Supplementary Online Content

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eTable 1. Demographic and Clinical Characteristics of the Auditory Steady-State Response (ASSR) Sample

eTable 2. Demographic and Clinical Characteristics of the Resting Electroencephalogram (EEG) Sample

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Demographic and clinical characteristics of the auditory steady-state response (ASSR) sample

Variable	HC (N=24)	SZ (N=24)	Statistic	*P*
Age [years]	44.1 (7.3)	46.0 (9.1)	t [46]= -0.78	0.439
Male / Female	20 / 4	20 / 4	X^2(1)= 0	1.000
Handedness [a]	0.79 (0.2)	0.81 (0.2)	t [46]= -0.38	0.710
Self SES [b]	2.25 (0.8)	3.42 (1.2)	t [39]= -3.72	0.001**
Parental SES [c]	2.46 (0.9)	2.83 (1.4)	t [41]= -1.11	0.275
Education [years]	14.2 (1.7)	13.5 (2.0)	t [46]= 1.33	0.188
MMSE [d]	28.8 (1.4)	28.9 (1.4)	t [46]= -0.51	0.615
WAIS-IV information subscale [e]	10.7 (2.6)	10.1 (2.7)	t [46]= 0.87	0.387
Duration of illness [years]		21.1 (9.7)		
Medication dosage [CPZ equiv, mg] [f]		426.39 (444.03)		
Medication type [AP / TP / TP+AP / Non] [g]		17 / 1 / 4 / 2		
SAPS - Positive Symptom Total [h]		9.33 (4.90)		
SANS - Negative Symptom Total [i]		9.38 (5.64)		

HC: Healthy Controls, SZ: Schizophrenia patients
[a] Handedness was measured by Edinburgh Handedness Inventory. [b c] SES: Socioeconomic Status, Higher scores indicate lower SES. [d] MMSE: Mini-Mental State Examination. [e] WAIS-IV: Wechsler Adult Intelligence Scale-Fourth Edition. [f] CPZ equiv: chlorpromazine equivalents. [g] TP: typical antipsychotics, AP: atypical antipsychotics, Non: non-medicated patient. [h] SAPS: Scale for the Assessment of Positive Symptoms. [i] SANS: Scale for the Assessment of Negative Symptoms. Mean (SD) are given for each variable. Asterisks (*) indicate statistically significant results: ** $p < 0.01$.

eTable 2. Demographic and clinical characteristics of the resting electroencephalogram (EEG) sample

Variable	HC (N=18)	SZ (N=18)	Statistic	*P*
Age [years]	44.1 (6.7)	45.4 (8.9)	t [34]= -0.51	0.614
Male / Female	14 / 4	15 / 3	X^2(1)= 0.18	0.674
Handedness [a]	0.78 (0.2)	0.77 (0.2)	t [34]= 0.22	0.829
Self SES [b]	2.17 (0.9)	3.28 (1.4)	t [34]= -2.92	0.006**
Parental SES [c]	2.39 (1.0)	2.83 (1.3)	t [34]= -1.11	0.273
Education [years]	14.5 (1.7)	13.5 (2.1)	t [34]= 1.61	0.115
MMSE [d]	28.9 (1.3)	28.9 (0.9)	t [34]= -0.89	0.380
WAIS-IV information subscale [e]	10.8 (2.7)	9.9 (2.8)	t [34]= 1.08	0.287
Duration of illness [years]		19.5 (9.5)		
Medication dosage [CPZ equiv, mg] [f]		408.27 (454.26)		
Medication type [AP / TP / TP+AP / Non] [g]		12 / 1 / 3 / 2		
SAPS - Positive Symptom Total [h]		10.06 (5.76)		
SANS - Negative Symptom Total [1]		8.77 (4.54)		

eAppendix. Methods and Results

Methods

Recruitment and diagnostic details

Thirty-one chronic schizophrenia patients (SZ; 4 females) and 30 healthy control subjects (HC; 4 females) participated in the study. Exclusion criteria for all participants were: 1) history of electroconvulsive therapy, 2) history of major head trauma or neurological illness including epilepsy, 3) lifetime history of substance dependence or a history of substance abuse within the past 5 years, 4) history of steroid use, and 5) estimated premorbid intelligence quotient (Wechsler Adult Intelligence Scale-IV [WAIS-IV][1]) below 75. All participants were right-handed and screened for normal hearing. HC were screened for the presence of an Axis-I disorder using the SCID-Non-Patient edition[2], and were also excluded if they reported having a first-degree relative with an Axis I disorder. SZ were diagnosed according to the DSM-IV Diagnostic Criteria (APA 1994). HC were recruited within the Boston metropolitan area from local newspaper, mass transit, and online advertisements. SZ were recruited from the Schizophrenia Center at the VA Boston Healthcare System. This study was approved by the Institutional Review Boards of the VA Boston Healthcare System and Harvard Medical School. After a detailed description of the study, each subject gave written informed consent to participate. Subjects were paid for their participation.

