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Psychiatry

KEY WORDS: Schizophrenia, gamma oscillation, ARMS

A STUDY TO CORRELATE EVOKED GAMMA OSCILLATIONS WITH CLINICAL AND DEMOGRAPHIC VARIABLES IN FIRST DEGREE RELATIVES OF PATIENTS OF SCHIZOPHRENIA WITH AT-RISK MENTAL STATE.

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ABSTRACT

Background: EEG has shown that schizophrenia is characterized by alterations in synchrony and oscillatory activity in a variety of paradigms, particularly in the gamma range. A study was conducted to correlate evoked gamma oscillations with clinical and demographic variables in first-degree relatives of patients of schizophrenia with At-risk mental states (ARMS) and healthy controls (HC). **Methods:** This was a Hospital-based, cross-sectional study conducted between 2017 to 2019. Right-handed, normal-hearing individuals of both genders, aged > 18 years, FDRs of patients meeting diagnostic criteria for schizophrenia, and age and sex-matched healthy controls were included in the study. All participants underwent EEG recording in a light-attenuated and sound-proof room with a supine position. P<0.05 was considered to be statistically significant. **Results:** The finding suggests no significant difference between the two groups regarding religion, education, occupation, socioeconomic status, family income, and habitat. The continuous variable (age) was compared using the T-test. Correlations of low gamma (30-45 Hz) spectral power between age and regions were statistically not significant among ARMS & HC. **Conclusions:** The finding suggests no significant difference between the two groups regarding religion, education, occupation, socioeconomic status, family income, and habitat.

BACKGROUND

The Greek word prodromos which means forerunner of an event. From this, the word prodrome is derived. Since the psychoses were first described and documented, it had been noticed that severe mental disorders Bleuler's concept of latent schizophrenia can be considered as one of the first fundamental works on prodromal phases.[1] ERPs originate from postsynaptic potentials (PSPs) in cortical pyramidal cells, resulting from the flow of ions across the cell membrane in response to neurotransmitters binding with receptors. When PSPs co-occur in similarly oriented neurons, the resulting field potentials summate, and the voltage can be detected instantaneously on the scalp. Thus, ERPs provide a direct, millisecond-resolution measure of neurotransmission-related neural activity. Event-related potentials can only be measured at the scalp when PSPs are simultaneously produced in thousands of similarly oriented neurons.

These varied abnormalities in schizophrenia may be due to a dysfunction in neural circuitry, which affects many brain systems, rather than to a lesion affecting a localized site. One model garnered much attention in the past decade is the disconnection hypothesis, which proposes that schizophrenia disrupts signaling among brain regions, systems, or cellular circuits. Disruption of neural synchrony and oscillations, for example, could have a marked impact on functional connectivity within and across brain regions. Findings from cellular, local field potential and electroencephalographic recordings suggest that gamma oscillations (>30 Hz) are essential for the integration of information within neural circuits; gamma oscillations have been associated with numerous perceptual and cognitive processes, including attention, memory, object recognition, word processing, and consciousness.

EEG has shown that schizophrenia is characterized by alterations in synchrony and oscillatory activity in a variety of paradigms, particularly in the gamma range. High-frequency oscillations in the gamma range (30-100 Hz) of the electroencephalogram (EEG) are known to be altered in schizophrenia.[2] Changes in evoked gamma range EEG are intriguing because gamma band activities have been associated with several critical cognitive functions. Earlier studies showed that the evoked gamma band response to auditory tones is poorly synchronized in schizophrenia.[3] Earlier studies show that young schizophrenia patients demonstrate significantly decreased evoked power in the gamma band.[4]

Early sensory evoked gamma oscillations like the early auditory gamma band response play a role in integrating early sensory and attentional or motivational processes.[5] Inhibitory fast-spiking, gamma-aminobutyric acid (GABA)-ergic, parvalbumin-positive interneurons have been suggested to be involved in the generation of gamma oscillations by synchronization of cortical glutamatergic pyramidal cells firing via negative feedback inhibition. Glutamate receptor deficiency of GABAergic interneurons reduced gamma power in an in vitro study, suggesting that a reduced GABAergic inhibition of glutamatergic pyramidal cells could be due to a decreased glutamatergic excitation of interneurons in terms of a disturbed feedback loop.[6]

With these, a study was conducted to correlate evoked gamma oscillations with clinical and demographic variables in first-degree relatives of patients of schizophrenia with At Risk Mental State (ARMS) & Healthy controls (HC).

