



## Resting-state theta-band connectivity and verbal memory in schizophrenia and in the high-risk state



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### ARTICLE INFO

#### Article history:

Received 9 October 2014

Received in revised form 8 December 2014

Accepted 10 December 2014

Available online 29 December 2014

#### Keywords:

Psychosis

Electroencephalography

Coherence

Neuropsychology

Default mode network

Multivariate interaction measure

### ABSTRACT

**Background:** Disturbed functional connectivity is assumed to underlie neurocognitive deficits in patients with schizophrenia. As neurocognitive deficits are already present in the high-risk state, identification of the neural networks involved in this core feature of schizophrenia is essential to our understanding of the disorder. Resting-state studies enable such investigations, while at the same time avoiding the known confounder of impaired task performance in patients. The aim of the present study was to investigate EEG resting-state connectivity in high-risk individuals (HR) compared to first episode patients with schizophrenia (SZ) and to healthy controls (HC), and its association with cognitive deficits.

**Methods:** 64-channel resting-state EEG recordings (eyes closed) were obtained for 28 HR, 19 stable SZ, and 23 HC, matched for age, education, and parental education. The imaginary coherence-based multivariate interaction measure (MIM) was used as a measure of connectivity across 80 cortical regions and six frequency bands. Mean connectivity at each region was compared across groups using the non-parametric randomization approach. Additionally, the network-based statistic was applied to identify affected networks in patients.

**Results:** SZ displayed increased theta-band resting-state MIM connectivity across midline, sensorimotor, orbitofrontal regions and the left temporoparietal junction. HR displayed intermediate theta-band connectivity patterns that did not differ from either SZ or HC. Mean theta-band connectivity within the above network partially mediated verbal memory deficits in SZ and HR.

**Conclusions:** Aberrant theta-band connectivity may represent a trait characteristic of schizophrenia associated with neurocognitive deficits. As such, it might constitute a promising target for novel treatment applications.

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### 1. Introduction

Since the introduction of the concept of schizophrenia as a disorder of disturbed communication across neural networks (Andreasen et al., 1998; Friston, 1999), several studies have confirmed alterations in brain functional connectivity in patients with schizophrenia (Liemburg et al., 2012; Lui et al., 2010; Woodward et al., 2011), mainly affecting connections between frontal and more posterior areas (Pettersson-Yeo et al., 2011).

Connectivity disturbances have been consistently associated with deficient performance in a variety of cognitive domains (Dauvermann et al., 2014), which represents a core feature of schizophrenia (Heinrichs and Zakzanis, 1998). Such neurocognitive deficits are already present in individuals at high risk for the disorder (Agnew-Blais and

Seidman, 2013; Bora and Murray, 2013). More importantly, they have been suggested to be more severe in high-risk individuals who will later develop a psychotic disorder compared to those who will not (De Herdt et al., 2013). Identification of the neural networks involved in this core component of schizophrenia might help clarify the pathophysiological mechanisms that eventually lead to emergence of psychotic symptoms, and promote the development of interventions aiming to prevent transition into a chronic and difficult-to-treat disorder.

Most earlier studies of connectivity in schizophrenia focused on task-related connectivity indices. However, it has been shown that spontaneous, “resting-state” activity of the brain also displays discrete spatiotemporal organization patterns that carry specific functional significance (Damoiseaux et al., 2006; Engel et al., 2001, 2013; Friston, 2005). Furthermore, as spontaneous brain activity influences the processing of incoming stimuli (Britz et al., 2009; Deco and Corbetta, 2011; Hipp et al., 2011), investigation of the resting-state allows a view into the underpinnings of cognitive and perceptual disturbances in schizophrenia while at the same time avoiding the known confounder of impaired task performance in patients. As a result, more recent

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studies on connectivity in schizophrenia and in the high-risk state have increasingly focused on the interactions within and between resting-state brain networks. Overall, the findings of these studies indicate complex dysconnectivity patterns in patients and high-risk individuals, where interactions of a brain area with others might be reduced or increased depending on the network studied (Allen et al., 2010; Guo et al., 2014; Liemburg et al., 2012; Lord et al., 2011; Manoliu et al., 2014; Shim et al., 2010).

All of the aforementioned studies of resting-state connectivity have employed functional magnetic resonance imaging (fMRI). A shortcoming of fMRI-based measures is that, due to their low time resolution, they cannot capture the fast dynamics of neuronal interactions, which occur on a millisecond time-scale (Uhlhaas, 2013). These dynamics involve neuronal oscillations across a broad frequency range, which appear to correspond in a frequency-specific manner to different spatial network configurations (Hillebrand et al., 2012; Hipp et al., 2012; Marzetti et al., 2013) and different aspects of stimulus processing (Leicht et al., 2013; Marco-Pallares et al., 2008). MEG and EEG provide the opportunity to study the spectral structure of neuronal activity with excellent temporal resolution and thus to characterize brain network properties in considerably greater detail compared to fMRI. Indeed, emerging evidence suggests that certain EEG connectivity measures, notably those based on phase correlations among signals, might reveal coupling patterns that are not captured by fMRI (Engel et al., 2013).

