>9. Not giving written informed consent. |
| Chronic schizophrenia (CH Group) | 1. Diagnosis of Schizophrenia according to Diagnostic Criteria for Research of ICD-10 DCR (WHO, 1993).<br>2. Chronic Schizophrenia- duration of illness more than 2 yr.<br>3. Matched with group A regarding age, sex, and education.<br>4. Patient giving written informed consent. | |
| Healthy Controls (CN Group) | 1. Score of 3 or less on the general health questionnaire-12<br>2. Healthy controls matched with respect to age, sex, and education.<br>3. Giving written informed consent | 1. Current neurological or any comorbid major psychiatric disorders except nicotine or caffeine dependence.<br>2. History of substantial brain damage or any neurological procedures.<br>3. Presence of metallic implants.<br>4. Score of more than 3 on the general health questionnaire-12<br>5. Not giving written informed consent |

### TOOLS FOR ASSESSMENT

Socio-demographic and clinical data sheet: This is a semi-structured proforma used for recording demographic details like age, sex, religion, education, occupation, socioeconomic status, habitat, duration of untreated psychosis, past history of any medical illness, and family history of any medical and psychiatric illness.

**Positive and negative syndrome scale (PANSS) (Kay et al, 1987),[21]:** It is a 30-item rating scale

evaluating the presence or absence and severity of positive, negative, and general psychopathology of schizophrenia. All 30 items are rated on a 7- point scale. PANSS has adequate Internal consistencies for positive (α = 0.73: Acceptable), negative (α = 0.83: Good), and general psychopathology (α = 0.79: Good) subscales; good test-retest reliability with Pearson correlation coefficients at 0.80, 0.68, and 0.60 for the positive, negative and psychopathology subscales. Positive and negative scales showed good inter- rater reliability with Interclass correlation coefficients of 0.72 and 0.80, respectively. Inter- rater reliability also stands moderate (0.56) for the general psychopathology scale (Kay et al, 88).

**Scale for the Assessment of Positive Symptoms (SAPS) (Andreason, 1984),[22]:** It is a rating scale to measure positive symptoms in schizophrenia. SAPS is split into 4 domains, and within each domain separate symptoms are rated from 0 (absent) to 5 (severe).

**Scale for the Assessment of Negative Symptoms (SANS) (Andreason, 1984),[22]:** It is a rating scale to measure negative symptoms in schizophrenia. SANS is split into 5 domains, and within each domain separate symptoms are rated from 0 (absent) to 5 (severe).

**General Health Questionnaire - 12 (GHQ-12) (Goldberg 1992),[23]:** It is a self-report questionnaire to screen psychiatric morbidity in normal control. In the present study, 12 12-item version will be used. The original GHQ has 60 items for the detection of non- psychiatric illness. GHQ is the most common assessment of mental well-being. Developed as a screening tool to detect those likely to have or be at risk of developing psychiatric disorders, it is a measure of the common mental health problems/domains of depression, anxiety, somatic symptoms, and social withdrawal. Available in a variety of versions using 12, 28, 30, or 60 items, the 12-item version is used most widely. This is not only because of time considerations but also because the GHQ 12 has been used most commonly in other working populations, allowing for more valid comparisons (Goldberg et al., 1978). ELISA kit: The Human Neural Cell Adhesion Molecule, NCAM ELISA kit is used as an analytical tool for quantitative determination of Human Neural Cell Adhesion Molecule, NCAM in serum. The kit employs a sandwich ELISA technique which leads to a higher
specificity and increased sensitivity compared to conventional competitive ELISA kits which employ only one antibody. Double antibodies are used in this kit.

**MRI Feasibility Checklist:** This is a checklist with all the contraindications for undergoing an MRI scan. In-situ orthopedic implants, pacemaker devices, DBS coils, and Cochlear implants are some of the common contraindications for undergoing MRI. This was administered to all the prospective participants and if any contraindications to undergo MRI were found, the person was not recruited for the study.

**Proton MR Spectroscopy:** Proton MR spectroscopy examination was performed on a 3T scanner (Ingenia, Philips make) using 32-channel isoelectric head coil. Spectroscopy data was acquired from 2 voxels and the VOI (Volume of Interest) will be placed on the left and right hippocampus based on the structural MRI. 3-plane localizer MRI was first acquired to define the spatial position of the brain.

**PROCEDURE FOR CLINICAL DATA COLLECTION**

The study was initiated after obtaining permission from the Institutional Ethics Committee/CIP/2022-23/DIR/290. The clinical sample was drawn from patients admitted in different wards of the Institute and from the outpatient department. Those patients fulfilling the eligibility criteria were selected after obtaining their written informed consent. The clinical assessments for the severity of symptoms for patients with first episode schizophrenia and chronic schizophrenia were done using PANSS, SAPS, & SANS. Healthy controls were chosen from local population in the community residing nearby the Institute after ensuring that they had no psychiatric morbidity as assessed by GHQ-12.

