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Topographic deficits in alpha-range resting EEG activity and steady state visual evoked responses in schizophrenia

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ABSTRACT

Deficits in both resting alpha-range (8–12 Hz) electroencephalogram (EEG) activity and steady state evoked potential (SSVEP) responses have been reported in schizophrenia. However, the topographic specificity of these effects, the relationship between resting EEG and SSVEP, as well as the impact of antipsychotic medication on these effects, have not been clearly delineated. The present study sought to address these questions with 256 channel high-density EEG recordings in a group of 13 schizophrenia patients, 13 healthy controls, and 10 non-schizophrenia patients with psychiatric diagnoses currently taking antipsychotic medication. At rest, the schizophrenia group demonstrated decreased alpha EEG power in frontal and occipital areas relative to healthy controls. With SSVEP stimulation centered in the alpha band (10 Hz), but not with stimulation above (15 Hz) or below (7 Hz) this range, the occipital deficit in alpha power was partially reverted. However, the frontal deficit persisted and contributed to a significantly reduced topographic relationship between occipital and frontal alpha activity for resting EEG and 10 Hz SSVEP alpha power in schizophrenia patients. No significant differences were observed between healthy and medicated controls or between medicated controls and schizophrenia. These findings suggest a potential intrinsic deficit in frontal eyes-closed EEG alpha oscillations in schizophrenia, whereby potent visual stimulation centered in that frequency range results in an increase in the occipital alpha power of these patients, which however does not extend to frontal regions. Future research to evaluate the cortical and subcortical mechanisms of these effects is warranted.

1. Introduction

Alpha-band (~8–12 Hz) oscillations are a prominent feature of the human waking electroencephalogram (EEG). While the neural mechanisms contributing to alpha oscillations are complex and yet to be fully characterized, alpha rhythms have been widely studied and are associated with a variety of fundamental brain processes, including perception and attention (Klimesch et al., 2007; Palva and Palva, 2007; Klimesch, 2012). An increase in alpha activity spontaneously occurs when we close our eyes, and this increase is most prominently observed in the resting EEG over occipital regions, as consistently demonstrated experimentally from the seminal studies by Berger (1929, 1930) to more recent EEG–fMRI investigations (Feige et al., 2005). Several studies aimed at characterizing the neuronal circuitry underlying this phenomenon have demonstrated a dynamic interplay among cortical and subcortical areas, including the occipital cortex, the frontal cortex, and the thalamus (Guillery and Sherman, 2002; Sherman, 2005; Wang et al., 2011; Vijayan and Kopell, 2012). The implication of subcortical regions, particularly the thalamus, in generating EEG alpha activity has been confirmed by studies using combined EEG–fMRI techniques (Zou et al., 2009; Sadaghiani et al., 2010; Liu et al., 2012; Scheeringa et al., 2012; Omata et al., 2013), whereas the involvement of the occipital and frontal cortices has been established by source modeling analysis of alpha-band brain oscillations recorded with EEG and MEG (Srinivasan et al., 2006).

Deficits in resting state, spontaneous EEG alpha-band power in schizophrenia have been demonstrated by numerous studies and have been observed in patients with chronic schizophrenia, first episode psychosis, prodromal schizophrenia, as well as relatives of schizophrenia probands. These deficits have also been identified during remission, and higher alpha may predict treatment response (Boutros et al., 2008; Javitt et al., 2008; Luck et al., 2011). However, it is still debated whether schizophrenia patients have a peak of alpha activity shifted to a lower frequency (Knott et al., 2001; Harris et al., 2006), or rather whether alpha deficits reflect a reduced ability to generate oscillations in this frequency band (Danos et al., 2001; Mathiak et al., 2011). One paradigm that allows entraining brain oscillations at a given frequency is the steady-state visual evoked potential (SSVEP). The SSVEP is a frequency and phase-locked EEG response to a visual stimulus constantly

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presented at a rapid rate (e.g., a light flicker), thereby measuring the visual system's ability to entrain the stimulus and its oscillatory characteristics (Vialatte et al., 2010). SSVEP deficits have been observed in patients with schizophrenia, most prominently in the alpha and beta frequency ranges (Krishnan et al., 2005; Brenner et al., 2009), and have been shown to implicate both the thalamus as well as frontal and occipital cortical regions (Butler et al., 2005; González-Hernández et al., 2014). In line with these findings, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) has recently recommended the SSVEP as a promising electrophysiological paradigm to be used in clinical trials in schizophrenia research (Butler et al., 2012).

Multiple key aspects of resting and event-related alpha activity in schizophrenia have not yet been fully explored. While prior studies have demonstrated effects in both occipital (Jin et al., 1995, 2000) and frontal (Rice et al., 1989; Wada et al., 1995) areas, these studies were performed with limited resolution EEG montages (19 channels or fewer). The recent availability of high-density EEG systems allows the characterization in greater detail of the topographic characteristics of alpha-range EEG deficits in schizophrenia. Furthermore, spontaneous and SSVEP recordings have not been concurrently evaluated to assess whether decreased alpha activity in schizophrenia reflects an intrinsic deficit to generate and entrain alpha-band oscillations, whether this intrinsic deficit is specific to the alpha range, and the extent to which a deficit can be reverted when adequately entrained. Finally, the effects of chronic exposure to antipsychotics on EEG alpha activity in non-schizophrenia patients, which could contribute to establishing the role of these medications as well as the specificity of alpha deficits in schizophrenia, are not well known.

