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Fluctuation of gamma-band phase synchronization within the auditory cortex in schizophrenia

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Abstract

Objective—To study the phase stability of the 40 Hz auditory steady-state response (ASSR) in Sz, and in addition, to investigate inter-hemispheric phase synchronization using ipsilateral and contralateral hemisphere gamma band ASSRs.

Methods—Whole head magnetoencephalography (MEG) was used to detect ASSR from both hemispheres in Sz patients and their control counterparts. Source localization, spatial and temporal filtering were performed to infer gamma band activity from the neural generators of the ASSR. The response gamma band phase stability relative to a reference signal was quantified using the phase synchronization index (PSI).

Results—Results indicated reduced phase synchronization of the ASSR and the stimulus reference signal in Sz patients compared to control subjects, in addition to reduced inter-hemispheric phase synchronization between contralateral and ipsilateral hemispheric responses in Sz patients.

Conclusions—Greater intra and inter hemispheric fluctuations of ASSR gamma band phase synchronization in Sz add to previous studies suggesting timing deficiencies within neural populations, possibly caused by impairments of neural network parameters.

Significance—This study provides experimental support that may aid in understanding the dynamics of neural phase synchrony caused by modifications of underlying neurotransmitter systems, as reflected in disease states such as schizophrenia.

Keywords

Magnetoencephalography; Gamma; Auditory evoked response; Steady state response; Synchronization; Complexity

1. Introduction

The human brain is an interconnected network composed of more than 100 billion neurons (Kandel, 2000). As such, methodologies based on the studies of complex systems may be beneficial in quantifying particular dynamical aspects, specifically synchronization, of the underlying neural assemblies. Phase synchronization amongst elements within an ensemble have long attracted researchers from diverse fields (Kuramoto, 1984; Winfree, 2001; Kori et

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al., 2008). Several models describing dynamical features of large populations of coupled limit cycle oscillators have been proposed (Kuramoto, 1984; Strogatz, 2000; Pikovsky et al., 2000), among which neural oscillators can be seen as a special example (Tass, 1997; Rosenblum et al., 2001; Netoff et al., 2005; Tsubo et al., 2007).

At a macroscopic level, the interplay of inhibitory and excitatory neural network configurations may lead to synchronized groups of neurons oscillating at a common frequency. One early example of such a large scale synchronization was the EEG detection of the spontaneous generation of 'idling' alpha rhythms in the occipital cortex during an eyes closed resting condition (Robinson et al., 2001). Experimental manipulation of these rhythms is difficult, given that these oscillatory rhythms are unstable in the sense that their spatiotemporal patterns vary throughout recording and occur only during resting conditions. However, one experimental method which can be used to study neural phase synchronization within a particular cortical area is via sensory stimulation at their respective neural network resonance frequencies. For the somatosensory, visual and auditory cortices these resonant frequencies are at approximately 24 Hz, 8 Hz and 40 Hz, respectively (Galambos et al., 1981). Although these resonances occur at other frequencies, the spectral peak is usually around the said frequencies in the normal human adult brain. For the primary auditory cortex, maximal phase synchronization of the neuronal population, the ASSR, occurs approximately 200–300 ms after stimulus onset and continues for the duration of the driving stimulus (Ross et al., 2000).

Neural networks can display synchronized oscillatory behavior under particular biophysical parameters (Crook et al., 1997) and network configurations (Kopell et al., 2000; Kopell and Ermentrout, 2004). As these parameters are varied, the network dynamical state, which includes its synchronized state, also varies (Rodriguez et al., 2004; Roopun et al., 2008; Stiefel et al., 2008; Basar and Guntekin, 2008). As an example, the 40 Hz ASSR can be modulated depending on the overall macroscopic state of its network, e.g., there is an increase in its amplitude upon increasing levels of arousal (Griskova et al., 2007) and a decrease during drowsiness (Picton et al., 2003). In addition, a correlation has been shown between the ASSR amplitude and neural maturation (Rojas et al., 2006). In Sz, studies indicate impairment in some of these biophysical parameters, such as glutamatergic excitatory NMDA receptors (Phillips and Silverstein, 2003; Roopun et al., 2008) and GABAergic inhibitory receptors (Benes and Berretta, 2001; Lewis et al., 2005), which as mentioned above, are involved in neural network function and regulation. Based on these findings of impaired biophysical parameters in Sz and their role in synchronization, in this paper, we hypothesize that Sz patients will display disruptions in the ability of the auditory cortex neural networks to maintain a synchronized state. This disruption will be reflected as disturbances of the 40 Hz ASSR relative phase, during the course of external stimulation.

