Clinical Neurophysiology 128 (2017) 867–874

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Altered effective brain connectivity at early response of antipsychotics in first-episode schizophrenia with auditory hallucinations

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ARTICLE INFO

Article history:
Accepted 3 February 2017
Available online 20 February 2017

Keywords:
Schizophrenia
Hallucination
Electroencephalogram
Dynamic casual modelling
Effective connection

HIGHLIGHTS

- We investigated the effective connectivity of cortical networks in patients with FES with auditory hallucinations using DCM of resting-state EEG data.
- Medicated patients showed improvement of frontotemporal connectivity.
- This study provides the first evidence of early drug response-related alterations in the effective connectivity of cortical networks in schizophrenia.

ABSTRACT

Objective: This study aimed to examine the alterations of cortical connectivity in first-episode schizophrenia (FES) with auditory hallucinations at early response of antipsychotics.
Methods: This was a nonexperimental control of medication study. We measured the cortical activity of 20 medicated patients with FES (medicated group), 19 nonmedicated patients with FES (nonmedicated group), and 22 healthy controls using electroencephalogram during eye-open resting state. Source reconstruction analysis was performed to determine the brain regions that showed significant group difference. A dynamic causal modelling (DCM) analysis was used to estimate the effective connectivity between sources.
Result: Both FES groups expressed increased activity in the right middle frontal gyrus (RMFG) and left/right superior temporal gyrus (L/RSTG) relative to that in the controls ($p < 0.05$), and the nonmedicated group presented even higher activity than the medicated group ($p < 0.05$). The effective connectivity from RMFG to LSTG was weaker in the nonmedicated group relative to that in the medicated group ($p < 0.01$), although patients in the medicated group showed no difference with healthy controls in RMFG to L/RSTG connections. The Bayesian model selection analysis found modulatory lateralization in the nonmedicated group.
Conclusion: The patients with FES showed frontotemporal hyperactivity and disconnectivity. The effective connections accompanied with modulation were improved when hallucination diminished at early response of routine medication.
Significance: This study provided the first evidence of early drug response-related alterations in effective brain connectivity.

1. Introduction

The core impairments in schizophrenia include positive symptoms, negative symptoms, and cognitive deficits. The most common symptom, auditory hallucination, appears in 70–75% of affected individuals (Nayani and David, 1996). According to

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http://dx.doi.org/10.1016/j.clinph.2017.02.004

patients with schizophrenia, the voices can be inside (i.e., pseudoform) or outside their heads. Disordered brain connectivity has long been suggested to be a central pathophysiological feature of schizophrenia (Andreasen et al., 1998; Friston, 1999). Recently, a number of neuroimaging and neurophysiological studies have made reference to hypoactivity (Ehrlich et al., 2012) or hyperactivity (Hoffman et al., 2011) in the frontal and temporal areas and their altered connectivity per se (Quintana et al., 2003; Kam et al., 2013) during auditory hallucinations. It is not clear, however, whether disconnectivity influences the progress of schizophrenia or whether it is an outcome of the illness or its treatment (Konrad and Winterer, 2008). A recent review of studies using structure neuroimaging and electrophysiology in first-episode schizophrenia (FES) demonstrated that there is evidence for altered connectivity in the early stage of this disorder (Begre and Koenig, 2008); Crossley et al. (2009) demonstrated increased superior temporal and middle frontal gyrus connectivity in patients with schizophrenia under working memory task. As these studies have largely been performed in patients with chronic schizophrenia, the question is whether the alterations in brain functional integration between regions are secondary to psychotic illness or its treatment. In the present study, the patients were all at their first presentation of psychosis, with typical auditory hallucinations. Our interest points were the alterations of neural network at the onset of disease and the early response of a 2-week treatment, namely the mechanism difference between the drug-naïve and the drug early onset state, which, to our knowledge, has seldom been reported.

Following the seminal proposition that communication within neuronal networks is mediated by synchronous neural oscillations (Engel et al., 2001; Fries, 2005; Singer, 1999), there has also been growing interest in the oscillatory mechanisms underlying these connectivity disturbances, as revealed by electroencephalogram and magnetoencephalography. Previous electrophysiological studies have demonstrated that dynamic causal modelling (DCM) can provide valid information on the mechanisms that represent potential key dimensions of psychiatric disease, e.g., excitation-inhibition balance and synaptic plasticity by N-methyl D-aspartate receptors or its regulation by neuromodulatory transmitters such as dopamine or acetylcholine (Moran et al., 2011; Schmidt et al., 2013). For example, there is evidence that links gamma- and alpha-band to neurotransmitter systems involving parvalbumin-positive GABAergic interneurons and glutamatergic pyramidal cells (Bartos et al., 2007; Sohal et al., 2009; Lozano-Soldevilla et al., 2014). The relationship between beta-band and dopaminergic system (Cagnan et al., 2015) has also been reported.