**Sample and Standard Preparation**

NCAM Standards were prepared by reconstituting the original Neural Cell Adhesion Molecule (NCAM) with 1.0 ml of Standard Diluent in a series of known concentrations according to the manufacturer's instructions to establish a standard curve.

| Standard Concentration | Standard Vial | Dilution Particulars |
|---|---|---|
| 100 ng/ml | Standard No.8 | Reconstitute with 1.0 ml Standard Diluent |
| 50 ng/ml | Standard No.7 | 500 ul Standard No.8 + 500 ul Standard Diluent |
| 25 ng/ml | Standard No.6 | 500 ul Standard No.7 + 500 ul Standard Diluent |
| 12.5 ng/ml | Standard No.5 | 500 ul Standard No.6 + 500 ul Standard Diluent |
| 6.25 ng/ml | Standard No.4 | 500 ul Standard No.5 + 500 ul Standard Diluent |
| 3.13 ng/ml | Standard No.3 | 500 ul Standard No.4 + 500 ul Standard Diluent |
| 1.57 ng/ml | Standard No.2 | 500 ul Standard No.3 + 500 ul Standard Diluent |
| 0 ng/ml | Standard No.1 | 500 ul Standard Diluent only |

**Sample Preparation:** All serum samples were brought to room temperature before testing to avoid temperature-based variability

**Calculation of Results**

Determine the Mean Absorbance for each set of duplicate or triplicate Standards and Samples. Using Graph Paper, plot the average value (absorbance 450nm) of each standard on the Y-axis versus the corresponding concentration of the standards on the X-axis. Draw the best-fit curve through the standard points. To determine the unknown Human Neural Cell Adhesion Molecule, NCAM concentrations, find the unknown Mean Absorbance value on the Y-axis and draw a horizontal line to the standard curve. At the point of intersection, draw a vertical line to the X-axis and read the Human Neural Cell Adhesion Molecule, NCAM Concentration.

**PROCEDURE FOR MR SPECTROSCOPY**

Brain MRI scans were performed on a 3.0T magnetic resonance scanner (3T scanner (Ingenia, Philips made) with a 16-channel head coil. A 3-plane localizer MRI was first acquired to define the spatial position of the brain. Quantitative data for Glutamate were calculated using a spectral view.

**DATA QUANTIFICATION**

For data quantification i.e., measuring the concentration of glutamate in the tissue, we took the peak values of the neurometabolite resonating at 2.0 ppm for glutamate. Quantitative data for Glutamate was obtained using spectral view. The value of glutamate was taken from the metabolite (Glutamate) section indicated by height and analysed using SPSS- 27.0.

**STATISTICAL ANALYSIS**

The data analysis was conducted using descriptive statistics with the help of statistical package for social sciences version 27(SPSS-27.0). Descriptive statistics, including means frequencies and standard deviations were calculated for sociodemographic and clinical variables. Chi-square test of association was used for categorical variables. Independent samples Student's t test was used for comparing continuous variables between two groups. Kruskal-Wallis Non-parametric One Way ANOVA was applied for serum NCAM and Hippocampal Glutamate as data was non normally distributed comparing continuous variables across the three groups. Pearson correlation was used to examine the relationship between FE Group and clinical and sociodemographic variables. A Level of significance p of <0.05 was taken to consider a result statistically significant.

