IS FASTER ALWAYS BETTER? RATE OF STIMULATION AFFECTS AUDITORY-EVOKED RESPONSES IN SCHIZOPHRENIA

by

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ABSTRACT

Schizophrenia patients exhibit characteristic problems in early stages of auditory information processing, which may be related to cognitive dysfunction present in the illness. These problems are related to schizophrenia patients' inherent inability to generate and/or maintain evoked oscillatory rhythms in response to both transient and repetitive (steady-state) stimuli. These oscillatory rhythms underlie cortical middle- and late-latency auditory evoked responses (MLAERs), P1 and N1, and evoked oscillatory responses at the driving frequency of steady-state stimuli (SSRs). These evoked responses are indices of abnormal sensory encoding and temporal integration ability in schizophrenia. These abnormalities may be attributed to some fundamental characteristics of schizophrenia patients' auditory systems – characteristics whose sum effect is to reduce the signal-to-noise ratio during auditory information processing. The present study examined the hypothesis that increasing the rate of stimulation, i.e. increasing the number of stimuli presented per unit time, would increase signal power sufficiently to normalize evoked oscillatory responses in schizophrenia patients. Steady-state stimuli at various rates (5, 20, 40, 80, and 160 Hz) were presented to 12 normal

and 12 schizophrenia subjects while 248 sensor whole-cortex magnetoencephalography was recorded. The FFT power and inter-trial phase coherence in the delta and theta bands underlying MLAERs and in the SSRs at the driving frequencies of the respective rates of stimulation were examined for differences between groups, hemispheres, and rates of stimulation. Results indicated that schizophrenia patients were able to generate essentially normal steady-state responses in response to stimuli with durations sufficiently long enough to allow build-up of the SSR. Steady-state stimuli may also enhance patients' auditory integration and encoding abilities, perhaps through increased signal strength, as indicated by a lack of schizophrenia-normal differences on low-frequency evoked oscillations subserving the P1 and N1 MLAERs. Finally, the observation that evoked power and inter-trial phase coherence play divergent but complementary roles with regard to MLAER-associated low-frequency evoked oscillatory activity in both normal and schizophrenia subjects was illustrated. Understanding the mechanisms responsible for deficits in the ability to evoke oscillatory responses could help in understanding the relationship between the neuropathology and symptoms of schizophrenia.

INDEX WORDS: Schizophrenia, magnetoencephalography, P1, N1, Steady-state, Auditory-evoked response

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CHAPTER 1

Introduction

Schizophrenia patients' problems in processing auditory information are theoretically related to both the symptoms and fundamental neuropathology of this illness (Clementz, Geyer, & Braff, 1998; Ford, 1999; Javitt, 2000; Light & Braff, 1999; Potter, Summerfelt, Gold, & Buchanan, 2006; Umbricht & Krljes, 2005). Auditory hallucinations, sensory and working memory deficits, and difficulty differentiating signal from noise in the auditory environment are important clinical and neuropsychological features of schizophrenia (Ford, 1999; Goldman-Rakic, 1994; Salisbury, Shenton, Griggs, Bonner-Jackson, & McCarley, 2002; Schultz & Andreasen, 1999).

Some characteristic auditory stimulus processing differences between schizophrenia and normal groups are manifested in the middle- and late-latency auditory evoked response (AER)[1] components, those that occur at latencies between 10–70 ms post-stimulus onset (middle-latency) and between 50–500 ms (late-latency). Of the middle- and late-latency auditory evoked responses (MLAERs), the P1 and N1 (at 50 and 100 ms post-stimulus, respectively) are the earliest components that consistently show schizophrenia-normal differences – their amplitudes are typically lower in schizophrenia than normal subjects (Clementz & Blumenfeld, 2001; Ford et al., 2001; McCarley, Faux, Shenton, Nestor, & Adams, 1991; Myles-Worsley, 2002; Shelley, Silipo, & Javitt, 1999).

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[1] To avoid awkward abbreviations, AER is used throughout this paper to refer to both auditory evoked potentials (AEPs) of EEG and auditory evoked fields (AEFs) of MEG. For instance, the N1 AEP is also referred to as N1m or M100 for MEG data. Since EEG and MEG provide complementary information on the same components, the conventional names of components, e.g. P1 and N1, will be used here.

The P1 and N1 MLAERs are the earliest cortical responses to auditory input (Huotilainen et al., 1998; Näätänen & Picton, 1987). Neural generators of both P1 and N1 have an estimated source location in superior temporal cortex – in the planum temporale just posterior to Heschl's gyrus (Lu et al., 2007; Naatanen & Picton, 1987; Reite, Teale, Zimmerman, Davis, & Whalen, 1988; Reite et al., 1988; Yvert, Fischer, Bertrand, & Pernier, 2005). Additionally, thalamocortical projections are thought to play a role in the generation of P1 and N1 MLAERs. P1 is generated primarily in layer IV (which receives input directly from specific afferent projections from the medial geniculate nucleus; MGN), with possible contributions from supragranular layer neurons in primary auditory cortex (Barth & Di, 1991; Barth, Kithas, & Di, 1993). N1 results from subsequent activation of both supra- and infra-granular layer pyramidal cells, due to both parallel thalamocortical projections and intralaminar projections (Barth & Di, 1991).

Functionally, P1 and N1 index early stages of stimulus processing in auditory cortex. Incoming auditory stimuli obligatorily evoke both high- and low-frequency oscillatory activity (e.g. gamma, delta, and theta bands) in superior temporal cortex (Basar, Rosen, Basar-Eroglu, & Greitschus, 1987; Klimesch, 1999; Pantev et al., 1991). Following onset of an auditory stimulus, these evoked oscillations have points of maximal deflection near 50 and 100 ms – points at which the combined activity of the underlying neural sources are recorded at the scalp as the P1 and N1 MLAERs (e.g. Clementz & Blumenfeld, 2001; Johannesen et al., 2005; Klimesch, 1999; Naatanen & Picton, 1987). These evoked oscillations (and concomitant AERs) are associated with initial neural registration of the stimulus (Karakas & Basar, 1998) and encoding of new sensory information (Klimesch, 1999; Naatanen & Picton, 1987).

AERs arise from stimulus-evoked phasic firing of discrete neural ensembles (Mazaheri & Jensen, 2006; Shah et al., 2004) and/or phase reorganization of the ongoing (background) oscillatory neural activity (Brandt, 1997; Jansen, Agarwal, Hegde, & Boutros, 2003; Makeig et al., 2002). Thus, AER amplitudes are a function of a) the number of neurons activated and/or strength of activity evoked in cortical neurons, and b) the amount of pre-stimulus (background) oscillatory activity. For example, there is a negative correlation between pre- and post-stimulus theta power, i.e. high pre-stimulus theta is related to low post-stimulus theta (and, therefore, low amplitude P1 and N1 AERs; Basar, Basar-Eroglu, Roschke, & Schutt, 1989; Klimesch, Sauseng, Hanslmayr, Gruber, Freunberger, 2007; Rahn & Basar,1993).

Reduced AER amplitudes in schizophrenia patients, then, may be attributed to some fundamental characteristics of their auditory processing systems. Schizophrenia patients have shown 1) left temporal lobe anatomical and functional abnormalities (McCarley, Shenton, O'Donnell, & Nestor, 1993; Rockstroh et al., 1998), particularly associated with MLAER (P1 and N1) generation (Clementz et al., 2003; Rockstroh et al., 1998), 2) reduced excitatory drive on cortical pyramidal neurons, mediated by dysfunctional glutamatergic transmission in thalamocortical circuits (Javitt, Steinschneider, Schroeder, & Arezzo, 1996; Meador-Woodruff, Clinton, Beneyto, & McCullumsmith, 2003), and 3) deficient coordination between modulatory GABAergic interneurons and pyramidal neurons (Benes & Berretta, 2001; Coyle, 2004) in temporal cortex. Additionally, schizophrenia patients have abnormally increased background low-frequency activity at rest (Clementz, Sponheim, Iacono, & Beiser, 1994), and during information processing (Winterer et al., 2000). The sum effect of these dysfunctional

characteristics in schizophrenia is reduced signal-to-noise ratio in their auditory processing system – due to increased pre-stimulus low-frequency noise, reduced signal power, and increased noise following stimulus presentation (Winterer & Weinberger, 2004; Winterer et al., 2000) – effects which may be attributed to or exacerbated by left hemisphere dysfunction.

While MLAER amplitudes are typically lower in schizophrenia than normal subjects, these differences occur in response to transient stimuli (stimuli presented at repetition rates slow enough to allow the intervening brain activity to return to baseline), especially after longer (e.g. > 3 s) inter-stimulus-intervals (Blumenfeld & Clementz, 2001; Shelley et al., 1999). Given the aforementioned information processing abnormalities, however, a transient stimulus may provide insufficient information for effective processing by schizophrenia patients. A significant determinant of N1 (and possibly P1) amplitude is density of information presented per unit time in the first 25 – 50 ms after stimulus onset (Forss, Makela, McEvoy, & Hari, 1993). Auditory N1 amplitude can normally be increased by presenting bursts of steady-state (i.e. temporally dense) stimuli with frequencies up to at least 320 Hz, suggesting that N1 indexes information integration over time (Forss et al., 1993; Naatanen & Picton, 1987; Ross, Picton, & Pantev, 2002). Thus, steady-state stimuli may provide patients' neuronal ensembles with sufficient information to more effectively process auditory input, i.e. increase the signal-to-noise ratio in their auditory system.

Steady-state stimuli are presented at a sufficiently rapid rate that the brain responses to successive stimuli begin to overlap (Picton, John, Dimitrijevic, & Purcell, 2003; Regan, 1989). The steady-state stimulus drives the neurons to respond at the

same frequency as the stimulus, which results in a periodic response with a constant phase relationship to the repeating stimulus, the so-called steady-state response (SSR; Picton et al., 2003; Stapells, Linden, Suffield, Hamel, & Picton, 1984). Neural sources of the auditory SSR reside primarily in supratemporal auditory cortex (Hari, Hamalainen, & Joutsiniemi, 1989; Mäkelä et al, 1990; Picton et al., 2003), and may overlap with sources of transient MLAERs (e.g. Moratti et al., 2007). Other potential neural contributors to SSRs reside in thalamus and subcortical structures (Kuwada et al., 2002; Mäkelä et al, 1990), especially at higher frequency (> 80 Hz) steady-state stimulation. While the exact mechanism behind the SSR is unknown, it is theoretically related to the brain's intrinsic oscillatory properties (Hutcheon & Yarom, 2000; Llinas, 1988) and non-linear interactions of the neural generators of the SSR (Azzena et al., 1995; Santarelli et al., 1995).

