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Inter and Intra-Hemispheric Resting EEG Coherence in Schizophrenia Patients

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Abstract
Schizophrenia is a chronic and disabling mental disorder characterized by distortions in thinking, perception, emotions, language, sense of self and behaviour. The oscillatory pattern of electrical activity generated by synchronized neuronal firing at rest might help in identifying the subjects of schizophrenia. Though various studies have tried to assess the underlying functional connectivity and its impairment in the patients of schizophrenia, the exact mechanism remains to be elucidated. The present study was conducted in the Department of Physiology in collaboration with the Department of Psychiatry, S. M. S. Medical College, Jaipur (Rajasthan). Twenty-one newly diagnosed schizophrenia patients aged 18-40 years from Psychiatry OPD were recruited as cases and an equal no. of age matched healthy subjects were recruited as controls from the accompanying attendants of patients. The inter and intra-hemispheric coherence among various brain areas was evaluated in delta, theta, alpha 1, alpha 2, beta 1, beta 2and gamma frequency bands. The resting EEG coherence was significantly reduced between various electrode pairs in schizophrenia patients in delta (C3-P3, P3-T3, F3-P3&P3-P4), theta (C3-P3, P3-T3, F3-P3&P3-P4), alpha-1(C3-P3, P3-T3& C4-T4), alpha-2 (C3-P3, P3-T3&C4-T4) and gamma (C3-P3& P3-P4) frequency bands as compared to healthy controls. The schizophrenia patients exhibit functional dysconnectivity in frontal, central, parietal and temporal regions that might underlie the impaired thought process in schizophrenia patients, especially in the left hemisphere.
Keywords: *Schizophrenia, Electroencephalogram (EEG), Coherence, Functional Connectivity, Inter-hemispheric and Intra-hemispheric.*

Introduction

Schizophrenia is a chronic and disabling mental disorder characterized by distortions in thinking, perception, emotions, language, sense of self and behavior. Schizophrenia has been reported to affect about 1 % of the population, with a considerable impact on the psychosocial functioning and quality of life[1],[2]. The unaffected siblings of schizophrenia

patients have also shown to exhibit cognitive and developmental abnormalities, suggesting a possible combination of genetic and environmental risk factors causing aberrant pattern of neuronal communications[3], [4].

Neural oscillations are the basis of functional connectivity among different brain areas. Defect in neural oscillations and synchronization has been implicated in the recent available literature as a pathophysiological mechanism in schizophrenia patients. This is also evident from the neuroimaging-based studies in schizophrenia patients[5]-[8]. However, the available literature reports mixed findings, with both increased and decreased functional connectivity in resting conditions[9]-[12].

Resting EEG Coherence

The oscillatory pattern of electrical activity generated by synchronized neuronal firing at rest might help in identifying the subjects of schizophrenia[13],[14]. Modalities like magneto encephalogram (MEG) and electroencephalogram (EEG) have made it possible to quantify the electrophysiological processes occurring among various neuronal pools, using network connectivity analysis. EEG technique has a good temporal resolution that provides an efficient way for exploring functional and effective connectivity between two distinct brain regions using coherence and phase synchrony. EEG coherence (range from 0 to 1) evaluates the consistency of relative amplitude and phase between signals detected in different brain areas within a specific frequency band. A consistent similarity in rise and fall of phase between two signals over the time, at different brain areas, within a specific frequency band suggests functional connectivity[15].

The psychotic disorders have underlying impaired thought process[16]-[19] and impaired autobiographical memory retrieval[19],[20]. These processes involve default mode network (DMN), [21]-[23] that are more active at rest than during task performance[24],[25]. The components of DMN are areas like precuneus, posterior cingulate cortex, medial prefrontal cortex and temporo-parietal junction[26, 27].

Though various studies have tried to assess the underlying functional connectivity and its impairment in the patients of schizophrenia, the exact mechanism still remains to be elucidated[28]-[30]. Most of the available literature on functional connectivity in schizophrenics did not take all the frequency bands into account for evaluation of EEG coherence. Thus, this study was an attempt to decipher the deranged functional neuronal connectivity in schizophrenia patients in terms of coherence across all frequency bands.

Material and Methods

The present study was conducted in the Department of Physiology in collaboration with the Department of Psychiatry, S. M. S. Medical College, Jaipur (Rajasthan). Twenty-one newly diagnosed schizophrenia patients, aged 18-40 years, according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV TR, 2000) attending OPD of the Department of Psychiatry, S M. S. Medical College, Jaipur were recruited as cases and an equal no. of age matched healthy subjects were recruited as controls from the accompanying attendants of patients. A prior clearance from institutional ethical committee was obtained and a written, informed consent was obtained from every subject before commencing any procedure.