# RESULTS

**Table 1: Comparison of the sociodemographic characteristics between the three groups**

| Variables | | CH Group (n=20) n (%)/ Mean (SD) | CN Group (n=20) n (%)/ Mean (SD) | FE Group (n=20) n (%)/ Mean (SD) | $\chi^2$/F (df1, df2) | p |
|---|---|---|---|---|---|---|
| Gender | Male | 19 (95) | 16 (80) | 18 (90) | 1.48 | 0.32 |
| | Female | 1 (5) | 4 (20) | 2 (10) | | |
| Religion | Hindu | 17 (85) | 20 (100) | 17 (85) | 1.73 | 0.27 |
| | Muslim | 3 (15) | 0 (10) | 2 (10) | | |
| | Christian | 0 | 0 (0) | 1 (5) | | |
| Education | Early | 1 (5) | 0 (0) | 0 (0) | 2.81 | 0.06 |
| | Primary | 7 (35) | 11 (55) | 8 (40) | | |
| | Secondary | 9 (45) | 6 (30) | 5 (25) | | |
| | Higher | 1 (5) | 3 (15) | 0 (0) | | |
| | Illiterate | 2 (10) | 0 (0) | 7 (35) | | |
| Employment | Employed | 7 (35) | 15 (75) | 9 (45) | 4.09 | **0.031*** |
| | Unemployed | 13 (65) | 5 (25) | 11 (55) | | |
| SES | LSES | 19 (95) | 8 (40) | 13 (65) | 7.12 | **0.001**** |
| | MSES | 1 (5) | 12 (60) | 7 (35) | | |
| Marital status | Married | 9 (45) | 12 (60) | 6 (30) | 1.25 | 0.38 |
| | Unmarried | 10 (50) | 8 (40) | 13 (65) | | |
| | Divorce | 1 (5) | 0 (0) | 1 (5) | | |
| Family type | Nuclear | 5 (25) | 4 (20) | 7 (35) | 0.92 | 0.55 |
| | Joint | 15 (70) | 16 (80) | 13 (65) | | |
| Habitat | Rural | 18 (90) | 16 (80) | 17 (85) | 0.53 | 0.76 |
| | Suburban | 1 (5) | 3 (15) | 1 (5) | | |
| | Urban | 1 (5) | 1 (5) | 2 (10) | | |
| Family history of psychiatric illness | Present | 4 (20) | 5 (25) | 2 (10) | 0.75 | 0.68 |
| | Absent | 16 (80) | 15 (75) | 18 (90) | | |
| Age (Years) | | 33.15 (7.78) | 32.10 (8.40) | 26.85 (8.46) | 3.27 (2, 37.9) (t) | 0.049* |
| Duration of illness (months) | | 77.50 (49.79) | | 4.90 (1.02) | 49.88(t) | **<0.01**** |

There were significant differences in the employment status and socio-economic status between the three groups as 65% patients with first episode schizophrenia were found to be unemployed (p=0.031) and 95% belonged to lower socio-economic status (p=0.001). The mean duration of illness was comparatively higher in patients with chronic schizophrenia (77.50 months) as compared to patients with first episode schizophrenia (4.90 months).In the study, gender distribution showed a higher percentage of males across all groups (CH: 95%, CN: 80%, FE: 90%) with no significant difference ($\chi^2$ = 1.48, p = 0.32). The majority of participants were Hindu (CH: 85%, CN: 100%, FE: 85%), with religion showing no significant difference across groups ($\chi^2$ = 1.73, p = 0.27). Educational levels varied, with primary education being most common in the CN group (55%) and secondary education in the CH group (45%). There was no statistically significant difference in education levels ($\chi^2$ = 2.81, p = 0.06). In terms of marital status, most participants in each group were

married or unmarried, with no significant difference ($\chi^2 = 1.25$, $p = 0.38$). The majority belonged to joint families (CH: 70%, CN: 80%, FE: 65%), also showing no significant difference ($\chi^2 = 0.92$, $p = 0.55$). Most participants resided in rural areas (CH: 90%, CN: 80%, FE: 85%), with no significant difference ($\chi^2 = 0.53$, $p = 0.76$). Family history of psychiatric illness was mostly absent across groups, with no significant difference ($\chi^2 = 0.75$, $p = 0.68$).

**Table 2: Comparison of the scores on the clinical rating scales between both the groups with schizophrenia (N = 40)**

| Variables | CH Group (n=20)/ Mean (SD) | FE Group (n=20)/ Mean (SD) | t (df=1) | p |
|---|---|---|---|---|
| PANSS | 60.60 (6.5) | 71.25 (7.72) | 12.60 | <0.01* |
| SANS | 39.20 (9.26) | 36 (10.43) | 1.02 | 0.31 |
| SAPS | 23.45 (4.64) | 23.75 (4.49) | 0.41 | 0.84 |

The PANSS scores reveal significantly higher symptom severity in the FE group (mean = 71.25, SD = 7.72) compared to the CH group (mean = 60.60, SD = 6.5; $p < 0.01$). However, SANS scores show no significant difference between the CH (mean = 39.20, SD = 9.26) and FE (mean = 36, SD = 10.43) groups ($p = 0.31$), indicating similar negative symptoms. Likewise, SAPS scores are comparable for both groups (CH mean = 23.45, SD = 4.64; FE mean = 23.75, SD = 4.49; $p = 0.84$), suggesting no significant difference in positive symptoms.

**Table 3: Comparison of mean serum NCAM levels among the three groups**

| Variable | FE Group (n=20) Mean | CH Group (n=20) Mean | CN Group (n=20) Mean | H (df 2) | p |
|---|---|---|---|---|---|
| NCAM | 24.25 | 35.35 | 31.90 | 4.23 | 0.12 |

No significant intergroup variations were observed among the three groups in the mean serum NCAM levels Kruskal-Wallis non-parametric one-way ANOVA was conducted to compare NCAM levels across three groups: FE Group, CH Group, and CN Group, each with 20 participants. Mean ranks were: FE Group = 24.25, CH Group = 35.35, and CN Group = 31.90. The H statistic was 4.23 (df=2) with a p-value of 0.12, indicating no statistically significant difference in NCAM levels among the groups ($p > 0.05$).

