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The auditory steady-state response (ASSR): a translational biomarker for schizophrenia

Brian F. O'Donnell[a,b,c,*], **Jenifer L. Vohs**[b,c], **Giri P. Krishnan**[d], **Olga Rass**[a], **William P. Hetrick**[a,b,c], and **Sandra L. Morzorati**[c]

[a]Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN 47405, USA

[b]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN 46222, USA

Larue D. Carter Memorial Hospital, Indianapolis, IN 46222, USA

[d]Department of Cell Biology and Neuroscience, University of California Riverside, Riverside, CA 92521, USA

6.1 Introduction

Schizophrenia (SZ) is a debilitating mental disorder associated with psychotic symptoms, such as hallucinations and delusions which affect nearly 0.8% of the population (Saha et al., 2005). Disturbances of auditory perception are among the most characteristic features of SZ. Interview measures of perceptual abnormalities, as distinct from hallucinations, indicate that auditory distortions are more frequent than distortions in any other sensory modality, occurring in 42% of patients with SZ compared to 17% of healthy adults (Bunney et al., 1999). Consistent with these subjective reports, behavioral measures of auditory processing have demonstrated deficits in time estimation (Carroll et al., 2009), spatial localization (Perrin et al., 2010), sound intensity discrimination (Bach et al., 2011) pitch discrimination (Leitman et al., 2008) and echoic memory (Strous et al., 1995). Event-related potential (ERP) findings suggest that auditory processing is affected within 50–200 ms of stimulus onset, including reduction of the P50 response to the first click of a paired click paradigm, impaired P50 gating, reduction of the auditory N100 component, and reduced mismatch negativity (see Hirayasu et al., 1998; Turetsky et al., 2007). Auditory hallucinations are a diagnostic criterion for SZ, and patients with auditory hallucinations show altered brain activation in left superior temporal gyrus and middle temporal gyrus compared to non-hallucinating individuals (Kuhn and Gallinat, 2010). Consequently, the auditory system can provide a window into one of the key neurobehavioral symptoms.

The neural mechanisms which produce symptoms of SZ remain poorly understood, but accumulating evidence suggests that disturbances in neural synchrony and oscillatory activity may contribute to failures of effective connectivity and neural integration in the illness (Uhlhaas and Singer, 2010; Whittington, 2008; Basar, 2011). While noninvasive

[*]Correspondence to: Dr. Brian F. O'Donnell, Department of Psychological and Brain Sciences, Indiana University, 1101 East 10th Street, Bloomington, IN 47405, USA, Tel.: 1 812 856 4164, bodonnel@indiana.edu.

measures currently cannot detect cellular signaling at the level of individual neurons and circuits in humans, the electroencephalogram (EEG) and magnetoencephalogram (MEG) can detect the synchronous activity of ensembles of neurons. Moreover, since both EEG and MEG are primarily generated by postsynaptic potentials, they are often highly sensitive to alterations in neurotransmission secondary to brain dysfunction or pharmacological manipulations (Luck et al., 2011). Thus, these measures have the potential to serve as biomarkers for disturbance of synchrony and oscillations in SZ.

6.1.1. Auditory steady-state responses

The auditory steady-state response (ASSR) is a type of ERP which can test the integrity of auditory pathways and the capacity of these pathways to generate synchronous activity at specific frequencies (Brenner et al., 2009). ASSRs are elicited by temporally modulated auditory stimulation, such as a train of clicks with a fixed inter-click interval, or an amplitude modulated (AM) tone. After the onset of the stimulus, the EEG or MEG rapidly entrains to the frequency and phase of the stimulus. Testing the capacity of auditory circuits to support entrainment provides a noninvasive method to determine the relationship of the power or phase of the output (EEG) to the characteristics of the periodic input. If the auditory system is unable to support neural synchronization, particularly at higher gamma frequencies (> 30 Hz), this would be evident in the amplitude or phase variability of the ASSR.

