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Augmented gamma band auditory steady-state responses: Support for NMDA hypofunction in schizophrenia

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Abstract

Individuals with schizophrenia (SZ) have deviations in auditory perception perhaps attributable to altered neural oscillatory response properties in thalamo-cortical and/or local cortico-cortical circuits. Previous EEG studies of auditory steady-state responses (aSSRs; a measure of sustained neuronal entrainment to repetitive stimulation) in SZ have indicated attenuated gamma range (≈40 Hz) neural entrainment. Stimuli in most such studies have been relatively brief (500–1000 ms) trains of 1 ms clicks or amplitude modulated pure tones (1000 Hz) with short, fixed interstimulus intervals (200–1000 ms). The current study used extended (1500 ms), more aurally dense broadband stimuli (500–4000 Hz noise; previously demonstrated to elicit larger aSSRs) with longer, variable interstimulus intervals (2700–3300 ms). Dense array EEG (256 sensor) was collected while 17 SZ and 16 healthy subjects passively listed to stimuli modulated at 15 different frequencies spanning beta and gamma ranges (16–44 Hz in 2 Hz steps). Results indicate that SZ have augmented aSSRs that were most extreme in the gamma range. Results also constructively replicate previous findings of attenuated low frequency auditory evoked responses (2–8 Hz) in SZ. These findings (i) highlight differential characteristics of low versus high frequency and induced versus entrained oscillatory auditory responses in both SZ and healthy stimulus processing, (ii) provide support for an NMDA-receptor hypofunction-based pharmacological model of SZ, and (iii) report a novel pattern of aSSR abnormalities suggesting that gamma band neural entrainment deviations among SZ may be more complex than previously supposed, including possibly being substantially influenced by physical stimulus properties.

Keywords

Auditory; Electroencephalography; Steady-state; Gamma; Beta; Theta; NMDA

1. Introduction

Auditory sensory processing abnormalities in schizophrenia (SZ) have been quantified with transient evoked responses (e.g., N/M100) to abrupt stimulus onsets (Rosburg et al., 2008)

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Appendix A. Supplementary data Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2012.04.003.

and auditory steady-state responses (aSSR) to repeating auditory stimulation (e.g., a 40 Hz steady-state stimulus is a repetition every 25 ms). Low N100 amplitude in SZ is one of the most replicated effects in this literature (Shelley et al., 1999; Blumenfeld and Clementz, 2001; Ford et al., 2001; Gilmore et al., 2004; Hamm et al., in press). Theoretically, deficiencies of excitatory drive on (Goff and Coyle, 2001) and/or coordination between (Benes and Berretta, 2001) neuronal ensembles supporting auditory stimulus processing cause these abnormalities in SZ. This issue is difficult to study using transient stimulation alone. Use of aSSRs, however, allows for evaluation of both transient responses and the synchronous oscillation of neural ensembles (Rockstroh et al., 1996; Hamm et al., 2011). Auditory SSRs in the 15–80 Hz range probe the ability of thalamo-cortical and local cortical circuits to entrain to repetitive stimulation (Picton et al., 2003; Krishnan et al., 2009). Previous research indicates SZ abnormalities on the 40–80 Hz aSSR in auditory cortex (Hamm et al., 2011; Tsuchimoto et al., 2011) that may be less prominent or absent at lower (20 Hz) stimulation rates (Brenner et al., 2009).

Auditory evoked responses (AERs) to transient stimuli have complex frequency compositions (Hong et al., 2008), involving stimulus locked alterations in oscillatory amplitudes and phase coherence across multiple frequency bands. Quantifying evoked response amplitudes only in the temporal domain (e.g., N100) may not capture this complexity. The few studies quantifying AER in the time/frequency domain in SZ indicate a deficiency of phase alignment and/or amplitude augmentation in low frequency ranges (below 10 Hz; Hong et al., 2008; Brockhaus-Dumke et al., 2008). An understanding how these low frequency AER deficits relate to auditory neural entrainment abnormalities measured by the aSSR has not been fully investigated.

