Baseline gamma power during auditory steady-state stimulation in schizophrenia

Kevin M. Spencer1,2*

1 Research Service, Veterans Affairs Boston Healthcare System, Boston, MA, USA
2 Department of Psychiatry, Harvard Medical School, Boston, MA, USA

INTRODUCTION
Oscillatory activity in the γ band (30–100 Hz) of the electroencephalogram (EEG) has been proposed to be sensitive to cortical circuit abnormalities in schizophrenia (e.g., Kwon et al., 1999; Spencer et al., 2003; Lewis et al., 2005). Fast-spiking local circuit interneurons that express the calcium-binding protein parvalbumin (PV) show several abnormalities in schizophrenia, including reduced synthesis of γ-aminobutyric acid (GABA; Lewis et al., 2005). PV interneurons play a major role in the genesis of γ oscillations in cortical circuits, as they exert powerful, precisely timed inhibition onto their target pyramidal cells and inhibitory oscillations in cortical circuits, as they exert powerful, precisely timed inhibition onto their target pyramidal cells and inhibitory interneurons (Whittington and Traub, 2003; Bartos et al., 2007; Whittington and Traub, 2009). Thus, γ oscillations may provide a sensitive biomarker for assessing the integrity of local circuit inhibition mediated by PV interneurons in schizophrenia (Woo et al., 2011).

Reduced function of N-methyl-D-aspartate receptors (NMDARs) may be an important neural substrate of schizophrenia leads to the prediction that γ activity should rather be increased in SZ, but data supporting this hypothesis have been lacking. One possibility is that baseline induced γ power is increased, an effect that might have gone unnoticed in studies of stimulus-locked oscillations. Here we addressed this question by re-analyzing the data from a previously published study on the 40 Hz auditory steady-state response (ASSR) in schizophrenia in which dipole source localization was used to examine γ responses in the left and right auditory cortices. Subjects were 16 HC and 18 chronic SZ, who listened to trains of clicks presented at 40 Hz during electroencephalogram recording. Independent component analysis was used to remove ocular artifacts. Power spectra were computed for the pre-stimulus baseline period. We found that baseline power was higher in SZ than HC at 40 Hz in the left auditory cortex. Baseline 40 Hz power in the left auditory cortex was also correlated with ASSR evoked power in SZ. Thus, γ oscillation abnormalities in schizophrenia may include abnormal increases in baseline power as well as deficits in evoked oscillations. These baseline increases could be the sign of NMDAR hypofunction on parvalbumin-expressing inhibitory interneurons, which would be consistent with acute NMDAR antagonism and genetic ablation models of schizophrenia.

Keywords: schizophrenia, gamma oscillation, auditory steady-state response, NMDA receptor

Several studies have reported deficits in γ oscillatory activity elicited by sensory stimulation or cognitive processes in schizophrenia patients (SZ) compared to healthy control subjects (HC). However, the evidence for cortical hyperexcitability and reduced function of N-methyl-D-aspartate receptors (NMDARs) on parvalbumin-expressing inhibitory interneurons in schizophrenia leads to the prediction that γ activity should rather be increased in SZ, but data supporting this hypothesis have been lacking. One possibility is that baseline induced γ power is increased, an effect that might have gone unnoticed in studies of stimulus-locked oscillations. Here we addressed this question by re-analyzing the data from a previously published study on the 40 Hz auditory steady-state response (ASSR) in schizophrenia in which dipole source localization was used to examine γ responses in the left and right auditory cortices. Subjects were 16 HC and 18 chronic SZ, who listened to trains of clicks presented at 40 Hz during electroencephalogram recording. Independent component analysis was used to remove ocular artifacts. Power spectra were computed for the pre-stimulus baseline period. We found that baseline power was higher in SZ than HC at 40 Hz in the left auditory cortex. Baseline 40 Hz power in the left auditory cortex was also correlated with ASSR evoked power in SZ. Thus, γ oscillation abnormalities in schizophrenia may include abnormal increases in baseline power as well as deficits in evoked oscillations. These baseline increases could be the sign of NMDAR hypofunction on parvalbumin-expressing inhibitory interneurons, which would be consistent with acute NMDAR antagonism and genetic ablation models of schizophrenia.

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The data set consisted of 18 SZ and 16 HC. Subjects were selected without regard for ethnicity, and met our standard inclusion criteria: (1) age between 18 and 55 years; (2) right-handed; (3) no history of electroconvulsive treatment; (4) no history of neurological illness, including epilepsy; (5) no history of alcohol or drug dependence, nor abuse within the last year, nor long duration (>1 year) of past abuse (DSM-IV criteria); (6) no present medication for medical disorders that would have deleterious EEG, neurological, or cognitive functioning consequences; (7) verbal IQ above 75; (8) no alcohol use in the 24 h prior to testing; and (9) English as a first language. SZ were diagnosed according to DSM-IV criteria.