Previous studies have supported the idea of timing dysregulation related to information processing, and consequent cognitive dysfunction, within varied regions of the Sz brain (Braff, 1993; Cadenhead et al., 1997; Wiser et al., 1998; Andreasen, 1999; Tononi and Edelman, 2000; Bob et al., 2008; Carroll et al., 2008). These functional deficits also include abnormalities within the gamma band in Sz (Lee et al., 2003; Hong et al., 2004; Roach and Mathalon, 2008; Ferrarelli et al., 2008), and in particular, several authors all noted reduced ASSR amplitude, power and inter-trial phase locking value (Kwon et al., 1999; Light et al., 2006; Teale et al., 2008; Spencer et al., 2008). Kwon et al. (1999) showed reduced EEG evoked gamma band power from a 40 Hz click train stimulus, in addition to an increased phase delay in the Sz group during stimulation. In Kwon's study, phase delay was calculated by a time difference comparison of the ASSR maximas to the presentation of the corresponding click. Light et al. (2006) verified Kwon's reduced EEG evoked gamma band power finding, while demonstrating reduced inter-trial phase locking in Sz. Inter-trial phase locking is a measure of the variation of the signal phase angles at a particular time point across trials. This analysis is

performed in order to demonstrate inter-trial phase synchronization deficits and is different from the phase measure in the Kwon study, which measured phase delay with regards to the stimulus reference signal. The MEG gamma band ASSR study by Teale et al. (2008) examined signals from the ASSR localized neural sources from both hemispheres due to monaural auditory stimulation. That study reported reduced gamma band evoked strength and inter-trial phase locking in both hemispheres. Spencer et al. (2008) showed that reduced EEG evoked gamma power and inter-trial phase locking is also present in first episode Sz patients. Their study also included hemispheric effects which demonstrated more pronounced decreases of inter-trial phase locking in the left hemisphere for the first episode Sz group. The current study, while presenting an analysis of previously published data by Teale et al. (2008), contributes additionally by investigating fluctuations of the gamma band auditory steady-state phase response with the stimulus reference signal between the Sz group and controls. Distinct to the Teale et al. (2008), Light et al. (2006) and Spencer et al. (2008) inter-trial phase-locking studies, here ASSR phase synchronization is examined and quantified using a reference 40 Hz signal and by doing so one can measure, on average, the ability of the underlying circuits to maintain a synchronized phase response with respect to the driving stimuli. Note that a 40 Hz reference signal was created since the stimulus pure tone is only modulated at 40 Hz and does not contain any power at this frequency. This viewpoint of examining the ASSR phase relative to the driving stimulus (relative phase) is somewhat similar to Kwon et al. (1999), but while this study slightly differs on imaging modality and stimulus type, it also includes source localization and subsequent spatial filtering; investigation of stability between contralateral and ipsilateral hemispheric phase synchrony; and also the use of circular statistics to quantify phase synchronization variability of the ASSR.

Various measures exist which can be used to calculate the relationship between the driving stimulus and the ASSR. For reviews and comparison of different measures see (Quiroga et al., 2002; Kreuz et al., 2007) for quantifying the interdependency of two signals. These measures include quantification of linear interdependency, such as coherence and cross-correlation (Robinson, 2003); nonparametric statistical tests (Maris et al., 2007); nonlinear measures based on trajectories within phase space topologies (Stam et al., 2003); information based statistics such as mutual information (Pereda et al., 2005), informational coherence (Klinkner et al., 2005; Shalizi et al., 2006) and entropy (Tass et al., 1998); and phase relationships as derived from various time-frequency transformations (Lachaux et al., 1999; Pikovsky et al., 2000; Rosenblum et al., 2001; Le Van Quyen et al., 2001). In this study we quantify stability of the relative phase over the duration of the ASSR based on a circular statistics measure, called the mean resultant length (Fisher, 1995). This measure has also been used as to quantify phase synchronization between two signals (Allefeld and Kurths, 2004), by calculating the mean resultant length of the phase differences distribution. It was referred to in previous literature as the phase synchronization index (Quiroga et al., 2002; Costa et al., 2006; Bob et al., 2008) and also by the *mean phase coherence of an angular distribution* (Mormann et al., 2000). The phase synchronization index (PSI) terminology will be used in this paper.

