Schizophrenia Research 152 (2014) 513–520

Contents lists available at ScienceDirect

Schizophrenia Research

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

Resting-state connectivity in the prodromal phase of schizophrenia: Insights from EEG microstates

Christina Andreou [a,*], Pascal L. Faber [b], Gregor Leicht [a], Daniel Schoettle [a], Nenad Polomac [a], Ileana L. Hanganu-Opatz [c], Dietrich Lehmann [b], Christoph Mulert [a]

[a] Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany
[b] The KEY Institute for Brain-Mind Research, University Hospital of Psychiatry, CH-8032 Zurich, Switzerland
[c] Developmental Neurophysiology, Center for Molecular Neurobiology, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany

ARTICLE INFO

Article history:
Received 10 September 2013
Received in revised form 22 November 2013
Accepted 10 December 2013
Available online 2 January 2014

Keywords:
Schizophrenia
At-risk mental state
Resting-state
Microstates
EEG
Connectivity

ABSTRACT

Introduction: Resting-state EEG microstates are thought to reflect the momentary local states and interactions of distributed neural networks in the brain. Several changes in resting-state EEG microstates have been described in acutely ill patients with schizophrenia, but it is not known whether these represent trait or state abnormalities. The present study aimed to investigate this issue by assessing EEG microstate characteristics in high-risk individuals (HR) and clinically stable first-episode patients with schizophrenia (SZ) with low symptom levels, compared to each other and healthy controls (HC).
Method: Participants were 18 HR, 18 SZ, and 22 HC subjects. 64-channel resting-state EEG recordings were used for microstate analyses. Microstates were clustered into four classes (A–D) according to their topography. Temporal parameters and topographies of microstates were compared among groups.
Results: Microstate class A displayed higher coverage and occurrence in HR than SZ and HC, while microstate class B covered significantly more time in SZ compared to both HR and HC. Microstate class B displayed an aberrant spatial configuration in SZ, and to a lesser extent also in HR, compared to HC, with patients exhibiting significantly higher activity in the vicinity of the left posterior cingulate.
Discussion: Microstate abnormalities observed in HR were similar to those previously reported in acutely ill patients with schizophrenia. Moreover, there was evidence that HR and SZ might share specific disturbances in brain functional connectivity. These findings raise the possibility that certain abnormalities in resting-state EEG microstates might be associated with an increased risk for psychosis.

1. Introduction

Schizophrenia is a severe disorder compromising multiple aspects of everyday functioning and quality of life (e.g. Bellack et al., 2007). These impairments often persist despite pharmacological treatment of psychotic symptoms (Hofer et al., 2006; Leifker et al., 2009). Accordingly, a growing body of research is devoted to correctly and timely identifying individuals at risk for schizophrenia, in order to prevent their transition into psychosis. In this context, several candidate clinical, neuropsychological and neurophysiological markers are being investigated, in the hope of increasing the specificity of risk detection.

It has been long suggested that the complex clinical and cognitive symptoms of schizophrenia are best explained in terms of large-scale neuronal networks rather than as a hypofunctionality of specific brain regions (Andreasen et al., 1998; Friston, 1999). In recent years, several such alterations in brain functional connectivity have been confirmed in patients with schizophrenia (e.g. Lui et al., 2010; Woodward et al., 2011; Liemburg et al., 2012). There is evidence that this might be the case in the high-risk state as well (Allen et al., 2010; Bloemen et al., 2010; Shim et al., 2010; Lord et al., 2011). However, these findings were obtained with hypothesis-driven analyses of specific brain networks, such that they are difficult to synthesize into a coherent account of the nature and topography of connectivity disturbances in the high-risk state. The present study adopts a more global approach, drawing from the well-described concept of EEG microstates, which has produced quite consistent results in patients with schizophrenia.

EEG microstates are periods, in which the EEG global field power displays a quasi-stable spatial configuration (Lehmann et al., 2005). Their duration is in the order of about 100 ms, which is compatible with the time range in which spontaneous mental operations occur (Lehmann et al., 2005; Nishida et al., 2013). Based on the premise that the brain exhibits a single state of coherent activity at any given time (Ashby, 1952; Dehaene and Naccache, 2001; Baars, 2002), it is assumed that EEG microstates capture the momentary local states and interactions of diverse distributed neural networks (Koenig et al., 2002). Indeed,

* Corresponding author at: University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany. Tel.: +49 40 7410 59460; fax: +49 40 7410 59805.
E-mail address: c.andreou@uke.de (C. Andreou).

0920-9964/$ – see front matter
http://dx.doi.org/10.1016/j.schres.2013.12.008

microstates of different topography have been associated with different types of spontaneous (Lehmann et al., 1998) and stimulus-driven mental processes (Koenig et al., 1998; Britz et al., 2009), and appear to correspond to different resting-state networks in simultaneous EEG-fMRI studies (Britz et al., 2010; Musso et al., 2010; Yuan et al., 2012).