The SZ and HC groups were matched on gender (all male), age [HC: 44.4 ± 6.8 years; SZ: 39.8 ± 10.5 years; t(32) = 1.47, p = 0.151], parental socio-economic status (Hollingshead, 1965), and handedness (all right-handed). All SZ were taking atypical antipsychotics, and one patient was also receiving a typical antipsychotic. Antipsychotic medication dosages were converted to chlorpromazine equivalents (Stoll, 2001), which ranged from 83 to 1200 (mean 450 ± 306). The mean age of onset for SZ was 26.1 years (±8.0). The total positive and negative symptom scores on the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (Andreasen, 1985) were 9.0 ± 4.2 and 13.9 ± 4.9, respectively.

**STIMULI AND EXPERIMENTAL DESIGN**

Subjects were seated in a quiet room in a comfortable chair in front of a computer monitor. Stimuli consisted of one hundred and fifty 40 Hz trains of 1 ms white noise clicks (500 ms duration, 1100 ms stimulus onset asynchrony), which were presented binaurally through headphones (70 dB sound pressure level). Subjects were instructed to look at the fixation cross on the monitor and listen to the stimuli.

**EEG RECORDING AND PROCESSING**

The EEG was recorded (0.05–100 Hz, 500 Hz digitization) with a Neuroscan Synamp amplifier using sintered Ag/AgCl electrodes in an electrode cap at 60 standard scalp sites (Chatrian et al., 1985), nosetip, and left earlobe, referenced to the right earlobe, and grounded at AFz. Bipolar vertical and horizontal electro-oculograms were recorded from electrodes above and below the right eye and at the left and right outer canthi, respectively. Electrode impedances were <10 kΩ. Single-trial epochs were extracted from −250 to +772 ms relative to stimulus onset and corrected for ocular artifacts (blinks and eye movements) with ICA (Makeig et al., 1996). Independent components accounting for ocular activity were identified via visual inspection. Vertical EOG components had topographies with maximal values around the most anterior sites and inverted polarity at the nosetip. Horizontal EOG components were maximal at lateral frontal sites and reversed polarity between the hemispheres. Next, epochs containing other artifacts were removed. The artifact criteria were: (1) > ±90 μV change in one time point; and (2) amplitude range within an epoch exceeding 200 μV. These criteria were visually tested and verified. Finally, the retained artifact-free single epochs were re-referenced to the average reference.
The number of epochs retained per subject was (mean ± standard deviation) 145 ± 7 for HC and 140 ± 12 for SZ.

**SOURCE LOCALIZATION**

Complete details can be found in Spencer et al. (2009). ASSR source localization was performed with Brain Electric Source Analysis (BESA) v5.1. The HC grand average ASSR was filtered from 13 to 100 ms to eliminate the transient auditory evoked potentials, and the 30–550 ms segment of the resulting waveform (the period of the ASSR) was used for dipole modeling with the standard BESA 4-shell (brain, scalp, skull, and cerebrospinal fluid) spherical head model (Figure 1A). The 5-dipole model consisted of two pairs of dipoles in the superior temporal plane of each hemisphere, and a deep midline dipole accounting for residual activity (Figure 1B). The residual variance of the model was 6.7%. The HC model was used for both the HC and SZ data. When the 5-dipole HC model was applied to the SZ grand average ASSR, the RV was 15.2%. This model is similar to other dipole models of auditory cortex activity (e.g., Herdman et al., 2002; Poulsen et al., 2007).

The dipoles that were oriented tangentially to the lateral scalp surface (but radially to the fronto-central scalp) were termed “LH tangential” and “RH tangential.” The complementary cortical dipoles that had less tangential orientations were termed “LH radial” and “RH radial” (although their orientations were not strictly radial). The deep midline dipole was termed “Residual”.

**POWER SPECTRUM ANALYSES**

The total spectral power of the pre-stimulus baseline period (−250 to 0 ms) was computed with the fast Fourier transform (FFT) using a 10% Hanning window. The FFT was applied to the single-trial epochs, and the single-trial power spectra were averaged to yield the baseline power spectrum (4 Hz frequency resolution). Power values were log_{10} transformed (Kiebel et al., 2009). Due to power line frequency (60 Hz) artifacts, the frequencies 56, 60, and 64 Hz were eliminated from analyses.

The post-stimulus ASSR evoked power and PLF measures were taken from the original study, in which those measures were computed using the Morlet wavelet transform (Tallon-Baudry et al., 1996). Evoked power and PLF were averaged within the time-frequency window of 30–550 ms and 38–50 Hz where the ASSR was maximal.

