Original Article

Mu-wave Activity in Schizophrenia: Evidence of a Dysfunctional Mirror Neuron System from an Indian Study

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ABSTRACT

Background: The 'mirror-neuron system' is thought to play an important role in automatic decoding of biological motions and interpretation of socially adaptive environmental stimuli. Accordingly, a dysfunction in this system in schizophrenia has been hypothesised to mediate the psychotic manifestations. **Materials and Methods:** As a part of an ongoing study, we evaluated the mirror neuron system using 'EEG mu-wave (8-13 Hz) suppression' paradigm in 15 drug naïve/drug free patients and compared the working to 15 age, sex and education matched controls. We also correlated the psychopathology scores on PANSS with the mu wave suppression in the schizophrenia patients, at baseline. We used high (192-channel) resolution EEG to record the mu rhythm while the subjects watched alternating sequences of a socially-relevant biological motion and white visual-noise on a custom made video-clip. **Results:** We found a significant difference in the degree of mu wave suppression between the two groups. We also found that the degree of mu suppression over right sensorimotor cortex at presentation correlated significantly and negatively with thought disorder in the patient group, and had a strong linear relationship. **Conclusion:** This study replicates past findings regarding a dysfunctional mirror neuron system in schizophrenia patients, and also emphasizes the role of rMNS in schizophrenic thought disorders.

Key words: *Electroencephalography mu waves, mirror neuron system, misattribution of agency, right hemisphere, schizophrenia, thought disturbance*

INTRODUCTION

Since they were described in the F5 sector of the macaque monkey ventral premotor cortex,[1,2] the mirror neuron system (MNS) has generated great interest in terms of its clinical significance with the identification of their unique ability to automatically understand others' motor acts.[3] Recent data point toward the existence of at least two main networks with mirror properties: the parieto-frontal mirror system involved in recognition of voluntary behavior; and limbic mirror system dealing with the recognition of affective behavior.[4] Within the system, various subsystem involved in separate but related functions have been described[5,6], as is the existence of "inter-hemispheric" differences in mirror neuron activity[7,8] have also been described; with the left hemisphere structures responding to actions[9] while the right hemisphere worked toward understanding intentions.[4,10,11]

The process of "intention" interpretation involves "simulation", in which the same areas of the brain as those required to perform the action, is activated[10]

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through a delicate and critical integration of the sensorimotor system.[12] Therefore, a disturbance in this ability might result in impaired monitoring of others and of self, leading to misattribution of agency giving rise to psychopathology in schizophrenia.[10,12]

Accordingly, an impaired functioning of the MNS, compared with normal people, has been demonstrated in patients with schizophrenia.[13,14]

As a part of an ongoing study, we evaluated the MNS function in schizophrenic patients and compared them to the control population. We aimed at replicating the past findings on the presence of dysfunctional MNS in schizophrenic patients and also to correlate the psychopathology with the functioning of this system. We also studied the MNS in the two hemispheres separately to further the knowledge regarding the differential functioning of the two. We hypothesized that if the functioning of the MNS of the right hemisphere (rMNS) determined the ability of the person to understand "intentions" behind actions,[10,11] then the rMNS function could reflect the severity of psychopathological manifestations, at least in the domains of thought disturbances and other positive symptoms.

Thus, we examined the MNS through the event-related de-synchronization of electroencephalography (EEG) mu waves (8-13 Hz), or "mu wave suppression", in response to observed biological motion.[15-18] Study objectives were to measure the mu wave suppression over the whole sensory motor cortex (SMC) and separately in the two hemispheres and understand its relationship within schizophrenia symptomatology.

MATERIALS AND METHODS

The study was conducted at a premier tertiary care psychiatric institute in the eastern part of India. It was approved by the institute's ethics committee and all the participants had given informed consent for the same. 15 drug naïve or drug free (at least 4 weeks for oral and 12 weeks for depot medications) right handed patients with a diagnosis of schizophrenia were recruited. 15 age, sex, education and mother-tongue matched right-handed controls were also recruited after obtaining informed consent. We matched for the education level and the mother because of the presumed role of the MNS in cognitive functioning, including planning and attention and in the development of language function. Exclusion criteria for both groups included a history of any other co-morbid psychiatric disorder, major neurological or medical illness; drug or alcohol dependence, except nicotine or caffeine use and electroconvulsive therapy in the past 6 months

Assessment

Relevant socio-demographic data were collected from the patients at baseline. The subjects were rated on Positive and Negative Syndrome Scale (PANSS)[19] to quantify their psychopathology and to follow them up through the study period of 4 weeks. The control group was assessed on the General Health Questionnaire and were included only if the score was <3.

