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Research Paper

Schizophrenia patients and 22q11.2 deletion syndrome adolescents at risk express the same deviant patterns of resting state EEG microstates: A candidate endophenotype of schizophrenia

Miralena I. Tomescu [a,*], Tonia A. Rihs [a], Maya Roinishvili [b], F. Isik Karahanoglu [c,d], Maude Schneider [e], Sarah Menghetti [e], Dimitri Van De Ville [c,d], Andreas Brand [f], Eka Chkonia [g], Stephan Eliez [e], Michael H. Herzog [h], Christoph M. Michel [a], Céline Cappe [h,i]

[a] Functional Brain Mapping Laboratory, Department of Fundamental Neuroscience, Geneva, Switzerland
[b] Institute of Cognitive Neurosciences, Agricultural University of Georgia, Tbilisi, Georgia
[c] Institute of Bioengineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
[d] Department of Radiology and Medical Informatics, University of Geneva, Geneva, Switzerland
[e] Office Médico-Pédagogique Research Unit, Department of Psychiatry, University of Geneva, Geneva, Switzerland
[f] Institute of Psychology and Cognition Research, University of Bremen, Bremen, Germany
[g] Department of Psychiatry, Tbilisi State Medical University, Tbilisi, Georgia
[h] Laboratory of Psychophysics, Brain Mind Institute, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
[i] Centre de recherche Cerveau et Cognition, Université de Toulouse, CNRS, UMR5549, Toulouse, France

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ABSTRACT

Schizophrenia is a complex psychiatric disorder and many of the factors contributing to its pathogenesis are poorly understood. In addition, identifying reliable neurophysiological markers would improve diagnosis and early identification of this disease. The 22q11.2 deletion syndrome (22q11DS) is one major risk factor for schizophrenia. Here, we show further evidence that deviant temporal dynamics of EEG microstates are a potential neurophysiological marker by showing that the resting state patterns of 22q11DS are similar to those found in schizophrenia patients. The EEG microstates are recurrent topographic distributions of the ongoing scalp potential fields with temporal stability of around 80 ms that are mapping the fast reconfiguration of resting state networks. Five minutes of high-density EEG recordings was analysed from 27 adult chronic schizophrenia patients, 27 adult controls, 30 adolescents with 22q11DS, and 28 adolescent controls. In both patient groups we found increased class C, but decreased class D presence and high transition probabilities towards the class C microstates. Moreover, these aberrant temporal dynamics in the two patient groups were also expressed by perturbations of the long-range dependency of the EEG microstates. These findings point to a deficient function of the salience and attention resting state networks in schizophrenia and 22q11DS as class C and class D microstates were previously associated with these networks, respectively. These findings elucidate similarities between individuals at risk and schizophrenia patients and support the notion that abnormal temporal patterns of EEG microstates might constitute a marker for developing schizophrenia.

1. Introduction

Schizophrenia is one of the most devastating mental disorders. Despite thorough and intensive research its pathogenesis is still largely unknown. To better understand the pathogenesis of schizophrenia and identify susceptible genes, endophenotypes are of crucial interest (Gottesman and Gould, 2003). Endophenotypes are neurophysiological or neurocognitive measures sensitive to the underlying genetic abnormalities rather than the current state of the disease. Endophenotypes are simple, easily quantified, closer to the gene expression and brain network disturbances, and more susceptible to gene discovery, improving prevention and early diagnosis.

A large body of literature has shown abnormal patterns of resting state in schizophrenia (Menon, 2011; Palaniyappan and Liddle, 2012). Both review papers found that the anterior cingulate and the frontoinsular cortex, as part of the salience resting state network (SN), play an important role in schizophrenia by integrating, detecting and filtering pertinent internal and external stimuli as well as recruiting the appropriate networks for sensory information processing. Both models propose that dysfunctional activation of the SN via aberrant engagement of the fronto-parietal central executive resting network (CEN) is

* Corresponding author at: Functional Brain Mapping Laboratory, Dept. of Fundamental Neurosciences, Campus Biotech, 9 Chemin des Mines, CH-1211, Geneva, Switzerland. Tel.: +41 22 379 0858.
E-mail address: ioana.tomescu@unige.ch (M.I. Tomescu).

