Published in final edited form as:

Neuroimage. 2009 October 1; 47(4): 1711–1719. doi:10.1016/j.neuroimage.2009.03.085.

Steady State and Induced Auditory Gamma Deficits in Schizophrenia

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Abstract

Steady state auditory evoked potential (SSAEPs) in the electroencephalogram (EEG) and magnetoencephalogram (MEG) have been reported to be reduced in schizophrenia, most consistently to frequencies in the gamma range (40 Hz and greater). The current study evaluated the specificity of this deficit over a broad range of stimulus frequencies and harmonics, the relationship between phase locking and signal power, and whether induced 40 Hz activity was also affected. SSAEPs to amplitude modulated tones from 5 to 50 Hz were obtained from subjects with schizophrenia (SZ) and healthy control subjects in 5 Hz steps. Time-frequency spectral analysis was used to differentiate EEG activity synchronized in phase across trials using Phase Locking Factor (PLF) and Mean Power (MP) change from baseline activity. In the SSAEP frequency response condition, patients with SZ showed broad band reductions in both PLF and MP. In addition, the control subjects showed a more pronounced increase in PLF with increases in power compared to SZ subjects. A noise pulse embedded in 40 Hz stimuli resulted in a transient reduction of PLF and MP at 40 Hz in control subjects, while SZ showed diminished overall PLF. Finally, induced gamma (around 40 Hz) response to unmodulated tone stimuli was also reduced in SZ, indicating that disturbances in this oscillatory activity are not confined to SSAEPs. In summary, SZ subjects show impaired oscillatory responses in the gamma range across a wide variety of experimental conditions. Reduction of PLF along with reduced MP may reflect abnormalities in the auditory cortical circuits, such as a reduction in pyramidal cell volume, spine density and alterations in GABAergic neurons.

Background

The electroencephalogram (EEG) and magnetoencephalogram (MEG) entrain to the frequency and phase of a repetitive auditory stimulus such as a series of clicks or amplitude modulated (AM) tones. This entrained activity is usually referred to as the steady state auditory evoked potential (SSAEP). The SSAEP, at least for frequencies below 50 Hz, is most likely generated by primary auditory cortex (Pastor et al., 2002; Picton et al., 2003). Over the last decade, a series of studies has used the SSAEP to assess auditory processing in schizophrenia (SZ) and have shown that the SSAEP is reduced in schizophrenia, most consistently in the 40 to 50 Hz range. Specifically, SSAEP studies in schizophrenia show reduction in power of the averaged

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SSAEP or Phase Locking Factor (PLF) across trials for the 40 Hz response to 40 Hz stimulation for both EEG (Kwon et al., 1999; Brenner et al. 2003; Light et al., 2007; Spencer et al., 2008a; Vierling-Claassen et al., 2008) and MEG recordings (Teale et al. 2008). While most studies have assessed chronic patients, the 40 Hz deficit has also been reported in first episode schizophrenia subjects (Spencer et al., 2008a). Analysis of topography and source analysis suggests that the deficit may be more pronounced for left hemisphere generators of the SSAEP (Spencer et al., 2008a; Teale et al., 2008). The 40 Hz harmonics of 20 Hz stimulation and the 20 Hz sub-harmonic to 40 Hz may also be affected (Spencer et al., 2008a; Vierling-Claassen et al., 2008). Hong et al. (2004) did not find a reduction in 40 Hz power in SZ subjects treated with atypical antipsychotics, but did demonstrate a 40 Hz deficit in first degree relatives, suggesting that this deficit may occur in populations with elevated genetic risk for schizophrenia. On the other hand, Brenner et al. (2003) reported that the 40 Hz SSAEP was unaffected in Schizotypal Personality Disorder, which is usually included in the schizophrenia spectrum. In summary, these data suggest that the 40 Hz SSAEP is usually reduced in SZ and first degree relatives, possibly indicative of a more general deficit in the generation of neural oscillations at gamma frequencies in the early auditory pathways or auditory cortex (Kwon et al., 1999). This deficit may be secondary to alterations of GABAergic inhibitory modulation within cortical circuits. GABAergic inhibitory interneurons appear to be important in producing gamma synchronization in local circuits, and can modulate firing rates of projection neurons (Whittington et al., 2000; Vierling-Claassen et al., 2008). In schizophrenia, GABAergic function may be disrupted by loss of GABAergic cells (Benes, 2000) or disturbed modulation by *N*-methyl-D-aspartate (NMDA) receptors (McCarley et al., 1999).