Patients underwent an EEG recording between 0900 and 1200 h on the day of their admission. The recording was carried out while the patient sat relaxed on a recliner inside a light and sound attenuated room, with the monitor being the only source of stimulus. An 18 min long video-clip [Figure 1] was played to them on a 17" LCD monitor placed five feet in front of the subjects at eye level. The clip had a 3 min sequence of white background at the beginning (W_1), two each of socially relevant biological motion (B_1 and B_2) and white visual noise (N_1 and N_2) for 3 min alternating with each other and a final sequence of white background (W_2) for 3 min. EEG was recorded under each of the sub-conditions while the patients watched the video. To ensure sustained attention on the task, the LCD screen turned red 6 times during the recording at random intervals and the patients were instructed to keep a count of the same. All accomplished this without a mistake. For the controls, the EEG was recorded on a mutually convenient day between 0900 and 1200 h, when they had not consumed tea/coffee/tobacco in the past 12 h.

The EEG was recorded using a custom made scalp cap with 192 Ag-AgCl electrodes (Electro-Cap International, Inc., Eaton, Ohio, USA) in accordance with the international 10-5 system.[20] Eye movement potentials were monitored using right and left electro-occulogram channels. Electrode impedance was kept <5 kΩ. EEG was filtered (time constant −0.1 s, high frequency filter −30 Hz) and digitized (sampling rate −512 Hz, 16 bits) using Neurofax EEG-1100K (Nihon-Kohden, Tokyo, Japan).

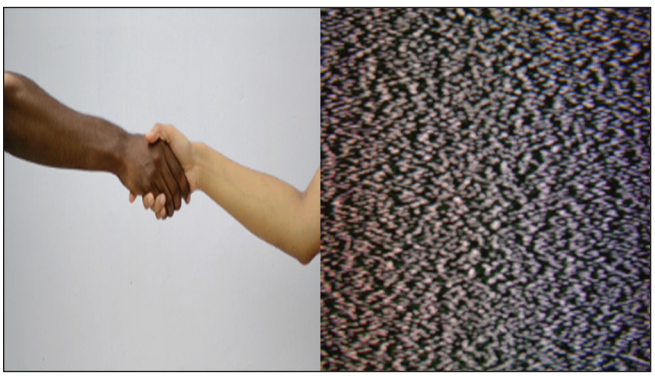

Figure 1: Biological Motion (Hand Movement) and Visual Noise

EEG analysis

Artefacts were visually identified and a 30 s relatively artefact-free EEG data clip was selected from each of the sub-conditions of biological motion and visual noise. The selected epochs were recomputed with common average reference. Spectral power was calculated using Fast Fourier Transformation, hamming window. The mu-wave suppression was calculated using the formula[14,21] Mu suppression = $\log_{10}$ (mu power in B/mu power in N) (eq. 1) and the average of the two conditions was considered ([$\log_{10}$ (B_1/N_1) + $\log_{10}$ (B_2/N_2)]/2). The analysis was carried out using Matlab-7 (The MathWorks, Inc., Natick, MA, USA) on leads C6, CCP6, FCC6h, C6h, CCP6h, FCC4, FCC2, C2, CCP2, C2h, FCCz, CCPz, C1h, FCC1, C1, CCP1, C3h, CCP3h, FCC3, FCC5h, C5h, CCP5h, C5, CCP5 and FCC5. Further, the right and left hemispheric leads were analyzed separately.

Statistical analysis

Statistical analysis of the data was carried out with SPSS v.16 (SPSS, Inc., Illinois, USA). Chi-square test was applied to study the two groups regarding their categorical variables. The two groups were compared using Man-Whitney U-test for mu suppression. The relationships between baseline mu suppression over the whole of SMC, over the right and the left hemispheric SMCs (rSMC and lSMC respectively) separately; and scores on PANSS subscales, the PANSS cluster scores[22] of Anergia (N1+N2+G7+G10), Thought Disturbance (P2+P3+P5+G9), Activation (P4+G4+G5), Belligerence (P6+P7+G8) and Depression (G1+G2+G3+G6) were investigated in bivariate exploratory analysis using Spearman's correlation [Table 1]. Linear regression analysis was performed to explore further the significant correlations.

