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Evaluation of spontaneous dense array gamma oscillatory activity and minor physical anomalies as a composite neurodevelopmental endophenotype in schizophrenia

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ABSTRACT

Objective: Minor physical anomalies (MPAs) and gamma oscillatory activity have been proposed as associated endophenotypes in schizophrenia. Combining these endophenotypes to create a composite endophenotype may help identify those at risk for schizophrenia better. The present study aims to investigate MPAs and gamma oscillatory activity in schizophrenia patients, their unaffected first degree relatives and healthy controls and appreciate whether they can be used together as a composite endophenotype.
Methods: This was a cross sectional family study conducted at a tertiary care mental health setup. Ninety participants including schizophrenia patients, their first degree relatives and controls (thirty each) were assessed for MPAs on the Extended Waldrop Scale. All participants underwent an awake, resting 192-channel EEG recording. Spectral power and coherence in 30–100 Hz gamma bands were estimated using Welch's averaged periodogram method. One-way ANOVA, chi square test were used for comparing socio-demographic-clinical variables. MANOVA supplemented by one-way ANOVAs (post hoc Tukey HSD) were done for comparison of spectral measures. Pearson's correlation, step-by-step linear discriminant functional and intra-familial correlation analysis were subsequently performed.
Results: An endophenotype pattern of finding was found for MPAs in the craniofacial region, the total number of MPAs, spectral power in right temporal region on all bands and in the right parietal region in 50–70 Hz and 70–100 Hz gamma bands. The three groups were most accurately classified when MPA total score, right temporal 30–50 Hz gamma power and right occipital 'intra hemispheric' 50–70 Hz gamma coherence were considered together than when considered independently. Significant intra familial correlation was seen for MPA total score and right temporal gamma 30–50 Hz power.
Conclusion: Composite evaluation of two developmentally linked markers i.e. MPAs and gamma spectral measures may prove useful in categorizing schizophrenia and identifying at-risk individuals.

1. Introduction

The endophenotype construct represents a promising approach in facilitating investigating schizophrenia (SCZ), a disorder that is now thought to be influenced by multiple genes as well as environmental factors. Neurodevelopmental hypothesis provides a valuable framework for genetic studies of endophenotypes in schizophrenia (Owen et al., 2011; Braff and Light, 2005). Morphological evidence of the neurodevelopmental insults has been consistently documented in schizophrenia patients in the form of minor physical anomalies (MPAs). MPAs are insignificant, fixed physical defects or deviations in appearance from essential physical characteristics and are of little functional significance (Tarrant and Jones, 1999). Although MPAs have been suggested to be associated with other neurodevelopmental and behavioral disorders, including but not limited to attentional disorders, autism, fetal alcohol syndrome, learning disabilities, and sensory impairment in general (Compton and Walker, 2009), the pattern of changes in these morphological characteristics, especially higher frequency, has been suggested to reflect neurodevelopmental

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defects that allow better characterization of schizophrenia patient subgroups (Akabaliev et al., 2011).

It has been proposed that developmental insults during the pre and postnatal period lead to abnormal neural synchrony resulting in the development of aberrant cortical networks. These abnormal cortical circuits are unable to support the maturation of gamma oscillations and the consequent reorganization of cortical networks during adolescence and early adulthood manifesting as cognitive dysfunction and psychotic symptoms (Uhlhaas et al., 2009; Uhlhaas, 2011; Uhlhaas and Singer, 2013). Gamma oscillatory activity (GOA) has been consistently found to be abnormal in schizophrenia patients and to be associated with positive and negative symptom, and cognitive domains (Shin et al., 2011; Leicht et al., 2011; Tikka et al., 2013). The developmental nature of higher frequency of MPAs and abnormal gamma oscillations in schizophrenia points to a possible association between these. Recently, it has also been found that spontaneous gamma power/synchrony is increased in schizophrenia patients having higher MPAs supporting the association between MPAs and GOA (Tikka et al., 2013). This investigation also suggested that schizophrenia patients having higher MPAs form a distinct sub-group of schizophrenia with neurodevelopmental origins having aberrant gamma activity.

MPAs are suggested as an endophenotype on account of the findings that MPAs present more in patients than healthy controls and are state-independent (Compton and Walker, 2009) and increased rates of MPAs are found in unaffected first degree relatives as well (Gassab et al., 2013; Aksoy-Poyraz et al., 2011; Compton et al., 2007; Xu et al., 2011). And recently, there is a suggestion that gamma oscillations might also serve as an intermediate phenotype as it is found to be abnormal in first degree relatives (FDRs) of patients with schizophrenia (Rass et al., 2012; Bandyopadhyaya et al., 2011). From a neurodevelopmental perspective, MPAs and GOA in combination may prove to be a more robust endophenotype of schizophrenia.

