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Is gamma band EEG synchronization reduced during auditory driving in schizophrenia patients with auditory verbal hallucinations?

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ABSTRACT

Auditory verbal hallucinations (AVH) in schizophrenia patients assumingly result from a state inadequate activation of the primary auditory system. We tested brain responsiveness to auditory stimulation in healthy controls (n = 26), and in schizophrenia patients that frequently (n = 18) or never (n = 11) experienced AVH. Responsiveness was assessed by driving the EEG with click-tones at 20, 30 and 40 Hz. We compared stimulus induced EEG changes between groups using spectral amplitude maps and a global measure of phase-locking (GFS). As expected, the 40 Hz stimulation elicited the strongest changes. However, while controls and non-hallucinators increased 40 Hz EEG activity during stimulation, a left-lateralized decrease was observed in the hallucinators. These differences were significant ($p = .02$). As expected, GFS increased during stimulation in controls ($p = .08$) and non-hallucinating patients ($p = .06$), which was significant when combining the two groups ($p = .01$). In contrast, GFS decreased with stimulation in hallucinating patients ($p = 0.13$), resulting in a significantly different GFS response when comparing subjects with and without AVH ($p < .01$). Our data suggests that normally, 40 Hz stimulation leads to the activation of a synchronized network representing the sensory input, but in hallucinating patients, the same stimulation partly disrupts ongoing activity in this network.

1. Introduction

About 70% of patients with schizophrenia patients have auditory verbal hallucinations (AVH); these voices often comment on inner aspects of the patients' live. In the absence of sensory input, AVH therefore are likely to involve top-down frontal functions (producing context related language), sensory areas (accounting for the compelling realness) and automatic perceptual processes making the voices immediately recognizable. The currently most accepted hypothesis on the biological mechanisms of AVH is thus that during inner speech, there is an abnormal co-activation of sensory and perceptual systems leading to a faulty misattribution of inner-psychic processes to external sources (Allen et al., 2008).

Research on the neurobiology of AVH has therefore emphasized a network perspective, trying to understand the unitary quality of AVH across multiple perceptual and cognitive domains as dysfunctional interactions among the involved functions and regions. AVHs correlate with reduced cortical gray matter in the left temporal lobe (e.g. Flaum et al., 1995; Gaser et al., 2004), and Heschl's gyrus (e.g. Gaser et al., 2004; Sumich et al., 2005; Hubl et al., 2010), whereas neuronal activity in similar regions seemed to be increased during the acute experience of hallucinations (e.g. Dierks et al., 1999; Hubl et al., 2007). Accordingly, inhibitory transcranial magnetic stimulation of the left temporal cortex diminished AVH (Jandl et al., 2006; Horacek et al., 2007). Recent studies investigating white-matter structural connectivity showed increased connectivity between left frontal language-related areas and temporal regions associated with auditory perception (Hubl et al., 2007; Shergill et al., 2007). Allen (Allen et al., 2008) therefore suggested a model in which an imbalance of bottom-up and top-down processes terminates in these erroneous perceptions.

Independent of schizophrenia, the issue of how information distributed across multiple cognitive–perceptual modules is transiently assembled into a unitary mental representation (the so called binding problem) has received widespread attention. The current hypothesis is that binding occurs when the different modules synchronize in the gamma (~40 Hz) frequency range (Gray and Singer, 1989; Singer and Gray, 1995). Additionally, there is a long-known link between gamma-band activity and auditory processing. When subjects hear sounds that repeat at a certain frequency, EEG spectral amplitude increases at that frequency (Galambos et al., 1981), which is called auditory steady-state response (ASSR). Interestingly, in healthy subjects, the ASSR is strongest in the gamma band around 40 Hz (Galambos et al., 1981) and has been localized to the auditory cortices (Pantev et al., 1991), and is strongly reduced when consciousness is lost (Plourde et al., 2008).

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The relation of gamma-band activity, auditory processing, and AVH in schizophrenia is thus interesting. However, only a few studies have specifically related gamma band activity to AVH. Spencer (Spencer et al., 2009) reported that the phase-locking of gamma-band steady-state responses in the left superior temporal lobe correlated positively with AVH, and Mulert et al., 2011, found that during 40 Hz stimulation, lagged coherence between left and right primary auditory cortices increased with the severity of AVH. Ford (Ford and Mathalon, 2005) however failed to find an association of gamma-band coherence during auditory–verbal integration and AVH.

The current study further investigated the relation of the 40 Hz steady state response and AVH. The novelty of the present study lays in the method to quantify synchronization. In previous studies, synchronization has either been defined as the stability of the relation between stimulus onset and EEG phase (e.g. Spencer et al., 2009; Uhlhaas and Singer, 2010) or as coherence with a 90° phase lag, avoiding problems of volume conduction (Mulert et al., 2011). Conceptually, binding is however assumed to occur thru simultaneous, non-lagged oscillations of different regions (Gray and Singer, 1989; Singer and Gray, 1995; Koenig et al., 2005b). This is neither assessed when investigating phase-locking to a stimulus, nor by lagged coherence, which explicitly discards simultaneous oscillations. We have thus proposed a method called *global field synchronization* (GFS) that estimates the amount of phase-locking among all active regions at a given frequency.