Studies using steady-state stimulation have revealed abnormalities in the oscillatory properties of schizophrenia patients' neural systems (Brenner, Sporns, Lysaker, & O'Donnell, 2003; Clementz, Keil, & Kissler, 2004; Gilmore et al., 2004; Krishnan et al., 2005; Kwon et al., 1999; Light et al., 2006). The most consistent finding is decreased ability to generate and maintain synchronous neural activity (i.e. an SSR), especially at gamma band frequencies. Abnormal gamma band synchronization in schizophrenia patients' auditory system is theorized to mediate inefficient transmission of transient information and temporal integration ability (Kwon et al., 1999; Light et al., 2006), abnormalities that could theoretically underlie hallucinatory phenomena (Spencer et al., 2004; Tass, 1997). Thus, while increasing the density of information presented to the auditory system (using steady-state stimulation) may benefit schizophrenia patients'

auditory registration and integration abilities (i.e. increase P1 and N1 amplitudes to equal that of normal subjects), there may be a physiological limit to this benefit. It may be the case that patients' auditory processing efficiency can benefit from increased stimulus density only up to a point (≤ 40 – 80 Hz), and stimulus densities above that level could lead to further difficulties with auditory processing.

We (Gilmore et al., 2004) investigated this possibility recording dense-array EEG while presenting schizophrenia and normal subjects with steady-state stimuli composed of a 1 kHz pure tone amplitude modulated at 10, 20, 40, or 80 Hz. Results showed that the amplitude of normal subjects' low-frequency evoked oscillations (i.e. delta and theta band activity) associated with the P1 and N1 MLAERs systematically increased as a function of increasing rate of stimulation. As stimulus density increased from one stimulus in the first 50 ms (10 Hz, effectively a transient stimulus for P1 and N1 measurement) to two stimuli in the first 50 ms (20 Hz), schizophrenia subjects' low-frequency evoked oscillation amplitudes also increased, such that there was effectively no difference when compared to the normal group. Schizophrenia subjects demonstrated a low ceiling on their ability to handle high density auditory information, however. Increasing stimulus density to three (40 Hz) or four (80 Hz) stimuli in the first 50 ms resulted in a failure to increase MLAER-associated oscillation amplitudes. Patients were also unable to sustain a SSR at 40 Hz (cf. Kwon et al., 1999). These results suggest that steady-state stimuli, up to a point, provide the extra information needed for schizophrenia patients to more effectively integrate auditory information; pass that point and schizophrenia patients' auditory integration systems may be further compromised.

Ours (Gilmore et al., 2004) was the first study to systematically examine the effect of rate of stimulation on early cortical AERs in schizophrenia patients. While addressing some important issues regarding patients' auditory registration and integration abnormalities, Gilmore et al. also raised some interesting questions. First, that study's use of electroencephalographic (EEG) data and spectral power measures that were averaged across sensors over the whole head addressed the global effects of steady-state stimulation on AER generation. The effect of rate of stimulation on activity specific to auditory cortex, however, as well as any possible hemispheric laterality effects, need to be investigated (voltage data in Gilmore et al. suggested abnormal left hemisphere N1 activity in schizophrenia patients). Second, with respect to the ability to sustain a SSR, Gilmore et al. focused on the 40 Hz response, as this response had been extensively studied in schizophrenia, and is theorized to be the preferred resonant frequency of the auditory system (Basar et al., 1987; Galambos, Makeig, & Talmachoff, 1981). Patients' ability to sustain SSRs at other, especially higher, rates of stimulation needs to be addressed, particularly when neural ensembles are given sufficient time to build-up the SSR. The majority of studies have used relatively short steady-state stimulation times (≤ 500 ms; Gilmore et al., 2004; Kwon et al., 1999; Light et al., 2006; Teale, Carlson, Rojas, & Reite, 2003), which may be insufficient to generate a stable SSR in schizophrenia patients. Finally, the role of phase coherence, the extent to which a stimulus serves to organize, or align, the phases of oscillatory responses, needs to be examined. Decreased phase coherence has been suggested to underlie patients' abnormal SSRs (e.g. Clementz et al., 2004; Kwon et al., 1999).

The present study will build upon and extend the findings of Gilmore et al. (2004) with regard to the ability of increased rate of stimulation to improve schizophrenia patients' auditory integration abilities. To address the aforementioned issues, the present study will use magnetoencephalography (MEG), which is particularly suited for study of the auditory cortex since neurons oriented perpendicular to the sylvian fissure (i.e. tangential to the surface of the skull) have been shown to be the major contributors to the magnetic fields evoked over primary auditory cortex (Hari, 1989; Zimmerman, Reite, & Zimmerman, 1981). This advantage, along with MEG's high temporal resolution, can provide a more accurate representation of the neural activity in auditory cortical substrates of P1 and N1 AERs and the SSR.

The information processing abnormalities in schizophrenia discussed earlier (reduced excitatory drive on cortical pyramidal neurons, deficient coordination between modulatory interneurons and pyramidal neurons, compromised temporal integration ability, etc.), and previous findings, lead to the present hypothesis that an abnormal functional relationship exists between the rate at which auditory stimulation is presented and the strength of the evoked response in patients' auditory cortices. In particular, this dysfunctional relationship may result from attempts by patients' brains to compensate for these processing abnormalities. Patients could attempt to overcome reduced excitatory drive on cortical neurons, for instance, by increasing the gain in the thalamocortical system. This compensatory mechanism might be successful in allowing more efficient processing of incoming auditory information, particularly more rapidly presented information (e.g. steady-state stimuli), thus equalizing patients' SSRs and phase coherence to the level of that of normal subjects, at least for rates below those in

the gamma band. This compensation may not work, however, for low frequency oscillatory neural responses (e.g. delta and theta bands, which are associated with the MLAERs) since low frequency noise will be increased along with the signal. Thus, low-frequency activity around the time of P1 and N1 AERs will remain characteristically smaller in schizophrenia patients than normal subjects, especially for faster rates of stimulation (≥ gamma band), since there may be a physiological limit on patients' brains to integrate incoming stimuli at such rapid rates (e.g. Kwon et al., 1999). Finally, these effects will be pronounced in left hemisphere, due to anatomical and functional abnormalities in patients' left temporal lobes (e.g. McCarley et al., 1993).

CHAPTER 2

Methods

Subjects

Twelve schizophrenia patients (Mean age=44 years, SD=8; 2 females; all right-handed) and 12 normal subjects (Mean age = 40 years, SD=10; 4 females; all right-handed) were recruited to participate in this study. Data were collected at the Brain Sciences Center located at the Minneapolis VA Medical Center. Schizophrenia patients were recruited from the outpatient clinics of the Minneapolis VA Medical Center, community support programs for the mentally ill, and a county mental health clinic. Normal subjects were recruited through announcements placed in the community, the Minneapolis VA Medical Center, and in newsletters for veterans and fraternal organizations. Subjects were absent of current alcohol or drug abuse, past drug dependence, a current or past central nervous system disease or condition, history of head trauma, or potentially confounding treatments (e.g. electroconvulsive therapy). The Structured Clinical Interview for DSM-IV (SCID-IV; First et al., 2002) was used to generate research diagnoses of schizophrenia, and the Scale for the Assessment of Negative Symptoms (SANS, Andreasen, 1981) and the Scale for the Assessment of Positive Symptoms (SAPS, Andreasen, 1983) were used to quantify the severity and extent of specific psychotic symptoms. All subjects provided written informed consent. This study was approved by the University of Georgia Institutional Review Board.

Stimuli and procedure

Steady-state stimuli consisted of 1500 ms duration bursts of broadband noise (bandpass filtered 500 – 4000 Hz) amplitude modulated at 5, 20, 40, 80, 120, or 160 Hz. (The 120 Hz stimulus was subsequently dropped from further processing due to technical issues). Amplitude modulation periodically varies the amplitude of the carrier noise burst based on a sinusoidal modulating signal at the desired frequency and, in the present study, 100% modulation depth. Broadband noise was used, as opposed to a pure tone carrier frequency, because the noise activates a broader region of the basilar membrane, resulting in greater amplitude of response (Picton et al., 2003). Noise bursts were presented binaurally through Etymotic insert earphones at 76 dB SPL.

To control attention to the task, unmodulated noise bursts lasting 1500 ms were presented on 10% of trials, to which subjects were required to respond with a button press. Unmodulated bursts were evaluated only for percentage correct responses and were not included in other analyses. Each frequency of steady-state stimulation (the 'driving frequency') was presented in a separate block, with each block consisting of 90 steady-state stimuli and 10 unmodulated noise bursts randomly intermixed with the steady-state stimuli, presented with an average 3 s ISI (range 2.7 – 3.3 s).

Data acquisition

Data were collected using a 248-channel axial gradiometer whole-cortex MEG system (Magnes 3600 WH, 4D-Neuroimaging, San Diego, CA, USA). The MEG sensor array is located within an electromagnetically shielded room to reduce environmental noise. To monitor unwanted subject motion, three frequency specific coils attached to the fiducial locations of the left and right preauricular points (just anterior to the tragus of

the ear, bilaterally) and the nasion (the skin over where the nasal bone joins the skull) were consecutively activated before and after data acquisition, thereby locating the head in relation to the sensors. A subject's data was considered unusable if coil positions collected at the beginning and end of the session differed by more than 5 mm in any plane (only one subject failed this criterion, and was not used in the study). Digitization of scalp and fiducial points were carried out with a Polhemus Fastrak 3-D digitizer (Polhemus, Colchester, VT, USA). MEG data were acquired at 1,017.25 Hz and filtered down to 0.1 – 400 Hz during acquisition.

Eye movements and eyeblinks were monitored using three electrodes placed around the right eye of each subject; they were located: (1) immediately lateral and superior to the supraorbital notch, (2) at the lateral canthus, and (3) over the center of the inferior orbital rim. The resulting electrooculogram (EOG) was also sampled at 1,017.25 Hz.

MEG data screening

MEG data were screened and segmented around stimulus triggers using BESA 5.0 software (MEGIS Software, Grafelfing, Germany). Raw data were inspected for bad channels and trials containing blink or cardiac artifacts. Bad channels were interpolated (no more than 5% of channels for any subject) using a spherical spline interpolation method (as implemented in BESA). If necessary, blink and cardiac artifacts were removed using Independent Components Analysis (EEGLAB 6.0; Delorme & Makeig, 2004). Trials containing activity greater than 3000 femtoTesla (fT) were eliminated from further processing. Data were resampled down to 1000 Hz and digitally bandpass filtered from 1 – 50 Hz for the 5, 20, and 40 Hz conditions, 1 – 100 Hz for the 80 Hz

condition, and 1 – 200 Hz for the 160 Hz conditions (zero phase filter; rolloff: 6 dB/octave for all highpass filters, 48 dB/octave for all lowpass filters). Trials consisted of 3000 ms epochs, beginning 500 ms prior to stimulus onset, averaged separately for each steady-state frequency within each subject.