Several methodological issues limit the interpretation of the specificity of this deficit to 40 Hz stimulation. While past studies suggest selective reduction to 40 Hz stimulation, most studies have measured responses from relatively few frequencies (20, 30 and 40 Hz). It is therefore possible that a broader survey of the stimulus frequencies may detect other frequency specific deficits. Second, most previous studies have used click stimuli, which have a more complex frequency composition than amplitude modulated tones. Amplitude modulated tones have power only at the carrier frequency and two side bands, while click stimuli have power at several harmonics. Brenner et al. (2003) used amplitude modulated tones across a broad range of frequencies and found that the group of patients with schizophrenia or schizoaffective disorder exhibited SSAEP deficits which extended to frequencies lower than the gamma range (≤ 30 Hz). This finding suggests that the specificity of the deficit in SZ may be influenced by stimulus characteristics. In the present study, amplitude modulated tones with frequencies ranging from 5 to 50 Hz with 5 Hz increments were presented to generate a Modulation Transfer Function (MTF) for measures of phase locking and overall power. The MTF is a function of some response measures with stimulus frequency. The MTF is often measured in animal studies for phase synchronization and firing rate of individual neurons or a population of neurons. Measuring MTF in SZ may thus provide possible links with these animal studies.

Previous studies have measured only phase locked activity captured by averaged SSAEPS or the application of the PLF. The mean trial by trial change in EEG power from baseline for different frequencies of stimulation has not been assessed, and this measure of Mean Power (MP) or Event Related Spectral Perturbation (Delorme et al., 2004) can evaluate overall amplitude of the evoked oscillations regardless of phase relationships. Moreover, since PLF is related to signal-to-noise ratio (Infantosi et al., 2006), the reduction in PLF could arise either due to increased inter-trial phase variability or due to reduction of MP. In this study, we evaluated the relationship of PLF to MP. Individual trials for each subject were classified based on MP into four sub-groups (high, medium-high, medium-low and low MP). PLF was measured in each of these power groups and then compared between schizophrenia and control subjects for all stimulation frequencies.

The SSAEP response in healthy adult subjects is largest to 40 Hz stimulation (Galambos et al., 1981; Rees et al., 1986; Ross et al., 2000), the same frequency which is most sensitive to schizophrenia. The SSAEP has been argued to represent the superposition of individual evoked potential responses to individual clicks, and the maximum response at 40 Hz to be due to optimal temporal spacing of individual responses (Galambos et al., 1981). Several findings argue against this hypothesis. First, the 40 Hz response in MEG evolves temporally 200 msec after stimulus onset (Ross et al., 2002) and phase synchronization continues after offset of a stimulus (Kwon et al., 1999; Santarelli et al., 1999). Second, the 40 Hz SSAEP can be disrupted by a brief noise pulse (Ross et al., 2005), and this effect persists longer than the offset of the pulse. Such a prolonged disruption of the 40 Hz oscillation cannot easily be simulated by an optimal spacing model and may indicate an inhibitory process which disrupts ongoing perceptual or binding processes (Ross et al., 2005). In the present study, the noise interruption paradigm developed by Ross and colleagues was used to test the ability of the SSAEP oscillations to recover from interruption by a brief noise pulse in SZ and control subjects. Third, a PET rCBF study (Pastor et al., 2002) demonstrated that activation in auditory cortex is larger to 40 Hz compared to frequencies above or below 40 Hz, and that 40 Hz was the only frequency which concurrently activates the auditory region of the ponto-cerebellum, a structure associated with cortical inhibition and timing. Finally, phase locking of the 40 Hz SSAEP has been reported to be enhanced by selective attention, whereas the 20 Hz SSAEP was not (Skosnik et al., 2007), suggesting differential sensitivity of 40 Hz to attentional modulation. These findings suggest that the 40 Hz SSAEP is in part due to an oscillatory process which can be differentiated from other SSAEP processes in terms of EEG and MEG amplitude, anatomic activation, and involvement in perceptual or attentional processes.