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responsible for impairments of sensory information processing in schizophrenia (Menon, 2011; Palaniyappan and Liddle, 2012). We speculate that aberrant activation of salience networks could in general result in a reduced activation of sensory processing networks by altered top-down control.

Large-scale neural networks are characterised by flexible dynamics that allow for rapid reorganisation to meet the demands of a constantly changing environment (Bressler, 1995). Such changes in the sub-second time scale can be traced in real-time by electroencephalography (EEG). The EEG microstates are recurrent topographic distributions of the ongoing scalp potential fields with temporal stability of around 80 ms. The spatial configuration (the topography) and the temporal parameters (mean duration, time coverage, occurrence) of the EEG microstates are consistent across many studies and recordings and only 4 resting state EEG microstate classes (A–D) are explaining more than 80% of the data (Khanna et al., 2014; Lehmann et al., 2005). EEG microstates are proposed to be electrophysiological signatures of the typical fMRI resting state networks (RSNs), of which the class C resting EEG microstate has been linked to the salience network (SN) and the class D microstate to the central executive resting state networks (CEN) (Britz et al., 2010).

A recent study revealed that EEG microstates show scale-free behaviour measured by an index of fractality; i.e., the Hurst exponent (Van de Ville et al., 2010). The scale-free properties of microstate transitions in healthy subjects are of interest since neuropsychiatric disorders could potentially lead to a perturbation of dynamics of EEG microstates and thus affect also their fractal characteristics. To the best of our knowledge the scale-free dynamics of microstates in schizophrenia have not yet been studied. Here, we would like to investigate if the temporal dynamics of EEG microstates in schizophrenia and 22q11DS individuals exhibit any perturbations in their fractal properties. Several papers investigating resting EEG in schizophrenia reported abnormalities of the temporal patterns in EEG microstates (Kikuchi et al., 2007; Kindler et al., 2011; Koenig et al., 1999; Lehmann et al., 2005; Nishida et al., 2013). Many studies show a decreased duration of microstate class D (Andreou et al., 2014; Kikuchi et al., 2007; Koenig et al., 1999; Lehmann et al., 2005; Nishida et al., 2011), while other studies reported a decreased duration of class B and increased presence of class C (Kikuchi et al., 2007; Nishida et al., 2011).

The 22q11.2 deletion syndrome (22q11DS) is a genetic syndrome where the deletion of the *locus* (q11.2) on the 22nd chromosome is associated with a 30 fold increased risk to develop schizophrenia in adulthood (Murphy et al., 1999). In a previous study, we found temporal patterns of EEG microstates in 22q11.2 deletion syndrome that are in line with the literature on schizophrenia and with models of resting state dysfunction (Menon, 2011; Palaniyappan and Liddle, 2012; Tomescu et al., 2014). We found decreased class D (previously associated with central executive network CEN) and increased class C (previously associated with SN) presence and deviant transitions between microstate classes in a group of 22q11DS adolescents compared with age-matched healthy individuals (Tomescu et al., 2014). Interestingly, aberrant activation of the anterior cingulate (a key structure of the SN) was also observed during auditory stimulation in the 22q11DS adolescents compared with controls (Rihs et al., 2013). The results of both the resting state study and the auditory paradigm can be integrated in a framework, in which perception is as a state dependent process where the momentary state of the brain influences the processing of incoming stimuli. Several studies show that the pre-stimulus EEG microstate configuration is associated with the perceptual outcome (Britz and Michel, 2010; Britz and Pitts, 2011; Britz et al., 2011, 2014). Consequently, the deviant temporal dynamics of resting EEG microstates could reflect perturbations in networks relevant for cognitive function and could be related to cognitive impairments observed in schizophrenia and 22q11 Deletion Syndrome.