2. Methods

2.1. Subjects

MEG recordings were obtained from 15 schizophrenics and 15 age-matched control subjects. In the schizophrenic group: mean duration of illness was 12.6 ± 7.6 years, 13 were male with a mean age of 37.9 ± 9.3 years. In the control group: 12 were male with a mean age of 34.8 ± 8.0 years. Age was not significantly different between groups. Diagnosis for both groups were obtained using a combination of information from medical records and the use of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995). Two of the control subjects and two of the patients were primarily left-handed as determined by the Annett Handedness Scale

(Annett, 1985). Following a full explanation of the experimental procedures, written informed consent was obtained from all subjects in accordance with the guidelines of the Colorado Multiple Institutional Review Board.

2.2. Stimuli

Magnetic field data were recorded using an array of 248 axial gradiometers (Magnes 3600 WH Biomagnetometer, 4-D Neuroimaging, San Diego), see Fig. 1. Subjects were seated in a supine position and watched a silent movie for consistency of alertness and attention during recording. An auditory stimulus consisting of a 40 Hz modulated (100% modulation) 1 kHz sine wave with a duration of 500 ms was presented to each ear on separate runs (Fig. 2a). Approximately 200 trials of data were recorded for each ear with an interstimulus interval of 3.5 sec. Each epoch was 800 ms with a 200 ms baseline, sampled at a frequency of 678.17 Hz. The initial bandwidth at acquisition was .1 to 200 Hz.

2.3. Data Analysis

Artifact free epochs were selected for each subject and subjected to a band pass Butterworth filter (4th order, forward and backward filter), from 35 to 45 Hz. Bad channels were excluded from all analyses, and trials were rejected based on peak to peak amplitude values within a defined time segment. The mean number of artifact free trials used in the control group was 203 ± 6 (mean $\pm$ 95% C.I.) trials, whereas 186 ± 15 trials were used in the patient group analysis. The number of artifact free trials used in the analysis did not significantly differ between groups. A single moving equivalent current dipole source model was applied across each subject averaged band passed filtered data during the steady-state window (250–500 ms after stimulus onset) for each hemisphere. Dipole fits in each hemisphere were computed using 37 channels clustered around the midpoint of a line connecting those channels with the minimum and maximum field amplitudes. Best fit sphere center coordinates were determined by fitting a sphere to the projection of these same 37 channels to the digitized head shape surface. The single source dipole localization was performed for each time point during the steady-state interval. Only dipoles with certain spatial and goodness-of-fit criteria (> 0.9) were chosen. For each hemisphere, the parameters of these best fitting equivalent current dipoles were averaged to obtain a statistical estimate of the ASSR dipole parameters. The average contralateral dipole coordinates (mm) in the MNI system for all subjects were: $-40, -29, 6$ for the left hemisphere; and $40, -32, 7$ for the right hemisphere, see Teale et al. (2008) for an illustration of the localized results. Each subject dipoles, one for each hemisphere, was then chosen as the neural source estimate for subsequent spatial filtering of the raw temporally unfiltered, unaveraged data, for a detailed description of the spatial filtering, see (Ross et al., 2000; Teale et al., 2008). The spatial filtering results produce an estimate of source strength for each individual subject from the contralateral and ipsilateral hemisphere responses as a function of time for each epoch. These epochs were then averaged (Fig. 2b) and subsequently convolved with a Morlet wavelet centered at 40 Hz to produce a gamma band spectral estimate of the data (Fig. 2c). A wave number of 6 was used for the wavelet, generating a 6.67 Hz standard deviation bandwidth at the 40 Hz resolution scale, in accordance with the time-frequency uncertainty principle (Mallat, 1989; Samar et al., 1995; Tallon-Baudry et al., 1996). The wavelet analysis produces a single point estimate of the signal's phase and amplitude at each time point. Fig. 3 shows the ASSR instantaneous phase plotted as a function of the reference signal phase.