EEG studies of aSSRs in SZ showing reduced gamma range responses have used relatively consistent stimulus parameters. Brief ‘click’ stimuli or sinusoidally modulated 1 kHz tones of 500–1000 ms duration have been presented with short interstimulus intervals (ISIs; 200–1000 ms). Broadband noise bursts, however, are known to elicit the most robust aSSRs (John et al., 1998), and the severity of SZ reductions in some auditory evoked responses depends on ISI (Rosburg et al., 2008). In addition, under certain conditions when measured with EEG, SZ have shown increased neural activation in sensory cortices during extended stimulation (Spencer et al., 2004; Clementz et al., 2008; Wang et al., 2010). Plourde et al. (1997) administered ketamine, an NMDA-receptor antagonist reproducing psychosis-like symptoms (Rujescu et al., 2006), to healthy individuals during prolonged stimulation at 40 Hz and observed an increase of the aSSR using EEG.

Hamm et al. (2011) using 1500 ms stimulation epochs, however, focused on a spatially constrained region of auditory cortex (measured with MEG) and found reduced 40–80 Hz aSSRs to amplitude modulated broadband noise (1500 ms ISI). Unlike MEG, EEG is sensitive to radial and more spatially distributed neural activity (Williamson and Kaufman, 1989). The present investigation used 1500 ms steady-state stimulation over a broad frequency range (16–44 Hz in 2 Hz steps) with 2700–3300 ms ISIs and measured low frequency AERs and aSSRs with EEG. This approach allowed for precise separation of aSSRs in the beta-gamma ranges (given that beta range aSSRs have been reported as normal in SZ) and quantification of extended (both tangential and radial) neural responses.

2. Methods

2.1. Subjects

Seventeen persons with DSM-IV SZ (Mean+/−SD: age 41.5+/−8.3 years, 6 females) and 16 healthy persons (H; 39.5+/−9.0 years, 7 females) participated. SZ were recruited through community advertisements and outpatient services of the Medical College of Georgia

(Augusta, GA) and Advantage Behavioral Health Systems (Athens, GA); healthy subjects were recruited from the community. SZ were diagnosed using the Structured Clinical Interview for DSM-IV (First et al., 1995). At testing time, 14 SZ were taking second-generation antipsy-chotics (average CPZ equivalent=355 mg/day+/−245), 3 were taking first-generation antipsychotics (5–10 mg/day Haloperidol), and 2 were unmedicated. Additionally, 7 SZ were taking antidepressants (6 SSRIs, 1 Buproprion), 2 were taking anticholinergics (Benzatropine), and 1 was taking an anxiolytic (Buspirone). All subjects were free of substance use disorders in the 6 months prior to testing. SZ were chronic patients (M duration=18.2 years, +/−7.88) with typical age of illness onsets (M=22.4 years, +/−10.0). All participants provided informed consent and were paid for their time. This study was approved by the UGA IRB.

2.2. Stimuli

Stimuli were 1500 ms broadband noise bursts (500–4000 Hz) amplitude modulated (sinusoidal shape, 100% depth) at one of 15 frequencies: from 16 to 44 Hz in 2 Hz steps. Stimuli were presented binaurally through Etymotic insert earphones (Etymotic Research, Elk Grove Village, IL) at 76 dB SPL. Stimuli were presented randomly with an average 3 s ISI (range 2.7–3.3 s) until 40 trials were collected for every modulation rate.

2.3. EEG recording

EEG data were recorded vertex-referenced using a 256 sensor Geodesic Sensor Net and NetAmps 200 amplifiers (Electrical Geodesics Inc.; EGI, Eugene, OR). Sensor impedances were kept below 50 kO, as is standard when using high input impedance amplifiers. Data were sampled at 500 Hz with an analog filter bandpass of 0.1–200 Hz.

2.4. Data screening

Sensors from the neck/face were excluded leaving 207 sensors for analysis. Raw data were inspected offline for bad sensors, which were interpolated (<5% for any participant) using a spherical spline interpolation method (BESA 5.0; MEGIS Software, Grafelfing, Germany). Data were segmented into single trial epochs beginning 750 ms before and ending 2250 ms after stimulus onset (750 ms following stimuli offset). Trials containing blink, saccade, or cardiac artifact were corrected using a spatial filtering algorithm in BESA (Ille et al., 2002). Trials with activity >150 mV were eliminated. Data were transformed to an average reference and bandpass filtered (zero phase) from 1 to 100 Hz.