EEG acquisition

All the subjects were instructed a day before to come for recording with their hairs washed and no oil applied on scalp. The procedure was explained in detail to every subject and recording was done in a sound attenuated room with dim light in sitting position on a wooden chair. 21 channel scalp electroencephalography was done according to International 10-20 system for EEG electrode placement[31].

Electrode impedance was kept below 5 kΩ and a band pass filter of 0.5-70.0 Hz, digitalized at sampling rate of 256 Hz was used. EEG recording

was done using Brain Electro Scan System (BESS, Axxonet System, Bengaluru) of the EEG was recorded using a stretchable cap and positioned on the subject's head according to the known anatomical landmarks. The EEG recordings were run for 5 minutes with subject at rest during eye closed session. The recorded EEG was visually inspected and edited manually for artefacts free data. The Interhemispheric (F3-F4, C3-C4, T3-T4, P3-P4, O1-O2) and intra-hemispheric (Right: F4-C4, F4-P4, C4-P4, F4-T4, C4-T4, P4-T4 and Left: F3-C3, F3-P3, C3-P3, F3-T3, C3-T3, P3-T3) coherence among various brain areas was evaluated in delta (0.5-4.0 Hz), theta (4.1-8.0 Hz), alpha 1 (8.1-10.0 Hz), alpha 2 (10.1-13 Hz), beta 1 (13.1-20.0 Hz), beta 2 (20.1-30 Hz) and gamma frequency bands (30.1-80 Hz).

Statistical Analysis

The tabulation and analysis of recorded data was done using Microsoft Excel 2016. The unpaired t-test was used for the mean coherence comparison between schizophrenia and control groups in various frequency bands. The level of statistical significance was assigned at p-value less than 0.05.

Table 1 Comparison of mean and standard deviation of Left Intra-hemispheric EEG coherence of schizophrenia patients with healthy controls

Electrode Pairs		F3-C3	C3-P3	P3-T3	F3-P3	F3-T3	C3-T3
Delta (0.5-4 Hz)	**Schizophrenia**	0.569 ± 0.268	0.306 ± 0.3*	0.24 ± 0.215*	0.217 ± 0.197*	0.455 ± 0.222	0.485 ± 0.236
	Control	0.602 ± 0.276	0.591 ± 0.258	0.472 ± 0.198	0.372 ± 0.215	0.517 ± 0.215	0.558 ± 0.217
Theta (4.1-8 Hz)	**Schizophrenia**	0.483 ± 0.268	0.214 ± 0.231*	0.151 ± 0.169*	0.122 ± 0.153*	0.316 ± 0.244	0.355 ± 0.262
	Control	0.509 ± 0.268	0.472 ± 0.241	0.345 ± 0.186	0.234 ± 0.181	0.382 ± 0.208	0.454 ± 0.2
Alpha-1 (8.1-10 Hz)	**Schizophrenia**	0.45 ± 0.254	0.171 ± 0.202*	0.139 ± 0.145*	0.147 ± 0.154	0.277 ± 0.208	0.31 ± 0.226
	Control	0.475 ± 0.256	0.353 ± 0.242	0.279 ± 0.222	0.169 ± 0.165	0.323 ± 0.263	0.429 ± 0.229
Alpha-2 (10.1-13Hz)	**Schizophrenia**	0.356 ± 0.219	0.159 ± 0.201*	0.106 ± 0.141*	0.13 ± 0.15	0.212 ± 0.189	0.244 ± 0.191
	Control	0.398 ± 0.234	0.297 ± 0.21	0.214 ± 0.173	0.132 ± 0.116	0.243 ± 0.219	0.354 ± 0.213
Beta-1 (13.1-20 Hz)	**Schizophrenia**	0.343 ± 0.218	0.158 ± 0.21	0.104 ± 0.179	0.119 ± 0.179	0.191 ± 0.197	0.214 ± 0.212
	Control	0.359 ± 0.243	0.281 ± 0.234	0.135 ± 0.154	0.111 ± 0.143	0.169 ± 0.192	0.202 ± 0.16
Beta-2 (20.1-30 Hz)	**Schizophrenia**	0.268 ± 0.182	0.121 ± 0.166	0.078 ± 0.125	0.089 ± 0.116	0.147 ± 0.149	0.182 ± 0.168
	Control	0.269 ± 0.221	0.225 ± 0.214	0.089 ± 0.109	0.09 ± 0.151	0.119 ± 0.14	0.132 ± 0.108
Gamma (30.1-50 Hz)	**Schizophrenia**	0.25 ± 0.172	0.109 ± 0.109*	0.072 ± 0.06	0.081 ± 0.063	0.176 ± 0.139	0.185 ± 0.145
	Control	0.217 ± 0.18	0.233 ± 0.189	0.099 ± 0.082	0.129 ± 0.136	0.116 ± 0.1	0.124 ± 0.096