The relative phase, $\phi_{n,m}(t) = (n\phi_s(t) - m\phi_r(t)) \bmod 2\pi$, where $\phi_s(t)$, $\phi_r(t)$ are the phases of the ASSR and reference signal respectively, was then calculated for the contralateral and ipsilateral hemisphere responses separately. In this study, a 1:1 frequency locking between the ASSR and reference signals are examined, therefore $n = m = 1$. The PSI, γ , is defined as:

$$\gamma \equiv \left| \left\langle e^{i\phi(t)} \right\rangle_t \right|$$

where the brackets denote the expected value (in this case, an average over time). This value measures 1 minus the (circular) variance of an angular distribution (Fisher, 1995). A small circular variance value (and hence large PSI, on the scale of [0,1]) would imply that the distribution of ϕ during the steady-state response was tightly clustered around some particular angle. If ϕ was not stable, meaning that the ASSR phase was not tightly locked to the reference phase but fluctuating, then one would expect the angular distribution to be broad implying a lowered PSI.

The PSI values were then subject to a type III sum of squares mixed design 2×2×2 ANOVA where the factors (levels) were diagnosis (control, Sz) by hemisphere (ipsilateral, contralateral) by ear of stimulus presentation (left, right), with the latter 2 factors being the repeated measures. Statistical analyses were conducted using the SPSS Statistics Package (SPSS, Inc). All null hypothesis significance testing was two-tailed and conducted at .05 alpha. All other analyses were performed using author written algorithms in Matlab (Mathworks Inc., Natick, Mass).

In addition to using the reference signal, phase synchronization between the ipsilateral and contralateral ASSRs were also calculated. The procedure followed exactly as above, with the relative phase now defined as, $\phi(t) = (\phi_{contra}(t) - \phi_{ipsil}(t)) \bmod 2\pi$, where $\phi_{contra}(t)$ and $\phi_{ipsil}(t)$ are the contralateral and ipsilateral hemisphere ASSR phase angles, respectively. Accordingly, the PSI values were then subject to a 2×2 mixed design ANOVA with diagnosis and ear of stimulation as the factors.

3. Results

Due to poor data quality (environment noise dominated data, with no measurable gamma band neural response), one control subject was excluded from all subsequent analysis. A histogram of $\phi(t)$ is shown in Fig. 4. The relative phase results from both reference types are shown, i.e., using the generated 40 Hz reference signal, and also the contralateral response as the reference for the ipsilateral hemisphere response.

Using the 40 Hz signal as the reference for the PSI calculation, there was a highly significant main effect of hemisphere on PSI values, $F(1, 27) = 24.05, p < .005$, indicating greater PSI in the contralateral hemisphere, with a mean(SE) PSI marginalized across diagnosis and ear of presentation, of .963(.007), compared to the ipsilateral (left) hemisphere, mean PSI = .858(.021). There was also a significant main effect of diagnosis, $F(1, 27) = 7.67, p < .05$, suggesting a reduced PSI in the Sz group, mean = .880(.015), compared to the control group, mean = .940(.016). All interaction effects were non-significant. Examining the ASSR phase synchronization between the contralateral and ipsilateral hemispheres, there was a significant effect of diagnosis on PSI, $F(1, 27) = 4.57, p < .05$, suggesting decreased PSI in the Sz group, mean = .770(.032), compared to the control group, mean = .870(.034). The diagnosis by ear of stimulus presentation interaction effect was non-significant.