MEG Analysis

In order to assess the frequency characteristics of the evoked (SSR and MLAER) responses, the averaged trials for each condition for each subject were submitted to a moving window Fast Fourier Transform (FFT) analysis. For each MEG sensor, each time point of the MEG data was multiplied by a 500-sample Hanning window (corresponding to 500 ms) beginning 250 ms before stimulus onset and ending 2250 ms post-stimulus onset (to account for the 250 ms time uncertainty in both directions). The Fourier components were calculated within this window at each time point as it was shifted, point-by-point, across the epoch. This resulted in a time-frequency spectral power distribution for each rate of stimulation with 2 Hz resolution (e.g. Figures 3, 4, & 7).

These data were then normalized by dividing the power value of each post-stimulus time-frequency point by the respective frequency's baseline power, calculated as the mean power from 200 to 20 ms pre-stimulus onset (Wilson et al., 2007; Wilson, Rojas, Reite, Teale, & Rogers, 2007). Using such a temporal window functioned to minimize the influence of filtering artifacts on baseline power calculations. For each hemisphere, a group of six channels with maximal normalized power at each driving frequency (determined by averaging over all steady-state conditions at the respective driving frequencies; see Figure 1) was then chosen for subsequent analyses.

For SSR analyses, the mean power of each driving frequency over the time range from 200 to 1500 ms post-stimulus onset (i.e. from 200 ms to stimulus offset) was determined per hemisphere for each participant. This post-stimulus window was chosen to focus analyses on the SSR rather than transient evoked components. For the transient responses (P1 and N1 MLAERs) of interest, normalized FFT power was averaged 1) within the delta and theta band frequency range (2 – 8 Hz) and 2) within the time range 50 – 250 ms post-stimulus. Figure 2 shows magnetic field topography maps at the peaks of P1 and N1.

For inter-trial coherence analyses (ITC; an indication that the source activity at a given time and frequency in single trials becomes phase-locked), the same moving window FFT approach described above was applied to the single trial data to estimate single trial power. ITC was determined by normalizing the phase vectors composed of the real and imaginary parts of the FFT components for each time-frequency step by the corresponding length of the vectors (i.e. amplitude of the FFT component). For each time-frequency step, the normalized phase vectors were added across trials of each rate of stimulation condition and subject. This sum of the phase vectors was divided by the corresponding number of trials, resulting in the Rayleigh statistic R (Jammalamadaka & SenGupta, 2001). The R value is bound between zero and one. The higher the ITC of an oscillatory response, the more unimodal is the distribution of the phase vectors, and the closer the value of R will be to one. R values close to zero represent uniform (random) orientations of the phase vectors.

Statistical Analysis

MLAERs (the mean power in the delta and theta bands averaged from 50 – 250 ms post-stimulus onset) were analyzed using a 2 x 2 x 5 mixed-model ANOVA, with Group (NP, SZ) as the between-subjects factor and Hemisphere (Left, Right) and Rate of stimulation (5, 20, 40, 80, 160 Hz) as the within-subjects factors. SSRs (mean power at each driving frequency from 200 to 1500 ms post-stimulus onset) were analyzed using a 2 x 2 x 4 mixed-model ANOVA, with Group (NP, SZ) as the between-subjects factor and Hemisphere (Left, Right) and Rate of stimulation (20, 40, 80, 160 Hz) as the within-subjects factors (the 5 Hz rate of stimulation was excluded as it is does not evoke a steady-state response). Statistical analyses of ITC (R-values) associated with the SSR and MLAERs in response to the 20, 40, and 80 Hz rates of stimulation were performed using a 2 x 2 x 3 mixed-model ANOVA, with Group (NP, SZ) as the between-subjects factor and Hemisphere (Left, Right) and Rate of stimulation (20, 40, 80 Hz) as the within-subjects factors.

CHAPTER 3

Results

Behavioral Results

Mean percent correct responses to the unmodulated noise bursts, averaged over all steady-state conditions, did not differ between the normal (Mean=96.7%, SD=3.9) and schizophrenia (Mean=93.3%, SD=5.4) groups, $t(22)=1.74$, $p=0.09$. Both groups were equally attentive to the task.

Time-Frequency Results

Time-frequency spectrograms resulting from FFT analyses are shown in Figures 3, 5, & 7. Figure 3 shows the broadband spectrogram (from 0 – 180 Hz), which encompasses both the low-frequency (MLAER) and driving frequency (SSR) responses, averaged over normal and schizophrenia groups, for each hemisphere and rate of stimulation.

Low-frequency evoked response. Figure 4 shows the normalized mean power associated with the early cortical MLAERs (the mean power in the delta and theta bands averaged from 50 – 250 ms post-stimulus onset) for each group, hemisphere, and rate of stimulation. For the MLAER-associated low-frequency activity, there was no significant effect or interaction involving Group. Thus, low-frequency oscillatory activity evoked by onset of the steady-state stimuli did not differ between the normal and schizophrenia subjects around the time of the P1 and N1 MLAERs. There was, however, a main effect of Rate of stimulation, $F(4,88)=5.51$, $p<0.001$, as well as an interaction between Rate and Hemisphere, $F(4,88)= 3.54$, $p=0.009$. Figure 5 shows the

MLAER time-frequency spectrograms, averaged over normal and schizophrenia groups (as there were no significant results involving group), for each hemisphere and rate of stimulation.

Steady-state responses. Figure 6 shows the normalized mean power at the driving frequency (the mean power over the time range from 200 to 1500 ms post-stimulus onset) for each group, hemisphere, and rate of stimulation. As with the low-frequency evoked responses, analyses of the mean power at each driving frequency revealed no significant effect or interaction involving Group. Thus, normal and schizophrenia subjects' steady-state response power was effectively equal. There were, however, main effects of Hemisphere, $F(1,22)=14.99$, $p<0.001$ and Rate of stimulation, $F(3,66)=65.66$, $p<0.001$, as well as an interaction between Hemisphere and Rate, $F(3,66)=13.99$, $p=0.01$. The SSR in the right hemisphere was stronger than that in the left hemisphere, for all driving frequencies above 20 Hz. Figure 7 shows the driving frequency time-frequency spectrograms, averaged over normal and schizophrenia groups (as there were no significant results involving group), for each hemisphere and rate of stimulation.

Inter-Trial Coherence (ITC) Results

Low-frequency evoked response. Figure 8 shows the mean R-values for the ITC associated with the early cortical MLAERs (the mean R-values in the delta and theta bands averaged from 50 – 250 ms post-stimulus onset) for each group, hemisphere, and rate of stimulation. For ITC underlying the P1 and N1 MLAERs, the only significant result was a main effect of Group, $F(1,22)=5.57$, $p=0.03$. Normal subjects had significantly greater inter-trial phase coherence associated with their MLAERs than did

schizophrenia patients. Figure 9 shows the MLAER time-frequency ITC spectrograms, averaged over left and right hemispheres and over all rates of stimulation (as there were no significant results involving these factors) for normal and schizophrenia groups.

Steady-state responses. Figure 10 shows the mean R-values for the ITC associated with the driving frequency (the mean R-values over the time range from 200 to 1500 ms post-stimulus onset) for each group, hemisphere, and rate of stimulation. The results of ITC analyses for the SSR mirrored those of the power analyses. Analyses revealed no significant effect or interaction involving Group for any driving frequency. Thus, inter-trial phase coherence was present for both normal and schizophrenia subjects' steady-state responses. As with the power analyses, there were main effects of Hemisphere, $F(1,22)=63.24$, $p<0.001$, and Rate of stimulation, $F(2,44)=82.43$, $p<0.001$, as well as an interaction between Hemisphere and Rate, $F(2,44)=11.55$, $p<0.001$. ITC in the right hemisphere was greater than that in the left hemisphere, and ITC was stronger for the 40 Hz driving frequency. Figure 11 shows the driving frequency time-frequency ITC spectrograms, averaged over normal and schizophrenia groups (as there were no significant results involving group), for each hemisphere and rate of stimulation.

CHAPTER 4

Discussion

The goal of the present study was to investigate the relationship between the rate of presentation of auditory stimuli and the ability of normal and schizophrenia subjects' auditory neural systems to integrate and process this information. This relationship was examined recording MEG while presenting auditory steady-state stimuli for 1500 ms at varying rates of stimulation and studying both the steady-state responses and evoked low-frequency oscillations associated with the MLAERs, P1 and N1. Further, analyses were constrained to activity in sensors over auditory cortex bilaterally, thus allowing examination of evoked responses emanating from these areas.

Results revealed no significant differences between schizophrenia and normal subjects on any measure except the inter-trial phase coherence underlying the MLAER-associated low-frequency evoked responses. Differences in the power of evoked low-frequency responses and the SSRs occurred only as a function of hemisphere and rate of stimulation. While these hemisphere and rate effects did not significantly differ between normal and schizophrenia subjects, both groups showed differing trends with regard to the power of the evoked low-frequency responses. Responses over normal subjects' left auditory cortex tended to increase as a function of increasing rate of stimulation, at least up until 80 Hz, while their right hemisphere responses peaked at 40 Hz. Schizophrenia subjects' right hemisphere responses remained relatively stable across all rates of stimulation. Their evoked responses were weaker, however, in left

hemisphere at the slower rates of stimulation, increasing to about equal the level of their right hemisphere responses at 40 Hz. Power and ITC of steady-state responses were generally stronger over right hemisphere for both normal and schizophrenia subjects (cf. Ross, Herdman, & Pantev, 2005), and the 40 Hz steady-state response was strongest in both groups, consistent with the theory that 40 Hz is the preferred resonant frequency of the auditory system (Basar et al., 1987; Galambos et al., 1981)..

Thus, the hypothesized normal-schizophrenia differences of the present study were not realized, except for the low-frequency ITC. The aforementioned trends in the data were, however, in line with present hypotheses that normal subjects' MLAERs would increase as a function of increasing rate of stimulation, that schizophrenia subjects would have a limit near 40 Hz on the capacity for steady-state stimuli to enhance their auditory integration abilities (as indexed by MLAERs), that longer steady-state stimuli would enhance patients' steady-state responses, and that schizophrenia subjects' left hemisphere responses would be compromised (as they tended to be for slower driving frequencies in the present study).