*Significant (p-value <0.05)

Table 2 Comparison of mean and standard deviation of Right intra-hemispheric EEG coherence of schizophrenia patients with healthy controls

Electrode Pairs		F4-C4	C4-P4	P4-T4	F4-P4	F4-T4	C4-T4
Delta (0.5-4 Hz)	**Schizophrenia**	0.263 ± 0.288	0.458 ± 0.33	0.447 ± 0.246	0.204 ± 0.24	0.259 ± 0.248	0.445 ± 0.288
	Control	0.245 ± 0.312	0.514 ± 0.333	0.451 ± 0.204	0.16 ± 0.176	0.254 ± 0.252	0.561 ± 0.286
Theta (4.1-8 Hz)	**Schizophrenia**	0.215 ± 0.276	0.344 ± 0.285	0.303 ± 0.239	0.134 ± 0.212	0.164 ± 0.229	0.292 ± 0.244
	Control	0.225 ± 0.266	0.411 ± 0.291	0.335 ± 0.186	0.138 ± 0.169	0.201 ± 0.203	0.418 ± 0.223
Alpha-1 (8.1-10 Hz)	**Schizophrenia**	0.222 ± 0.262	0.273 ± 0.264	0.273 ± 0.21	0.098 ± 0.119	0.125 ± 0.157	0.253 ± 0.233*
	Control	0.208 ± 0.253	0.346 ± 0.268	0.309 ± 0.211	0.078 ± 0.136	0.148 ± 0.183	0.42 ± 0.21
Alpha-2 (10.1-13 Hz)	**Schizophrenia**	0.159 ± 0.233	0.251 ± 0.238	0.221 ± 0.177	0.091 ± 0.13	0.109 ± 0.141	0.213 ± 0.175*
	Control	0.154 ± 0.195	0.28 ± 0.214	0.232 ± 0.16	0.053 ± 0.099	0.109 ± 0.152	0.379 ± 0.233
Beta-1 (13.1-20 Hz)	**Schizophrenia**	0.167 ± 0.243	0.247 ± 0.239	0.215 ± 0.192	0.092 ± 0.142	0.1 ± 0.161	0.189 ± 0.188
	Control	0.14 ± 0.215	0.278 ± 0.241	0.171 ± 0.165	0.066 ± 0.158	0.091 ± 0.181	0.242 ± 0.196
Beta-2 (20.1-30 Hz)	**Schizophrenia**	0.118 ± 0.194	0.224 ± 0.23	0.172 ± 0.156	0.069 ± 0.109	0.071 ± 0.114	0.139 ± 0.151
	Control	0.12 ± 0.183	0.235 ± 0.221	0.137 ± 0.152	0.059 ± 0.135	0.061 ± 0.111	0.174 ± 0.162
Gamma (30.1-50 Hz)	**Schizophrenia**	0.135 ± 0.189	0.188 ± 0.197	0.144 ± 0.114	0.094 ± 0.135	0.081 ± 0.115	0.125 ± 0.115
	Control	0.125 ± 0.131	0.252 ± 0.215	0.153 ± 0.134	0.098 ± 0.119	0.089 ± 0.101	0.179 ± 0.146

*Significant (p-value <0.05)

Table 3 Comparison of mean and standard deviation of Inter-hemispheric EEG coherence of schizophrenia patients with healthy controls