RATIONALE OF THE STUDY

Research has shown that schizophrenia is characterized by changes in synchrony and oscillatory activity, particularly in the gamma range, as observed through EEG. High-frequency oscillations in the gamma range (30-100 Hz) of the electroencephalogram (EEG) are known to be altered in schizophrenia. A study was conducted to investigate the correlation between evoked gamma oscillations and clinical and demographic variables in first-degree relatives of patients with schizophrenia who are at risk of developing the condition (ARMS), as well as in healthy controls (HC). This research is critical to understanding the correlations in low gamma (30-45 Hz) spectral power between age and regions in ARMS and HC.

METHODS

This was a Hospital-based, cross-sectional study conducted in a tertiary referral center in India conducted between 2017 to 2019. The tertiary referral center for psychiatric patients has a wide catchment area, including the country and neighboring countries like Nepal and Bangladesh. The study followed a purposive sampling strategy. Thirty first-degree relatives of

schizophrenia patients who qualified for ARMS were assessed using CAARMS. They were taken as a study sample, and the same number of healthy individuals of both genders were considered as controls.

Right-handed, normal-hearing individuals of both genders, aged > 18 years, FDR of patients meeting diagnostic criteria for Schizophrenia, as per ICD-10-DCR, those FDRs who fulfilled the criteria of ARMS as assessed by using Comprehensive Assessment of ARMSs were included in the study. FDR's having epilepsy or any organic brain disorder, history of any significant medical illness or major psychiatric illness, and those who did not submit the consent were excluded from the study. It is a semi-structured proforma used for recording demographic details like age, sex, religion, education, occupation, socioeconomic status, and habitat, as well as clinical data such as duration of illness, past history of any medical illness, family history of medical or psychiatric illness, and pre-morbid temperament. It also includes details of physical examination and, finally, the patient's diagnosis according to ICD-10 DCR and treatment received.

Family interviews for genetic studies, seven comprehensive assessments of at-risk mental state (CAARMS), eight social and occupational functioning assessment scales (SOFAS), 9, and handedness preference schedules, Hindi version 10, were also considered as per the standard protocol. FDRs of patients with schizophrenia fulfilling the inclusion and exclusion criteria were selected by purposive sampling. And 30 HCs were taken. Written informed consent was taken. Socio-demographic and clinical data were collected from all the study participants, and handedness was assessed using a sidedness bias schedule (SBS) –Hindi version. A detailed physical examination was also done, followed by an assessment of FIGS. All participants (FDR) were assessed by CAARMS and, based on the ARMS group's cut-off with ARMS taken, 30 samples of ARMS were then compared to healthy control by EEG-ERP.

All participants underwent EEG recording at the tertiary referral center for psychiatric patients. They were advised to avoid using tea, coffee, or nicotine for at least one hour before recording. The individual's hair was washed thoroughly with a glycerin-free soap and allowed to dry. The recording was done in a light-attenuated and sound-proof room, with the patients in the supine position. The subjects were asked to remain relaxed and to minimize motor movements during the recording.

Statistical Analysis

Appropriate statistical measures were applied using a statistical package for Social Sciences version 24.0 (SPSS-24.0). Different statistics, such as t-test and chi-square test, were used. P<0.05 was considered to be statistically significant.

RESULTS

Comparative information about socio-demographic characteristics of experimental and healthy control (HCs) in discrete variables like religion, education, occupation, socioeconomic status, family income, and habitat were given in Table 1. The finding suggests no significant difference between the two groups regarding religion, education, occupation, socio-economic status, family income, and habitat, and the continuous variable (age) was compared using the T-test. The active group consists of 30 ARMS with a mean age of 29.63 years (S.D. = 6.59), and the HC group consists of 30 patients with a mean of 30.00 years (S.D. =5.02).

