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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.

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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) 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

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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 antipsychotics (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

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