Electrode Pairs		F3-F4	C3-C4	P3-P4	T3-T4	O1-O2
Delta (0.5-4 Hz)	**Schizophrenia**	0.286 ± 0.293	0.384 ± 0.297	0.288 ± 0.29*	0.328 ± 0.207	0.797 ± 0.169
	Control	0.274 ± 0.286	0.447 ± 0.309	0.572 ± 0.273	0.285 ± 0.192	0.705 ± 0.168
Theta (4.1-8 Hz)	**Schizophrenia**	0.232 ± 0.288	0.27 ± 0.246	0.202 ± 0.231*	0.184 ± 0.2	0.667 ± 0.246
	Control	0.241 ± 0.239	0.277 ± 0.211	0.408 ± 0.258	0.144 ± 0.124	0.603 ± 0.172
Alpha-1 (8.1 - 10 Hz)	**Schizophrenia**	0.316 ± 0.275	0.192 ± 0.184	0.182 ± 0.181	0.134 ± 0.079	0.691 ± 0.25
	Control	0.26 ± 0.318	0.234 ± 0.206	0.284 ± 0.237	0.126 ± 0.099	0.579 ± 0.189
Alpha-2 (10.1 - 13 Hz)	**Schizophrenia**	0.204 ± 0.233	0.134 ± 0.171	0.148 ± 0.169	0.14 ± 0.118	0.617 ± 0.278
	Control	0.218 ± 0.264	0.159 ± 0.176	0.195 ± 0.213	0.149 ± 0.107	0.517 ± 0.208
Beta-1 (13.1 - 20 Hz)	**Schizophrenia**	0.158 ± 0.219	0.12 ± 0.178	0.13 ± 0.179	0.143 ± 0.141	0.585 ± 0.281
	Control	0.125 ± 0.21	0.116 ± 0.183	0.17 ± 0.204	0.118 ± 0.109	0.448 ± 0.188
Beta-2 (20.1 - 30 Hz)	**Schizophrenia**	0.089 ± 0.128	0.072 ± 0.107	0.109 ± 0.148	0.109 ± 0.097	0.559 ± 0.261
	Control	0.089 ± 0.16	0.098 ± 0.171	0.153 ± 0.21	0.09 ± 0.058	0.441 ± 0.194
Gamma (30.1 - 50 Hz)	**Schizophrenia**	0.125 ± 0.179	0.11 ± 0.142	0.097 ± 0.103*	0.123 ± 0.104	0.498 ± 0.257
	Control	0.107 ± 0.109	0.135 ± 0.161	0.211 ± 0.199	0.101 ± 0.061	0.476 ± 0.185

*Significant (p-value <0.05)

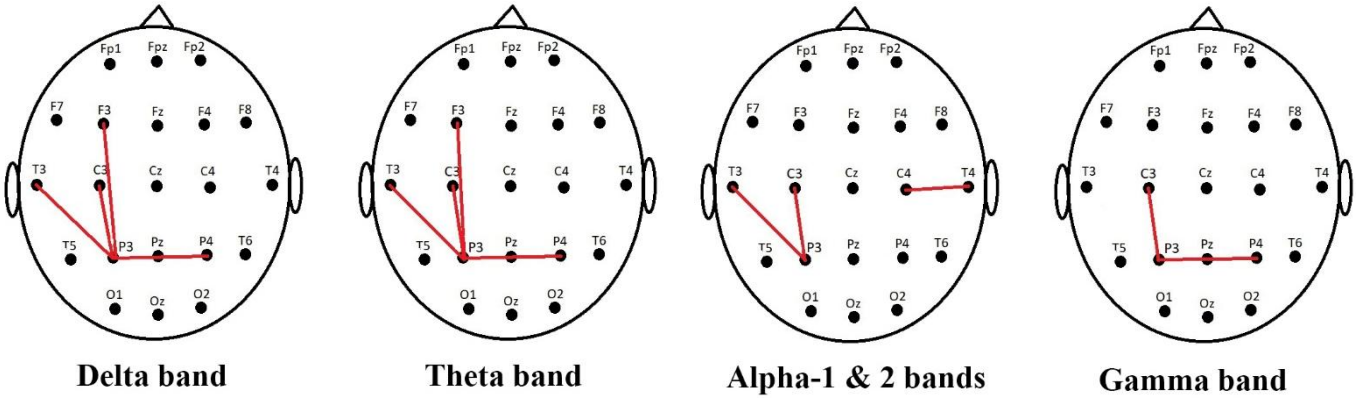

Figure 1 EEG head map depicting the functional connectivity using coherence between different electrode areas

Discussion

Schizophrenia is a chronic and a disabling mental disorder with a considerable impact on the psychosocial functioning and quality of life[32]. Defect in neural oscillations and their synchronization has been suggested as a pathophysiological mechanism in schizophrenia patients in recent available literature. This deranged functional connectivity in schizophrenics, was evaluated in the present study, using intra and interhemispheric EEG spectral coherence among various frequency bands.

Intra-hemispheric resting EEG Coherence

The present study showed significantly reduced left intra-hemispheric coherence in delta (C3-P3, P3-T3 and F3-P3), theta (C3-P3, P3-T3 and F3-P3), gamma (C3-P3) bands in schizophrenics as compared to healthy controls in resting state. The coherence in alpha-1 and alpha-2 bands in C3-P3 and P3-T3 electrode pairs was also significantly lower in schizophrenics as compared to healthy controls (Table 1, Figure 1). The present study also showed significantly lower right intra-hemispheric resting EEG coherence in C4-T4 electrode pair in alpha-1 and alpha-2 bands in schizophrenia patients as compared to controls (Table 2, Figure 1).

