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Resting-state EEG in schizophrenia: Auditory verbal hallucinations are related to shortening of specific microstates

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ABSTRACT

Objective: Abnormal perceptions and cognitions in schizophrenia might be related to abnormal resting states of the brain. Previous research found that a specific class (class D) of sub-second electroencephalography (EEG) microstates was shortened in schizophrenia. This shortening correlated with positive symptoms. We questioned if this reflected positive psychotic traits or present psychopathology.
Methods: Resting-state EEGs of frequently hallucinating patients, indicating on- and offset of hallucinations by button press, were analyzed. Microstate class D duration was related to spontaneous within-subject fluctuations of auditory hallucinations.
Results: Microstate D was significantly shorter in periods with hallucinations.
Conclusions: Microstates of class D resemble topographies associated with error monitoring. Its premature termination may facilitate the misattribution of self-generated inner speech to external sources during hallucinations.
Significance: These results suggest that microstate D represents a biological state marker for hallucinatory experiences.

1. Introduction

The brain's information processing is state dependent, in other words, the state of the brain is the fate of the incoming information. The brain's resting state follows replicable norms and probably thereby defines the functionally appropriate available perceptual-cognitive repertoire (John et al., 1988). Deviations from these norms are typically associated with specific alterations and dysfunctions of the subject's perception and/or cognition (John et al., 1988).

It is well known that auditory verbal hallucinations (AVH) are very dynamic on a minutes or sub-minutes time scale. In fMRI (Dierks et al., 1999; Allen et al., 2008) as well as EEG studies (Hubl et al., 2007; Ford et al., 2008) these dynamics have been successfully used to investigate neurophysiologic changes associated with the presence of hallucinations, helping to identify their functional neuroanatomy.

EEG-resting state data can be efficiently parsed into sub-second time epochs with quasi-stable field topography, so called microstates (Lehmann et al., 1987) that assumingly correspond to transiently stable distributed neural networks. These microstates are separated by rapid changes of scalp field topography. Since different scalp fields must have been produced by differently activated neural populations, it is appropriate to assume that different microstates correspond to different brain functions (Lehmann et al., 2010). Indeed, in spontaneous EEG as well as in event-related potential data, it has been shown that topographically distinct classes of microstates represent different modes of information processing, such as visual imagery, or abstract thought (Lehmann et al., 1998, 2010; Koenig et al., 1998). Furthermore, the observed sequence of microstates can be efficiently clustered into a small number of microstate classes. These microstate classes are repeatedly observed within one subject, and were also shown to replicate well across subjects (Koenig et al., 2002), which suggests that there

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is a limited number of preferred network configurations both within and across subjects. Recent studies have shown that EEG microstates are closely related to specific resting state networks, as measured by BOLD-fMRI (Britz et al., 2010; Musso et al., 2010).

When studying resting-state EEG microstates in patients with schizophrenia, concise and well replicable differences to normative data were reported. In several independent samples, a specific class of microstates with a fronto-central distribution (see maps as shown in Table 1: class D), was consistently shorter in schizophrenic patients when compared to healthy controls (Koenig et al., 1999; Strelets et al., 2003; Lehmann et al., 2005; Kikuchi et al., 2007). This shortening was correlated to positive psychotic symptoms (Koenig et al., 1999).

However, because all of these previous studies investigated between-group differences or within differences across a time-span of several weeks, it remained unclear whether the effect is a marker of proneness to paranoid-hallucinatory experiences, whether it represents neurobiological features of the abnormal experiences themselves, or whether it is a more general indicator of having a schizophrenic mind set.

To resolve this issue, we analyzed microstates in the ongoing EEG of patients with schizophrenia that frequently experience AVHs, and that were able to indicate during the recording whether or not those experiences were present. We focussed on AVHs because among all types of paranoid experiences, hallucinations are those that are easiest to indicate by the patients (e.g., Dierks et al., 1999; Hubl et al., 2007; Raij et al., 2009; Diederen et al., 2010). Our hypothesis was that microstate D was shortened during phases with AVHs as compared to phases without hallucinations. Mean duration, mean number of microstates per second and percentage of total analysis time occupied of all microstate classes in periods with AVH compared to periods without AVH were computed and evaluated.