The ASSR is generated by activity within the auditory pathway. The ASSR for modulation frequencies up to 50 Hz is generated from the auditory cortex based on EEG (Pantev et al., 1996; Herdman et al., 2002), MEG (Ross et al., 2002) and animal studies (Dolphin and Mountain, 1992; Conti et al., 1999). Higher frequencies of modulation (> 80 Hz) are thought to originate from brainstem areas (Herdman et al., 2002). The type of stimulus may also affect the region of activation within the auditory cortex. Amplitude modulated (AM) tones and click train stimuli are commonly used stimuli to evoke the ASSR (Picton et al., 2003). AM tones are generated by temporally modulating a tone (or sine wave) using another sine wave modulation resulting in variation of the amplitude of the tone over time. The frequency of the tone is referred to as the carrier frequency and the frequency of the modulation envelope is called the modulation frequency. The click train stimuli, on the other hand, consist of clicks which are brief but broad spectrum sound stimuli. Thus, the click stimulus has several harmonics, while the modulation frequency of AM tones has only one peak at the stimulus frequency. Due to tonotopic mapping of the auditory cortex, the carrier frequency or the frequency content in individual stimuli determines the region of the auditory cortex that is activated. In the case of the AM tones, only a small region that responds to the carrier frequency responds, while click stimuli activate a larger area. This is reflected in the amplitude of the ASSR responses, as clicks generate higher amplitude ASSR than AM tones. The mechanisms of generation of ASSRs differ as a function of frequency, but likely represent both the superposition of individual evoked potentials to each click or cycle of modulation, as well as intrinsic oscillatory processes in the auditory pathways. For further discussion of this issue, see Krishnan et al. (2009).

6.1.2. Time-frequency analysis of ASSRs

Entrainment is apparent in the ASSR averaged in the time domain (Fig. 1A and B), but the frequency response can be more accurately quantified using time-frequency analysis. One approach is to apply a Fast Fourier Transform (FFT) to the period of stimulation, or to the ASSR averaged across stimulus periods to improve signal to noise by isolating phase locked activity (Fig. 1C). The FFT decomposes the time domain ASSR into a sum of sinusoidal waveforms varying in power and phase. A power spectrum displays the coefficients for each frequency measured by the FFT as a graph of power values (usually in microvolts^2), as shown in Fig. 1C. In Fig. 1, the ASSR was elicited by a 40 Hz amplitude modulated tone (1 s duration) with a 1000 Hz carrier frequency. The power spectrum in Fig. 1C shows a prominent peak in power at 40 Hz, which has a larger value in the control group compared to the group of patients with SZ. The ASSR in humans shows a peak response at about 40–45 Hz (Fig. 2).

More recently, signal analysis procedures have allowed trial-to-trial differentiation of phase consistency of the ASSR, and change in power from baseline. The phase locking factor (PLF), or inter-trial phase coherence, is a measure of phase synchronization of EEG activity across trials at particular temporal intervals and frequencies (Delorme and Makeig, 2004). In order to compute PLF, a baseline normalized spectrogram is first obtained by applying FFT using a time sliding window on single trial data. This results in a time-frequency transform consisting of a complex number for every time point, frequency and trial. This complex output is divided by its complex norm (absolute value), which is then averaged across trials. The complex norm of this averaged value results in PLF for different time and frequency points. PLF values can range from 0 (absence of synchronization) to 1 (perfect synchronization, or phase reproducibility across trials at a given latency). In contrast, mean power (MP) difference from baseline (also called event-related spectral perturbation (ERSP) measures the power in a frequency band relative to baseline. MP is obtained by first subtracting the power from the prestimulus baseline period and then averaging across trials. This measure represents the average change in power at a given frequency from the mean baseline power and so can detect changes in power that are induced by, but are not necessarily phase-locked to, stimulus onset. Fig. 1D and E show time-frequency plots comparing MP (or ERSP) and PLF (inter-trial coherence) for subjects with and without SZ to the 40 Hz AM tone.

6.1.3. ASSRs in schizophrenia

ASSRs are usually reduced in power or phase locking in patients with schizophrenia to 40 Hz stimulation (Table 1). Kwon et al. (1999) first reported that SZ patients showed a reduction in the ASSR. Short, 500 ms click trains were used to elicit the ASSR at three frequencies: 20, 30 and 40 Hz. Patients with schizophrenia showed a reduction in power at 40 Hz, but not at 20 or 30 Hz. Moreover, patients showed delayed onset of phase synchronization and delayed desynchronization to the 40 Hz click trains. Subsequently, a reduction in 40 Hz power or PLF in SZ has been observed in most (Light et al., 2006; Vierling-Classen et al., 2008; Wilson et al., 2008; Spencer et al., 2009; Mulert et al., 2011) but not all (Hong et al., 2004) studies. Thirty and 40 Hz PLF ASSR reductions have been observed in first episode SZ (Spencer et al., 2008) and in adolescents with a diagnosis of a