More clear-cut results were found with regard to steady-state responses. Schizophrenia subjects' SSRs were essentially equal to that of normal subjects, across rates of stimulation and hemispheres. This finding was consistent with the present study's hypothesis that the short stimulation times (≤ 500 ms) used in previous studies may be insufficient to generate a stable SSR in schizophrenia patients, especially at higher frequencies. Supporting evidence for this hypothesis comes from Clementz, Keil, & Kissler (2004). Using visual steady-state stimuli with longer (2, 4, and 6 s) stimulation times, Clementz et al. (2004), demonstrated that patients' SSRs have a delayed buildup

from the time of stimulus onset to their maximum amplitudes. Patients' SSR amplitudes differed from normal for the first second following stimulus onset, suggesting that it may take this long to reach a stable SSR. For the one second preceding stimulus offset, patients' SSR amplitudes did not differ from normal for the 2 s and 4 s stimulation times, but the groups did differ for the 6 s stimulation time. These results suggest that, while schizophrenia patients' SSR may take time to buildup, they may be able to sustain the response for a longer period (at least 4 – 6 s). Thus, steady-state stimuli presented for a sufficient time period may allow patients' neural ensembles to more successfully process and integrate the incoming information. While the present study did not specifically address possible delayed buildup of the SSR in the auditory system, patients' SSR power and ITC, averaged over stimulation time, were equalized to those of normal subjects with the 1.5 s duration stimulus.

A study recently completed in our lab (Clementz & Gilmore, 2007, in preparation) also presented 1.5 s auditory steady-state stimuli at various driving frequencies, between 16 and 44 Hz, to normal and schizophrenia subjects. The resultant SSRs in that study were actually stronger in schizophrenia than in normal subjects. In addition, the low-frequency (delta and theta) evoked responses associated with the P1 and N1 MLAERs were smaller in schizophrenia subjects. Thus, in response to steady-state stimulation, schizophrenia subjects had increased driving frequency power, yet their low-frequency evoked power remained reduced compared to that of normal subjects. Further, schizophrenia subjects had increased low-frequency activity, around 4 Hz, that was not time-locked to the onset of the stimulus and was present both pre- and post-stimulus onset.

The results of this previous study (Clementz & Gilmore, 2007 in preparation) added evidence for our hypotheses that 1) schizophrenia patients suffer from a constitutional information processing dysfunction related to weak signal strength and compromised signal-to-noise-ratio in their auditory systems, and 2) patients may have developed a possible compensatory mechanism that their brains use in an attempt to overcome this deficiency. These propositions are in accord with a prevailing theory that schizophrenia is associated with 1) reduced excitatory drive on cortical pyramidal neurons, mediated by hypofunctional glutamatergic NMDA receptor transmission in thalamocortical circuits (Coyle, Tsai, & Goff, 2003; Javitt, 2007; Javitt et al., 1996; Meador-Woodruff et al., 2003) and 2) deficient coordination between modulatory GABAergic interneurons and pyramidal neurons (Benes & Berretta, 2001; Coyle, 2004).

An effect of NMDA hypofunction on neural processing is reduced excitatory drive on cortical glutamatergic neurons from thalamocortical afferents, i.e. reduced signal power. This inherently reduced signal power results in the consistently lower than normal cortical evoked responses to transient stimuli in schizophrenia (e.g. Butler et al., 2005; Butler et al., 2007). NMDA hypofunction also plays a role in schizophrenia patients' reduced ability to generate and maintain oscillatory activity, including steady-state responses (Grunze et al., 1996; Kwon et al., 1999; Phillips & Silverstein, 2003). While not completely understood, it is theorized that inhibitory local circuit neurons in the thalamocortical loop play a major role in the primary generation of oscillatory, especially high frequency (≥ gamma), rhythms, while NMDA-receptor activity has a role in controlling their strength, duration, and synchronization (Phillips & Silverstein, 2003), through recurrent input to inhibitory GABA-ergic neurons (Grunze et al., 1996; Kwon et

al., 1999). Consequently, with regard to steady-state responses, reduced NMDA-receptor activity is at the core of why schizophrenia patients typically generate weaker SSRs with decreased phase coherence that are unable to be maintained over a long period, and that take longer to return to baseline following stimulus offset (Brenner et al., 2003; Clementz et al., 2004; Gilmore et al., 2004; Krishnan et al., 2005; Kwon et al., 1999; Light et al., 2006).

Hypotheses of our previous study (Clementz & Gilmore, 2007, in preparation), and of the present study, were based on the theory that the neural disturbances found in schizophrenia are actually a result of patients' brains attempting to overcome this constitutional NMDA-receptor dysfunction. Over the course of development, schizophrenia patients' brains attempt to compensate for reduced excitatory drive by increasing gain control in the thalamocortical system. Increasing the gain serves to increase the power of the incoming signal. As an analogy, consider an amplifier system such as a home or car stereo system. Gain controls on an amplifier are essentially volume controls that allow adjustment of the incoming signal to the amplifier so that the amplifier works well with the receiver (the receiver is the unit that ties together the various components of the system; appropriate in the present context, the receiver is sometimes called the "head unit"). If the head unit has a low voltage output, turning the volume all the way up may still be insufficient to drive the amplifier to full power (Singmin, 1999). As with a low voltage amplifier system, the schizophrenia brain has insufficient input signal power (reduced excitatory drive), originating early in the information processing stream, at or before the level of thalamus (Butler et al., 2005; Leavitt et al., 2007; Meador-Woodruff et al., 2003). Increasing the gain in the

thalamocortical system, then, should strengthen incoming signal power and increase the cortical evoked responses of schizophrenia patients to be at least equal to those of normal subjects. This result, unfortunately, is not always the case, because there is not a simple linear relationship between increasing gain and signal power. Increasing the gain in a system does increase signal, but it also increases noise (Motchenbacher & Connelly, 1993), resulting in a paradoxical decrease in signal-to-noise-ratio, especially at lower frequencies. Given the 1/f nature of noise in neural systems (the power spectral density of the noise is proportional to the reciprocal of the frequency (f), i.e. noise in low frequency bands is stronger than noise in higher frequency bands; Buzsaki, 2006), low frequency noise, in the same bands as the MLAERs P1 and N1, is increased. Previous findings of smaller AERs to transient stimuli (Clementz & Blumenfeld, 2001; Ford et al., 2001; McCarley et al., 1991; Myles-Worsley, 2002; Shelley et al., 1999) and increased low frequency background noise (Clementz et al., 1994) in schizophrenia are in accord with this theory.

Results of our previous studies (Clementz & Gilmore, 2007, in preparation; Gilmore et al., 2004) were also in accord with this theory. These studies found that steady-state stimuli apparently increased the incoming signal power such that 1) patients' MLAER-associated low-frequency activity was increased to essentially equal that of normal subjects (at least below gamma band driving frequencies), 2) low-frequency background "noise" was increased in patients, and 3) longer duration steady-state stimuli resulted in stronger driving frequency responses (SSRs) in patients, a possible indication that patients' thalamocortical systems are being overdriven – a consequence of increasing the gain in the system.

Using the same 1500 ms duration noise burst steady-state stimuli as in Clementz and Gilmore (2007, in preparation), the present study had a different outcome. There were no indications of the maladaptive consequences related to increased gain, as seen in previous studies (i.e. no indications of increased low-frequency noise, of overdriven thalamocortical loops, etc.). It is important, then, to consider the differences between these studies that may account for the observed results. The main difference is in the data collection techniques used. These previous studies used EEG, while the present study used MEG. Thus, different results may be a function of the differing sensitivities of each method to particular neural activity.

MEG is preferentially sensitive to superficial tangential currents, whereas EEG also obtains significant contributions from deep and radial sources (Fuchs et al., 1998; Lounasmaa, Hamalainen, Hari, & Salmelin, 1996). EEG auditory evoked potentials typically have a widespread distribution, whereas evoked auditory magnetic fields are more localized to the general area of the primary auditory cortex and diminish rapidly in amplitude as a function of increasing distance between the sensors and the source (Reite, Edrich, Zimmerman, & Zimmerman, 1978). Thus, MEG is sensitive to auditory cortical sources without influence of neural activity outside this area. Figure 1 nicely illustrates this point. Both P1 and N1 magnetic fields have distinct dipolar patterns over superior temporal cortex bilaterally. P1 and N1 potential topographies as recorded with EEG, however, typically show more widespread dipolar patterns, with one pole being distributed over central superior areas of the head and the opposite pole located inferiorly on either side of the head. The general implications of these facts are that auditory EEG data contain neural activity from outside of auditory cortex, while auditory

MEG data is specific to those auditory cortex neurons oriented tangentially to the surface of the skull (e.g. Edgar et al., 2003; Huang et al., 2003). It seems to be the case, then, that there are strengths and weaknesses for both EEG and MEG with regard to investigating dysfunctional gain control in schizophrenia patients' thalamocortical systems.

Low-frequency oscillatory activity (i.e. delta, theta, alpha) is typically generated in areas outside primary auditory cortex, both cortical and subcortical (e.g. Klimesch, 1999; Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007; Timofeev & Steriade, 1996). The increased low-frequency activity seen in EEG recordings of schizophrenia patients, then, may not be specific to their auditory processing systems, but a more general dysfunction that simply interferes with normal generation of auditory evoked responses. Lack of normal-schizophrenia differences in low-frequency evoked power in the present study lends support to this proposition. The auditory cortical neural ensembles to which MEG is most sensitive may in fact operate normally, or not be as susceptible to the processing deficiencies found in schizophrenia patients, and only without interference from sources of noise outside auditory cortex can this be detected.

These different sensitivities of EEG and MEG also affect detection of the SSR. As discussed earlier, SSRs arise from the interaction between glutamatergic and GABA-ergic neurons in periodically recurrent thalamocortical loops. Thus, unlike P1 and N1 MLAERs, whose sources reside almost exclusively in supratemporal auditory cortex (Lu et al., 2007; Naatanen & Picton, 1987; Reite et al., 1988), generators of auditory SSRs reside in supratemporal auditory cortex (Hari et al., 1989; Mäkelä et al, 1990) as well as in thalamus and subcortical structures (Kuwada et al., 2002; Mäkelä et al, 1990).

In this instance, EEG's ability to "see" beyond superficial cortical sources allows a more complete picture of the mechanisms underlying the SSR, and particularly, the maladaptive consequences of increased gain in schizophrenia patients' thalamocortical systems. This could account for the findings of stronger SSRs in schizophrenia patients than normal subjects using EEG in Gilmore and Clementz (2007, in preparation), and the equalization of SSRs between normal and schizophrenia subjects in the present study using MEG. MEG only detects the cortical end of the thalamocortical loop, missing an important piece of the overall picture.

Given these strengths and weaknesses of EEG and MEG, the method which would seem to yield the best and most precise information about auditory processing abnormalities in schizophrenia is the simultaneous combination of EEG and MEG. Combination of EEG and MEG would also serve to enhance the ability to localize the intracranial sources of these evoked responses. It is important to note that the data from these studies (Clementz & Gilmore, 2007; Gilmore et al., 2004; the present study) were analyzed in sensor space, i.e. potentials and fields recorded at the sensors, or time-frequency analyses derived from these potentials and fields. Source localization, using equivalent current dipoles or distributed source configurations, may provide more precise information regarding the activity of the neural activity subserving the MLAERs and SSRs.