Gamma range activity can also be elicited by unmodulated, sustained auditory stimuli. For example, an unmodulated pure tone generates oscillations at 40 Hz (Ross et al., 2002). The sources of this response appear to differ from SSAEP sources based on source analysis of MEG recordings (Ross et al., 2002). Similar gamma oscillations to pure tones are seen in primate studies with multiunit recordings (Brosch et al., 2002). Using MEG, Teale et al. (2008) reported a reduction in 40 Hz PLF in SZ to brief (500ms) pure tone stimuli. We used this paradigm to test whether EEG gamma oscillations induced by a stimulus were similarly reduced in power in SZ.

In summary, the following hypotheses were tested: 1) SSAEP measures of MP and PLF elicited by amplitude modulated tones would be reduced in schizophrenia, and this reduction would be largest for frequencies of stimulation proximal to 40 Hz; 2) Harmonics and sub-harmonics at 40 Hz would be affected in SZ; 3) The reduction in PLF for schizophrenia will be higher for highest MP group compared to the lower MP groups; 4) Patients with SZ would show slower recovery to interruption of the 40 Hz SSAEP by an embedded noise pulse; 5) Gamma activity induced by an unmodulated tone would also be reduced in SZ. These results would extend previous SSAEP studies by examining the specificity of the 40 Hz deficit to auditory stimuli, evaluate oscillatory characteristics of the response, and test whether the deficit generalized to indicators of induced as well as entrained activity.

Methods

Subjects

Twenty one (8 female) schizophrenia subjects (SZ) and 21 healthy, non-psychiatric control (10 female) subjects participated in this study. The mean age of the SZ group was 42.6 years (SD 10 years) and 40.0 years (SD 11 years) for the control group. Clinical diagnoses were obtained from the SCID I structured interview (First et al, 1997) and chart review using DSM-IV criteria. Subjects with a history of electroconvulsive therapy, neurologic illness, alcohol use in the past 24 hours, visual impairment, or head trauma were excluded. In addition, subjects

with a history of drug or alcohol dependence (based on DSM-IV criteria) were excluded for this study. Finally, all subjects were screened for pure tone hearing threshold and only subjects with a threshold of 30 db SPL or lower were included in the study. While all the SZ subjects were taking atypical antipsychotics, three subjects were also taking haloperidol decanoate injections once every 3 weeks.

Experimental Design

The MTF was obtained using amplitude modulated (AM) tones with a 1000 Hz carrier frequency and modulation frequencies of 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 Hz. The AM tones are defined as follows:

$$S(t) = (1 + m_a \sin(2\pi f_m t)) \sin(2\pi f_c t)$$

where t is time, m_a is modulation depth, and f_m and f_c are modulation and carrier frequencies. The modulation of the carrier frequency was 100% ($m_a = 1$). The tones were one second in duration, the interstimulus interval was 900 ms and 90 trials were presented for each frequency. All stimuli were presented binaurally at 80 db SPL using insert earphones. Subjects were randomly assigned to one of four different orders of stimulus presentation.

In the noise pulse condition, a brief noise pulse was added to the 40 Hz AM tone 500 ms after onset. The 40 Hz AM tone was one second in duration, the interstimulus interval was 1000 ms and 90 trials were presented. Figure 1b shows the stimuli with noise embedded in 40 Hz AM tone. The noise pulse was obtained by filtering a white noise for frequencies below 1500 Hz, in order to prevent overlap with carrier frequency. The amplitude of the noise varied based on a Gaussian function in time with the center of the Gaussian aligned to 500 ms of the 40 Hz AM tone, at a minimum in AM tone with the standard deviation of the Gaussian function of 5 ms. In the induced gamma condition, a 1000 Hz tone with one second duration was presented. The tone was one second in duration, the interstimulus interval was 1000 ms and 90 trials were presented.

In order to control for attentional effects, subjects were asked to perform a visual detection task during the auditory stimulation. The visual detection task involved presenting numbers (0 – 9) in the center of the screen. Subjects were asked to respond to a target number (7) by a button press. The target appeared 10% of the total trials, and each stimulus was presented for 150 ms with a 1000 ms interstimulus interval.