2. Methods

2.1. Subjects

The investigation included nine right handed patients (three female) with an ICD-10 diagnosis of paranoid schizophrenia (F20.0, eight patients) or an acute polymorphic psychotic disorder (F23.0, one patient) (WHO, 2004) who frequently experienced AVH. Age ranged between 21 and 54 years (mean 35.2 ± 11.7 years). Only patients without relevant medical disorders (except their psychiatric diagnosis) were included. All patients included in the study were taking either a typical antipsychotic medication (two patients: haloperidol) or an atypical antipsychotic (six patients: olanzapine, risperidone or quetiapine) in conventional dosages. Four received additional benzodiazepine (diazepam, lorazepam) or benzodiazepine-like (zolpidem) treatment. Because we used an intra-individual design, we did not expect that differences in medication would affect the results. Only patients with sufficiently preserved cognitive function to indicate the on- and offset of their AVH by button press were investigated. This approach allows collecting data from a clinically relatively homogeneous sample, but also explains the limited number of investigated subjects. The approach is conservative in the sense that if patients are included that fail to appropriately signal the AVHs, it would bias the analysis towards negative results.

The investigation was conducted in accordance with the declaration of Helsinki and approved by the canton's ethics committee. All patients gave their written informed consent before participating in the study.

Clinical Global Impression Scale (CGI) (NIMH, 1976) and Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987) were used to assess psychopathology. Additionally, hallucinations, fulfilling the Schneiderian first rang symptoms, were rated using the Oulis auditory hallucinations rating scale (Oulis et al., 1995).

2.2. EEG recording

The EEG was recorded using Ag/AgCl electrodes attached to the scalp at 74 regularly spaced, standard positions of the international 10-10-system. Impedances were kept below 10 kΩ. The recording reference electrode was at electrode position Cz. Electrocardiography and electrooculography were recorded for artefact monitoring. All signals were amplified, bandpass-filtered between 0.3 and 70 Hz, digitized at 250 Hz and stored using a BrainScope EEG system (M&I, Prague).

EEG was recorded for about 8 min. Subjects were instructed to listen and attend to their voices (AVH) and indicate the beginnings and endings by a button press, which was marked in the EEG and used to divide the data into periods with and without AVH.

2.3. Data analysis

The microstate analysis followed the standard procedure used in earlier work (Koenig et al., 2002). The EEG data analysis was conducted in BrainVision Analyzer. The continuous EEG was visually inspected for artefacts, and artefact-free periods were divided into 2 s epochs. The selected EEG epochs were digitally band pass filtered from 2 to 20 Hz. Global Field Power (GFP), which quantifies the overall potential variance across the set of electrodes, was computed at each sample in time. Since topography remains stable around peaks of GFP and changes during the troughs, only topographies at momentary maxima of the GFP were further analyzed. A modified version of the K-mean clustering algorithm (Pascual–Marqui et al., 1995) was instructed to seek four classes of microstate topography and to assign each EEG topography to one of these classes. This number of classes has previously been found to be optimal, using a cross validation criterion, and was maintained for compatibility with previous studies.

Microstate class topographies were computed individually and averaged across subjects using a permutation algorithm that maximized the common variance over subjects (Koenig et al., 1999). Within each subject, microstates were identified as continuous epochs within which all topographies were assigned to the same class. The obtained microstate classes were labelled A–D according to their similarities to the previously reported microstate class topographies. Mean duration, mean number of microstates per second and percentage of total analysis time occupied of all four microstate classes in periods with AVH were compared to periods without AVH. Based on the hypothesis raised in the introduction, shortening of microstate class D duration was statistically tested using a confirmatory one-tailed, paired *t*-test. For the other comparisons, where no a priori-hypothesis was available, two-tailed *t*-tests were applied. To exclude possible effects of non-normal distributions or small samples, a bootstrap for paired samples test (based on 1000 bootstrap samples, two-tailed) and a non-parametric Wilcoxon signed-rank test were calculated (two-tailed) when a significant result was obtained. Statistics was carried out in SPSS 16.0.

3. Results

3.1. Clinical measures

The patients' mean PANSS total score was 80.7 (SD: 11.9), mean positive scale was 22.8 (SD: 4.8) and mean negative scale was 16.8 (SD: 2.57). The mean CGI was 6.1 (SD: 0.9), indicating a severe degree of acuity of the symptoms. The analysis of the Oulis auditory hallucinations rating scale indicated that in eight patients the AVH were