4. Discussion

The purpose of this study was to investigate both intra and inter hemispheric ASSR phase stability in patients with schizophrenia. It was hypothesized that schizophrenic patients will display greater fluctuations of the ASSR phase leading to increased circular variance of the relative phase distribution, as compared to their control counterparts. Using the 40 Hz reference signal, greater fluctuations of the ASSR phase, as quantified by a reduced PSI, was found in

the Sz group. In addition, Sz patients also demonstrated reduced phase synchronization between contralateral and ipsilateral hemisphere responses during auditory stimulation. These findings support the conclusions in the Kwon et al. (1999) study of abnormalities in the entrainment of gamma-band oscillations in the auditory cortex of schizophrenics.

A reduction in 40 Hz evoked response strength with a simultaneous increase of activity at a different frequency, in particular, at 20 Hz has been demonstrated (Vierling-Claassen et al., 2008). One assumption made in the current study is that in both groups the auditory steady-state neural generators respond to the stimulus at the same dominant frequency, around 40 Hz. It is important to check this assumption because a constant rate of change of the relative phase during the ASSR window, i.e. a response at a different frequency from the driving stimulus, can produce a larger variance in the angular distribution of the relative phases, based on the defined $n = m = 1$ frequency locking used in the calculations. Therefore, to identify any potentially different response frequencies between groups, hence a possible bias to the relative phase angular distributions, a linear regression model was generated to test for slope differences in the relative phases during the ASSR interval between groups. Results indicated that the effect size, R^2 , of the group regression slopes were extremely small in all stimuli cases, indicating that the same dominant frequency response was observed in both groups and therefore was not a factor contributing to the observed relative phase distribution differences.

Another factor which could affect the PSI calculation is the neural response phase angle estimation in the situation of low signal to noise ratio (Dobie and Wilson, 1993, 1994). As discussed below, ASSR amplitude reductions have been found in Sz populations (Kwon et al., 1999; Teale et al., 2008; Spencer et al., 2008). While the PSI calculation is amplitude independent, it is still important to check whether the SNR in the Sz ASSR are sufficiently high for accurate phase angle estimation. Simulations were therefore performed to determine the SNR required for accurate phase estimation in the current study. These levels were then compared with the Sz group SNR for the ASSR contralateral and ipsilateral hemisphere responses. The simulation consisted of generating a 40 Hz signal with known phase embedded in white noise at various amplitudes, thus generating varying signal to noise levels. This mixed signal was filtered using the exact same temporal filter used in the current study and accuracy of the resulting estimated phase was determined using the PSI, by comparison with the known original 40 Hz signal phase. For each SNR, 5000 realizations of white noise were generated whose resulting PSI values were then averaged. The simulations indicate 99% accurate phase estimation at $\text{SNR} \geq 1$. Examining 40 Hz ASSR from left and right ear stimuli and from both hemispheres, the minimum Sz group mean SNR was 1.9 for the left hemisphere ipsilateral response. Therefore, based on this value, lowered Sz SNR levels does not appear to be a contributing factor for the decreased PSI values in the Sz patients.

Previous group studies have found reduced ASSR amplitudes in Sz populations compared to controls (Kwon et al., 1999; Teale et al., 2008; Spencer et al., 2008). A recent study by Teale et al. (2008) suggested that this reduction in the averaged-data amplitude may partially be explained by a lack of strict inter-trial timing to the stimulus. Possibly related to this idea of inter-trial response timing inconsistency, is the idea of a reduction in the synchronization of the neural population generating the ASSR. MEG does not have the sensitivity to measure magnetic fields from individual cells and can only detect activity from synchronized pyramidal neurons (Hamalainen et al., 1993). Therefore, a reduction in neural synchronization within the neuronal ensemble can lead to a reduction in detected mean field strengths and consequently equivalent current dipole amplitude estimates. Realistic modeling of neural networks have shown the role of biophysical parameters in the nature and degree of neural synchronization (Crook et al., 1997; Kopell and Ermentrout, 2004; Vierling-Claassen et al., 2008) and their phase interactions with stimuli (Galan et al., 2005; Gutkin et al., 2005). Certain aforementioned biophysical parameters, such as axonal delay, can be modulated by GABAergic inhibitory