This study utilized high-density EEG recordings of spontaneous eyes-closed and multiple SSVEP (7 Hz, 10 Hz and 15 Hz) conditions in schizophrenia patients, healthy controls, and other psychiatric patients taking antipsychotic medications. It was hypothesized that schizophrenia patients would demonstrate decreased EEG alpha power in occipital and frontal regions at rest compared to both control groups, and that these deficits would be partially reverted by 10 Hz SSVEP in the occipital area where the alpha-specific sensory information is initially processed, but not in the frontal region where subsequent long-range propagation of this information is required.

2. Methods

2.1. Subjects

Thirteen schizophrenia patients, 13 healthy controls, and 10 non-schizophrenia patients receiving antipsychotic medication were recruited (see Table 1 for demographic information). After providing informed consent, all subjects underwent a screening interview. The Structured Clinical Interview for DSM-IV-TR (First et al., 2002a) was administered by a psychiatrist (MJP) to assess psychiatric diagnoses of patients. Diagnoses for schizophrenia (SZ) patients were paranoid (N = 3), undifferentiated (N = 7), and residual (N = 3). Diagnoses for medicated control (MC) patients were unipolar depression (N = 4), bipolar depression (N = 4), and anxiety disorders (N = 2). All 13 SZ and 10 MC patients were receiving second-generation antipsychotic medication for a history of psychotic features confirmed during the structured interview. Schizophrenia patients were further evaluated with the Positive and Negative Syndrome Scale (PANSS). All subjects were between 18 and 55 years of age. Exclusion criteria for all subjects were identifiable neurologic disorders, substance use disorders within the last 6 months, or diagnosed sleep disorders. An additional exclusion criterion for healthy control subjects was personal psychiatric history or the presence of a first-degree relative with a psychiatric diagnosis, assessed with a non-patient version of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (First et al., 2002b). The study was approved by the University of Wisconsin–Madison Human Subjects Institutional Review Board.

Table 1
Demographic and clinical data.

	HC	SZ	MC	p^*
N	13	13	10	
Sex (m/f)	10/3	8/5	2/8	0.02
Age	38.2 (11.2)	33.2 (10.7)	36.5 (8.8)	0.47
Medication dose		470.7 (345.5)	337.6 (225.2)	0.30
Years since onset		10.5 (6.9)		
PANSS—composite		40.3 (4.3)		
PANSS—positive		20.1 (3.4)		
PANSS—negative		20.2 (1.9)		

HC, healthy control; SZ, schizophrenia; MC, medicated (non-schizophrenia) control; PANSS, Positive and Negative Syndrome Scale. Values are displayed as mean (standard deviation). * p-value represents one-way ANOVA or independent samples t-test result, where applicable.

2.2. Recording procedure

Subjects were outfitted with a 256 channel high-density EEG net (Electrical Geodesics Inc., Eugene, OR). For each recording, subjects were seated in a reclining chair and were asked to relax and sit comfortably while upright with eyes closed, minimizing eye movement or muscle tension. Two minutes (120 s) of resting wakefulness were recorded, followed by 2 min each of several photic stimulation conditions to obtain steady state visual evoked potential (SSVEP) measures. For the SSVEP recordings, a diode photo stimulator (model PS33-PLUS, Grass Technologies, Warwick, RI) placed approximately 90 cm in front of the subject continuously emitted a sinusoidally modulated light stimulus for 120 s at theta (7 Hz), alpha (10 Hz), and beta (15 Hz) frequencies, counterbalanced across flickering frequency conditions. SSVEP sessions were pseudo-randomized with at least 5 min between sessions in order to avoid either order or carry-over effects. Luminance of the sinusoidal light flicker ranged from 300 cd/m^2 at trough to 800 cd/m^2 at peak. EEG signals were digitized and sampled at 500 Hz with a vertex reference.

2.3. EEG processing and analysis

EEG recordings were band-pass filtered between 0.5 and 50 Hz. Channels located on the face and neck, which are most prone to muscle contamination, were initially removed to increase signal-to-noise ratio of subsequent analysis (Goncharova et al., 2003). EEG data were then segmented into 4-second epochs. Muscle and eye-movement artifacts were further removed for individual channels and/or epochs using semi-automatic procedures with amplitude-based threshold detection and visual inspection in EGI NetStation and MATLAB (Mathworks, Natick, MA). Removed channels were interpolated via spherical spline estimation. Combined spontaneous and SSVEP recordings were then subjected to Independent Component Analysis (ICA) using the EEGLAB plug-in (Delorme and Makeig, 2004) in MATLAB to identify and remove characteristic eye, muscle, and cardiac artifacts (Hulse et al., 2011). After ICA, individual session recordings were again visually inspected to remove residual artifacts and then re-referenced to the global average. The amount of data retained for analysis following all artifact removal procedures for the four recording conditions was comparable across the three groups (channels: 94.2 ± 4.8%, 94.0 ± 5.7%, and 93.2 ± 5.1% (mean ± standard deviation) for HC, SZ, and MC, respectively, p = .669; epochs: 57.4 ± 20.4%, 55.0 ± 16.0%, and 55.7 ± 18.0%, p = .836). Spectral power was then computed via Fast Fourier Transform (Welch's averaged modified periodogram, Hamming window; Supplementary Fig. 1), yielding a frequency resolution of 0.25 Hz.

For correlations with clinical variables, alpha power was defined as the average 8–12 Hz power, and peak frequency for each participant was defined as the frequency corresponding to the highest amplitude point in the global (185 channels) average spectrum between 7 and

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