Neuroscience Letters 604 (2015) 145–150

Contents lists available at ScienceDirect

Neuroscience Letters

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

Research paper

Electroencephalographic connectivity analysis in schizophrenia

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HIGHLIGHTS

- Our aim was to investigate electroencephalogram connectivity in schizophrenia.
- We conducted a mutual information (MI) analysis in baseline and active conditions.
- Patients with schizophrenia show a higher brain connectivity.
- Controls show higher MI values in the baseline condition. This increased connectivity was not present in the patients group.
- The results support the “dysconnection hypothesis” in schizophrenia.

ARTICLE INFO

Article history:
Received 11 March 2015
Received in revised form 30 May 2015
Accepted 30 July 2015
Available online 1 August 2015

Keywords:
Electroencephalographic connectivity
Schizophrenia
Mutual information

ABSTRACT

The aim of the present study was to further investigate the electroencephalogram (EEG) connectivity in schizophrenic patients by means of mutual information (MI), an analysis capable of detecting both the linear and nonlinear components of EEG. 19-lead EEGs were recorded in stable schizophrenic patients ($N = 17$) and healthy controls ($N = 17$) in two different conditions: closed eyes (CE) and open eyes (OE). In patients, higher MI values were observed in temporal-parietal-occipital regions compared with controls. In controls, an increase in brain connectivity in frontal regions was observed in the CE condition. This increase was not present in patients. Our results suggest that patients with schizophrenia present changes of brain connectivity that can be detected through MI analysis.

1. Introduction

Although the etiology of schizophrenia is far to be understood, according to current pathophysiological theories this disease can be explained with the “dysconnection hypothesis”. According to this hypothesis the core pathology of schizophrenia is an impaired neuromodulation of synaptic plasticity, manifested as an abnormal functional integration of neural systems (dysconnectivity) [1–3]. Different histological, biochemical and neuroimaging studies have been used to outline this phenomenon and results showed either increased [4–6] and decreased [4–6] connectivity patterns in distributed brain networks that often correlate with cognitive deficits. In spite of the growing interest on this phenomenon, the exact nature of aberrant connectivity patterns has not yet been fully clarified.

Recently, the human brain activity during resting state has attracted considerable attention in neuroscience. The brain resting state is thought to be an energetically costly condition that allows the brain to allocate resources and prepare itself for changes in internal and external environments. Therefore, the investigation of functional connectivity during resting state may reveal an intrinsic functional disintegration between brain regions.

Functional connectivity between and within brain hemispheres has been intensively studied using the electroencephalogram (EEG) as a non invasive technique that provides insight into cortical rhythms and neuronal oscillations. Among the several EEG methods to study cortical connectivity, such as synchronization, correlation, or coherence, the information transmission and functional connectivity can be widely investigated with mutual information (MI) analysis [7]. MI comes from information theory proposed by Vastano and Swinney [8] and can be defined as a measure of the amount of information gained about one system from the measurement of another. MI measures the entropy of an input and the conditional equivocation entropy of the input given a specific output that is known or can be estimated. The major advantage of MI is that this

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http://dx.doi.org/10.1016/j.neulet.2015.07.045
0304-3940/

Table 1
Demographic and clinical features.

	Patients	Controls
Demographic caracteristics		
Sample (N)	17	17
Gender	10 Males; 7 female	9 Males; 8 female
Age (years)	34.7 ± 10.3	36.5 ± 13.9
Education (years)	12.1 ± 3.2	15.8 ± 4.1
Psychiatric assessment		
Onset of schizophrenia (years)	24.5 ± 6.2	–
Duration of illness (years)	9.8 ± 7.7	–
CPZ equivalent (mg/die)	212 ± 112	–
CGI-S	4.0 ± 0.8	–
PANSS	58.2 ± 19.4	–
GAF	65.3 ± 14.3	–

CPZ equivalent = chlorpromazine equivalents; CGI-S = Clinical Global Impression-Severity Scale; PANSS = Positive and Negative Syndrome Scale; GAF = Global Assessment of Functioning.

method considers both the linear and nonlinear dependencies of information transmission among those brain regions. MI has a maximum value when the two time series are completely the same, and a zero value if the system is completely independent of the other. Since its introduction, MI has been used in different fields as a measure of coupling or information transmission between different systems. Several studies have already applied this approach in various clinical and experimental situations [9–12]. Different studies have investigated MI in schizophrenia, but no definitive conclusions have been outlined [11,13].

By taking all these considerations into account, the aim of the present study was to investigate brain connectivity by means of MI in patients with schizophrenia and healthy controls in two different conditions: a baseline condition recorded with eyes closed, and an active condition recorded with eyes open. Mutual information index in the multi-channel EEG was computed between all pairs of electrodes (19 × 19). Given the results of previous studies, we expected a difference between the two groups in terms of MI. However, in the light of the contradictory findings in the literature regarding increased or decreased connectivity, we intended for this investigation to be an exploratory analysis.