Inter-hemispheric resting EEG coherence

The interhemispheric comparison of resting EEG coherence at parietal region (P3-P4) in delta, theta and gamma bands revealed significantly lower coherence in schizophrenia patients as compared to healthy controls (Table 3, Figure 1).

Several studies have tried to assess the functional connectivity in schizophrenics and suggested reduced EEG spectral coherence in various frequency bands at different brain regions[33]. The

reduced coherence shows the lack of brain synchronization in schizophrenia patients. John et al. (2002) also reported significantly lower inter-hemispheric coherence values across the central and parietal regions in the eyes closed condition and across central regions in the eyes open condition[34].

Schizophrenics have shown poor performance on cognitive task. This dysfunction and the psychopathology of schizophrenia might be attributable to the cortical hyperactivation and reduced spontaneous and induced gamma coherence [35]. The aberrant functional organization leading to poor performance of cognitive activation task in schizophrenia patients has also been linked to altered alpha band coherence[36].

Phase lag index is another useful parameter to assess functional connectivity. EEG analysis in schizophrenia patients using phase lag index has also revealed reduced functional connectivity of beta (frontal region) and gamma bands (throughout scalp). Moreover, this dysfunctional connectivity in schizophrenics did not vary with symptoms severity or antipsychotic treatment[37]. However, the negative symptoms in schizophrenia patients have shown association with lower interhemispheric alpha coherence between hemispheres and between right parietal and frontal regions[38].

Ray and Ram (2012) suggested both a deficit and excess in neural connections that may be attributable to a compensatory change in schizophrenics with formal thought disorder. This neural disconnection was indicated by reduced intra hemispheric coherence in schizophrenia patients with FTD and reduced interhemispheric coherence in those without FTD provides[39]. These findings might explain the variable results of EEG coherence reported in various studies done on schizophrenia patients. This could also explain the findings of the present study where a reduced intra and inter hemispheric coherence was observed in various frequency bands.

A recent study has also indicated higher intra-hemispheric coherence in healthy controls as compared to schizophrenia patients in Beta-1 band [40]. Yeragani et al. (2006) also reported reduced coherence during the wake stage in patients with schizophrenia in beta as well as gamma frequency bands[41]. An EEG spectral coherence study among cortical areas involved in the auditory information processing suggested significantly reduced coherence in upper alpha band in schizophrenics with history of auditory hallucination, as compared to healthy controls in C3–C4, C5–C6, Ft7–Ft8 and Cp5–Cp6 electrode pairs[42]. The reduced EEG coherence in schizophrenia patients is also a potentially heritable trait predisposing the unaffected siblings to genetic risk of schizophrenia [43].

Functional dysconnectivity in left hemisphere in schizophrenia

The brain exhibits a hemispheric asymmetry, with different function designated to different brain hemispheres. The findings of the present study indicate at a greater dysfunctional connectivity in terms of reduced intra-hemispheric EEG coherence (C3-P3, P3-T3 and F3-P3) in left hemisphere as compared to right. Previously available data also indicates at overall more left hemisphere dysfunction and overactivation[44].

This dysfunction is also evident from a meta-analysis study of tensor imaging studies in schizophrenia patients, that suggested reduction in left frontal and left temporal deep white matter tracts. The greater number of electrode areas involved in the present study over left hemisphere might be explained by this finding, that suggests an altered brain asymmetry leading to functional disconnection in schizophrenia patients[45].

All the above studies fully or partially support the findings of the present study, that indicate a functional disconnection over frontal, parietal and temporal regions. The available literature on functional connectivity in schizophrenia suggests mixed findings. Many studies have also reported increased coherence at rest in schizophrenia patients in various frequency bands that contrasts with findings of the present study but suggest another possible mechanism underlying impaired inter and intra-hemispheric functional connectivity [46]-[49].

Conclusion

The schizophrenia patients exhibit functional dysconnectivity in frontal, central, parietal and temporal regions. This impairment in connectivity was greater over left hemisphere, that might account for the impaired thought process, logical reasoning, perception and language in schizophrenia patients.

Limitations of the Present Study

This study did not take into account the association between symptoms of schizophrenia and coherence. A large-scale study considering symptoms of schizophrenia in future is needed for a better understanding of the underlying defect in functional connectivity.

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