Int. J. Devl Neuroscience 50 (2016) 39–46

Contents lists available at ScienceDirect

International Journal of Developmental Neuroscience

journal homepage: www.elsevier.com/locate/ijdevneu

Schneiderian first rank symptoms in schizophrenia: A developmental neuroscience evaluation

Sai Krishna Tikka*, S.Haque Nizamie, Archana Kumari Das, Nidhi Agarwal, Nishant Goyal

KS Mani Center for Cognitive Neurosciences and Department of Psychiatry, Central Institute of Psychiatry, Kanke, Ranchi 834006, Jharkhand, India

ARTICLE INFO

Article history:
Received 26 December 2015
Received in revised form 3 February 2016
Accepted 15 February 2016
Available online 4 March 2016

Keywords:
Schizophrenia
Self disorders
FRS
Gamma spectral-power
Self-monitoring
BDNF

ABSTRACT

Introduction: Self disorders in schizophrenia have been suggested to have distinct neurobiological underpinnings. Using comprehensive neuro-scientific assessments including a neurophysiological, a neurochemical and a neuropsychological marker, this study assesses disordered-"self" in schizophrenia.
Methods: Twenty schizophrenia patients with first rank symptoms (FRS;FRS+), 20 patients without FRS (FRS−) and 20 healthy controls (HC) were assessed for psychopathology, especially on specially designed FRS score sheets with a narrow and a broad definition. Resting state electroencephalography was acquired using 256-electrodes; gamma spectral-power was measured in 8 regions of interest. Serum BDNF and self-monitoring were also assessed. Comparative and correlation analysis were conducted in addition to a step-wise discriminant function analysis.
Results: FRS+ group with greater positive symptom score and a lower negative symptom score, showed significantly increased gamma spectral power, especially on right hemispheric regions, along with lower BDNF levels and lower scores on self-monitoring compared to FRS− and HC. Serum BDNF levels and gamma spectral power in the region corresponding right inferior parietal lobule were identified as predictors that most accurately classified the defined groups.
Conclusions: Schizophrenia patients satisfying the criteria of presence of first rank symptoms represent a distinct neurodevelopmental subgroup with associated features of predominantly positive symptoms, significantly lower neurotrophin levels, aberrant resting state brain activity in the heteromodal association cortex and performing poorer on self-monitoring tasks.

1. Introduction

Conscious living as- one, single, defined unit of experience and action, in time has been conceptualized as 'self'(Jaspers et al., 1997). This construct refers to the personal attribution of "mineness," "myness," "for-me-ness," or "ipseity" (Zahavi, 2005). Schizophrenia patients have been found to be characteristically deficient in the sense of "ipseity" of the field of awareness (Sass and Parnas, 2003). Historically, phenomenological research suggests that this deficiency may be a core marker of schizophrenia. While Emil Kraepelin regarded "disunity of consciousness" a fundamental feature, Eugen Bleuler considered experiential "ego disorders" among the pathognomonic symptoms; and Karl Jaspers described the sense of "self-presence" being fundamentally weakened in schizophrenia patients (Parnas and Henriksen, 2014). Most importantly, Kurt Schneider's first-rank symptoms (FRS) that form a basis for current day's categorical nomenclature of schizophrenia underpin a consideration that self awareness undergoes radical change in patients with schizophrenia (Schneider and Hamilton, 1959). Although substantial amount of phenomenological research highlights the 'self' perspective, interest in empirical biological research in this context is relatively new and sparse.

FRS, whose presence has been the inclusion criteria for presence of self disturbances among patients with schizophrenia, have been proposed to have specific regional brain localization. Both functional and structural neuroimaging studies suggest that FRS might be particularly localized to right parietal regions. While structural magnetic resonance imaging (MRI) data suggests volume and cortical thickness deficits in right inferior parietal lobule (rIPL) (Danivas et al., 2009; Venkatasubramanian et al., 2011), functional MRI studies reveal functional hyperactivation in the rIPL, specifically right brodmann's area 40 (Ganesan et al., 2005). Moreover, increased

* Corresponding author.
E-mail address: cricsai@gmail.com (S.K. Tikka).

http://dx.doi.org/10.1016/j.ijdevneu.2016.02.001
0736-5748/

blood flow on positron emission tomography (PET) (Franck et al., 2002) and increased spectral power in gamma frequency range on high-resolution electroencephalography (hEEG) (Tikka et al., 2014) have also been associated with FRS in schizophrenia patients in these regions. Pertinently, increased gamma spectral power, especially on the right hemisphere, has been linked developmentally (Tikka et al., 2015).

Among other developmental neural correlates, deficient brain derived neurotrophic factor (BDNF) levels in the blood has been linked to presence of FRS (Kalmady et al., 2013). Interestingly, BDNF gene polymorphisms have been found be underlying cortical volume deficits in rIPL as well (Nemoto et al., 2006). Predictably, neurocognitive correlates of FRS found are impairments in self-monitoring (Waters and Badcock, 2010) as FRS has been conceptualized as having an underlying defective "self internal monitoring system" (Frith et al., 2000). Interestingly, these high-level cognitive functions like self-awareness have been found to be associated significantly with gamma oscillations as well (Yamagishi and Anderson, 2013).