RESULTS

The study sample included 15 patients, of which 12 were males and 3 were females. Out of a total of 15 subjects, 8 had studied until intermediate or above. The mean age of the study subjects was 28.87 ± 6.8 years and the control was 28.01 ± 6.3 years. The mean duration of illness was 55.13 ± 50.4 months. Four subjects were drug naïve whereas 11 were drug free according to the inclusion criteria upon induction into the study. Table 2 shows the results from the Chi-square test, in which the two groups were found to be similar to each other in all aspect except for the residence, where we found that a significantly higher number of control subjects lived in an urban area. This was due to a selection of the controls from around the institute.

Table 3 shows the results of the Mann-Whitney U-test. We found that there existed a significant difference between the mu wave suppression in response to biological stimuli between the schizophrenic patients and the control subjects and this difference also existed when the MNS of the two hemispheres were analyzed separately.

A bivariate correlation [Table 1] analysis to explore the relationship between the psychopathology scores at presentation and the baseline mu suppression, using Spearman's correlation, showed a significant negative correlation between the mu wave suppression over the rSMC and the thought disturbance at presentation ($\rho = -0.647$, $P < 0.01$).

In regression analysis, a linear model emerged between the thought disturbance at presentation and the degree of mu wave suppression at rSMC and yielded a beta of −0.631, adjusted R^2 value of 0.398 and $P = 0.012$ [Table 4].

DISCUSSION

The ability to automatically process biological motion stimuli develops at very early stages in human life[14]

Table 1: Spearman's Correlation coefficients (ρ) for the psychopathology measures and mu suppression at presentation (*N* = 15)

Variables	Global SMC Mu suppression at presentation	Right hemispheric Mu suppression at presentation	Left hemispheric Mu suppression at presentation
Duration of illness	−0.449	−0.402	−0.397
PANSS positive score	0.362	−0.154	0.353
PANSS negative score	−0.279	0.038	−0.281
PANSS global score	0.280	0.165	0.258
PANSS total score	0.097	−0.039	0.080
Anergia cluster score	−0.142	0.250	−0.190
Thought disturbance cluster score	−0.031	−0.647**	−0.009
Activation cluster score	0.334	−0.256	0.395
Belligerence cluster score	0.321	0.128	0.480
Depression cluster score	−0.144	0.082	−0.163

** $P < 0.01$. PANSS – Positive and negative syndrome scale; SMC – Sensory motor cortex

and with sensorimotor maturation, the activity in this system has been found to mature.[16] Though some controversy exists,[23] available data overwhelmingly favor the role of MNS in understanding goals and intentions behind actions[3,5,10,12,24] and in the ability to empathize.

Past studies conducted on schizophrenic patients[13,14] have found a dysfunction in the MNS at presentation, even in those who were drug naïve. The main finding of the present study was that the patient group significantly differed from the control group in terms of the degree of mu wave suppression over the SMC. This degree of mu wave suppression over SMC has been reliably demonstrated to be a marker for the activation of the SMC-MNS in past[14,21] and hence the results indicate that SMC-MNS functioning is significantly different in schizophrenia.

The second significant finding was of a negative correlation between the mu wave suppression (degree of activation of the MNS) over rSMC and the thought disturbance cluster on PANSS. The thought disturbance cluster consists of 4 sub-scores (3 positive and 1 general psychopathology scale) of conceptual disorganization, hallucinatory behavior, grandiosity and unusual thought content. The thought disturbance score also showed similar (negative) trends with the whole MNS and lSMC MNS mu suppression but did not reach statistical significance. As discussed earlier, MNS essentially enables a person to place himself into others' shoes and mediate the construct of empathy. The rMNS is more important for understanding "intentions",[4,10] monitoring own action, distinguishing self from others[6,13] and in experiencing the attributes of agency while performing an action.[25] It has been suggested that an ability to "empathize" was at the heart of developing psychosis[26] and strong Mu suppression over SMC has been demonstrated in the past in actively psychotic Schizophrenia Spectrum disorder patients[27] compared with those in remission and healthy controls; which also correlated with psychotic symptom severity. Thus, our finding essentially means that a better functioning rMNS led to a higher degree of initial thought disturbances in these patients, possibly through a higher degree of empathy "contaminating"[13] the self and breaking down the "self-others" boundary.[24] The involvement of the right hemisphere in schizophrenic thought disorder was recognized long ago when it was found that lesions here led to schizophrenia-