Correlations of low gamma (30-45 Hz) spectral power between age and regions were statistically not significant among ARMS (Table 2). When age and region correlated, statistically, there was no significant difference with high gamma (45-60 Hz) spectral power between age and regions among ARMS (Table 3). There was no significant correlation between low gamma power with CAARMS and SOFAS. There was a positive relation in CAARMS frequency between left and right frontal low gamma and SOFAS A and B with left and right parietooccipital in low gamma and SOFAS B in Right central gamma. The Rest of all have negative correlation but no significant correlation between regions of low gamma spectral power (30-45 Hz) with CAARMS and SOFAS (Table 4). Statistically, there was no significant correlation between high gamma power and CAARMS and SOFAS. There was a positive relation between right frontal gamma with CAARMS frequency and SOFAS A and B with left and right parietooccipital in high gamma and SOFAS B with left and right central gamma. The rest of them have a negative correlation but no significant correlation between regions of high gamma spectral power (45-60 Hz) with CAARMS and SOFAS (Table 5). In the correlation between CAARMS and SOFAS, as the CAARMS score increases, there is a decline in socio-occupational functioning (Table 6).

Variable		ARMS (n=30) Mean ± SD/n (%)	HC (n=30) Mean ± SD/n (%)	t/χ^2	p
Age (in years)		29.63 ± 6.59	30.00±5.02	-0.242	0.809
Education (in degree)	Secondary/Higher Secondary	14 (46.7%)	14 (46.7%)	.000	1.000
	Graduate /above	16 (53.3%)	16 (53.3%)		
Socioeconomic status	Low	16 (53.3%)	17 (56.7%)	1.138[f]	0.553
	Middle	14 (46.7%)	12 (40.0%)		
	High	0 (0.0%)	1 (3.3%)		
Habitat	Rural	12 (40.0%)	14 (46.7%)	0.271	0.602
	Urban	18 (60%)	16 (53.3%)		
Family Income (in rupees)	0-20000	18 (60%)	17 (56.7%)	0.119	0.942
	20000-50000	7 (23.3%)	7 (23.3%)		
	>50000	5 (16.7%)	6 (20%)		
Religion	Hindu	25 (83.3%)	28 (93.3%)	1.456	0.228
	Islam	5 (16.7%)	2 (16.7%)		
Occupation	Employed	17 (56.7%)	19 (63.3%)	1.112[f]	0.561
	Unemployed	1 (3.3%)	0 (0.0%)		
	Other	12 (40%)	11 (36.7%)		

Table 1. Comparison of Sociodemographic Data Between the Groups

Regions	r	p
Left Frontal Gamma1	0.266	0.156
Right Frontal Gamma1	0.278	0.137
Left Central Gamma1	0.178	0.346
Right Central Gamma1	0.168	0.376
Left Parieto Occipital Gamma1	0.099	0.604
Right Parieto Occipital Gamma1	0.133	0.483

Table 2. Correlations of Low Gamma (30-45 Hz) Spectral Power in Between Age and Regions in ARMS

r=Pearson Correlations with age; P=NS; *Significant at <0.05 level

Regions	r	p
Left Frontal Gamma2	0.293	0.117
Right Frontal Gamma2	0.304	0.102
Left Central Gamma2	0.146	0.441
Right Central Gamma2	0.167	0.378
Left Parieto Occipital Gamma2	0.099	0.604
Right Parieto Occipital Gamma2	0.110	0.563

Table 3. Correlations of High Gamma (45-60 Hz) Spectral Power in Between Age and Regions Among ARMS

r=Pearson Correlations with age; P=NS; *Significant at <0.05 level

Regions	CAARMS intensity	CAARMS frequency	CAARMS total	SOFAS A	SOFAS B	SOFAS C
Left Frontal Gamma1	-0.018	0.004	-0.010	-0.099	-0.060	-0.164
Right Frontal Gamma1	-0.009	0.021	0.003	-0.123	-0.104	-0.125
Left Central Gamma1	-0.153	-0.110	-0.134	-0.071	-0.023	-0.172
Right Central Gamma1	-0.165	-0.120	-0.145	-0.046	0.004	-0.163
Left Parieto Occipital Gamma1	-0.188	-0.146	-0.169	0.078	0.146	-0.133
Right Parieto Occipital Gamma1	-0.193	-0.154	-0.175	0.084	0.159	-0.145