With involvement of specific neural networks (rIPL) and distinct neurophysiological (gamma oscillations) and cognitive (self-monitoring) domains, this study hypothesizes FRS to represent a distinct clinical dimension from other psychotic symptom dimensions. With the conventional treatment strategies, it has been found that schizophrenia patients with FRS, especially during the acute phase, have a poorer long-term outcome than schizophrenia patients without FRS (Rosen et al., 2011); perhaps suggesting a need to consider alternate treatment strategies that can specifically target the specific brain regions.

Aim of the index study was to compare a comprehensive set of neuroscience variables- hEEG gamma oscillations, blood BDNF and self-monitoring deficits between schizophrenia patients with and without FRS and, healthy controls.

2. Methods

The study was approved by the Institute Ethics Committee of Central Institute of Psychiatry (CIP), Ranchi, India. This study is a part of the parent study, registered in the clinical trials registry India (CTRI-2014-12-005280) prior to recruitment of subjects. 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

Two schizophrenia patient groups, with sample size of 20 each, were included—those with FRS (FRS+) and those without FRS (FRS−). Patients were recruited by purposive sampling from various inpatient wards of CIP. 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), on a stable dose of antipsychotic medications were recruited. These patients were recruited within a week of admission in the hospital for first episode or for an acute exacerbation or relapse; all patients were deemed 'symptomatic'. *Presence of FRS was operationally defined as having elicited one or more narrow defined FRS or two or more widely defined FRS on 2 or more mental status interviews spaced over 2–3 days*. 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 six months. The healthy control 'HC' group included twenty right-handed, age matched subjects, recruited among the hospital staff and community living in the vicinity of CIP.

2.2. Tools

2.2.1. Clinical assessments

Relevant socio-demographic and clinical data was collected from all the participants. Handedness was assessed using the Sidedness Bias Schedule (SBS)—Hindi version (Mandal et al., 1992). Severity of psychopathology in patients was evaluated by administering the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). FRS were assessed according to definitions given by Mellor (1970) and also on their modified wide and narrow definitions (O'Grady, 1990). A specifically constructed score sheet was used to assess FRS on frequency, preoccupation, conviction and interference with routine activities on a five point likert scale (Appendix A). Healthy controls were screened with General Health Questionnaire (GHQ)-12 (Goldberg and William, 1998); only those with scores less than three were included.

2.2.2. Self-monitoring task

Self-monitoring was assessed based on an adaptation from the series of drawing tests given by Stirling et al. (2001). Patients had to generate drawings of simple designs and subsequently 'identify' their own drawings (from drawings of the same design by other people) in a recognition paradigm. In drawing test 1, designs to be drawn were randomly selected by the experimenter and the patient drew them out-of-sight. In drawing test 2, designs were chosen by the experimenter and the patient drew in full view. Drawing tests 1 taps self-monitoring mechanisms, whereas drawing test 2 is a control test that primarily assesses recognition memory.

2.2.3. Serum BDNF

Blood samples were drawn from all subjects after >12 h overnight fast. Serum was allowed to clot in a serum separator tube (for about 4 h) at room temperature; then centrifuged at approximately 1000 × *g* for 15 min. Samples were stored at −80° C. Serum BDNF was quantified using enzyme-linked immunosorbent assay (ELISA) kit (Boster Biological Technology Co., ltd, CA, USA) with sensitivity of <2 pg/mL (Range—31.2 pg/ml–2000 pg/ml). The absorbances were measured with an automated microplate reader at 450 nm.

2.2.4. EEG recording

All participants underwent an EEG recording. Recording was carried out between 0900 and 1200 h at the KS Mani Centre for Cognitive Neurosciences, CIP. Participants were advised to avoid use of tea, coffee or nicotine for at least one hour before recording. In a light and sound attenuated room, ten minutes of resting state EEG was recorded for each participant, while sitting, eyes closed, on a reclining chair. EEG was acquired on the Geodesic EEG System 400 (Electrical Geodesics, Inc., Eugene, Oregon, USA) system with 256 EEG channel Geodesic Sensor Nets; electrodes placed according to the international 10–10 system of electrode placement (Fig. 1). Eye movement potentials were monitored using right and left electro-oculogram (EOG) channels. Electrode impedance was kept <50kΩ. EEG was filtered (time constant—0.1 sec, high frequency filter—120 Hz) and digitized (sampling rate—256 Hz) using Net Station 5.1 software (Electrical Geodesics, Inc., Eugene, Oregon, USA).

2.3. Analysis

2.3.1. Spectral power and coherence analysis

First sixty-second epoch of artifact-free EEG data as visually selected from each recording after carefully excluding segments