Table 2: Comparison of the socio-demographic variables between patients and control (*N* = 30)

Variable	Group		χ^2	df	*P*
	Patient (*n* = 15)	Control (*n* = 15)			
Sex					
Male	12	12	0.000	1	0.674
Female	3	3			
Residence					
Rural	8	5	8.462	2	0.015
Semi urban	4	0			
Urban	3	10			
Religion					
Hindu	12	10	0.682	1	0.682
Islam	3	5			
Education					
Illiterate	1	1	1.077	4	0.898
Primary	1	1			
Secondary	5	5			
Intermediate	2	2			
Graduate and above	6	6			
Marital status					
Married	6	9	1.886	2	0.390
Unmarried	8	6			
Divorced	1	0			
Monthly family income					
<5000	4	4	0.786	2	0.675
5000-10,000	5	3			
>10,000	6	8			

Table 3: Comparison between patient group and control group (*N* = 30)

	Ranks				Mann-Whitney U
Variable	Group	*n*	Mean rank	Sum of ranks	
Global SMC Mu suppression at presentation	Patient	15	21.93	329	16.00**
	Control	15	9.07	136	
Right hemispheric Mu suppression at presentation	Patient	15	20.47	307	38.00**
	Control	15	10.53	158	
Left hemispheric Mu suppression at presentation	Patient	15	19.4	291	54.00**
	Control	15	11.6	174	

**$P < 0.01$; *$P < 0.05$. SMC – Sensory motor cortex

Table 4: Linear regression analysis of relation between rSMC Mu wave suppression at presentation and thought disturbance cluster score of PANSS (dependent variable)

Model	Beta	*t*	*P*	*R*	R^2	Adjusted R^2
Right hemisphere Mu suppression at presentation	−0.631	−2.931	0.012*	0.631	0.398	0.352

rSMC – Right sensory motor cortex; PANSS – Positive and negative syndrome scale; *Significance <0.05

like thought patterns, with understanding based on "personalization",[28] mis-symbolization of the real world and impaired self-monitoring of verbalization.[24,29,30] We also found a strong linear relationship between the thought disorder score and the rSMC mu suppression, with a negative slope. This has not been reported in the past and we believe this relationship further strengthens our conclusion of the "contamination of self".

It has been long suggested that schizophrenia might actually be a disorder involving altered functioning of various neuronal circuits. Abnormal neuronal positioning, abnormal synaptic architecture, and aberrant neuronal connections[31] along with various neurotransmitters abnormalities in dopamine, glutamate, gamma-aminobutyric acid and acetylcholine have been implicated[16,31] in their development. The view that schizophrenia is a neurodevelopmental disorder is now well endorsed. If the MNS dysfunction was responsible for psychopathology, and if the functioning of this system was already established in infancy, then why did the psychopathology manifest now? Recently, dopamine has emerged as the neurotransmitter system responsible for the optimal functioning of the cortical circuits, particularly through gamma band synchronization.[32] It has been demonstrated that dopamine levels in the brain and the performance of the circuits have an "inverted-U" shaped relationship, with higher dopamine levels leading to decreased efficiency of these,[33] probably through an alteration in the excitability of the fast-spiking interneurons.[32] We propose that an increase in brain dopamine levels during the schizophrenic state possibly disrupts the MNS circuit, leading to manifest psychopathology.

However, this proposal is at a nascent stage. There has been no research, to the best of our knowledge, on these lines with a prospective study design and hence this would need support from future studies on this line.

CONCLUSION

This article reports a replication of the finding of a dysfunctional MNS system in schizophrenic patients compared to normal controls, in an Indian study. We matched the control subjects for education status as well as the mother tongue, which are improvements over the previous studies, thus giving a better picture of the actual differences without being confounded by the cognitive abilities. The study adds to the current literature on the role of rMNS in schizophrenic thought disorder and proposes that the rSMC MNS might be the "holy grail" in the thought disorder manifestations.

Overall, the findings add to the growing literature on the MNS and schizophrenic psychopathology.

Limitations

The present study suffered from several limitations as a small sample size, a failure to include more drug naïve patients and patients of the female gender. The findings also need replication in large scale studies to be concurred. In future, we propose a study with a prospective design to evaluate the MNS functioning, in order to investigate the MNS function as a trait in schizophrenia.

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