An important positive result in the present study with regard to a difference between normal and schizophrenia groups was found in the inter-trial phase coherence underlying the MLAER-associated low-frequency evoked responses. Schizophrenia subjects showed significantly lower ITC than normal, regardless of hemisphere or rate

of stimulation. Therefore, patients demonstrated a generally reduced capacity to generate synchronized, phase-locked low-frequency oscillations in response to the onset of a steady-state stimulus. This reduced ITC is in contrast to the lack of schizophrenia-normal differences in power of the evoked low-frequency responses. These divergent results suggest that evoked power and inter-trial coherence measures may reflect related but different aspects of the auditory information processing system (e.g. Light et al., 2006). One relevant theory posits that phase alignment serves a filtering function that enhances the signal-to-noise ratio in neural systems (e.g. Moratti et al., 2007; Steinmetz et al., 2000). In the present context, the reduced ITC subserving evoked low-frequency activity in auditory cortex, accompanied by normal ITC at the driving frequency of the steady-state stimulus, found in the present study may be a measure of the dysfunctional attempt at increasing signal power through gain control in schizophrenia patients' thalamocortical systems. Comparing single-trial power changes with the present ITC results could more definitively determine the relationship between power and phase in generation of oscillatory activity in schizophrenia.

Conclusions

The present study illustrated the complex relationship between rate of stimulation, evoked oscillatory rhythms, and the mechanisms underlying these oscillations in both normal and schizophrenia subjects. Results indicated that schizophrenia patients are able to generate essentially normal steady-state responses in response to stimuli with durations sufficiently long enough to allow build-up of the SSR. Steady-state stimuli may also enhance patients' auditory integration and encoding

abilities, perhaps through increased signal strength, as indicated by a lack of schizophrenia-normal differences on low-frequency evoked oscillations subserving the P1 and N1 middle- and late-latency auditory-evoked responses. Given the trends in the evoked low-frequency data, though, larger sample sizes may be warranted to see these results solidified. Finally, the observation that evoked power and inter-trial phase coherence play divergent but complementary roles with regard to MLAER-associated low-frequency evoked oscillatory activity in both normal and schizophrenia subjects was illustrated.

A limitation of this study is that the medications of the schizophrenia patients were not taken into account. The roles, if any, that the different classes of neuroleptic medications play in the relationship between rate of stimulation and evoked oscillatory rhythms needs to be addressed. Previous studies have shown both a relationship (Hong et al., 2004) and lack of a relationship (Kwon et al., 1999) between medication status and evoked oscillations, particularly in the gamma band. Hong et al. (2004) found that patients taking atypical antipsychotics had stronger 40 Hz evoked power than normal subjects, while Kwon et al. (1999) found no correlation between evoked gamma power and medication status of schizophrenia patients. Thus, the extent to which medication affects these measures needs further investigation.

Taken together with our previous studies (discussed above), the present study also illustrated the strengths and weaknesses of EEG and MEG, and their sensitivities to different, but complementary neural activity. Particularly, to most thoroughly test the hypothesis of dysfunctional adaptive neural gain control in schizophrenia will require the

use of both techniques, preferably simultaneously to enhance source localization ability of both superficial cortical and deeper subcortical and thalamic sources.

This hypothesis is important because dysfunctional adaptive neural gain control is theoretically responsible for schizophrenia patients' inherent inability to generate and/or maintain evoked oscillatory rhythms in response to both transient and repetitive (steady-state) stimuli. Oscillatory activity is theorized to support communication, both short- and long-range, among neural ensembles (Başar et al., 2001; Klimesch, 1999; Ribary, 2005). Theta frequencies have been associated with sensory encoding and memory performance (Klimesch, 1999; Klimesch et al., 2004). Gamma range frequencies, in particular, are critical for efficient cortico-cortical communication (Rodriguez et al., 1999, Traub et al., 1996), assessment of the temporal dynamics of cortical networks (Kaiser & Lutzenberger, 2005), and perceptual "binding", the integration of information into a particular percept (Joliot, Ribary, & Llinas, 1994; Pantev et al., 1991; Traub et al., 1996). These and other cognitive domains subserved by neural oscillations (e.g. sensory encoding, working memory, long-term memory, attention) are those in which schizophrenia patients have shown deficits (Ford, 1999; Goldman-Rakic, 1994; Salisbury et al., 2002; Schultz & Andreasen, 1999). Thus, reduced ability to generate and/or maintain oscillatory neural responses in schizophrenia must underlie their cognitive deficits. Understanding the mechanisms responsible for these deficits could help in understanding the relationship between the neuropathology and symptoms of schizophrenia.

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Figure 1. MEG sensors over each hemisphere showing highest FFT values

MEG sensors over each hemisphere showing highest FFT power grand averaged over groups and all rate of stimulation conditions. Small circles represent locations of MEG sensors, projected onto the scalp.

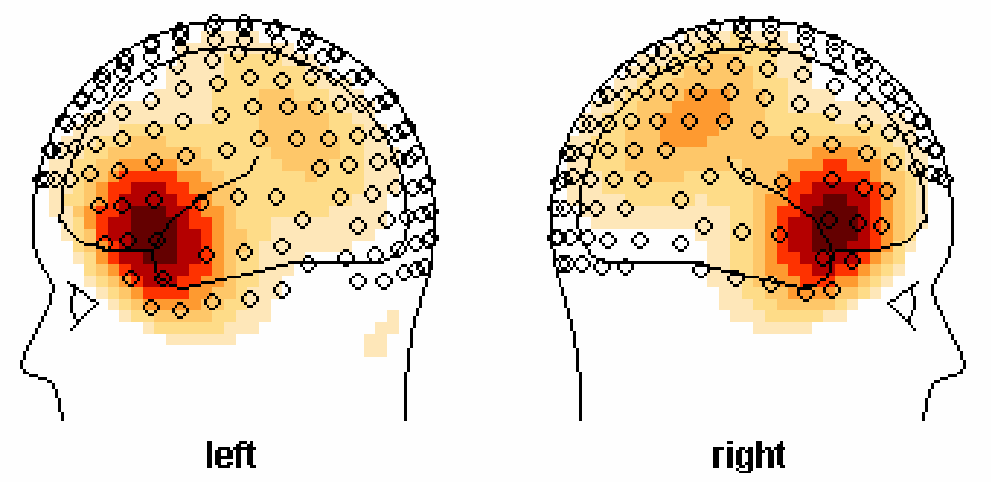

Figure 1. MEG sensors over each hemisphere showing highest FFT values

Figure 2. Magnetic field topography for P1 and N1 AERs projected onto scalp

Averaged magnetic field topographies at the peak of the P1 and N1 AERs projected onto the scalp of the normal (NP) and schizophrenia (SZ) groups. Scale, in femtoTeslas (fT), is shown at lower right.

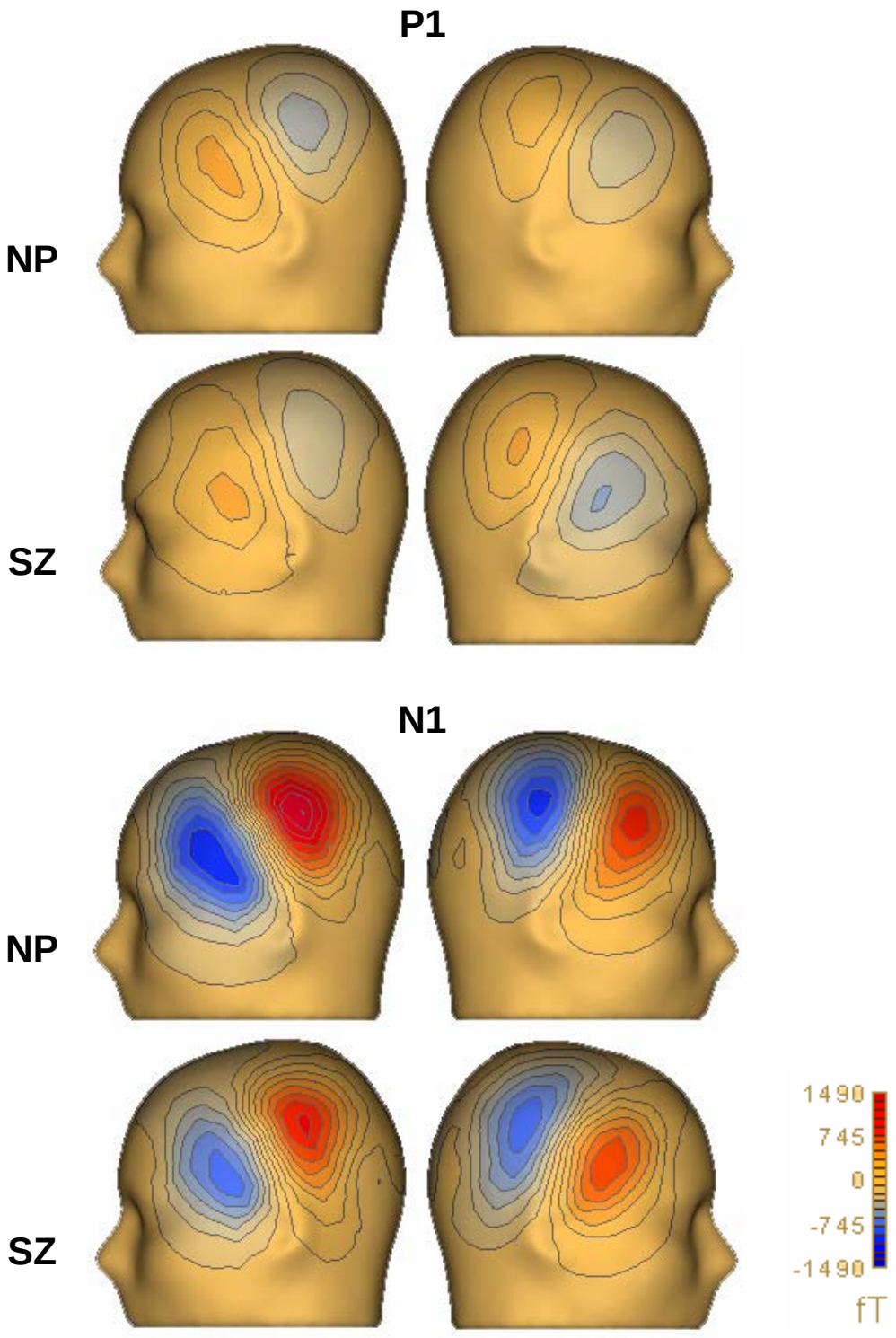

Figure 2. Magnetic field topography for P1 and N1 AERs projected onto scalp

Figure 3. Broadband time-frequency power spectrogram (from 0 – 180 Hz)

Broadband time-frequency power spectrograms, averaged across normal and schizophrenia groups, at each rate of stimulation (5, 20, 40, 80, & 160 Hz), averaged over sensors in left (LH) and right (RH) hemispheres. Time is on the x-axis (-250 – 2250 ms; stimulus onset at 0 secs and offset at 1.5 secs marked by vertical dashed lines), frequency is on the y-axis (from 0 – 180 Hz; tick marks indicate each rate of stimulation). Colors represent $\log_{10}$ transformed FFT power (scale shown at right) at each time-frequency point.