For all conditions, continuous electroencephalographic (EEG) recordings were acquired with a 29-channel cap (10–20 system; Falk Minow Services, Munich, Germany) and sampled at 1000 Hz using SYNAMPS bioamplification system (Neuroscan Inc., El Paso, TX) with a high-pass filter of .1 Hz and low-pass of 100 Hz. Scalp leads were referenced to the nose. Vertical (VEOG) and horizontal eye movements (HEOG) were also recorded. Electrode impedance was maintained below 10 kohm.

Signal Processing and Statistical Analysis

PLF and MP measures—The continuous EEG was segmented based on stimulus type with a baseline of 300 ms and a 1000 ms of the stimulus period. The EEG segments were baseline adjusted by subtracting the average value of EEG sampled 300 ms prior to stimulus presentation from the whole segment. Ocular movement artifact correction was applied using Gratton's algorithm (Gratton et al., 1983) implemented by Vision Analyzer software (Brain Products, GmbH). The trials were then screened for artifacts by rejecting trials in which any sample point exceeded a voltage criterion of $\pm 150 \mu\text{V}$. In order to estimate power and phase across trial with high temporal resolution, a Hilbert transform was used. Before applying the Hilbert transform,

a least square linear-phase FIR filter (using *firls* function in Matlab) was used to filter each trial with a fixed filter order of 250. Individual trials from each stimulating frequency were filtered with a ± 1 Hz bandwidth and center frequencies at the stimulus frequency (f), harmonic ($2*f$) and sub-harmonic ($f/2$) of stimulus frequency. For the 40 Hz stimuli with noise and unmodulated tone stimuli, the trials were filtered at ± 1 Hz centered on 40 Hz (39–41 Hz).

The Phase Locking Factor (PLF) and Mean Power (MP) were estimated from the Hilbert transformed single trials. The PLF is the average of normalized phase across trials for every time point and frequency, and is given as:

$$PLF(f, t) = \frac{1}{K} \left| \sum_{k=1}^K \frac{H_k(f, t)}{|H_k(f, t)|} \right|$$

where f is frequency, t is time, k is trial, K is number of trials and $H(f, t)$ is the complex output of the Hilbert transform at frequency f and time t . The PLF is a Rayleigh test of circular variance which tests for uniformity of phase which was first introduced by Jervis et al. (1983) and has been used in several studies (Tallon-Baudry et al., 1996; Delorme et al., 2004; O'Donnell et al., 2003; Light et al., 2007). The MP was computed by first obtaining power for each trial and time point and then subtracting the mean value of the baseline period (–300 ms to 0 ms) from entire trial duration. The MP provides the measure of change in power during the stimuli compared to the baseline period and is equivalent to Event Related Spectral Perturbation (ERSP) (Delorme et al., 2004). In order to measure the interaction between MP and PLF, PLF was computed in sub-group of trials which varied on MP (Figure 5 illustrates this technique). First, the single trials were sorted based on mean MP value from the period of stimulation. The sorted trials were then divided into four MP groups (High, Mid-High, Mid-Low and Low) each with equal number of trials. Mean PLF values were computed for each category of MP trials.

Modulation Transfer Function (MTF)—The MTF of PLF and MP is the function of these response characteristics across wide range of frequencies. The PLF and MP were estimated for each stimulating frequency to generate the MTF at stimulus, harmonic and sub-harmonic frequencies of interest. Figure 2 shows the scalp distribution of the mean values of these measures over the entire stimulation period across the head. Both the PLF and MP showed a peak power at frontal and central electrodes for all stimulus frequencies. For an overall test of whether the SSAEPs were affected by SZ, a mean of PLF and MP across the whole stimulus period was computed for each stimulus frequency. Because the signal was usually largest at or around fronto-central regions, the following sites were selected for further statistical analysis: Fz, FCz, F3, F4, C3, C4 and Cz. ANOVA with the within subjects factors of channel (7) and stimulus frequency (10) and the between subjects factor of group (2) was used to analyze PLF and MP values in the Modulation Transfer Function condition. Greenhouse-Geisser corrections were used when applicable. Since previous studies (Spencer et al., 2008a; Vierling-Claassen et al., 2008) have shown changes in harmonics and sub-harmonics for 20 and 40 Hz, we compared these responses in a separate one-way ANOVA between groups. A repeated measure ANOVA was used to determine the relationship between MP on PLF between groups for channel Cz. The within subjects factors were MP groups (4: low to high) and stimulus frequency (10), and the between subjects factor of group (2).