All statistical tests were two-tailed with α = 0.05. For ANOVAs, the Greenhouse-Geisser correction for inhomogeneity of variance (Keiselman and Rogan, 1980) was applied for factors with more than two levels and is reflected in the reported p values. The non-parametric Spearman’s ρ was used for correlation analyses.

**RESULTS**

Previously, we identified abnormalities in the RH tangential and LH radial dipoles in the SZ group, so these sources were the focus of our analyses. For the RH tangential dipole, baseline power appeared to be slightly increased in SZ compared to HC from 36 to 72 Hz (Figure 2B), but this effect was not significant (t_{32} = 0.669, p = 0.509), nor did 40 Hz baseline power differ between groups (t_{32} = 0.502, p = 0.619). For the LH radial dipole, baseline power appeared to be increased in SZ compared to HC from 16 to 100 Hz (Figure 2A). This broadband increase was marginally significant (t_{32} = 1.89, p = 0.069). At 40 Hz, baseline power was significantly increased in SZ. (t_{32} = 2.14, p < 0.05).

Given the evidence suggesting that increased baseline activity may be related to psychotic symptoms, particularly hallucinations, we examined correlations between LH radial dipole baseline 40 Hz power and psychotic symptom scales (Total Positive Symptoms, Global Rating of Hallucinations, and Auditory Hallucinations) of the SAPS. None of these correlations approached significance, even at uncorrected levels (p < 0.0791, p < 0.783).

To examine whether the increased LH 40 Hz baseline power in SZ developed during the course of the session, the baseline power values for the LH radial dipole were averaged for the first through fifteenth sets of the single trials (e.g., trials 1–30, 30–60, etc.) and analyzed in an ANOVA with the design Group × Quintile. The main effect of Group was significant [F(1,32) = 4.48, p < 0.05], the main effect of Quintile was marginally significant [F(4,32) = 2.23, p = 0.089] and the Group × Quintile interaction was not significant [F(4,32) = 0.230, p = 0.878]. In exploratory post hoc tests we examined whether increased baseline power in SZ was significant in each quintile. Baseline power was significantly increased in the first and second quintiles (p < 0.05) and marginally significant in the fourth and fifth quintiles (p < 0.078), but the...
Winterer et al. (2000) were engaged in performing an oddball task. We found that pre-stimulus baseline power during auditory just with deficits in $\rho$ power correlated with age of onset or medication dosage in SZ (all socio-economic status in either subject group, nor was baseline power correlated with age of onset or medication dosage in SZ (all $p$s < 0.154, $p_s > 0.585$).

**DISCUSSION**

We found that pre-stimulus baseline power during auditory steady-state stimulation at 40 Hz was increased at 40 Hz in the left auditory cortex of chronic SZ relative to HC. Baseline 40 Hz power was correlated with ASSR evoked power but not PLF in SZ. Baseline power at 40 Hz was not correlated with antipsychotic dosage, demographic measures, or positive symptoms in the SZ. While baseline power appeared to be increased in SZ across a wide frequency band (16–100 Hz), the effect was significant just at 40 Hz, the ASSR stimulation frequency. A question for future studies is whether the broadband power increase would be significant with a larger sample size.

Winterer et al. (2000) also reported an increase in non-stimulus locked oscillatory activity in schizophrenia. They found this effect at low frequencies, in the delta and theta bands. In contrast, baseline power at low frequencies was not reduced in the present study. There are several differences between the two studies that could account for these different findings, including: (1) the subjects in Winterer et al. (2000) were engaged in performing an oddball task, while our ASSR experiment involved passive listening; and (2) auditory steady-state stimulation is designed to tap into the resonance of auditory cortex circuits in the y band, while the oddball task is not known to engage neural circuits with specific resonant frequencies. It is an interesting question whether active task performance would change the frequency of the baseline power increase in SZ.

The finding of increased baseline $\gamma$ power in SZ also adds to the growing body of evidence that schizophrenia is associated not just with deficits in $\gamma$ activity, but pathological increases as well. Positive correlations between $\gamma$ measures and psychotic symptoms have been reported in several of our studies (Spencer et al., 2004, 2008b, 2009, Mulert et al., 2011), and one study found increased $\gamma$ phase locking in patients relative to controls during visual steady-state stimulation (Ritzansky et al., 2010). However, to our surprise, we did not find any correlations between baseline $\gamma$ power and psychotic symptoms, even though LH radial dipole PLF was positively correlated with auditory hallucinations in this sample (Spencer et al., 2009).