2.5. Data analysis

From 500 ms pre-stimulus onset to 500 ms post-stimulus offset (allowing 250 ms padding at the beginning and end of epochs), 500 ms windows centered on each sample of EEG data for each trial was multiplied by a 250-sample Hanning window (500 ms). The window was shifted in one-sample (2 ms) steps and a Fast Fourier Transform (FFT; 2-Hz resolution) was calculated at each step (Brenner et al., 2009). Stimulus induced phase locking and changes in power were then isolated in the EEG data (presented in Supplementary Figs. 1 and 2) and analyzed in 4 steps.

2.5.1. The presence of an aSSR was tested for frequencies between 8 and 88 Hz (in 2 Hz steps; covering sub- and second harmonics of driving frequencies) for each sensor, subject, and condition (16- to 44-Hz) during the last 1000 ms of stimulation (to reduce influence of stimulus onset responses) using circ-T values (Victor and Mast, 1991; Hamm et al., 2011; see “Circular T-Test” section of Supplementary materials). Results showed aSSRs at the driving frequencies for 14 stimuli (18- through 44-Hz) and at harmonics for 6 stimuli (18-

through 28-Hz). Stimuli modulated at 16-Hz did not evoke an aSSR. Therefore, a total of 20 aSSRs were used in subsequent analyses.

2.5.2. To determine scalp topographies of aSSRs as a function of frequency, average FFTs within each aSSR frequency (20 total from above) were computed for the last 1000 ms of stimulation. Evoked spectral power was then calculated and standardized across sensors before averaging across subjects in order to capture relative spatial magnitude and minimize the influence of single subjects and frequencies with large responses. A Principal Components Analysis (PCA; Kaiser normalization; PROMAX rotation; Dien, 2010) with 207 observations (sensors) and 20 variables (frequencies) was calculated. Because PCA results were equivalent between groups (same number of components and patterns of factor weights and structures), an overall PCA, which indicated two significant components, was used for subsequent analyses (Fig. 1A; see “Principal Components Analysis for Factor Retention” section of Supplementary materials). The first component included all aSSRs at driving frequencies (18–44 Hz) with FCz maximum. The second component included all aSSRs at frequencies harmonic to driving frequencies (36–56 Hz) with F5 and F6 maxima.

2.5.3. PCA was used to evaluate whether aSSRs demonstrated shared variance as a function of frequency. Evoked spectral power values were averaged within-subjects across the 10 sensors with the highest factor scores from the PCA-based topographies. These values were standardized across frequencies within subjects. This yielded a matrix with 33 observations (subjects) and 14 or 6 variables (for driving and second harmonic aSSRs, respectively). PCA was calculated on this matrix; results indicated two components for driving frequency (separate beta and gamma components) and one component for the second harmonic (Fig. 1B; see “Principal Components Analysis for Factor Retention” section of Supplementary materials). Subsequent analyses were conducted on these component scores rather than individual driving frequencies.

2.5.4. Inter-trial coherence (ITC) and single trial power (STP) were calculated for the component scores. ITC quantifies consistency of oscillatory phase across trials (Jammalamadaka and SenGupta, 2001; Hamm et al., 2011). FFT-derived complex numbers at each time and frequency point for each trial were divided by their absolute values, then summed across trials and divided by the number of trials (see “Adjustment of Inter-trial Coherence” section of Supplementary materials). The absolute value of this result (ITC) is bound between 0 and 1 (1 indicating perfect phase alignment). STP quantifies magnitude of oscillatory activity, and was analyzed as change in power from baseline in decibels (Delorme and Makeig, 2004; see “Baseline Power Comparison” section of Supplementary materials).

Analysis of low frequency AERs was accomplished by creating single trial windows from 500 ms pre- to 500 ms post-stimuli onsets using the same procedure as for the aSSRs. Subsequently, ITC and STP values were calculated for 2–12 Hz to quantify the frequency composition of the AER across driving frequencies.