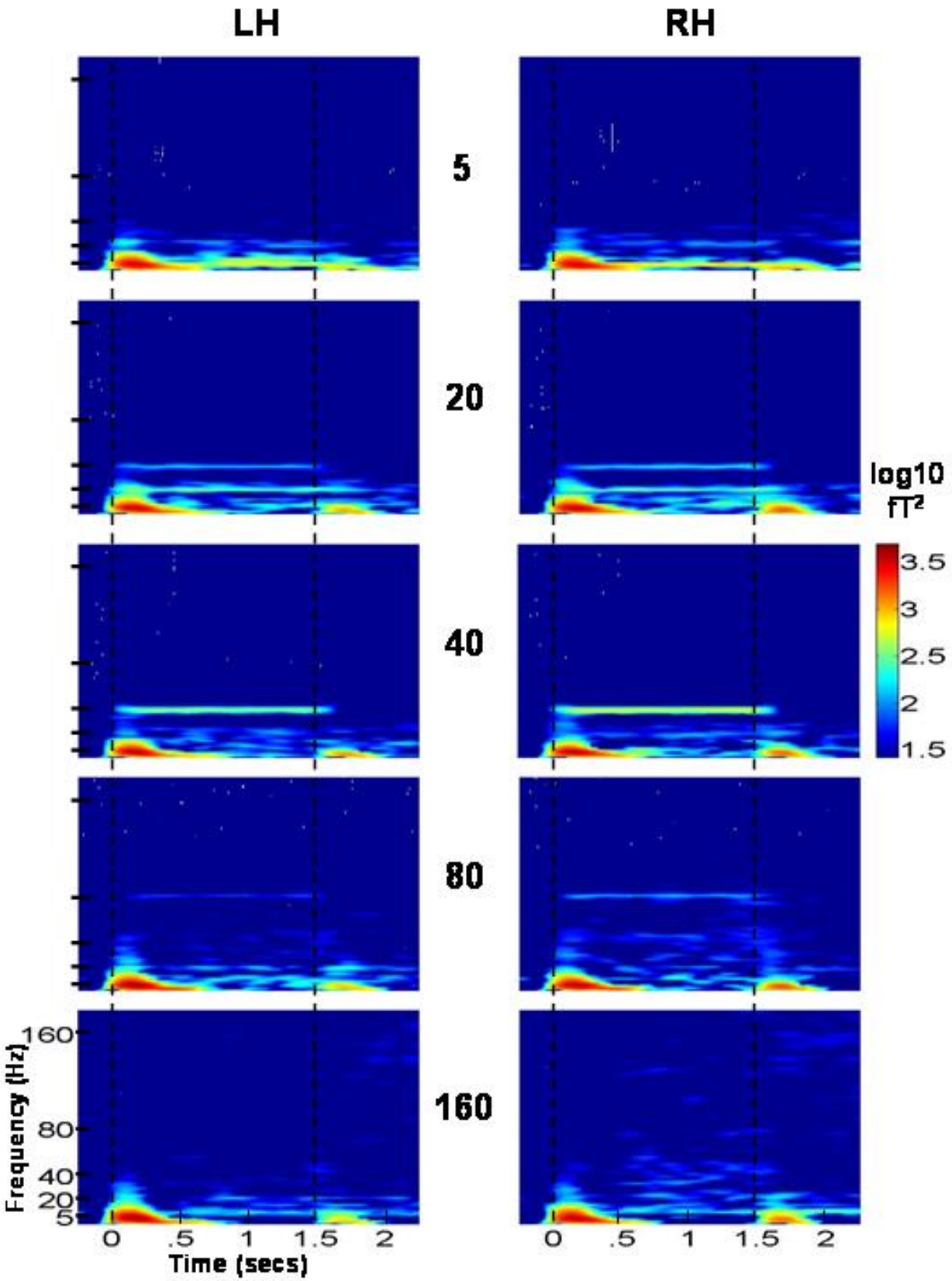

Figure 3. Broadband time-frequency power spectrogram (from 0 – 180 Hz)

Figure 4. FFT power (mean ± standard error bars) associated with the P1 and N1 MLAERs

Normalized FFT power (fT^2; mean ± standard error bars) associated with the middle- and late- latency auditory evoked responses (MLAERs) averaged 1) within the time range 50 – 250 ms post-stimulus and 2) within the delta and theta bands (2 – 8 Hz), for each rate of stimulation. NP=normal subjects, SZ=schizophrenia subjects, L=sensors over left hemisphere, R= sensors over right hemisphere.

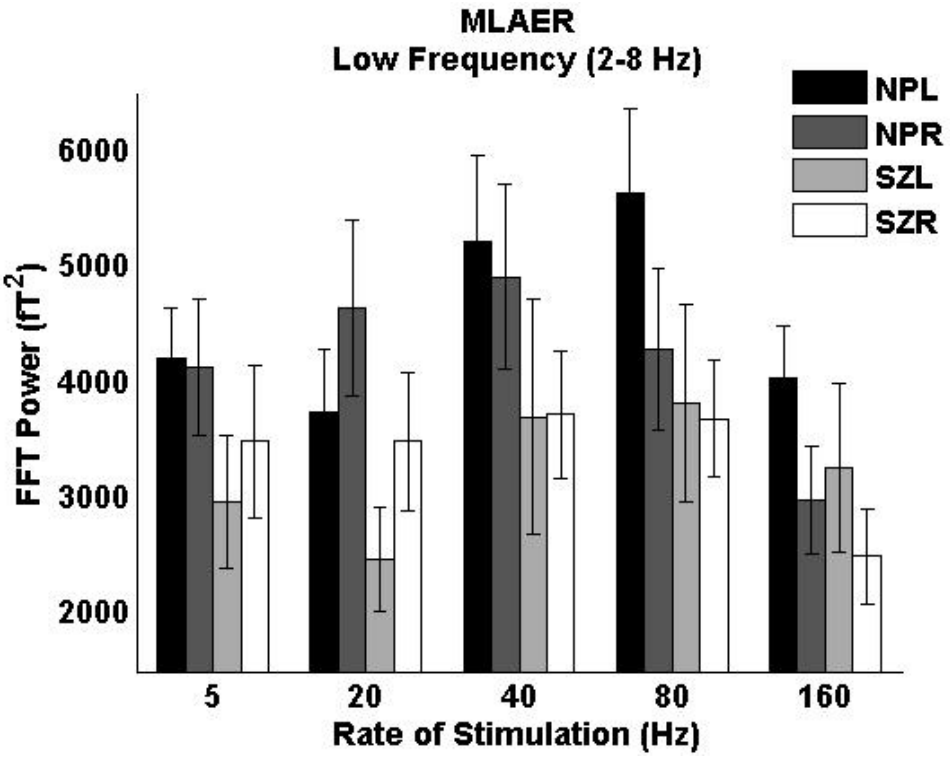

Figure 4. FFT power (mean ± standard error bars) associated with the P1 and N1 MLAERs

Figure 5. Time-frequency power spectrograms from 0 – 16 Hz

Low-frequency time-frequency power spectrograms, averaged across normal and schizophrenia groups, at each rate of stimulation (5, 20, 40, 80, & 160 Hz), averaged over sensors in left (LH) and right (RH) hemispheres. Time is on the x-axis (-250 – 2250 ms; stimulus onset at 0 secs and offset at 1.5 secs marked by vertical dashed lines), frequency is on the y-axis (from 0 – 16 Hz; scale is shown on lower left spectrogram). Colors represent $\log_{10}$ transformed FFT power (scale shown at right) at each time-frequency point.

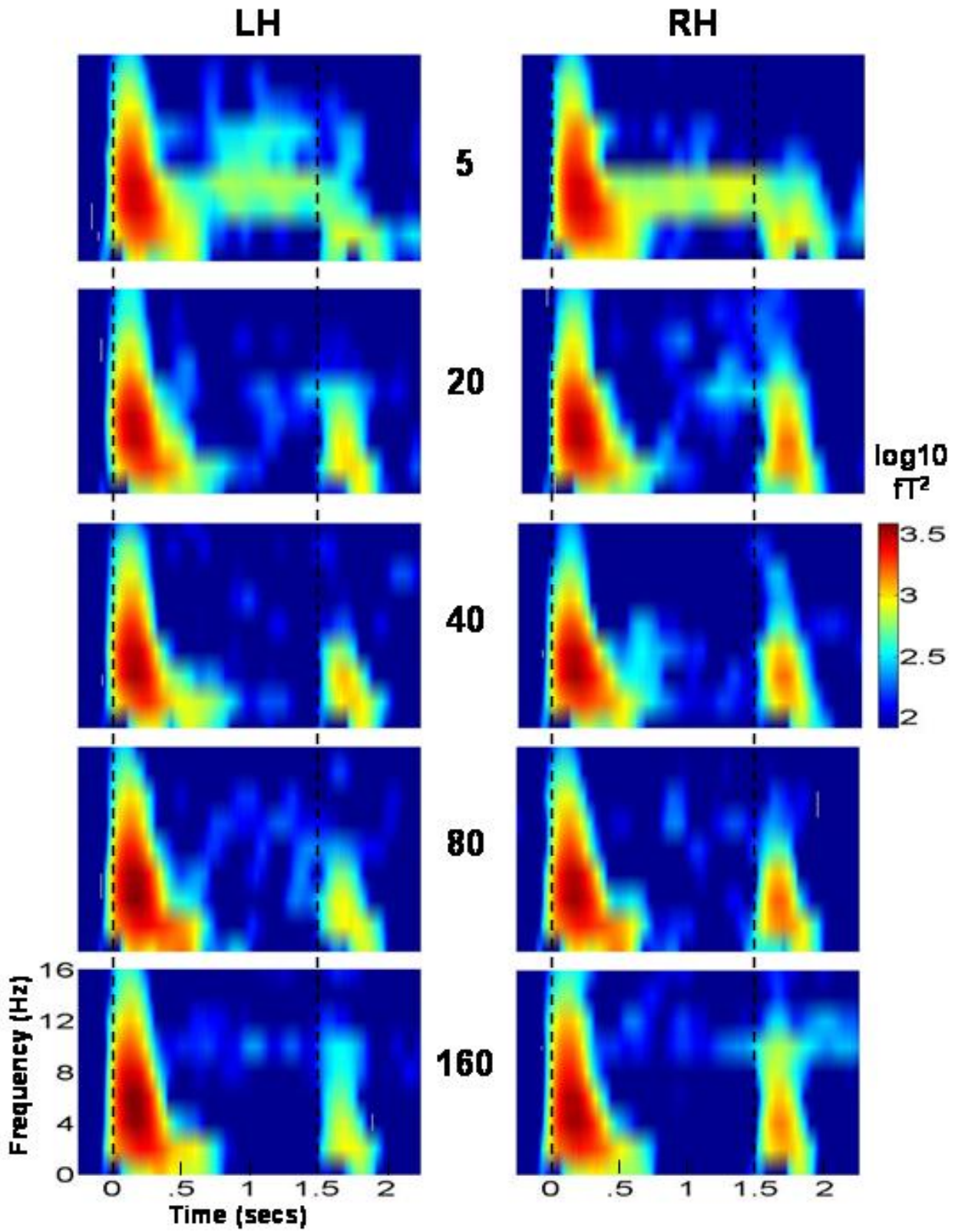

Figure 5. Time-frequency power spectrograms from 0 – 16 Hz

Figure 6. FFT power (mean ± standard error bars) at each driving frequency

Normalized FFT power (fT^2; mean ± standard error bars) averaged over the 200 – 1500 ms post-stimulus time at the respective driving frequency for each rate of stimulation.