Under the hypotheses that AVH arise from an excessive coactivation of internal mental representations with sensory systems, and that co-activation of remote, but functionally related brain regions is mediated by phase-locking of gamma-band activity, we expected that gamma-band GFS during auditory driving would show deviations that are selective to patients prone to AVH in contrast to patients that do not experience AVH and to healthy controls. To provide links to the existing literature, we also analyzed EEG scalp spectral amplitude maps and estimates of spectral amplitudes in regions of interest.

2. Methods

2.1. Subjects

Healthy controls (C; n = 26, 17 females, mean age 34.9), patients with schizophrenia and AVH (H; n = 18, 9 females, mean age 40.8), and patients with schizophrenia without AVH (N; n = 11, 3 females, mean age 36.9) were investigated. All subjects were right-handed (based on the Edinburgh Handedness Inventory (Oldfield, 1971)), reported normal hearing, and showed normal binaural auditory thresholds. Only subjects without relevant medical disorders (except for their psychiatric diagnosis) were included, based on their medical history and medical and neurological examination. All patients met the F20 criteria of the ICD10.

Patients were carefully assigned to group H or N. Patient group H was defined by hearing voices at least 4 times/week for the last 4 weeks and perceiving AVH in every of their acute exacerbation of schizophrenia, but not necessarily during the time of measurement. Patient group N was defined by the absence of any report of AVH, neither at time of investigation nor in any of their prior episodes. Symptoms were assessed in extensive (partly semistructured) interviews with a special focus on the perception of AVH. Patients' records and interviews of third parties (nurses, relatives, etc.) on the medical history were evaluated, too.

PANSS (Kay et al., 1987) and CGI (NIH, 1970) were used to assess psychopathologic symptoms severity. Hallucinations were rated using the Oulis Auditory Hallucinations Rating Scale (Oulis et al., 1995) that measures 25 clinical characteristics of auditory hallucinations based on observer ratings. The character of the hallucinations fulfilled the criteria of the Schneiderian first-rank symptoms of voices referring to the patient in the second or third person or in the form of a commentary.

None of the participants reported substance abuse at least 4 weeks before the investigation except sporadic cannabis consumption. Medication was assessed and compared with CPZ equivalents (Kroken et al., 2009, see also Supplementary Table 1). Duration of the disorder and date of the first episode were also evaluated.

The investigation was conducted in accordance with the Declaration of Helsinki and approved by the Cantons Ethics Committee. All subjects gave their prior written informed consent.

2.2. Experimental setup and EEG recording

The experiment was conducted within 24 h after the psychopathological assessment. 74 silver/silver chloride electrodes were placed at the subject's head at standard positions of the extended 10–20 system. Impedances were kept below 10 kΩ. For artifact monitoring, 2 additional electrodes were placed below each eye. Cz served as recording reference. The subject was comfortably seated in an electrically and sound-shielded recording chamber.

Auditory stimulation consisted of trains of 1 ms rectangular pulses given at a rate of 20, 30 and 40 Hz. Trains were presented thru a loudspeaker set to 84 dB. Each train lasted 500 ms, followed by 700 ms of silence. For each frequency, 150 trains were presented, resulting in a 3 min block for each frequency. The sequence of blocks (20, 30 and 40 Hz) was randomized across subjects. Subjects were instructed to close their eyes, sit still and pay no special attention to the tones. During the experiment, the EEG was continuously digitized (512 Hz sampling rate, 0.3–70 Hz bandpass) and stored using a BrainScope EEG system (M&I, Prague). The entire recording lasted about 10 min.

2.3. Data preprocessing

All EEG data was submitted to an ICA-based correction of eye-movements (Delorme et al., 2007), recomputed to average reference, and periods with remaining artifacts were eliminated by visual inspection. Channels containing excessive artifacts were interpolated (Perrin et al., 1989). The recordings were segmented into 500 ms epochs (256 datapoints) immediately preceding (silent condition) or following the onset of the auditory stimulation (stimulation condition). All epochs were frequency transformed (FFT, 2 Hz resolution), retaining the complex values.

2.4. Feature extraction

The EEG analysis quantified mean spectral amplitudes on the scalp and in pre-determined intracerebral regions of interest (ROIs), and the amount of phase-locking across channels as function of group and condition. All analyses were limited to the frequency of stimulation. Mean spectral amplitude maps were obtained by averaging the absolute values of the FFT transformed EEG across all segments of a condition and subject. Global EEG spectral amplitude was defined as the norm (across channels) of these spectral amplitude maps. Intracerebral spectral amplitude was estimated using the sLORETA software (Pascual-Marqui, 2002) that was based on a boundary elements head model derived from the MNI152 template, and an initial set of 6239 voxels of $5 \times 5 \times 5$ mm size that covered all cortical gray matter. The LORETA analysis was limited to ROIs derived from selected Brodman areas, whose coordinates were converted from Talairach to MNI space. These regions were: left and right Heschl's gyrus (BA41 and BA42), left and right superior temporal gyrus (BA22), left and right angular gyrus (BA 39), left and right interior frontal gyrus (BA44 and BA45), and bilateral anterior cingulum (BA32). For each ROI, condition and subject, mean spectral amplitude was computed across voxels and segments.

For the analysis of phase-locking, we used the global field synchronization (GFS) measure, which is a global frequency domain index of