Individual phenotypes identify various discrete types of genetic and environmental risk. As multiple deficits co-aggregate in the families of patients with schizophrenia reflecting a common variant of genetic risk, combining these variables has been proposed so as to create a composite or multivariate endophenotype and to better identify genetic risk (Turetsky et al., 2007). There is a certain lack of literature on MPAs and GOA together as a composite endophenotype i.e. these two measures being investigated in a family study. Hence, we attempted to explore these two measures together and ascertain whether they can be used together as a composite endophenotype for schizophrenia. As it is essential to characterize an illness variable in unaffected family members to qualify for an endophenotype (Gottesman and Gould, 2003) we conducted this investigation in a genetically-informative family study setting.

2. Methods

The study was approved by the Institute Ethics Committee of Central Institute of Psychiatry (CIP), Ranchi, India. Written informed consent was taken from all the participants (and their legally qualified representatives in case of patients) before enrolling them for the study.

2.1. Participants

Patients were recruited by purposive sampling from the outpatient services of CIP. Thirty right-handed, male patients in the age group of 18–50 years, having a diagnosis of schizophrenia as per ICD-10 DCR (World Health Organization, 1992), who were either drug naïve or drug free (for at least 4 weeks for oral and 12 weeks for depot medications) were taken up for the study in the schizophrenia 'SCZ' group. Patients having history of neurological illness, significant head injury, co-morbid substance dependence (excluding nicotine and caffeine), other psychiatric disorder, disruptive behavior (suicidal or homicidal) that warranted immediate intervention, or history of electroconvulsive therapy within previous 6 months were excluded. Thirty first degree relatives (one first degree relative each of participants in patient group) of either sex aged between 18 and 50 years were also recruited. Seventeen subjects in the 'FDR' group were siblings of corresponding subjects in the 'SCZ' group; 6 were parents and 7 were off springs. The healthy control 'HC' group included thirty right-handed age matched subjects, recruited from the hospital staff and community living in the vicinity of CIP. *None of the participants from the present study is common with our earlier published data* (Tikka et al., 2013).

2.2. Clinical assessment

Socio-demographic and clinical data were collected from all the participants using a specially designed data-sheet. Sidedness Bias Schedule (SBS) – Hindi version (Mandal et al., 1992) was used to assess handedness. Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was administered to assess baseline severity of psychopathology. General Health Questionnaire (GHQ)-12 (Goldberg and William, 1998) was used for screening healthy controls and first degree relatives; those with scores of 3 or more were excluded from the study. Assessment of MPAs in all the participants was done using a modified version of the Waldrop scale – Extended Waldrop scale (EWS) (Mehes, 1988). All the 55 items in EWS were assessed except for mandible size, due to logistic difficulties in getting the required X-ray mandible (occipito-mental view) done. Items on the EWS were grouped into those in the head and face region – 33 items and elsewhere in the body – 21 items, and were scored as absent or present. One author (S.K.T.), a trained rater, assessed MPAs in all the participants of the study.

2.3. EEG recording

All participants had an EEG recording between 0900 – 1200 hrs at the K S Mani Centre for Cognitive Neurosciences, Central Institute of Psychiatry. Participants were advised to refrain from taking tea, coffee or nicotine for at least an hour before the recording. Resting state EEG was recorded from each participant for ten minutes while reclining in a chair with eyes closed. A 192-Ag-Ag/Cl-electrode customised scalp cap (Electro-Cap International, Inc., Ohio, U.S.A.) with electrodes placed according to the 10-5 International System of electrode placement and referenced to linked ear lobes was used. Eye movements were recorded using right and left Electro-occulogram (EOG) channels. Electrode impedance was maintained below 5 kΩ. EEG was acquired using Neurofax EEG-1100 K (Nihon-Kohden, Tokyo, Japan) with a time constant of 0.1 sec, high frequency filter of 120 Hz and at a sampling rate of 512 Hz (16 bits).

2.4. Spectral power and coherence analysis

Following visual inspection, first sixty-second epochs of artefact-free EEG data were selected. Any EEG segments with eye movement, blink, electromyogram, movement, electrode, or perspiration artifacts, or drowsiness changes were excluded. Two authors (NP and NG), who were blind to the clinical status of the participants, independently examined the selected epochs for final approval. The selected epochs were re-referenced to the common average reference. Welch's averaged periodogram method was used for computing spectral power (expressed in μV, fast Fourier transform routine, Hanning window) and cross-spectral coherence