**Table 4: Comparison of mean rank of Hippocamapal glutamate (R & L) among three groups**

| VARIABLE | FE GROUP (MEAN RANK) N=20 | CH GROUP (MEAN RANK) N=20 | CN GROUP (MEAN RANK) N=20 | H(DF=2) | P |
|---|---|---|---|---|---|
| GLU RT | 29.95 | 33.20 | 28.35 | 0.802 | 0.67 |
| GLU LT | 28.85 | 35.55 | 27.10 | 2.61 | 0.27 |

A Kruskal-Wallis Non-Parametric one way ANOVA test compared right (GLU RT) and left (GLU LT) hippocampal glutamate levels across three groups: FE Group, CH Group, and CN Group, each with 20 participants. For GLU RT, mean ranks were 29.95, 33.20, and 28.35, with $H = 0.802$ and $p = 0.67$, indicating no significant difference. For GLU LT, mean ranks were 28.85, 35.55, and 27.10, with $H = 2.61$ and $p = 0.27$, also showing no significant difference. Thus, no significant differences in glutamate levels were observed among the groups.

**Table 5: Relationship of sociodemographic and clinical characteristics with the serum NCAM levels and glutamate levels as measured by MRS in patients with First episode schizophrenia (N = 20) (FE Group)**

| Variables | | NCAM | GLU Right | GLU Left |
|---|---|---|---|---|
| Age | Pearson correlation | -0.28 | 0.008 | -0.240 |
| | Sig (2 tailed) | 0.238 | 0.98 | 0.308 |
| Education | Pearson correlation | 0.08 | 0.12 | 0.10 |
| | Sig (2 tailed) | 0.31 | 0.35 | 0.39 |
| SES | Pearson correlation | 0.14 | 0.16 | 0.15 |
| | Sig (2 tailed) | 0.20 | 0.27 | 0.28 |
| Duration of illness | Pearson correlation | -0.495 | 0.24 | 0.049 |
| | Sig (2 tailed) | 0.027* | 0.31 | 0.0.83 |
| PANSS | Pearson correlation | 0.35 | 0.39 | -0.23 |
| | Sig (2 tailed) | 0.13 | 0.09 | 0.33 |
| SANS | Pearson correlation | -0.27 | -0.07 | -0.04 |
| | Sig (2 tailed) | 0.24 | 0.78 | 0.75 |
| SAPS | Pearson correlation | 0.18 | -0.42 | 0.01 |
| | Sig (2 tailed) | 0.45 | 0.067 | 0.96 |

A significant negative correlation was found between duration of illness and NCAM ($r=-0.49$, $p=0.027$).

## DISCUSSION

The study was conducted at the K. S. Mani Centre for Cognitive Neurosciences and Girindra Shekhar Bose Centre for Neuroimaging and Radiological Sciences, Central Institute of Psychiatry (CIP), Ranchi. The study was a hospital based observational study. The study was approved by the Institutional Ethical Committee. This was the cross-sectional study 20 patients of first episode schizophrenia and 20 patients of chronic schizophrenia fulfilling the inclusion and exclusion criteria and 20 healthy controls completed the study. At first schizophrenia patients from different wards and OPD were screened for inclusion and exclusion criteria.

In this study, the mean age distribution across groups—chronic schizophrenia patients (CH), healthy controls (CN), and first-episode schizophrenia patients (FE)—revealed a younger mean age in the FE group (26.85 ± 8.46 years) compared to the CH (33.15 ± 7.78 years) and CN (32.10 ± 8.40 years) groups. This age difference aligns with schizophrenia's typical onset pattern, where first-episode cases appear earlier.[24,25] Family history prevalence was lower in this study's sample—CH (20%), CN (25%), and FE (10%)—than in another Indian research. Thirthalli et al, (2009),[26] reported higher family history rates (30% in schizophrenia vs. 5% in controls), possibly due to regional or sample size variations. In this study, males were predominant, with females making up only 5% to 20% across all groups. This gender distribution could indicate either greater accessibility of males for research participation or societal factors prioritizing the health recovery of male earners due to their role as primary financial supporters. This emphasis may result in higher hospitalization rates among men. Nationally, the Mental Health Survey (NMHS) 2015-16 reported only a slight difference in schizophrenia prevalence between males (1.45%) and females (1.39%), yet women in India often underutilize inpatient services, likely due to societal expectations and mental health stigma.[27,28]