The data from 6 HC and 7 SZ were excluded due to excessive artifacts (3 HC, 2 SZ), bad channels (1 HC, 2 SZ), or less than 100 recorded epochs (2 HC, 3 SZ), resulting in a final sample of 24 (4 females) HC and 24 (4 females) SZ (see eTable 1 for demographic and clinical data). A subset of 18 HC and 18 SZ also had resting-state EEG data (see eTable 2). HC were matched to SZ in both subsets on age, handedness[3], parental socioeconomic status[4], education years, Mini-Mental State Examination score, and information subscale of the WAIS-IV (a measure of premorbid intelligence). Hospital records indicated that all of the SZ but 2 were receiving antipsychotic medication at the time of the experiment. Antipsychotic medication dosages were converted to chlorpromazine equivalents using the values from Stoll et al.[5] for typical and Woods et al.[6] for atypical antipsychotics. Symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS)[7] and the Scale for the Assessment of Negative Symptoms (SANS)[8].

Stimuli and procedures

Subjects were seated in a quiet dim room in a comfortable chair 1 m in front of a computer monitor. During the ASSR task, three blocks of click trains (500 ms duration, 800 ms inter-train interval) were presented binaurally through headphones at 70 dB sound pressure level. The click train rates were 20, 30, and 40-Hz, each presented within a single block, and the order of the blocks was counterbalanced across subjects. Subjects were instructed to view the fixation cross on the monitor and listen to the stimuli. Resting-state EEG was recorded for 3 minutes in a separate session. Subjects were instructed to close their eyes and relax. The first minute of the recording period was excluded from analysis.

EEG recording and processing

The EEG was recorded (DC-100 Hz bandpass filter, 512 Hz digitization rate) with an Active-Two system (Biosemi B.V.) using active electrodes in an electrode cap at 71 scalp sites. During data acquisition the DC offsets were kept below 25 mV and all channels were referred to the system's internal loop (CMS/DRL electrodes). Bipolar vertical electro-oculogram and horizontal electro-oculogram channels were derived from electrodes Fp1 and an electrode below the left eye, on the left and right outer canthi, respectively. Epoching and filtering of continuous EEG data were performed with BrainVision Analyzer 2.0.1 (Brain Products GmbH). A 0.1 Hz high-pass filter was used to remove skin

potentials and other slow artifacts[9]. Single-trial epochs were extracted from -500 ms pre-stimulus to 800 ms post-stimulus for ASSR analyses. Non-overlapping 1000 ms epochs were selected for resting-state EEG analyses.

Further processing was performed in MATLAB (Mathworks, Inc.) and IDL (Exelis Visual Information Solutions). Ocular, cardiac, and muscle artifacts were removed using ICA, as implemented in the *runica* program from EEGLAB[10]. ICs representing artifacts were identified based on their topographic, temporal, and spectral signatures[11-13]. Additional artifact criteria were: 1) > +/- 90 μV change in one time point, and 2) amplitude range within an epoch exceeding 200 μV. Artifact-free single epochs were re-referenced to the average reference. For ASSR and baseline γ analysis, the number of artifact-free epochs retained per subject for each stimulation rate (20, 30, and 40-Hz) was (mean $\pm$ standard deviation) 139$\pm$13, 139$\pm$14, and 139$\pm$12 for HC and 138$\pm$13, 138$\pm$13, and 139$\pm$12 for SZ, respectively. The number of epochs retained per subject for resting-state EEG analysis was 141$\pm$21 for HC and 139$\pm$27 for SZ.

Source analysis

Dipole source localization of the ASSR was performed using Brain Electric Source Analysis (BESA) v5.1.8 (BESA, GmbH). Following artifact correction, the HC grand average 40-Hz ASSR was filtered from 13 to 100 Hz to eliminate the transient auditory evoked potentials, and the 30–530 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. 1-A). ASSR sources were localized with a 4-dipole model consisting of tangential and radial pairs of dipoles in the superior temporal plane of each hemisphere (LH: left hemisphere, RH: right hemisphere) (Figure. 1-B). 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 other pair of dipoles that had more radial orientations were termed "LH radial" and "RH radial" (note that their orientations were not strictly radial). During the dipole fitting process, the tangential and radial dipoles in each hemisphere were constrained to have the same locations but free orientations. The locations of the dipole pairs in each hemisphere were constrained to be symmetric. This model is similar to other dipole models of auditory cortex activity[14-16]. The residual variance of the HC model was 10.4%. The HC model was used for both the HC and SZ data. When the HC model was applied to the SZ grand average 40-Hz ASSR the residual variance was 20.6%.