Microstate topographies can be clustered into four prototypical configurations (see Fig. 1, 'ND'), shown to be very reliable both within- and between-subjects across the entire life span (Koenig et al., 2002). These four 'classes', labeled A–D, have been suggested to represent preferred network configurations in the brain (Kindler et al., 2011). With use of simultaneous EEG-fMRI it has been shown (Britz et al., 2010) that the four typical microstates of spontaneous EEG correspond to distinct fMRI resting-state networks: a network consisting of superior and middle temporal areas implicated in phonological processing (class A), a visual network consisting of bilateral extrastriate areas (class B), an insular-cingulate network thought to be involved in own-body representation (class C), and a right-lateralized frontoparietal network associated with attention reorientation (class D).

In resting-state EEG, each microstate class is characterized by a set of temporal parameters (e.g. mean duration or frequency of occurrence, see also Section 2.1) that fall within the range of well-described age-dependent norms in healthy individuals (Koenig et al., 2002). Deviances from these norms have been described in several psychiatric and neurological disorders (Dierks et al., 1997; Strik et al., 1997; Stevens and Kircher, 1998; Kikuchi et al., 2011; Fingelkurts et al., 2012; Nishida et al., 2013), and are thought to reflect disturbed information processing in patients. In schizophrenia, a number of abnormalities in resting EEG microstates have been reported in acutely ill patients, especially shortened duration of two microstate classes (B and D) (Koenig et al., 1999; Strelets et al., 2003; Lehmann et al., 2005; Nishida et al., 2013) and increased frequency of occurrence of another (class A) (Koenig et al., 1999; Lehmann et al., 2005; Nishida et al., 2013), compared to healthy controls. These findings are associated with the presence of positive symptomatology and have been suggested to reflect disturbed information processing in patients (Koenig et al., 1999; Lehmann et al., 2005). For example, since microstate class D corresponds to a frontoparietal network associated with attention (Britz et al., 2010), it is assumed that its shortening marks a breakdown of self-monitoring processes involved in source attribution of inner speech, resulting in the emergence of hallucinations (Kindler et al., 2011). However, it is not clear whether these deviant microstates mirror the state of the brain during the psychotic experience, or rather correspond to abnormalities in the organization of functional networks that predispose the individual to such experiences. The former has been suggested for class D, the microstate most consistently found to be shortened in patients with schizophrenia (Kindler et al., 2011), but less is known about the trait or state nature of other microstate abnormalities in schizophrenia.

Since individuals at high risk for developing schizophrenia often exhibit clinical or cognitive symptoms of the illness in attenuated form (Klosterkotter et al., 2008; Keshavan et al., 2011), it is conceivable that these individuals might also exhibit some of the microstate abnormalities encountered in patients with schizophrenia. So far, this assumption has not been investigated. The present study aimed to assess EEG microstate characteristics in high-risk individuals compared to healthy controls and first-episode patients with schizophrenia. In order to more adequately discriminate trait effects from those of specific symptoms, the high-risk population was compared not to acutely ill patients, but to stable patients with similarly low symptom levels.

2. Materials and methods

The present study was part of a larger project investigating resting-state and task-related brain connectivity in the prodromal phase and

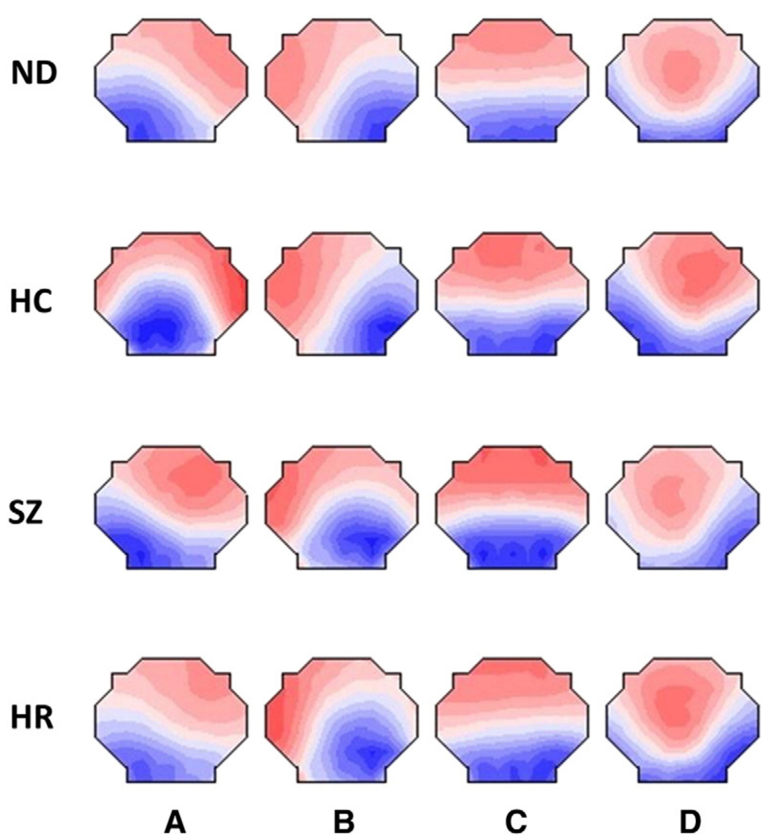

Fig. 1. Spatial configuration of the four microstate classes (A–D). Upper row: normative data (ND; Koenig et al., 2002). Lower rows: microstate configurations in patients with schizophrenia (SZ), high-risk individuals (HR) and healthy controls (HC).