Pure tone induced gamma activity and noise pulse effects on gamma activity—

For pure tone stimuli, mean activity at 40 Hz from channel Cz was used for analysis. Average responses (PLF and MP) were computed for every 100 ms period, which were then compared between the groups using repeated measure ANOVA with the within subjects factor of time interval (10) and the between subjects factor of group (2). For noise pulse stimuli, a mean

measure of response before (300–500 msec) and after the noise (600–1000 msec) was computed which was then compared between group (2) by time (2) ANOVA.

Results

Amplitude Modulated Tones

The interpolated scalp topography for the mean PLF and MP values at the frequency of stimulation was most prominent in the fronto-central electrodes for each of the amplitude modulated tones (Figure 2). Figure 3 shows the temporal dynamics of the PLF and MP over the stimulus period for all stimulus frequencies. The diagnostic groups differed for both PLF and MP across frequencies of stimulation. The repeated measure ANOVA on mean PLF over the stimulus period showed significant effects for channel ($F(6,222)=17.59, p<0.001$), stimulus frequency ($F(9,333)=13.28, p<0.001$), group ($F(1,37)=6.36, p=0.02$) and stimulus frequency by channel ($F(54,1998)=6.45, p<0.001$). The ANOVA for MP showed a significant effect for stimulus frequency ($F(9,333)=13.28, p=0.02$) and group ($F(1,37)=3.99, p=0.05$).

Figure 4 shows the PLF and MP for fundamental, harmonic and sub-harmonic frequencies from channel Cz. The 10 Hz reduction in PLF was seen mainly in early period (0 to 200 ms) after stimulus onset and corresponded to the transient onset potential (Figure 3). Analysis of harmonics and sub-harmonics for 20 and 40 Hz showed no significant difference between groups for PLF and MP (Harmonics - 20Hz (40Hz response): PLF - $F(1,41)=2.32, p=0.13$; MP - $F(1,41)=0.91, p=0.34$, 40Hz stimuli (80Hz response): PLF - $F(1,41)=2.17, p=0.15$; MP - $F(1,41)=0.07, p=0.78$, Sub-harmonics - 20Hz stimuli (10Hz response): PLF - $F(1,41)=0.22, p=0.64$; MP - $F(1,41)=0.02, p=0.88$, 40Hz stimuli (20Hz response): PLF - $F(1,41)=3.17, p=0.08$; MP - $F(1,41)=1.69, p=0.20$). The 20 Hz response to 40 Hz stimuli, showed a trend for higher PLF in HN than SZ ($p=0.08$).

Figure 5a shows the method of segregating trials by MP, and the PLF values computed within these categories. Figure 5b shows the relationship between mean power and PLF for control subjects and SZ patients. PLF increased with MP in control subjects, particularly for 40 to 50 Hz stimuli. This relationship was attenuated in schizophrenia, resulting in larger PLF difference between groups particularly at higher power levels. The ANOVA on PLF for different MP levels showed a significant effect for group ($F(1,36)=9.14, p=0.005$), stimulus frequency ($F(9,324)=14.45, p<0.001$), power level ($F(3,108)=23.43, p<0.001$), an interaction between power level and stimulus frequency ($F(27, 972)=2.33, p=0.004$) and an interaction between power level and group ($F(3, 108)=2.88, p=0.04$).

Noise Pulse Condition

The responses of the SSAEP to the noise pulse at Cz are shown in Figure 6. In the control group, the noise resulted in a reduction in PLF and MP at 500–600 ms, followed by an increase in the PLF and MP for period (600–900 ms) after the noise. In SZ there was an overall reduction in PLF across the stimulus period. The ANOVA using average values before and after the noise showed significant group difference for PLF ($F(1,40)=5.66, p=0.02$) with no interactions, while the MP did not differ between groups ($F(1,40)=2.09, p=0.15$).

Unmodulated Tones

The MP and PLF at 39–41 Hz for the unmodulated tone are shown in Figure 7. The MP at 40 Hz showed significant difference between groups ($F(1,38)=4.7, p=0.03$), with the control group higher than SZ group. Group differences were significant at 0 to 300 ms and 400 to 500 ms in Cz in independent t-tests as shown in Figure 7. The ANOVA for PLF at 40 Hz showed no difference between the groups ($F(1,38)=0.9, p=0.76$).