Table 4. Correlation of Low Gamma Spectral Power (30-45 Hz) with CAARMS and SOFAS

CAARMS= comprehensive assessment of at-risk mental states SOFAS= social and occupational functioning assessment scale (in this scale, SOFAS A= highest score in the past year OR score at baseline/last assessment, SOFAS current score & SOFAS C = difference between Score A and B)

Regions	Caarms Intensity	Caarms Frequency	Caarms Total	Sofas A	Sofas B	Sofas C
Left Frontal Gamma2	-0.041	-0.010	-0.028	-0.062	-0.023	-0.144
Right Frontal Gamma 2	-0.035	0.004	-0.018	-0.084	-0.061	-0.112
Left Central Gamma2	-0.192	-0.156	-0.177	-0.059	0.009	-0.216
Right Central Gamma 2	-0.196	-0.161	-0.182	-0.034	0.031	-0.193
Left Parieto Occipital Gamma2	-0.178	-0.143	-0.163	0.033	0.107	-0.174
Right Parieto Occipital Gamma2	-0.181	-0.146	-0.167	0.025	0.111	-0.213

Table 5. Correlation of High Gamma Spectral Power (45-60Hz) with CAARMS and SOFAS

CAARMS= comprehensive assessment of at-risk mental states SOFAS= social and occupational functioning assessment scale (in this scale, SOFAS A= highest score in a past year OR score at baseline/last assessment, SOFAS current score & SOFAS C = difference between Score A and B)

Variables	SOFAS A	SOFAS B	SOFAS C
CAARMS intensity	-.837	-.863	-.446
CAARMS frequency	-.850	-.865	-.485
CAARMS total	-.848	-.868	-.469

Table 6. Correlation of CAARMS with SOFAS

CAARMS= comprehensive assessment of at-risk mental states
SOFAS= social and occupational functioning assessment scale (in this scale, SOFAS A= highest score in past year OR score at baseline/last assessment, SOFAS current score & SOFAS C = Difference between Score A and B)

DISCUSSION

Evoked gamma oscillations and at-risk mental state in first-degree relatives of patients of schizophrenia and to correlate evoked gamma oscillations with clinical and demographic variables in first-degree relatives of patients of schizophrenia with ARMS. In this study, FDRs of patients with schizophrenia fulfilling the inclusion and exclusion criteria were selected by purposive sampling. And 30 healthy controls were taken. Written informed consent was taken from them. Socio-demographic and clinical data were collected from all the study participants, and handedness was assessed using a sidedness bias schedule (SBS)–Hindi version. A detailed physical examination was also done, followed by an assessment of FIGS. All participants (FDR) were assessed by CAARMS, and based on the cut-off for the ARMS group, 30 samples of ARMS were taken to compare with 30 HCs on EEG-ERP.

First-degree relatives of schizophrenia patients and healthy control groups were compared on their age, religion, education, occupation, habitat, socio-economic status, and family income. The finding suggests that there was no significant difference between the two groups regarding religion, education, occupation, socioeconomic status, family income, and habitat (Table 1), and they were adequately matched. Most of the study samples had a predominance of Hinduism, which might reflect the fact that Hinduism is the religion of the majority in India. Being a Government Tertiary Hospital, most patients who attend the services belong to families hailing from rural habitats. A similar finding was observed by 11 that 80% of schizophrenia patients come from rural backgrounds.

Study samples in both groups were educated up to secondary or higher secondary graduation, which reflects the adequate level of education in both groups. There was no significant difference between the ARMS group and controls when occupation was compared. 60% of the first-degree relatives of schizophrenia were found to be employed, which indicates adequate functioning of FDR, while 40% of them were engaged in either unskilled work or were not working at all. HCs were taken from the tertiary health care campus and residents of Ranchi. They were all male, and most of them were well-educated and employed.