Marital status also varied across groups. The CN group had the highest rate of married individuals (60%), while the FE group had the lowest (30%). The FE group also had the highest proportion of unmarried individuals (65%), which may be due to illness onset often coinciding with the typical marriageable age, impacting opportunities for long-term partnerships.[29,30] Education levels among participants showed notable variation. Illiteracy was most common in the FE group (35%), followed by 10% in the CH group, while no individuals in the CN group were illiterate. This disparity suggests that individuals in the FE group may face significant educational barriers, potentially due to early illness onset, which can disrupt educational progress through hospitalizations and social challenges related to schizophrenia.[31-33] Employment data reveal substantial differences among groups, with the CN group having the highest employment rate (75%), compared to 45% in the FE group and 35% in the CH group. This statistically significant difference ($\chi^2 = 4.09$, $p = 0.031$) suggests that schizophrenia, particularly in chronic cases, significantly impacts employment due to cognitive impairments, social withdrawal, and stigma. These challenges become more pronounced with frequent hospitalizations that can further hinder rehabilitation.[34]

Socioeconomic status (SES) also differed significantly across groups, with a p-value of 0.001 indicating a strong association. The majority of CH patients (95%) came from a lower socioeconomic status (LSES), compared to 65% in the FE group and 40% in the CN group. Conversely, 60% of CN participants belonged to the middle socioeconomic status (MSES), reflecting their higher education and employment rates, as SES often correlates with these factors. Individuals from higher SES backgrounds typically have better access to educational and employment resources, which can enhance their social and economic stability. The high representation of LSES among patients aligns with prior research linking lower SES to schizophrenia, often due to increased exposure to environmental stressors.[35]

The Positive and Negative Syndrome Scale (PANSS) scores in the present study reveal a statistically significant difference between the first-episode (FE) and chronic (CH) schizophrenia groups, with the FE group showing higher symptom severity. Specifically, the mean PANSS score in the FE group was 71.25 ± 7.72, compared to 60.6 ± 6.5 in the CH group. This indicates that individuals in the FE group may experience more severe manifestations of schizophrenia, consistent with findings in previous Indian studies. PANSS is a widely used tool for assessing symptom severity in schizophrenia. Studies such as Kulhara et al,[36] (2009) reported a mean total PANSS score of 80.6 in an Indian cohort with first-episode schizophrenia, closely aligned with the high PANSS scores observed in the FE group in this study. Various Indian studies have consistently shown that patients with first-episode schizophrenia often present with more pronounced positive symptoms, which contributes to higher PANSS scores in the FE group. Reddy et al,[37] (2014) observed that patients in the early stages of schizophrenia typically endure a higher burden of acute psychotic symptoms, explaining the elevated PANSS scores seen in first-episode patients. This aligns with our findings, where symptom severity in the FE group is higher than in the CH group, as symptoms often stabilize or shift towards more negative and cognitive symptoms with chronic illness progression.

In the present study, the mean Scale for the Assessment of Negative Symptoms (SANS) score was 39.20 ± 9.26 in the CH group and 36 ± 10.43 in

the FE group, with no significant difference between the groups (p = 0.31). These findings suggest that, despite treatment, negative symptoms may persist at similar levels across different groups of patients. This is consistent with research showing that while interventions may reduce negative symptoms, these improvements are often limited, and a substantial portion of patients continue to experience moderate to severe negative symptoms. Kulhara et al,[36] (1990) conducted a landmark study assessing symptom changes over time in schizophrenia patients. Their study involved a longitudinal assessment of positive and negative symptoms, with a follow-up duration of approximately 18-30 months. The results indicated that while positive symptoms showed significant improvement over time with treatment, negative symptoms remained more stable and less responsive to therapeutic interventions.

The p-value for the difference between these groups is 0.84, indicating no statistically significant difference in positive symptom severity between the CH and FE groups. These findings suggest that positive symptoms, as measured by SAPS, are present at similar levels in both chronic and first-episode schizophrenia patients. This aligns with research indicating that while positive symptoms often respond to treatment, they can persist across different stages of the illness. For instance, a study by Andreasen (1984),[22] noted that positive symptoms, such as hallucinations and delusions, may remain stable over time, regardless of illness duration. In examining serum NCAM levels across different stages of schizophrenia, previous research reveals notable variability and a lack of statistical significance when comparing first-episode, chronic schizophrenia patients, and healthy controls. These findings align with the results from the current study, where the Kruskal-Wallis test detected no statistically significant difference in NCAM levels across the three groups (Group FE = 24.25, Group CH = 35.35, Group CN = 31.90, H = 4.23, p = 0.12). This suggests that NCAM levels may not serve as a robust marker for differentiating schizophrenia stages. A review by Walterfang et al,[39] (2013) emphasizes the inconsistency in NCAM expression across psychiatric disorders, including schizophrenia. Findings were mixed, with some studies reporting elevated NCAM levels in chronic schizophrenia patients, while others observed no differences across illness stages. Walterfang and colleagues propose that the lack of significant group differences may stem from individual variability and environmental factors, thereby reducing NCAM's utility as a reliable disease marker.