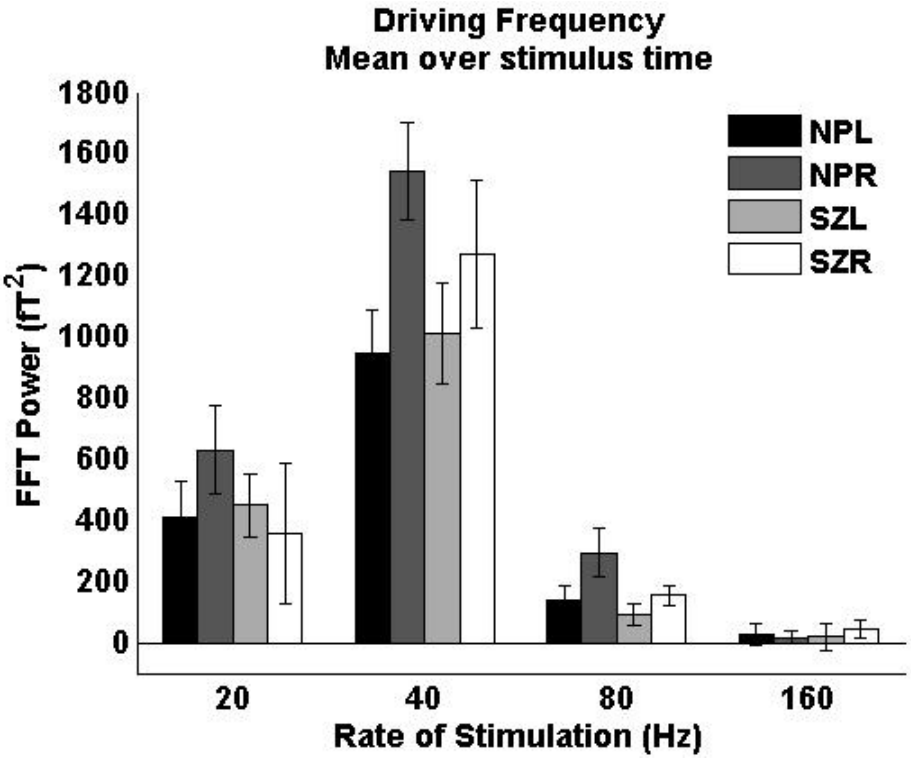

Figure 6. FFT power (mean ± standard error bars) at each driving frequency

Figure 7. Time-frequency power spectrograms at each driving frequency

Time-frequency power spectrograms, averaged across normal and schizophrenia groups, centered on the respective driving frequencies (DF) for each rate of stimulation (20, 40, 80, & 160 Hz), averaged over sensors in left (LH) and right (RH) hemispheres. Time is on the x-axis (-250 – 2250 ms; stimulus onset at 0 secs and offset at 1.5 secs marked by vertical dashed lines). Frequency is on the y-axis, centered on the respective driving frequency and spanning a +/- 4 Hz range (e.g. spectrogram for the 20 Hz rate of stimulation is centered on the DF of 20 Hz and spans from 16 Hz to 24 Hz). Colors represent $\log_{10}$ transformed FFT power (scale shown at right) at each time-frequency point.

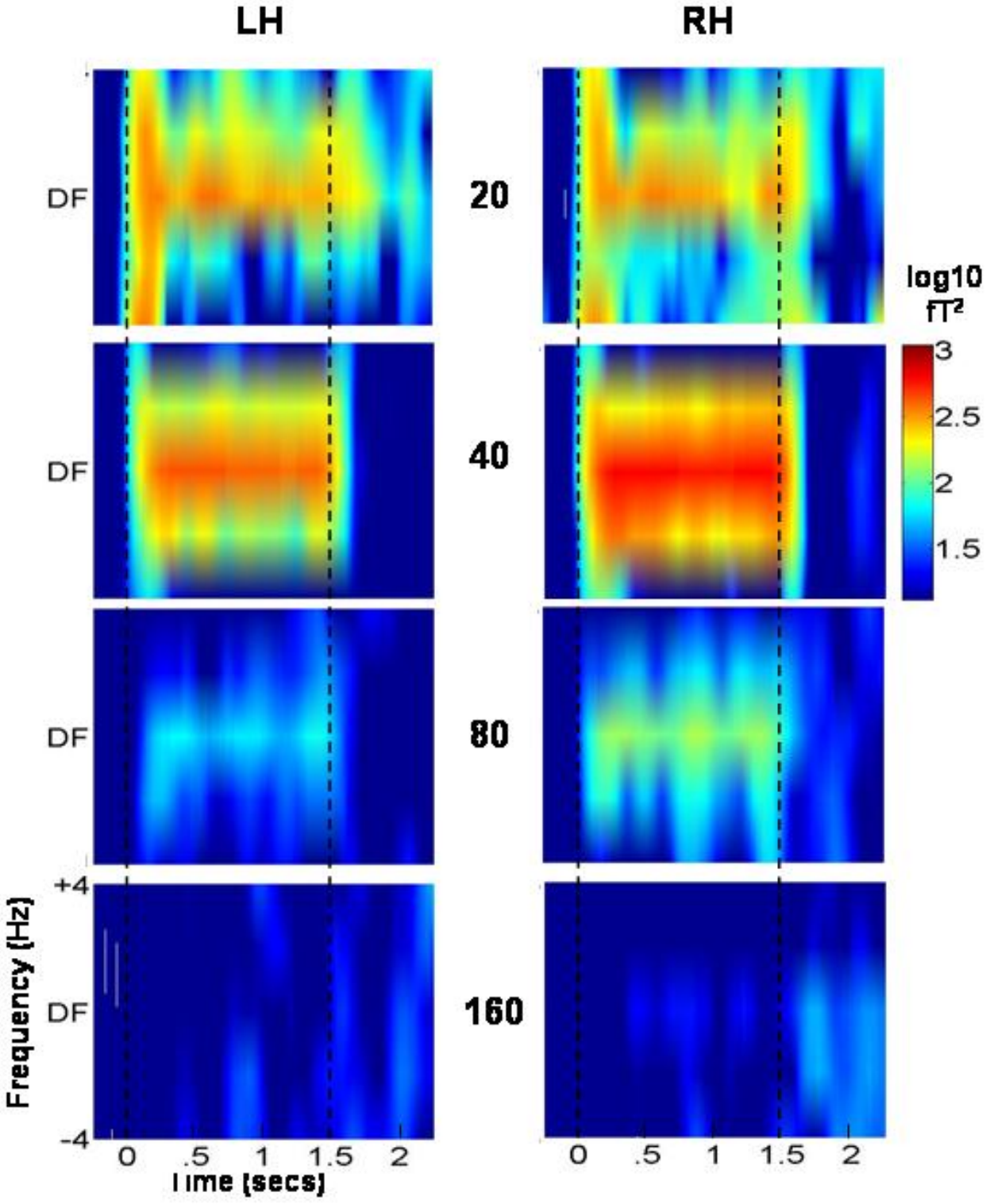

Figure 7. Time-frequency power spectrograms at each driving frequency

Figure 8. ITC (mean ± standard error bars) associated with the P1 and N1 MLAERs

ITC (R-values; mean ± standard error bars) associated with the MLAERs averaged 1) within the time range 50 – 250 ms post-stimulus and 2) within the delta and theta bands (2 – 8 Hz), for the 20, 40, and 80 Hz rates of stimulation.

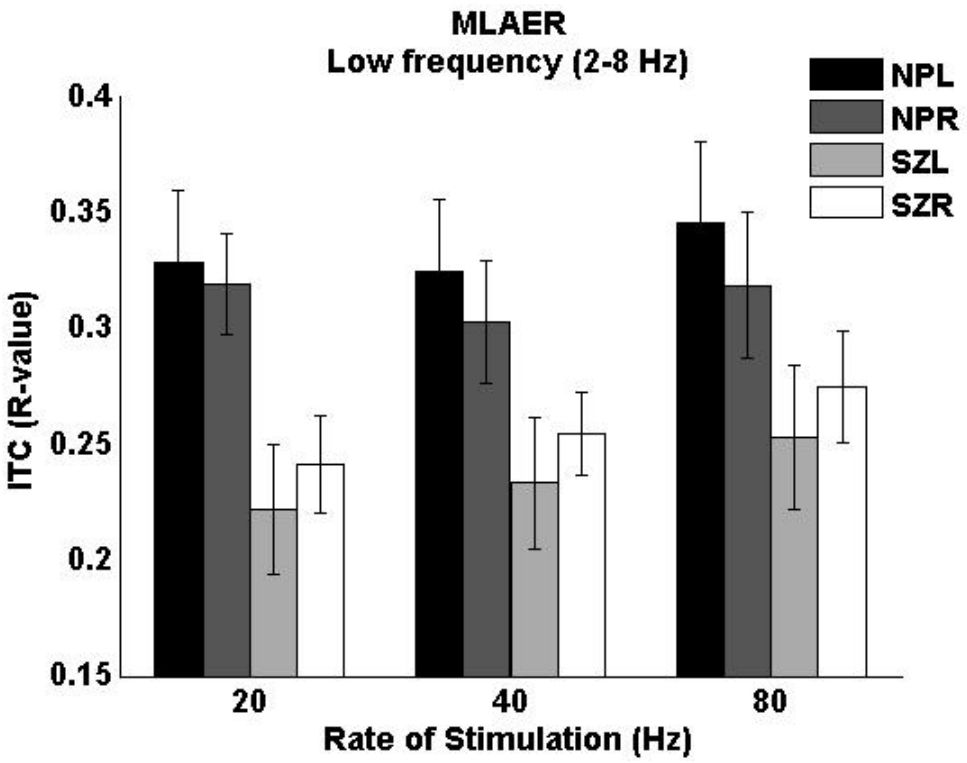

Figure 8. ITC (mean ± standard error bars) associated with the P1 and N1 MLAERs

Figure 9. Time-frequency ITC spectrogram from 0 – 16 Hz

Low-frequency time-frequency inter-trial phase coherence (ITC) spectrograms for normal (NP) and schizophrenia (SZ) subjects, averaged across hemispheres and the 20, 40, and 80 Hz rates of stimulation. Time is on the x-axis (-250 – 2250 ms; stimulus onset at 0 secs and offset at 1.5 secs marked by vertical dashed lines), frequency is on the y-axis (from 0 – 16 Hz; scale is shown on left spectrogram). Colors represent R-values (scale shown at right) at each time-frequency point.