2.6. Statistical analysis

For driving frequency aSSR (18–44 Hz) ITC and STP values were analyzed in two steps: (i) a Group Membership (SZ, H) by Rate of Stimulation (beta, gamma factors) by Time (first, second, and third 500 ms bins during steady-state stimulation) mixed-model ANOVA to evaluate neural responses to auditory driving, and (ii) a Group Membership by Rate of Stimulation mixed-model ANOVA for evaluating neural activity at the driving frequency remaining in the 500 ms following stimulus offset to determine if there were differences in how the groups recovered from steady-state stimulation. Second harmonic aSSR (36–56 Hz) ITC and STP values were analyzed using the same two steps but without the Rate of

Stimulation factor. Low frequency AERs occurred in the 2–8 Hz range during the first 400 ms following stimulus onset (Fig. 2). ITC and STP values in this range (using the 10 sensors that best captured these responses) were analyzed with a Group Membership (SZ, H) by Rate of Stimulation (beta, gamma) mixed-model ANOVA. Greenhouse–Geisser correction was used when sphericity was violated (Mauchly, 1940).

3. Results

SZ and H had similar numbers of usable trials (t's<1.6, p's>.12) for beta (SZ M=100, SD=12; H M=108, SD=17) and gamma (SZ M=238, SD=25; H M=258, SD=45) driving frequencies.

3.1. Steady-state responses

On STP at the driving frequency during stimulation, there was only a Group Membership by Rate of Stimulation interaction that was at trend significance level, $F(1,31)=4.0$, $p=.054$. The groups did not differ significantly on STP at either stimulation frequency (although SZ were lower than H on beta power, $d=-0.50$, and higher than H on gamma power, $d=0.54$), but SZ had a significant difference between beta and gamma STP ($d=1.15$), $t(16)=5.2$, $p<.05$, that was less dramatic among H ($d=0.69$), $t(15)=1.9$, $p>.05$. There were no other significant effects involving Group Membership on STP (Fig. 3A).

On ITC at the driving frequency during stimulation, there was only a significant main effect of Group Membership, $F(1,31)=5.3$, $p<.05$. SZ had higher ITC than H across driving frequencies ($d=0.69$). There were no group differences in post-stimulus ITC at the driving frequency (Fig. 3B). On ITC at the harmonic aSSR, there was also a significant main effect of Group Membership, $F(1,31)=4.4$, $p<.05$. SZ had higher ITC for the harmonic than did H ($d=0.70$). There were no other significant effects involving Group on ITC (see "Alternative Analysis Approach" section of Supplementary materials).

3.2. Stimuli onset responses

There was a main effect of group for STP at stimuli onset, $F(1,31)=4.3$, $p<.05$. H had significantly higher STP than SZ from 2 to 8 Hz during this interval ($d=0.69$). This same effect, however, was not significant for ITC, $F(1,31)=0.49$, $p>.05$. There were no other significant effects involving Group Membership on either STP or ITC (Fig. 2).

4. Discussion

Neural responses for SZ to steady-state stimuli across beta and low gamma frequencies were evaluated. SZ showed two deviations of interest: (i) augmented induced activity (STP) in relation to gamma versus beta range stimulation that was not present for H (see Fig. 3), and (ii) reduced low frequency (2–8 Hz) induced activity in relation to stimuli onset. The former effect occurred in relation to significantly stronger phase locking of oscillatory responses for SZ, which was more dramatic for responses in the gamma range ($d=-.84$) than in the beta range ($d=-.53$). These findings are consistent with pharmaco-patho-physiological models of SZ that invoke NMDA-receptor hypofunction (Rujescu et al., 2006; Javitt, 2007).

There is evidence for both augmented (Spencer et al., 2004; Clementz et al., 2008; Flynn et al., 2008; Farzan et al., 2010; Hamm et al., in press) and attenuated (Ferrarelli et al., 2008; Teale et al., 2008; Brenner et al., 2009; Hamm et al., 2011) gamma-range oscillations in SZ. Eleven of 13 previous studies of gamma range aSSRs in SZ indicated reductions compared to H, and 8 of 9 studies found no SZ difference for beta range aSSRs (Tsuchimoto et al., 2011; Rass et al., in press; see Hamm et al., 2011 for a review). Hong et al. (2004) showed that only SZ taking second-generation antipsychotics had enhanced gamma range responses.

Perhaps medication effects played a role in the current results (13 out of 17 subjects were taking second generation antipsychotics), but it is improbable that this feature accounts for between-study differences in aSSR results. SZ samples of Spencer et al. (2004), Krishnan et al. (2009), and Teale et al. (2008) were completely medicated with second-generation antipsychotics, but they all reported gamma range aSSR reductions.