The mean age of the first-degree relatives, those who are at risk mental state, and the controls in the present study for the active group were 29.63 ± 6.59 years, and for the control healthy group, 30.00 ± 5.02 years (Table 1), which was similar to a study done in the past. Schizophrenia patients' FDR taken who qualified for ARMS based on the CAARMS and SOFAS scales. The mean scores of CAARMS and SOFAS subscales were as follows: for CAARMS intensity 4.33±4.13, CAARMS frequency and duration 4.56±4.14, CAARMS total 8.93±8.23, SOFAS A 88.93±1.50, SOFAS B 61.76±1.22, SOFAS C 27.16±0.46. Our study showed a decline in the SOFAS scale as the scores on the CAARMS scale increased. A 12-month longitudinal study in which demographic, clinical, and neuropsychological data were acquired from 102 anti-psychotic naive UHR and 61 healthy controls, of whom 80 UHR and 58 controls provided valid EEG data during a passive auditory task. The study showed that the FDR, despite not

having symptoms of schizophrenia, were unemployed. This could be due to the defects in verbal memory, verbal fluency, and executive functioning working memory in ultra-high-risk samples that could also affect their socio-occupational functioning.[12] This could explain the poor socio-occupational functioning in the ARMS group.

The Kruskal-Wallis test was performed for region-wise comparison between 3 groups: ARMS vulnerability group, APS, and HCs. In low gamma power (30-45 Hz) and high gamma power (45-60 Hz, there was no statistically significant difference in gamma power between 3 groups. Some studies in the past also failed to find substantial differences in gamma power between first-degree relatives of schizophrenia patients and healthy controls.[13] But, a few studies on visual oddball tasks showed gamma (30 – 38 Hz) phase locking following target stimulus was significantly lower for schizophrenia patients in the occipital region but not in their FDRs.[14] It has been suggested that such deficits may be related to disturbances in the ability of the visual cortex to generate gamma oscillations or impaired attentional modulation by the DLPFC.[15]

Correlations of low gamma (30-45 Hz) and high gamma (45-60 Hz) spectral power between age and regions, there was no significant correlation in gamma power between age and regions in ARMS. Past studies by 16 also found no significant difference in gamma power (30-100 Hz) with age and areas, which supported our findings. However, some EEG studies that looked at gamma oscillations (30–50 Hz) during rest found that schizophrenia patients and their biological relatives had increased power in gamma oscillations compared to healthy controls, which were most prominent in the frontal and temporal regions in contrast to our findings.[17]

In this study, low gamma spectral power (30-45 Hz) and high gamma spectral power (45-60 Hz) with CAARMS and SOFAS, there was no significant correlation between low gamma and high gamma spectral power with CAARMS and SOFAS. A study by Grent et al., 2018 Found that the Low gamma band (30-46 Hz) in the resting state has no relation with CAARMS, which supports our finding. Clinical high-risk participants found moderately increased middle frontal and occipital cortex in high gamma-band power (64-90 Hz) in resting state. We also saw a correlation between CAARMS and SOFAS. As the CAARMS score increased, socio-occupational functioning declined, which could be explained by a subtle ongoing cognitive deficit that may be seen in at-risk subjects.

LIMITATIONS AND CONCLUSIONS

The study has several limitations that should be acknowledged. First, the sample is overrepresented in North India, which may limit the generalizability of the findings to participants from other parts of the country. This study includes only male first-degree relatives of patients with schizophrenia. thus gender-specific results could not be generalizable for the whole schizophrenic population. A more diverse sample encompassing regions such as the West and South of India would have enhanced the study's comprehensiveness. First-degree relatives of schizophrenia patients (ARMS) and HC groups were compared regarding their age, religion, education, occupation, habitat, socioeconomic status, and family income. The findings suggest no significant difference between the two groups regarding religion, education, occupation, socioeconomic status, family income, and habitat.

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Ethical Approval and Informed Consent:
The study received approval from the Institutional Ethics Committee. Only those participants who willingly agreed to take part in the study and provided informed consent were recruited.

Declaration of Conflicting Interests:
The authors have stated that they have no potential conflicts of interest regarding the research, authorship, and/or publication of this article.

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KEY MESSAGES

1. Gamma range oscillations (30-100 Hz) in EEG are altered in schizophrenia.
2. No significant correlations in low gamma (30-45 Hz) spectral power were found between age and regions in ARMS and HC.

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