Since resting state activity seems to suggest aberrant salience and attention processing in the 22q11DS adolescents (Rihs et al., 2013; Tomescu et al., 2014), we ask whether we find similar patterns in schizophrenia patients. We specifically investigate whether there are similar differences for classes C and D microstates in 22q11DS individuals, with a genetic high-risk for developing schizophrenia, and in schizophrenia patients.

2. Methods

2.1. Subjects and procedure

This study assembled two cohorts recruited and EEG recorded under similar conditions in Switzerland and Georgia.

The cohort from Geneva was recruited at the Office Medico-Pedagogique; for more details about the inclusion/exclusion criteria of participants see Tomescu et al., 2014. Fifty-eight participants between 12 and 19 years old, 30 patients with 22q11DS (16.5 ± 2.5 years old, mean ± s.d., 17 females) and 28 healthy individuals (15.6 ± 2.3 years old, mean ± s.d., 14 females) were included. At the time of the recording, none of the 22q11DS met the diagnostic criteria for schizophrenia, however, patients were expressing psychotic symptoms (assessed by interview of the psychiatrist S.E. with the patient and parent/caregiver): 12 patients had no psychotic manifestation, 1 had isolated psychotic symptoms, 4 patients had less than one psychotic episode per month, 9 patients had at least one episode per month and 4 patients had psychotic episodes at least once per week.

The second cohort included 54 participants between 18 and 54 years old, 27 control adults (34.2 ± 8 years old; mean ± s.d.; 22 males) and 27 chronic schizophrenia patients (34.5 ± 9.5 years old; mean ± s.d.;14 males). Inpatients (n = 7) came from the Tbilisi Mental Health Hospital; outpatients (n = 20) were recruited in the Neuropsychiatric Dispensary and the Psychosocial Rehabilitation Centre in Tbilisi, Georgia. Diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (DSM-IV) criteria, based on SCID-CV (Structured Clinical Interview for DSM-IV, Clinician Version). The severity of psychotic symptoms was assessed using the scale for assessment of positive (SAPS (Andreasen, 1984b)) and negative symptoms (SANS (Andreasen, 1984a)). The chronic schizophrenia patients in this study expressed positive symptoms with score values: min 3, max 16, mean = 8.7, s.d. = 3.3, and negative symptoms with score values: min 3, max 24, mean = 10.4, s.d. = 5.4. The duration since the schizophrenia diagnosis varied between 1 and 28 years with a mean duration of 10.8 years, s.d. 8.5. With one exception, all patients were treated with either clozapine (10/15/50 mg), haloperidol (10/15/30 mg), trifluoperazine (6/10/20 mg), risperidone (2/4/6 mg), quetiapine (100 mg), olanzapine (10/15 mg), fluphenazine (25 mg), chlorprothixen (12,5/25 mg) or zuclopenthixol (20 mg). Some patients were prescribed more than one antipsychotic drug. The chlorpromazine (CPZ) mean equivalent dose for the patients was 526.02 mg (s.d. = 401.6 mg). Two patients received trazodone (14 mg), 5 amitriptyline (20/25/100 mg), 1 paroxetine (20 mg), 1 fluvoxamine (50 mg), 1 citalopram (40 mg), 3 diazepam (5/10 mg), and 13 trihexyphenidyl (2/4/6 mg). The controls were recruited from the general population to match the patients with respect to age, education, and gender (see Table 1). All participants gave their informed consent before the experiment. All procedures complied with the Declaration of Helsinki and were approved by the local ethics committee.

2.2. EEG data acquisition

The EEG data were acquired mostly in the afternoon or early evening, always in a darkened, electrically shielded room. Participants were sitting in a comfortable, upright position and were instructed to