2. Methods

In the present study, we used the same subjects used in a previous study [14]. 23 patients with schizophrenia were recruited from the Department of Neuroscience, Section of Psychiatry, Outpatients Clinics and the Department of Mental Health ASL 1 Ospedale Maggiore San Giovanni, Turin, Italy. They all fulfilled formal Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [15] diagnostic criteria for schizophrenia. The diagnosis was confirmed by two expert clinicians using the Structured Clinical Interview for DSM-IV (SCID) [16]. At the time of study entry, patients had been clinically stable for at least 6 months as judged by the treating psychiatrist. Patients were evaluated using a semi-structured interview to assess demographic and clinical features (Table 1). Subjects were excluded if they had a current disorder other than schizophrenia on axis I of the DSM-IV-TR (screened with the SCID), a current or past co-diagnosis of autistic disorder or another pervasive developmental disorder, a history of severe head injury (coma ≥ 48 h), or a diagnosis of a psychiatric disorder due to a general medical condition. All the patients were receiving antipsychotic medication with a second generation antipsychotic (SGA) at the time of assessment.

Written informed consent was obtained from all subjects after a complete description of the study. The study was performed in accordance to the ethical standards of the Declaration of Helsinki and was approved by our ethics committee.

EEG recordings were carried out in different days. Six patients were discarded, due to unanalyzable EEG recording (electrocardiogram interference, muscular artifacts) ($N = 2$), inability to follow the instructions of the experimental protocol ($N = 3$) and protocol interruption ($N = 1$). The EEG of the final 17 patients was analyzed and compared with that of a sample of 17 sex and age-matched healthy volunteers without history of psychiatric or neurological diseases. All patients were right-handed, whereas one control was left-handed.

2.1. Psychiatric assessment

Overall severity of illness was rated using the Clinical Global Impression-Severity Scale (CGIS-S)[17]. Current levels of psychopathological symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), a rater-administered 30-item scale for measuring Positive Symptoms, Negative Symptoms, and General Psychopathology subscales [18]. The Global Assessment of Functioning (GAF) was used to quantify patients' psychological, social and occupational/educational functioning [19].

2.2. EEG recording

Subjects sat in a comfortable chair and EEG data were recorded using a 19-channel EEG (Galileo System, EBNeuro, Firenze, Italy). Nineteen electrodes were applied to the scalp in accordance with the 10–20 international system with linked common ear reference. Impedance was less than 2 kΩ in each active lead. Data were collected and digitized at a sampling rate of 1024 Hz, with a low frequency filter of 3 Hz, an high frequency filter of 30 Hz, in each channel. EEG recordings were carried out in two different conditions: a baseline period of 5 min with eyes closed (CE) and an active period of 4 min with eyes open (OE). All EEGs were visually inspected off-line by three independent experimenters in order to discard EEG artifacts. 16-s epochs (16384 data point) without artifacts were selected for each condition.

2.3. Mutual information and statistical analysis

We used MI analysis as a measure of functional connectivity or coupling among different brain regions. Mutual information comes from information theory and is a measure of the amount of information gained about one system from the measurement of another. If T is the set of messages sent through an instrument, $t1$, $t2$, $t3$, ..., tn, and the associated probabilities $PT(t1)$, $PT(t2)$, $PT(t3)$, ..., $PT(tn)$, the average amount of information gained from the measurement of T is the entropy H of the system:

$$H(T) = \Sigma_j P_{RT}(r_j|t_i) \log P_{RT}(r_j|t_i) = \Sigma_j \left(\frac{P_{RT}(r_j|t_i)}{P_T(t_i)}\right) \log\left(\frac{P_{RT}(r_j|t_i)}{P_T(t_i)}\right)$$

where $P_{RT}(r_j/t_i)$ is the probability that a measurement of r will yield r_i given that the measured value of t is t_i. Then, by averaging $H(R/t_i)$ over t_i, the uncertainty of r for a given measurement of t is:

$$H(R|t_i) = \Sigma_{ij}\left(\frac{P_{RT}(r_j|t_i)\log(P_{RT}(r_j|t_i))}{P_T(t_i) = H(R,T)H(T)}\right)$$

where

$$H(R,T) = \Sigma_{ij} P_{RT}(r_j|t_i) \log P_{RT}(r_j|t_i)$$

We define the mutual information as the amount by which a measurement of T reduces the uncertainty of R.

MI among all pairs of electrodes (19 × 19) was calculated. In order to consider the connectivity between an electrode, and thus, the underlying brain region, and all the other electrodes we used the following criterion, as previously done by Benedetti et al. [20].