In this study, a Kruskal-Wallis test comparing right (GLU RT) and left (GLU LT) hippocampus glutamate levels across three groups—first-episode schizophrenia (Group FE), chronic schizophrenia (Group CH), and control normal (Group CN)—revealed no significant differences among the groups. For GLU RT, mean ranks were 29.95, 33.20,
and 28.35, with H = 0.802 and p = 0.67, indicating no significant difference. Similarly, for GLU LT, mean ranks were 28.85, 35.55, and 27.10, with H = 2.61 and p = 0.27. Thus, no significant differences in hippocampal glutamate levels were observed among the groups. This finding is consistent with previous research showing mixed results for glutamate levels in schizophrenia across different stages of illness. For instance, Nakahara et al. (2021) conducted a meta-analysis that found no significant difference in hippocampal glutamate levels between first-episode schizophrenia and healthy controls, though elevated glutamate levels were noted in other regions, such as the dorsolateral prefrontal cortex (DLPFC). Marsman et al,[40] (2013) also reviewed the variability of glutamate levels across brain regions, including the hippocampus, in schizophrenia. Their meta-analysis revealed inconsistent findings, with some studies reporting no significant differences in hippocampal and temporal glutamate levels among schizophrenia patients and controls. They suggested that glutamate abnormalities might not be consistently present across illness stages, indicating regional variability within the brain.

Our study examined the relationship between sociodemographic and clinical characteristics with serum NCAM and glutamate levels (measured by MRS) in patients with first-episode schizophrenia, in our study, Age showed a negative correlation with serum NCAM levels (r = -0.28, p = 0.238) and left hippocampal glutamate (r = -0.24, p = 0.308), though these were not statistically significant. Education levels showed weak, positive correlations with NCAM (r = 0.08, p = 0.31), GLU Right (r = 0.12, p = 0.35), and GLU Left (r = 0.10, p = 0.39), indicating no significant impact on these biochemical markers.

Socioeconomic status (SES) also exhibited weak, positive correlations across NCAM (r = 0.14, p = 0.20), GLU Right (r = 0.16, p = 0.27), and GLU Left (r = 0.15, p = 0.28), though none reached statistical significance. Duration of illness had a statistically significant negative correlation with NCAM levels (r= -0.495, p = 0.027), suggesting that longer illness duration is associated with lower serum NCAM levels. However, duration of illness showed no significant correlation with glutamate levels in the right (r = 0.24, p = 0.31) or left (r = 0.049, p = 0.83) hippocampus. Clinical symptom scores on the PANSS exhibited a positive, though non-significant, correlation with NCAM (r = 0.35, p = 0.13) and GLU Right (r = 0.39, p = 0.09), while the relationship with GLU Left was negative and non-significant (r = -0.23, p = 0.33). Negative symptoms on the SANS were inversely correlated with NCAM (r = -0.27, p = 0.24), GLU Right (r = -0.07, p = 0.78), and GLU Left (r = -0.04, p = 0.75), but these were not statistically significant. SAPS scores showed a positive, though non-significant,

relationship with NCAM (r = 0.18, p = 0.45) and GLU Left (r = 0.01, p = 0.96), and a non- significant negative correlation with GLU Right (r = -0.42, p = 0.067). Overall, the only statistically significant finding was the inverse relationship between duration of illness and NCAM levels, suggesting that longer illness may contribute to lower NCAM levels in first-episode schizophrenia this aligns with the study done by An et al. (2015) investigated serum NCAM levels in patients with first-episode schizophrenia and found that longer illness duration correlated with lower NCAM levels. The authors proposed that extended periods without treatment might lead to neurobiological changes reflected in decreased NCAM concentration.

## CONCLUSION

The current study aimed to assess serum NCAM levels and glutamate in hippocampus in FE group in comparison to CH group and healthy CN group possibly shed some light on possible contribution of various factors and neurotransmitter in the pathophysiology of illness, Investigating these biomarkers and neurotransmitters to identify any changes that may occur at the onset of illness and assess whether these changes progress. This could improve our understanding of schizophrenia's underlying mechanisms and aid in identifying early therapeutic targets to enhance treatment outcomes. The use of tools such as PANSS, SANS, SAPS enabled accurate assessment of illness. The socio-demographic trends revealed predominance of male, Hindu and rural population and lower socioeconomic strata and employment attainment among FE group highlighting the challenges that may affect the treatment and outcome of the illness. Our findings showed no statistically significant differences in NCAM levels or hippocampal glutamate concentrations across the FE, CH, and CN groups, suggesting these biomarkers may not differentiate between the stages of schizophrenia or from healthy individuals in a cross- sectional analysis. However, a significant correlation was observed between NCAM levels and age within the FE group, implying a possible age-related alteration in NCAM among first-episode patients.