Stimulus parameter features, however, could account for some differences between the present and past EEG studies of gamma range aSSRs in SZ. Of 7 studies reporting 40 Hz reductions and/or normal 20 Hz aSSRs in SZ, 5 used 500 ms trains of 1 ms click stimuli and 2 used 1000 ms trains of sinusoidally-modulated 1 kHz tones. The current study used 1500 ms of sinusoidally-modulated broadband noise. The current study also had 3000 ms ISI, while previous studies used less than 1000 ms. Hamm et al. (2011) had stimulus parameters comparable to the current study but, like the other MEG aSSR investigations (Teale et al., 2008; Vierling-Claassen et al., 2008; Tsuchimoto et al., 2011), found reductions at 40 Hz in SZ. The MEG studies, however, used source analyses to measure auditory cortex signals. Perhaps these studies demonstrate that specific auditory cortical neurons contributing to the aSSR have suboptimal gamma-range activations in SZ. More cortically distributed sources, including radially oriented neurons contributing to aSSRs, may be prone to exuberant activation in SZ under prolonged, spaced, and aurally dense stimulation.

The present findings are consistent with theories of NMDA-receptor hypofunction in SZ (Javitt, 2007). NMDA antagonists produce abnormalities consistent with those reported here among SZ, with attenuated low frequency and augmented gamma oscillations (Ehrlichman et al., 2009), and larger effects for phase locked (similar to ITC) than for non-phase locked gamma (STP; Lazarewicz et al., 2009). Ketamine administration to healthy humans disrupts transient induced oscillations (Hong et al., 2010) and prolonged aSSRs (Plourde et al., 1997) in a manner congruent with the current results. In vitro and in vivo investigations of gamma oscillations sometimes differ on NMDA antagonist results (Cunningham et al., 2006), probably highlighting the importance of thalamo-cortical networks in NMDA modulation of gamma (Ferrarelli and Tononi, 2011).

NMDA receptor function is critical for normal gamma modulation; inactivation of these receptors causes increased gamma baseline amplitude and prolonged gamma duration in vivo (Carlen et al., 2011). For shorter stimulation periods, NMDA disruption most likely affects the GABA-a receptor-mediated inhibition that normally serves to sharpen and synchronize local circuits in gamma oscillation (Gonzalez-Burgos and Lewis, 2008, in press). GABA-b receptors are more distal to synapses than GABA-a receptors, can be activated by leakage from adjacent synapses (Kohl and Paulsen, 2010), and are more sensitive to prolonged GABA release associated with extended stimulation (Dutar and Nicoll, 1988). Unlike GABA-a, GABA-b activation has the net effect of inhibiting gamma oscillations (Brown et al., 2007). In a system with proper NMDA-mediated excitation of GABAergic cells, longer stimulus trains should reduce aSSR magnitudes. Interestingly, reduction of GABA-b mediated-inhibition is theorized to underlie impaired modulation of gamma oscillations in SZ (Farzan et al., 2010).

GABA-a and GABA-b receptors also vary in their relative distributions. GABA-a receptors are more prevalent in thalamic medial geniculate nucleus; GABA-b receptors are more broadly distributed in thalamus and cortex (Bowery et al., 1987). MEG studies specifically measuring auditory cortex signals (e.g. Hamm et al., 2011), therefore, could yield different aSSR results from EEG studies examining broad cortical entrainment. This would be especially true during prolonged broadband auditory stimulation which promotes accumulation of synaptic GABA and would exuberantly activate GABA-b receptors (Lambert and Wilson, 1994).