Several studies have reported various EEG/MEG scalp-level connectivity abnormalities in schizophrenia, with results indicating reduced phase synchronization in the beta and gamma frequency range (Kam et al., 2013; Kikuchi et al., 2011; Uhlhaas and Singer, 2010), but increased connectivity in lower frequency bands (Kam et al., 2013), in patients compared to healthy controls. However, scalp-level analyses are limited in their usefulness for drawing inferences regarding the underlying sources of electrical activity in the brain, due to known methodological problems associated with reference electrode placement and volume conduction. So far, few studies have assessed EEG/MEG connectivity at the source level in schizophrenia. In the gamma-band range, reduced task-related (Mulert et al., 2004), but intact resting-state connectivity has been reported (Rutter et al., 2013). In the lower frequencies, one study (Hinkley et al., 2011) reported a complex pattern that included region-specific increases and decreases of alpha-band connectivity in patients, whereas another study (Lehmann et al., 2014) observed decreased connectivity in the alpha-band, and increased connectivity in the delta/theta band, in patients. Clearly, more work is needed until these results can be integrated into a coherent account of connectivity disturbances in schizophrenia. Critically, so far there is very little information on the networks affected at different frequency ranges, and whether abnormalities are present before illness onset.

The aim of the present study was to evaluate EEG resting-state source-level connectivity across a wide range of frequencies in high-risk individuals compared to first-episode patients with schizophrenia and healthy controls. A second aim was to investigate to what extent resting-state connectivity disturbances contribute to the cognitive deficits that characterize schizophrenia and the high-risk state. An important consideration when investigating EEG/MEG connectivity is that measures of brain interaction may be distorted by signal mixing due to volume conduction and, for EEG, to the use of a common reference (Hipp et al., 2012; Nolte et al., 2004; Stam et al., 2007). Therefore, for the present study we used a multivariate interaction measure that maximizes both invariance with respect to volume spread and the detection of true neuronal interactions (Ewald et al., 2012).

## 2. Materials and methods

The present study was part of a larger ongoing project investigating resting-state and task-related brain connectivity in schizophrenia by

means of EEG, MEG, and simultaneous EEG–fMRI. Participant samples consisted of 28 individuals at high-risk for psychosis (HR), 19 patients with first-episode schizophrenia (SZ), and 23 healthy controls (overlapping with previous publications; Andreou et al., 2014, in press). Only first-episode patients were included in the SZ group, in order to avoid confounds related to chronicity and long-term antipsychotic drug treatment. Moreover, only stable SZ were included in analyses, in order to adequately discriminate trait effects from those of specific acute symptoms.

SZ and HR individuals were recruited through the Psychosis Center of the Department of Psychiatry of the University Medical Center Hamburg-Eppendorf. Exclusion criteria for all participants were current substance abuse or dependence, and presence of major somatic or neurological disorders. For healthy control subjects, additional exclusion criteria were any previous psychiatric disorder or treatment, and a family history of psychotic disorders. Inclusion/exclusion criteria were assessed with a semi-structured interview conducted by a clinical psychiatrist or trainee with at least 4 years of clinical experience. The study was conducted in accordance with the Declaration of Helsinki; all participants were required to sign an informed consent form prior to entering the study.

First-episode status was defined as having received the first diagnosis and psychiatric treatment less than a year prior to study participation, and presence of psychotic symptoms in any form for no more than five years. SZ patients were either (a) stable outpatients (defined as no change in antipsychotic treatment in the past two months) or (b) stabilized inpatients after antipsychotic treatment of at least 6-weeks' duration, shortly before discharge.

The high-risk state was defined according to criteria of the Early Detection and Intervention program of the German Research Network on Schizophrenia (GRNS) (Wolwer et al., 2006). These include (a) basic symptoms, defined as the presence of at least two subjective cognitive or perceptual disturbances with a score of  $\geq 3$  on the Schizophrenia Proneness Instrument (Schultze-Lutter et al., 2007); (b) presence of either a positive family history for psychotic disorders or schizotypal personality disorder, plus decline of at least 30% in the Global Assessment of Functioning scale (APA, 2000); (c) presence of attenuated positive symptoms or brief, limited and intermittent psychotic symptoms, as assessed with the Structured Interview for Prodromal Syndromes and the Scale of Prodromal Symptoms (Miller et al., 2003). In the present study, the above criteria were fulfilled in  $n = 10$ ,  $n = 3$  and  $n = 23$  HR subjects, respectively (please note that more than one criterion might apply to the same subject). Demographic characteristics of the three groups, and clinical characteristics of SZ and HR groups, are presented in Table 1.

Diagnosis of schizophrenia in patients was established with the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Severity of clinical symptomatology was assessed with the Positive and Negative Syndrome Scale (Kay et al., 1987). Subjects also underwent neuropsychological testing with an extensive battery that included tests of memory, attention, and executive functioning (see Supplementary Material for a complete list of the tasks). Neurocognitive performance data were available for 20 HC, 17 SZ and 26 HR.

### 2.1. EEG recording and analyses

A detailed account of EEG recording, electrode placement and computation methods is provided in the Supplementary Material. Recordings took place in a sound-attenuated and electrically shielded room. Continuous EEG activity was recorded while subjects were seated comfortably with their eyes closed. Participants were monitored for electroencephalographic signs of drowsiness (Hegerl et al., 2008) for the whole duration of the recording (5 to 10 min). Recordings were conducted at a sampling rate of 1000 Hz with 64 Ag/AgCl electrodes mounted on an elastic cap (ActiCaps, Brain Products, Munich, Germany), using the Brain Vision Recorder software version 1.10 (Brain Products, Munich,

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