While the increase of baseline power in the present study appeared across a broad range of the EEG spectrum in SZ, it was significant just at 40 Hz, the frequency of the steady-state stimulation. This suggests that the circuits underlying the LH radial ASSR dipole continued to oscillate at the stimulation frequency even when the steady-state stimulus was not being presented, although the oscillations were no longer phase-locked to the preceding stimulus. Presumably the enhanced 40 Hz baseline activity occurred in response to multiple presentations of the steady-state stimulus, which raises the question of how this effect developed over time during the session. We found some evidence that the 40 Hz baseline power effect was present as early as the first ~30 trials of the session, but the results were not conclusive. It could be that the increase in 40 Hz baseline power occurs very rapidly and reaches ceiling within the first 30 trials.

Some other questions to be investigated are whether the increase in baseline power occurs only for stimulation in the $\gamma$ band, and why an ASSR source in the LH but not the RH showed increased baseline $\gamma$. Structural and functional abnormalities of the left temporal lobe are strongly associated with auditory hallucinations, a hallmark symptom of schizophrenia (reviewed in Hugdahl et al., 2009), but few studies have examined whether auditory cortex microcircuitry abnormalities are also lateralized (e.g., Chance et al., 2008). The present data suggest that NMDAR hypofunction may be present on PV interneurons in the primary auditory cortex in the LH but not the RH in schizophrenia.

Increased baseline $\gamma$ power may be due to reduced function of NMDARs on fast-spiking PV interneurons. NMDAR antagonism increases pyramidal cell activity but decreases the activity of fast-spiking interneurons (Homayoun and Moghadam, 2007), presumably via the disinhibition of pyramidal cells by reduced NMDAR-mediated tonic excitation of fast-spiking interneurons. Increased $\gamma$ due to NMDAR antagonism could be caused by the same mechanism, as suggested by a computational model of NMDAR antagonism, which showed both increased cortical excitability and increased $\gamma$ activity when the NMDAR inputs to fast-spiking interneurons were reduced (Spencer, 2009). One possible explanation for these effects is that the decrease of tonic excitatory input to fast-spiking PV interneurons may increase the interneurons’ sensitivity to fast 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated excitatory input from pyramidal cells, and hence increase the synchronization of local circuits by PV interneurons in the $\gamma$ frequency range. We note also that a recent study by Yizhar et al. (2011) used in vivo optogenetic methods to demonstrate that increased baseline $\gamma$ power can be caused by an increase in the excitation/inhibition ratio in neurons. Such a shift in the excitation/inhibition balance could in principle also result from NMDAR antagonism.
The present finding provides a link between clinical studies and NMDAR hypofunction animal models of schizophrenia. The acute administration of NMDAR antagonists to rodents in vivo produces behavioral and cognitive abnormalities that are considered to be comparable to schizophrenia symptomatology (e.g., hyperlocomotion, attention and working memory deficits; reviewed in Amann et al., 2010), increased cortical excitability (Homayoun and Moghaddam, 2007), and increased baseline γ power (Ma and Leung, 2000, 2007; Pinsault, 2008; Ehrlichman et al., 2009; Hakami et al., 2009; Lazarewicz et al., 2010). Additionally, Hong et al. (2010) found that acute ketamine administration in humans increased the power of a sensory-evoked γ oscillation, and the genetic ablation of NMDARs on PV interneurons in vivo increases motor cortex excitability to transcranial magnetic stimulation. J. Physiol. 574, 485–496.


It should be noted that one of the difficulties in analyzing non-stimulus locked oscillations, particularly in the higher frequency bands, is that these oscillations are prone to contamination by muscle and ocular artifact (Kerr et al., 2010; Shackman et al., 2010). Thus, a finding of increased γ power from scalp electrode recordings during baseline or resting states could be due to non-EEG sources, even with stringent artifact rejection criteria (Shackman et al., 2010). We sought to overcome this potential confound by using a paradigm in which baseline power changes were expected at a particular frequency (40 Hz). In addition, we utilized ICA to remove artificial activity across the frequency spectrum, and employed source localization to focus on brain areas of interest. While we did find that baseline power tended to be increased across a wide frequency band in patients, the effect was significant only at 40 Hz. Therefore, we are confident in the validity of this effect.

Oscillatory activity in the γ band may be sensitive to the integrity of local circuit inhibition and factors that modulate the efficacy of this inhibition, such as NMDAR functionality. The present findings provide a link between human and animal model data in the study of the neural substrates of schizophrenia, and suggest that particular measures of γ activity may prove to be sensitive to particular cortical circuit abnormalities in neuropsychiatric disorders that can also be studied with animal models. Thus, measures of γ oscillations may prove to be useful biomarkers for translational research.

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