After the dipole model was constructed from the HC grand average ASSR data, the single-epoch source waveforms for each dipole were estimated in BESA by applying the dipole model to each single epoch. In this way, the scalp EEG data were spatially filtered to yield estimates of activity in the positions of the dipoles in the auditory cortex. Then, the wavelet and FFT analyses were performed on the resulting single epochs for each dipole in each subject for the all of the ASSR and resting state data.

Time-frequency and power spectrum analyses

The ASSR was analyzed using the Morlet waveform transform ($f_0/\sigma_f = 6$), which was applied to the single-trial epochs in 1 Hz steps from 1-100 Hz at each time point from -200 to 800 ms to yield time-frequency maps of phase locking factor (PLF) and evoked power[18]. PLF measures the variance of phase across single trials, and ranges from 0 (random distribution) to 1 (perfect phase locking). Evoked power measures the power of the average evoked potential in which the contribution of non-stimulus locked activity is minimized. Pre-stimulus baseline values (-100 to 0 ms) were subtracted from each time-frequency map.

Spontaneous γ activity in the ASSR data was measured as induced power during the baseline (-500 to 0 ms) and during the ASSR period (30-530 ms). First, the fast Fourier transform (FFT; 500 ms width, 10% Hanning window) was applied to the single-trial epochs and the resulting single-trial power spectra were averaged to yield total power, which includes both induced and stimulus-locked evoked power. Next, evoked power was calculated as the power spectra of the averaged single epochs using the FFT. Finally, the evoked power spectra were subtracted from the total power spectra to yield induced power spectra. Spontaneous γ activity in the resting-state data was measured as total power (since there was no stimulus-evoked activity) with the FFT as above from non-overlapping 1000 ms epochs.

Results

Correlations between baseline and ASSR period induced γ power

To test the extent to which baseline and ASSR period induced γ were related, these measures were correlated within each subject group for the 40-Hz stimulation condition (Bonferroni correction: 2 dipoles × 2 hemispheres × 2 subject groups). In HC, induced γ power in the baseline and ASSR periods was highly correlated for each hemisphere and dipole (LH tangential: $\rho = 0.960$, $p < 0.001$; LH radial: $\rho = 0.918$, $p < 0.001$; RH tangential: $\rho = 0.974$, $p < 0.001$; RH radial: $\rho = 0.957$, $p < 0.001$, corrected). In SZ, induced power in baseline and ASSR periods was also highly correlated for each hemisphere and dipole (LH tangential: $\rho = 0.943$, $p < 0.001$; LH radial: $\rho = 0.883$, $p < 0.001$; RH tangential: $\rho = 0.991$, $p < 0.001$; RH radial: $\rho = 0.977$, $p < 0.001$, corrected).

Correlations between resting γ and ASSR induced γ power

There were no significant correlations between resting γ power and induced γ power in the baseline and ASSR periods in either group (Bonferroni correction: 2 dipoles × 2 hemispheres × 3 stimulation frequency conditions × 2 periods × 2 subject groups): HC, $\rho<|0.552|$, $p>0.816$ corrected; SZ, $\rho<|0.353|$, $p>0.125$ uncorrected.

Correlations between ASSR PLF and evoked power

Previously we reported that 40-Hz ASSR PLF and evoked power were correlated in HC, but not in an LH auditory cortex source in SZ[16]. Examining these relationships in the present data, we computed correlations between ASSR evoked power and PLF for each dipole at each stimulation frequency (Bonferroni correction: 2 dipoles × 2 hemispheres × 3 stimulation frequencies × 2 subject groups). In HC, PLF and evoked power were correlated for each dipole and stimulation frequency ($0.599<\rho<0.911$, $p<0.036$). In SZ, PLF and evoked power were also correlated for each dipole and stimulation frequency ($0.546<\rho<0.905$, $p<0.048$), except for the LH dipoles during 40-Hz stimulation (LH tangential: $\rho=0.257$, $p=0.904$; LH radial: $\rho=0.177$, $p>0.99$), and the LH tangential dipole during 20-Hz stimulation ($\rho=0.374$, $p=0.288$).

Correlations between γ measures and antipsychotic medication dosage

No significant or trend-level correlations were found between any γ measures (ASSR evoked power and PLF, induced γ, and resting-state γ) and antipsychotic medication dosage (chlorpromazine equivalents) even at uncorrected p levels (evoked power: $-0.247 < \rho < 0.268$, $p > 0.158$; PLF: $-0.214 < \rho < 0.294$, $p > 0.173$; induced γ: $-0.062 < \rho < 0.272$, $p > 0.199$; resting-state γ: $-0.149 < \rho < 0.296$, $p > 0.233$). These results did not change appreciably when the 2 non-medicated SZ were removed from the analyses.

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