DCM can explain measured data through a network model that consists of a several dynamically interacting sources. This network model is inverted using a Bayesian approach, and one can make inferences about connections between sources through this approach (Friston et al., 2003; Stephan et al., 2007). The DCM for cross-spectral densities used for steady-state responses has been previously reported (Penny et al., 2009; Friston et al., 2012, 2014). The canonical microcircuit (CMC)-type neural mass model is a refinement of the Jansen and Rit convolution models and explicitly accommodates the neuronal sources of forward and backward connections in cortical hierarchies (Bastos et al., 2012).

Second-generation antipsychotic medications with fewer side effects relative to first-generation antipsychotics are associated with rapid improvement of positive psychotic symptoms in patients with FES (Sanger et al., 1999; Lieberman et al., 2003; Schooler et al., 2005). Atypical antipsychotics produce high temporal cortex D2/D3 occupancy, which is involved in antipsychotic efficacy (Stone et al., 2009). In clinical practice, an early response of atypical antipsychotics was observed within 2 weeks in patients with schizophrenia (Leucht et al., 2005; Levine and Leucht, 2012). A recent research reports that a short-term effect of antipsychotic treatment can increase regional synchronous neural activity in the frontal and temporal areas (Lui et al., 2010). However, the relevant mechanism of effective connection change in the brain at the early response stage of antipsychotics, i.e., after 2 weeks of medication in patients with FES, is still unclear.

The first aim of the present study was to examine the difference in brain activity between drug-naïve patients with FES and patients with the onset response of medication. We used electroencephalography to obtain time-frequency oscillations across all electrodes and determine the source location by the source reconstruction method. We then used DCM (Friston et al., 2003; Moran et al., 2009) to estimate the effective connections that these regions exerted on each other. Effective connection is distinct from functional connection, which reflects nondirectional correlations between activation in different regions with each other. Our principal hypotheses were as follows: (1) on the basis of the results of source analysis, the regional activities would be different between medicated and nonmedicated patients with FES and (2) the connectivity exerted by altered regions would be different between medicated and nonmedicated patients with FES. Evidence would be given for brain network alteration when the patient responds to routine medication.

2. Methods

2.1. Participants

The study was approved by the Ethics Committee of Second Affiliated Hospital of Zhejiang University School of Medicine, and all participants gave their written informed consent to participate.

Patients at their first presentation of psychosis were recruited from the psychiatry department of Second Affiliated Hospital, Zhejiang University School of Medicine. A total of 45 patients were enrolled; however, on the basis of their cooperation during the study period, 39 of them completed the entire experiment and analyzable data were obtained for these patients, which were included in a later analysis. The patients were diagnosed as having paranoid schizophrenia with auditory hallucinations in the acute phase according to the ICD-10 criteria (WHO, 1992) after a semi-structured clinical interview. The patients had experienced their first acute episode 1.50–4.50 months (mean 2.78 ± 1.01) before the EEG recording and met the DSM-5 (American Psychiatric Association, 2013) criteria for paranoid schizophrenia when subsequently reassessed 6 months after first presentation. Nineteen patients were drug naïve. The other 20 had been treated with atypical antipsychotics for approximately 2 weeks at chlorpromazine-equivalent mean dosage of 446.23 mg/day. Retrospectively, before treatment, the medicated patients with FES (hereafter, medicated group) had no difference in disease duration and symptom severity compared to nonmedicated patients with FES (hereafter, nonmedicated group) (Table 1). We only recruited hallucinating patients, which made the comparison focused, and the medication was non-experimental controlled. The severity of clinical symptoms in the medicated and the nonmedicated groups before medication and on the day of EEG recording was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) by an experienced psychiatrist trained in its use.

Twenty-two healthy volunteers from the medical staff and the local community were recruited. They received a semi-structured clinical interview to exclude any current or lifetime evidence of psychiatric disorder.

The sociodemographic data of the three groups were matched (Table 1), and subjects who had a history of neurological disorder or met the DSM-5 criteria for substance abuse disorder were