Discussion

While gamma range SSAEP deficits have been detected in both first episode and chronic patients with schizophrenia, previous studies have typically tested only a few frequencies of stimulation and focused on measures sensitive to impaired phase locking of the response. This study compared the Modulation Transfer Function of the SSAEP for PLF and MP measures in control and SZ subjects for a broad range of frequencies (5–50 Hz). The MP showed an increase around 40 Hz similar to the PLF. Thus, the resonance of the auditory cortex to 40 Hz stimuli as seen in averaged or phase locked activity (Galambos et al., 1981; Picton et al., 2003; Ross et al., 2000) was accompanied by an increase in power of oscillation for individual trials. While the deficit for PLF and MP in SZ was largest in the 35 to 45 Hz range, the overall ANOVA indicated a broad band deficit in the SSAEP. Similar results were found by Brenner et al. (2003) for amplitude modulated tones. The reduction of PLF around 40 Hz in SZ replicates several previous studies (Kwon et al., 1999; Light et al., 2007; Brenner et al., 2003; Vierling-Claassen et al., 2008; Spencer et al., 2008a). In the only MEG study of the SSAEP, Teale et al. (2008) found a reduction in PLF to a 40 Hz AM tone, along with an increase in induced 40 Hz activity. The measure of induced MEG activity is not readily compared to measures of EEG activity in other studies, and warrants further investigation. There was also reduction of 10 Hz PLF in SZ in the present study, which was seen primarily in the early period (0–200 ms), suggesting a deficit in the transient evoked responses. Similar findings have been reported by Gilmore et al., 2004, in which the N1 response was maximally reduced at 10 Hz stimulation in SZ.

Analysis of the harmonics and sub-harmonics of PLF showed a trend for reduced sub-harmonic for 40 Hz in SZ. There was no increase of 20 Hz response to 40 Hz stimulation as reported in the recent MEG study by Vierling-Claassen et al. (2008). Stimulus characteristics may contribute to these differences among studies. The current study used AM tones whose envelope is a sine wave with no power in harmonics. In contrast, the click stimuli used in previous studies has a non-sinusoidal envelope with power in multiple harmonics and a more complex EEG spectral response.

In this study, a novel approach was used to measure the relationship of MP to PLF values. PLF values were measured at different levels of MP. This analysis showed that the PLF was proportional to MP. While some authors (Makeig et al., 2004) have argued that PLF and measures of power are independent measures, the present results indicate that these measures are related in the SSAEP, particularly at 40 Hz and higher frequencies of stimulation. These results are consistent with an assumption that EEG is generated from linear system in which PLF is related to SNR (Infantosi et al., 2006). The control subjects showed a greater increase in PLF with power than the patient group, as indicated by a group by power interaction. Thus the reduction in PLF in SZ may be primarily due to reduced power in evoked oscillations as opposed to increased phase variability across trials. Overall, this finding along with the absence of increased responses in harmonics or sub-harmonics among SZ subjects suggests that the reduced SSAEP in SZ arise from reduced ability to generate oscillations especially around 40 Hz.

Several previous studies have shown the role of attention on the power of SSAEP response, especially at 40 Hz (Skosnik et al., 2007; Griskova et al., 2007). However, most studies of the SSAEP schizophrenia have not controlled for attentional effects. In this study, all subjects performed a concurrent visual detection task to minimize attention to the auditory stimuli. Consequently, the differences between groups in the SSAEP are unlikely to be secondary to attentional factors which differ between control and SZ subjects.

The reduction of 40 Hz PLF and MP due to a concurrent noise pulse in control subjects replicates the findings from previous study by Ross et al., 2005. A brief noise pulse caused a transient reduction in the SSAEP in control subjects. SZ showed attenuation of the SSAEP prior to and after the noise pulse compared to control subjects. This result shows further evidence of generalized impairment of 40 Hz responses in SZ.