Single trial power showed a Group by Frequency interaction driven by gamma-relative-to-beta enhancement rather than reduction/augmentation of one band. This is consistent with the hypothesis that changes in GABA recovery (Gonzalez-Burgos and Lewis, 2008) shift the relative dominance of beta versus gamma oscillations (Vierling-Claassen et al., 2008). Our beta/gamma shift for SZ was opposite of that reported by Vierling-Claassen et al. (2008) likely due to our use of more prolonged, aurally dense stimulation. In healthy interneuron–pyramidal cell assemblies, GABAergic release from inhibitory interneurons theoretically yields shorter GABA-induced current during short duration, narrow band stimulation (increased gamma/beta ratio) and longer GABA-induced current during long duration, broadband stimulation (decreased gamma/beta ratio). This shift may be less pronounced in SZ due to a combination of altered GAT1-mediated GABA transfer and GAD67-mediated GABA synthesis (Gonzalez-Burgos and Lewis, 2008), both of which could be downstream effects of altered NMDA receptor function (Gonzalez-Burgos and Lewis, in press). Studies of short versus long interval and of narrow versus broad bandwidth steady-state stimulation in the same SZ subjects are needed to test this thesis. Synchronous neural oscillations are critical for efficient perceptual processing (Romo et al., 2003), so determining conditions under which SZ deviate (high or low) on this parameter could be a fruitful area of investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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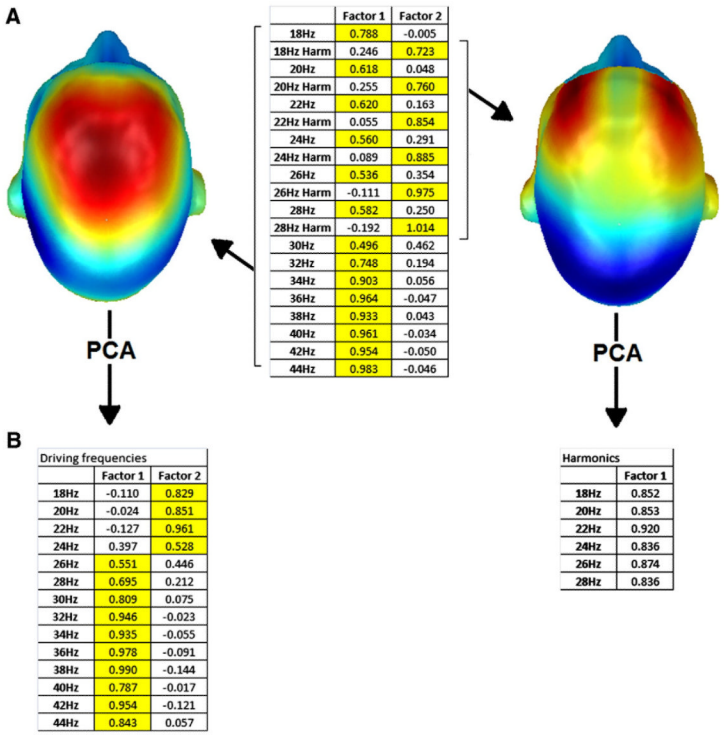

	Factor 1	Factor 2
18Hz	0.788	-0.005
18Hz Harm	0.246	0.723
20Hz	0.618	0.048
20Hz Harm	0.255	0.760
22Hz	0.620	0.163
22Hz Harm	0.055	0.854
24Hz	0.560	0.291
24Hz Harm	0.089	0.885
26Hz	0.536	0.354
26Hz Harm	-0.111	0.975
28Hz	0.582	0.250
28Hz Harm	-0.192	1.014
30Hz	0.496	0.462
32Hz	0.748	0.194
34Hz	0.903	0.056
36Hz	0.964	-0.047
38Hz	0.933	0.043
40Hz	0.961	-0.034
42Hz	0.954	-0.050
44Hz	0.983	-0.046

Driving frequencies		
	Factor 1	Factor 2
18Hz	-0.110	0.829
20Hz	-0.024	0.851
22Hz	-0.127	0.961
24Hz	0.397	0.528
26Hz	0.551	0.446
28Hz	0.695	0.212
30Hz	0.809	0.075
32Hz	0.946	-0.023
34Hz	0.935	-0.055
36Hz	0.978	-0.091
38Hz	0.990	-0.144
40Hz	0.787	-0.017
42Hz	0.954	-0.121
44Hz	0.843	0.057

Harmonics	
	Factor 1
18Hz	0.852
20Hz	0.853
22Hz	0.920
24Hz	0.836
26Hz	0.874
28Hz	0.836

Fig. 1.

Results from a Principal Components Analysis (PCA) of auditory steady-state response (aSSR) power across stimulus frequency and EEG sensors (A) reveal separate topographies for driving frequency aSSRs (left) and harmonic aSSRs (right). Results from a secondary PCA of aSSR power across stimulus frequency and subjects (B) reveal two factors or “frequency bands” for driving frequency aSSRs (left) and one factor for harmonic aSSRs (right).