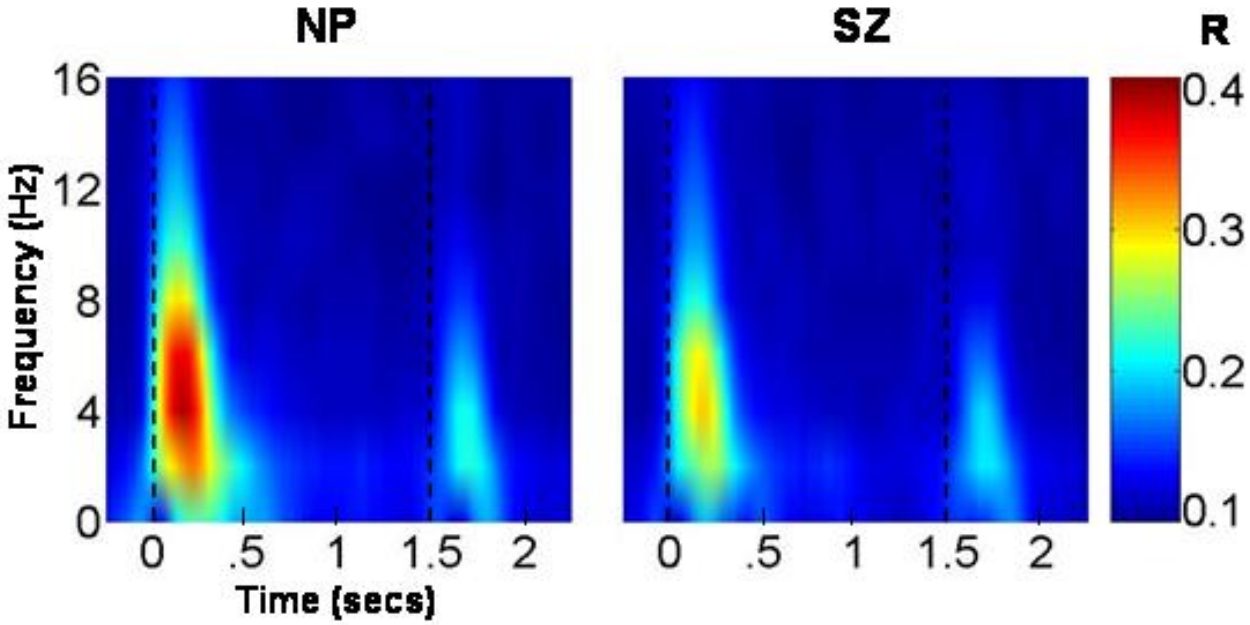

Figure 9. Time-frequency ITC spectrogram from 0 – 16 Hz

Figure 10. ITC (mean ± standard error bars) at each driving frequency

ITC (R-values; mean ± standard error bars) averaged over the 200 – 1500 ms post-stimulus time at the respective driving frequency for the 20, 40, and 80 Hz rates of stimulation.

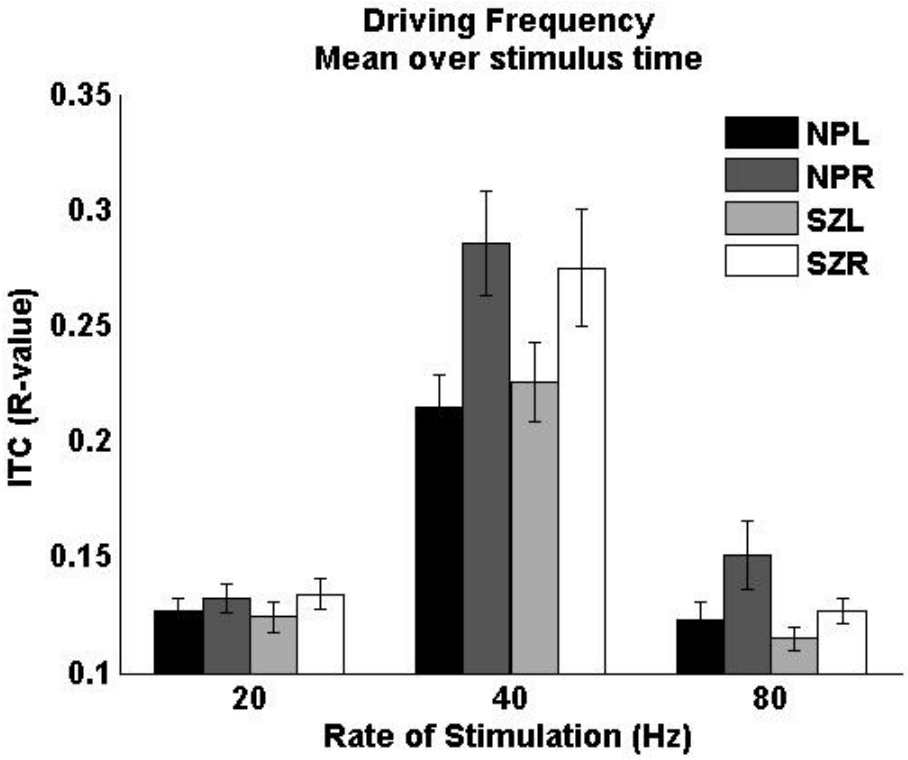

Figure 10. ITC (mean ± standard error bars) at each driving frequency

Figure 11. Time-frequency ITC spectrograms at each driving frequency

Time-frequency ITC spectrograms, averaged across normal and schizophrenia groups, centered on the respective driving frequencies (DF) for each rate of stimulation (20, 40, & 80 Hz), averaged over sensors in left (LH) and right (RH) hemispheres. Time is on the x-axis (-250 – 2250 ms; stimulus onset at 0 secs and offset at 1.5 secs marked by vertical dashed lines). Frequency is on the y-axis, centered on the respective driving frequency and spanning a +/- 4 Hz range. Colors represent R-values (scale shown at right) at each time-frequency point.

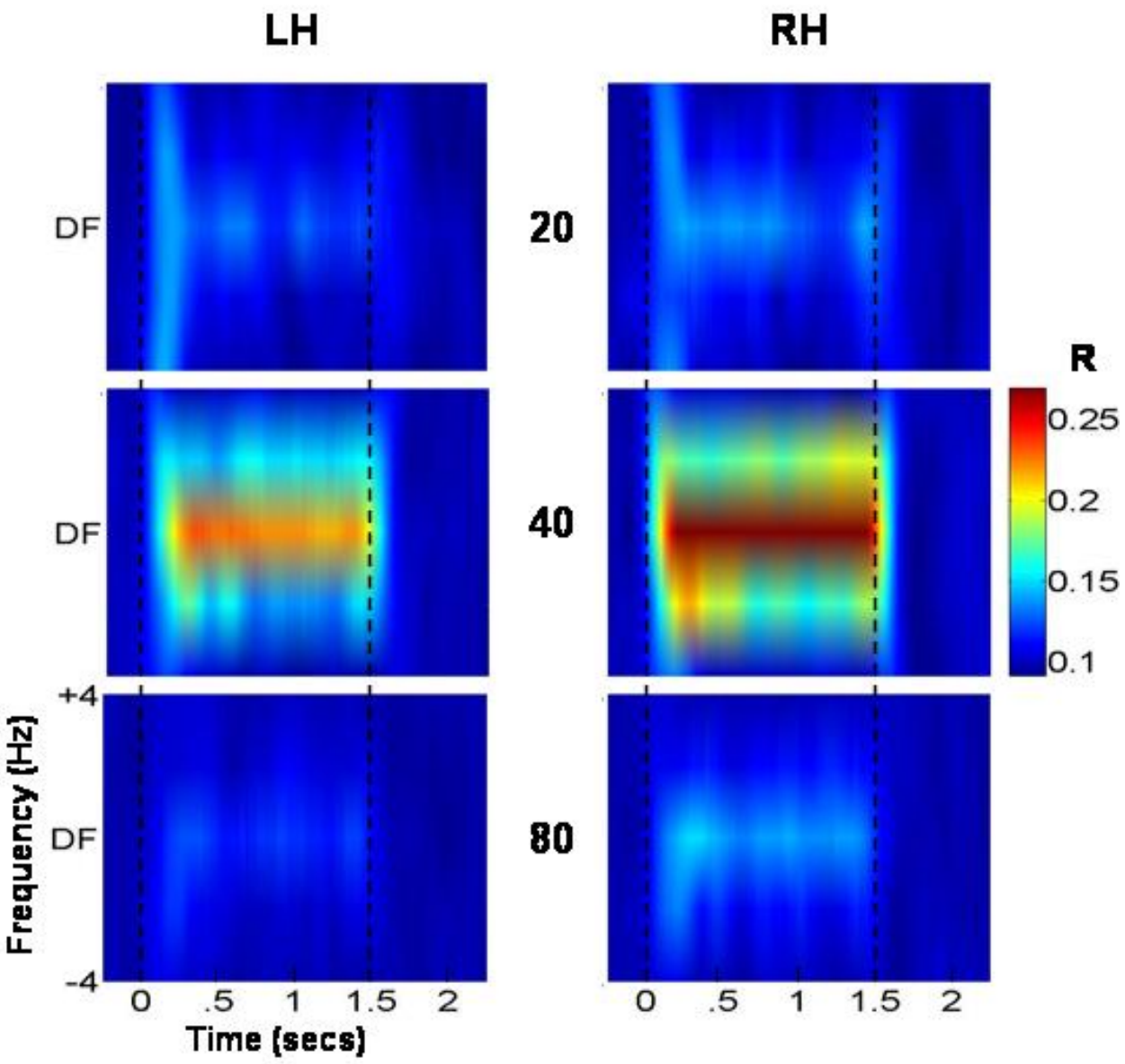

Figure 11. Time-frequency ITC spectrograms at each driving frequency