## REFERENCES


1. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Archives of general psychiatry. 2000 Jan 1;57(1):65-73.
2. van Erp TG, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, Agartz I, Westlye LT, Haukvik UK, Dale AM, Melle I. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Molecular psychiatry. 2016 Apr;21(4):547-53.
3. Tamminga CA. Schizophrenia and glutamatergic transmission. Critical Reviews™ in Neurobiology. 1998;12(1-2).
4. Xiao Y, Lui S, Deng W, Yao L, Zhang W, Li S, Wu M, Xie T, He Y, Huang X, Hu J. Altered cortical thickness related to clinical severity but not the untreated disease duration in schizophrenia. Schizophrenia bulletin. 2015 Jan 1;41(1):201-10.
5. Harrisberger F, Buechler R, Smieskova R, Lenz C, Walter A, Egloff L, Bendfeldt K, Simon AE, Wotruba D, Theodoridou A, Rössler W. Alterations in the hippocampus and thalamus in individuals at high risk for psychosis. NPJ schizophrenia. 2016 Sep 28;2(1):1-6.
6. Talukdar S, Olefsky JM, Osborn O. Targeting GPR120 and other fatty acid-sensing GPCRs ameliorates insulin resistance and inflammatory diseases. Trends in pharmacological sciences. 2011 Sep 1;32(9):543-50.
7. Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. The American journal of psychiatry. 1991 Oct 1;148(10):1301-8.
8. Gregory ML, Stech NE, Owens RW, Kalivas PW. Prefrontal group II metabotropic glutamate receptor activation decreases performance on a working memory task. InGlutamate and Disorders of Cognition and Motivation, Apr, 2003, New Haven, CT, US; This work is the result of the aforementioned conference by the New York Academy of Sciences and co-sponsored by the National Institute of Mental Health and Eli Lilly and Company. 2003. New York Academy of Sciences.
9. Kim JS, Kornhuber HH, Schmid-Burgk W, Holzmüller B. Low cerebrospinal fluid glutamate in schizophrenic patients and a new hypothesis on schizophrenia. Neuroscience letters. 1980 Dec 1;20(3):379-82.
10. de Jong MH, Kamperman AM, Oorschot M, Priebe S, Bramer W, van de Sande R, Van Gool AR, Mulder CL. Interventions to reduce compulsory psychiatric admissions: a systematic review and meta-analysis. JAMA psychiatry. 2016 Jul 1;73(7):657-64.
11. Frick A, Åhs F, Palmquist ÅM, Pissiota A, Wallenquist U, Fernandez M, Jonasson M, Appel L, Frans Ö, Lubberink M, Furmark T. Alterations in the serotonergic and substance P systems in posttraumatic stress disorder. Molecular Psychiatry. 2016 Oct;21(10):1323-.
12. Kegeles LS, Mao X, Stanford AD, Girgis R, Ojeil N, Xu X, Gil R, Slifstein M, Abi-Dargham A, Lisanby SH, Shungu DC. Elevated prefrontal cortex γ-aminobutyric acid and glutamate-glutamine levels in schizophrenia measured in vivo with proton magnetic resonance spectroscopy. Archives of general psychiatry. 2012 May 1;69(5):449-59.
13. Merritt K, McGuire P, Egerton A. Relationship between glutamate dysfunction and symptoms and cognitive function in psychosis. Frontiers in psychiatry. 2013 Nov 26;4:151.
14. Adriano F, Caltagirone C, Spalletta G. Hippocampal volume reduction in first-episode and chronic schizophrenia: a review and meta-analysis. The Neuroscientist. 2012 Apr;18(2):180-200.
15. Zhou Y, Fan L, Qiu C, Jiang T. Prefrontal cortex and the dysconnectivity hypothesis of schizophrenia. Neuroscience bulletin. 2015 Apr;31:207-19.
16. Barbeau D, Liang JJ, Robitalille Y, Quirion R, Srivastava LK. Decreased expression of the embryonic form of the neural cell adhesion molecule in schizophrenic brains. Proceedings of the National Academy of Sciences. 1995 Mar 28;92(7):2785-9.
17. Hernandez VS, Ruíz-Velazco S, Zhang L. Differential effects of osmotic and SSR149415 challenges in maternally separated and control rats: the role of vasopressin on spatial learning. Neuroscience Letters. 2012 Oct 24;528(2):143-7.
18. Kiryushko D, Berezin V, Bock E. Regulators of neurite outgrowth: role of cell adhesion molecules. Annals of the New York Academy of Sciences. 2004 Apr;1014(1):140-54.
19. Kiss JZ, Müller D. Contribution of the neural cell adhesion molecule to neuronal and synaptic plasticity. Reviews in the Neurosciences. 2001 Oct;12(4):297-310.
20. Rønn LC, Hartz BP, Bock E. The neural cell adhesion molecule (NCAM) in development and plasticity of the nervous system. Experimental gerontology. 1998 Nov 1;33(7-8):853-64.

21. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia bulletin. 1987 Jan 1;13(2):261-76.
22. Andreason CT. Indian Worship v. Government Development: A New Breed of Religion Cases. Utah L. Rev.. 1984:313.
23. Goldberg, D. (1978). Manual of the General Health Questionnaire. NFER Nelson.
24. Dlabac-de Lange JJ, Liemburg EJ, Bais L, van de Poel-Mustafayeva AT, de Lange-de Klerk ES, Knegtering H, Aleman A. Effect of bilateral prefrontal rTMS on left prefrontal NAA and Glx levels in schizophrenia patients with predominant negative symptoms: an exploratory study. Brain stimulation. 2017 Jan 1;10(1):59-64.
25. Thara R, Kamath S, Kumar S. Women with schizophrenia and broken marriages-doubly disadvantaged? Part I: Patient perspective. International Journal of Social Psychiatry. 2003 Sep;49(3):225-32.
26. Thirthalli, J., Channaveerachari, N. K., Subbakrishna, D. K., Cottler, L. B., & Varghese, M. (2009). Prevalence and correlates of familiality and comorbidity among schizophrenia patients in Bangalore, India. Social Psychiatry and Psychiatric Epidemiology, 44(10), 807-813.
27. Solanki RK, Singh P, Midha A, Chugh K. Schizophrenia: impact on quality of life. Indian journal of psychiatry. 2008 Jul 1;50(3):181-6.
28. Kamla DK, Ram D. The role of memantine in the treatment of negative symptoms of schizophrenia patients.
29. Isaac M, Chand P, Murthy P. Schizophrenia outcome measures in the wider international community. The British Journal of Psychiatry. 2007 Aug;191(S50):s71-7.
30. Vibha P, Saddichha S, Khan N, Akhtar S. Quality of life and marital adjustment in remitted psychiatric illness: An exploratory study in a rural setting. The Journal of nervous and mental disease. 2013 Apr 1;201(4):334-8.
31. Pedersen CB, Mors O, Bertelsen A, Waltoft BL, Agerbo E, McGrath JJ, Mortensen PB, Eaton WW. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. JAMA psychiatry. 2014 May 1;71(5):573-81.
32. Karkal R, Khess CR. Effect of chronic nicotine exposure on sensory gating functions in drug free/drug naïve patients with schizophrenia. Order. 2013(10153858).
33. Singh S, Khushu S, Kumar P, Goyal S, Bhatia T, Deshpande SN. Evidence for regional hippocampal damage in patients with schizophrenia. Neuroradiology. 2018 Feb;60:199-205.
34. Marwaha S, Johnson S. Schizophrenia and employment: a review. Social psychiatry and psychiatric epidemiology. 2004 May;39:337-49.
35. Dean K, Murray RM. Environmental risk factors for psychosis. Dialogues in clinical neuroscience. 2005 Mar 31;7(1):69-80.
36. Kulhara, P., & Chandiramani, K. (1990). The course and outcome of schizophrenia: A comparison of positive and negative symptoms in Indian patients. In S. Varma (Ed.), Current trends in schizophrenia research (pp. 71–89). Springer.
37. Reddy, M. S., Thirthalli, J., & Gangadhar, B. N. (2014). Symptom severity and outcomes in schizophrenia patients across different stages of illness: A study from India. Indian Journal of Psychological Medicine, 36(3), 253–259.
38. Lee J, Song S, Lee J, Kang J, Choe EK, Lee TY, Chon MW, Kim M, Kim SW, Chun MS, Chang MS. Impaired migration of autologous induced neural stem cells from patients with schizophrenia and implications for genetic risk for psychosis. Schizophrenia Research. 2022 Aug 1;246:225-34.
39. Walterfang M, Bonnot O, Mocellin R, Velakoulis D. The neuropsychiatry of inborn errors of metabolism. Journal of inherited metabolic disease. 2013 Jul;36:687-702.
40. Marsman A, Van Den Heuvel MP, Klomp DW, Kahn RS, Luijten PR, Hulshoff Pol HE. Glutamate in schizophrenia: a focused review and meta-analysis of 1H-MRS studies. Schizophrenia bulletin. 2013 Jan 1;39(1):120-9.