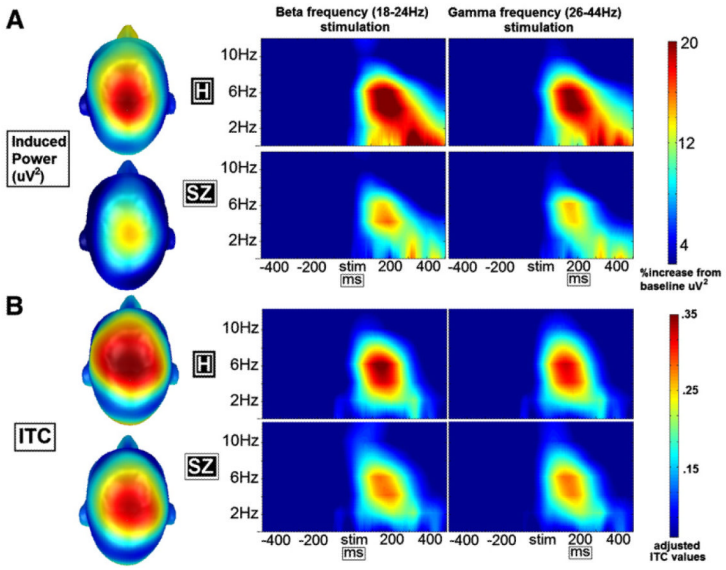

Fig. 2.

Plots of single trial power (A) indicate that H have significantly more stimulus induced oscillatory power in theta/low-alpha frequencies (2–8 Hz) in the 50–400 ms post stimulus period. This difference did not vary with stimulus frequency. Plots of intertrial phase coherence (B; ITC) indicate that although H have, on average, slightly more ITC in theta/low-alpha frequencies (2–8 Hz) in the 50–400 ms post stimulus period than SZ, this difference was not significant and did not vary significantly with stimulus frequency.

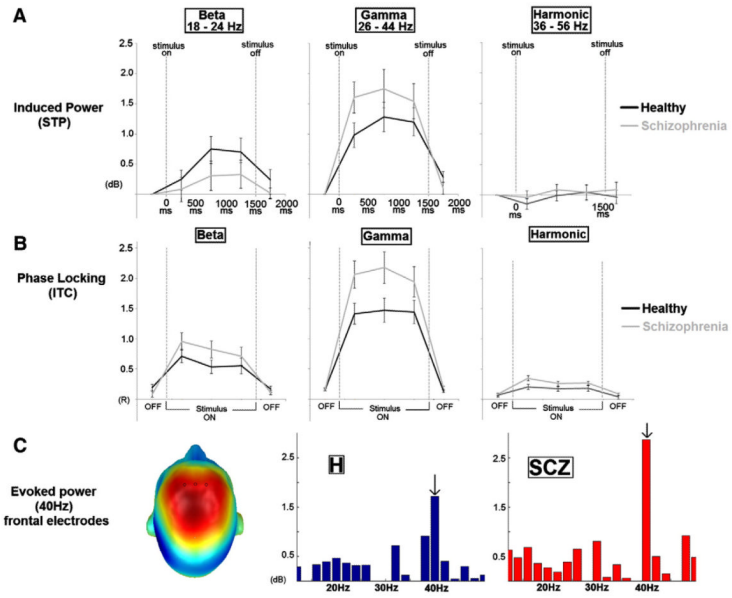

Fig. 3.

Plots of single trial power (STP; A) reveal a trend level (p=.054) frequency by group interaction for driving frequency aSSRs; SZ have a more dramatic beta/gamma difference. Plots of STP at the harmonic frequencies reveal no significant increases from baseline in either group. Plots of intertrial phase coherence (ITC; B) reveal larger values in SZ for all stimulation period ITC values regardless of frequency band (gamma or beta) or relationship to the stimulus (driving or harmonic). Examination of evoked power to 40 Hz stimulation (C) with methods analogous to previous aSSR studies reveals a trend level augmentation (p=.055) for SZ in line with the conclusions of the main analysis approach (see “Alternative Analysis Approach” section of Supplementary materials).