Forty Hz activity to unmodulated tones was found to be reduced in SZ. The 40 Hz response to pure tone has been observed in MEG studies (Ross et al., 2002) and in animal studies (Brosch et al., 2002). Teale et al. (2008) and Roach et al (2008) reported a reduction of PLF in MEG responses at 40 Hz activity to a 500 msec or shorter pure tone in SZ, which was localized to a left hemisphere source especially for 0–100 msec. However, Spencer et al. (2008b) did not show any reduction in SZ for pure tone stimuli (70 ms long). A longer stimulus (1 sec) was used in this study, and long duration reduction in MP without concurrent changes in PLF was observed. Differences in stimulus duration and type of measure (MEG vs EEG) may have contributed to these differences between studies. Overall, this evidence suggests alteration in auditory processing to unmodulated tones in schizophrenia in addition to the more widely reported changes in the SSAEP.

In order to determine the neural mechanisms in schizophrenia responsible for the 40 Hz deficit, pathological and animal studies need to be considered. The single neuron responses to repetitive auditory stimuli have been widely studied in animals from different sites within the auditory pathway (Joris et al., 2004). In these studies, the response characteristics to repetitive auditory stimuli are often recorded across a wide range of frequencies to generate the MTF of phase synchrony and firing rate. Recent studies have revealed two different population of neurons in the auditory cortex, one population which synchronizes for low stimulus frequencies (less than 50 Hz) and the second population which increase in firing to high stimulus frequencies (above 50 Hz) (Lu et al., 2001). Although the link between the scalp recorded EEG responses to single neuron or local population activity is not well characterized, responses around 40 Hz in EEG are highly phase locked and may thus originate primarily from the synchronous population, which may be altered in schizophrenia. Further studies are required to verify this relationship.

Post-mortem studies have shown reduction in spine density, pyramidal cell volume in auditory cortex and chandelier type inhibitory interneurons in pre-frontal cortex in schizophrenia (Lewis et al., 2005; Sweet et al., 2009). While the interneurons in auditory cortex have not been assessed in schizophrenia, similar changes may be present. One computational modeling study, assuming that reduction of chandelier type GABAergic interneurons increases the variability of GABA time constants, showed that SSAEP responses in SZ will have reduced 40 Hz response and an increase in 20 Hz response (Vierling-Claassen et al., 2008). In this study we found reduction in 40 Hz but no increase in 20 Hz response at fundamental or sub-harmonic frequency in PLF and MP. This study instead found reduced PLF along with reduction in MP in SZ for 40 Hz, which suggest reduced ability to generate oscillations. Such a deficit could arise from reduction in pyramidal cell volume and spine density or desynchronized firing of neurons in the auditory cortex primarily for 40 Hz with no increase in other frequencies. Thus, further computational studies could help identify the relationship between neuropathological findings and SSAEP responses in schizophrenia.

Acknowledgments

We are grateful for support from the Indiana University College of Arts and Sciences Dissertation Award (GK), NIMH 1 RO1 MH62150 (BFO), NIMH R01 MH074983 (WPH), NARSAD (Brenner) and the Indiana University Foundation (BFO, WPH).

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Figure 1.

a. Plot of 40 Hz AM tone with its FFT. b. Plot of the noise stimuli.

Figure 2.
Head plots of interpolated mean PLF and MP values over the one second stimulus period from healthy control and schizophrenia groups for all stimulus frequencies.

Figure 3. Time-frequency spectrograms for PLF and MP for all stimulus frequencies recorded from channel Cz for each group.

Figure 4.

The modulation transfer function (MTF) for the SSAEP recorded from the healthy control (HC) and schizophrenia (SZ) groups. The MTFs for the fundamental, harmonic, and subharmonic for each stimulus frequency are displayed. Each data point is the mean value across the entire stimulus period averaged across subjects within the group. The error bars indicate standard errors.

Figure 5.

a. Illustration of the analysis of the relationship of PLF values to MP level on a single control subject. b. Plots of the PLF-MP relationships for each frequency of stimulation for HC and SZ groups.

Figure 6.

a. PLF and MP averaged for 100 ms periods from HC and SZ subjects during the noise interruption condition. The noise pulse occurred at 500 ms after stimulus onset. The error bars indicate standard errors. b. Pre-noise and post-noise mean values for both groups.

Figure 7.

Mean PLF and MP at 40 Hz for 100 ms periods obtained to the unmodulated tone stimuli from HC and SZ subjects. Error bars indicate standard errors.