interneurons, such as chandelier cells (Lewis et al., 2005). Using postmortem tissue samples, Pierri et al. (1999) demonstrated reduced densities of chandelier neurons axon terminals in the dorsolateral prefrontal cortex in the schizophrenic brain. Konopaske et al. (2006) also performed a similar tissue examination in the auditory association cortex, but found a non-significant reduction in density. As Konopaske et al. (2006) mentions, this finding in schizophrenia could have been partially masked by an increased volume reduction in gray matter around that region, thus affecting the density measurement. More relevant to the anatomical area studied here, Sweet et al. (2007) found reduced pyramidal axon terminal densities in feedforward pathways in the primary auditory cortex. In addition, they also found a reduction in dendritic spine density in both primary and secondary auditory cortices (Sweet et al., 2009). This decreased anatomical density combined with their functional role supports the hypothesis of reduced gamma band phase synchronization during the ASSR paradigm within auditory cortex ensembles in Sz, as suggested in this study.

In future work, the equivalent current dipole source model may then serve as an effective order parameter, with appropriate spatial filtering, which may be useful to quantify the degree of local synchronized neural states. Drug manipulations acting on various neurotransmitter system may then serve as a useful variable, within paradigms incorporating neural network resonances, to examine synchronization disruptions within local neural populations of the schizophrenic brain.

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Figure 1.

Above figure shows a typical subject averaged MEG data from all 248 sensors as a function of time (stimulus onset, ms). Auditory stimulus was delivered to the left ear. Below figure shows a contour plot of the waveform topography at 400 ms. The open-circle nodes represent the MEG sensors positions, which have been projected onto a 2-D map. Positive x and y axes point toward the right ear and nose, respectively. The MEG sensors clearly detect the neural responses from the contralateral and ipsilateral hemispheres.

Figure 2.

Data from a representative subject. (a) Plot of the 40 Hz amplitude modulated 1 kHz auditory tone as a function of time (msec). (b) Subject averaged (≈ 180 trials) source strength (nA-m) as a function of stimulus onset (msec). Localization followed by spatial filtering was performed, in order to calculate the auditory neural response source strength. The auditory M100 evoked field is clearly visible around 80 – 100 msec, followed by the auditory steady-state response (ASSR). (c) Wavelet (temporal) filtering of (b) around 40 Hz provides a point estimate of the response amplitude and phase as a function of time (shown in blue). A 40 Hz reference signal (thin black line) is overlaid during a segment, denoted between the red dashed lines, of the ASSR. Fluctuation of the ASSR phase during the denoted segment was calculated by comparison with the reference signal phase, see Fig. 3 for a plot of all subjects response phases as a function of the reference phases.

Figure 3.

Phase state plot of ASSR phase (radians), ϕ_s , with respect to the reference phase, ϕ_r during the steady-state interval from 300–500 msec. The black + and red o, are responses from the contralateral and ipsilateral hemispheres, respectively. The left (a,c) and right (b,d) columns are responses from left and right ear stimulation, respectively. The upper (a,b) and lower rows (c,d) are responses from all subjects within the control and Sz groups, respectively. From this raw data, an increased variability of the ipsilateral response phase with respect to the reference phase can be observed. A diagonal line would imply perfect phase synchrony. An index of phase synchronization was used to quantify this ASSR phase variability with the reference phase.

Figure 4.

Distribution of the zero-mean ASSR relative phase, $\phi_m(t)$. For visualization purposes, the mean relative phase within the ASSR interval was subtracted from $\phi(t)$. Y-axes normalized by total number of phases within respective sample, N_t ; bins widths were 0.1 radians for figure. Blue and red lines denote control and Sz groups respectively. Solid and dashed lines denote contralateral and ipsilateral hemispheric responses respectively. The figures within the left (a,c) and right (b,d) columns are derived from left and right ear stimulation, respectively. Relative phase values in figures (a),(b) were derived when the stimulus was used as the reference signal, whereas in figures (c),(d) the relative phase was computed as the difference between the phases from the contralateral and ipsilateral responses. A statistical measure of the circular variance of these distributions is the PSI, where a larger variance (lower PSI) represents greater fluctuation of the auditory steady-state phase response with respect to perfect synchrony.