psychotic disorder (Wilson et al., 2008) indicating that the deficit is probably not due to chronic illness or long-term medication effects. Type of stimulus may affect the specificity of the deficit to gamma range (> 30 Hz) frequencies. Studies which used AM tones rather than clicks to elicit the ASSR have found that power was reduced from 11 to 82 Hz (Brenner et al., 2003), and both power and PLF were reduced from 5 to 50 Hz (Krishnan et al., 2009). Hamm et al. (2011) used broad-band noise bursts and found that 5, 40 and 80 Hz ASSRs were attenuated in SZ, while 20 Hz was unaffected. Similar to findings by Hamm et al. (2011), unpublished data from the Krishnan et al. (2009) study also revealed an 80 Hz ASSR deficit in SZ. There is also evidence that the ASSR 40 Hz deficit is associated with genetic risk, although not with schizotypal personality characteristics. In the only study to examine first-degree relatives of SZ patients, Hong et al. (2004) reported that relatives showed a reduction in 40 Hz power. In contrast, individuals with schizotypal personality disorder, a phenotype which shares symptoms with schizophrenia, did not show a deficit in power at 42 Hz or at any other frequency between between 11 and 82 Hz (Brenner et al, 2003).

ASSR deficits in 30–40 Hz range are suggestive of auditory cortex disturbances. Auditory cortex involvement in SZ has also been indicated by both imaging and neuropathological findings. Reduction of the grey matter volume of the posterior superior temporal gyrus, including auditory cortex, is a consistent neuroanatomical finding in SZ (Shenton et al., 2001). At the cellular level, Sweet et al. (2003) have reported reduction of the volume of pyramidal neurons in the deep layer of primary and secondary auditory cortex in postmortem tissue from patients with SZ.

6.1.4 Summary

Patients with SZ have typically demonstrated a deficit in ASSR power or PLF, which is most consistent at 40 Hz. This deficit is apparent for both EEG and MEG ASSR measures and is present at the first psychotic episode. The disturbance in synchrony affects a broader range of frequencies when AM tones, rather than clicks, are used as stimuli. Since the auditory cortex is the primary generator for scalp recorded ASSRs in the 40 Hz–50 Hz frequency range, these electrophysiological findings are convergent with other imaging data, demonstrating abnormalities in auditory cortex anatomy and function. The 40 Hz deficit also appears in first-degree relatives, suggesting that it may reflect genetic risk or shared environmental factors, but not in individuals with schizotypal personality disorder.

6.2. Cellular mechanisms, pharmacology and animal models

ASSRs demonstrate alterations in a key system affected by SZ, the auditory pathways and auditory cortex. The interpretation of this deficit and its value as a biomarker depend in part on understanding the cellular mechanisms responsible for synchrony and oscillatory activity within neural networks, and how these are disturbed by putative pathophysiological processes. Consequently, in vitro and in vivo studies of neurobiological mechanisms in animal models will likely play a critical role in further understanding cellular mechanism and evaluating novel treatments in both preclinical and clinical stages of development. Gamma range oscillatory activity (30–80 Hz) has been widely studied across a range of mammalian species (Ehrlichman et al., 2009; Lazarewicz et al., 2010).

6.2.1. Generation of gamma oscillations

Neural oscillations are a putative mechanism for sensory, attentional, mnemonic and motoric processes (Singer, 1999; Basar, 2011. A number of models have been developed to identify important components and network properties associated with neural synchronization. Data from both in vitro and in vivo investigations support the role of synaptic inhibition in the generation of neuronal oscillations, either in an interneuronal network or in a reciprocal excitatory–inhibitory loop (Wang, 2010).

In vitro studies suggest that two major cell types, excitatory principal neurons and inhibitory interneurons, and two specific receptor types, gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA), are critical for neural synchronization (Roopun et al., 2008) in the gamma frequency range. It was originally postulated that among interneuron networks, precise, in-phase firing modulates excitatory glutamatergic pyramidal neuron activity (Whittington et al., 1995; Gray and McCormick, 1996; Traub et al., 1996; Whittington, 2008).

Once activated by glutamatergic (NMDA) receptors, GABAergic interneurons generate post-synaptic interneuronal potentials (Traub et al., 1996) and engage in ongoing mutual inhibition and a recurrent feedback loop (Whittington et al., 1995). It has since been demonstrated that trains of fast, somatic inhibitory post-synaptic potentials mediated by the $GABA_A$ receptor are present in all forms of gamma oscillations (Roopun et al., 2008). High frequency synchronization is likely propagated through networks in a cycle of GABAA mediated inhibition followed by rebound excitation and then inhibition (Lewis and Gonzalez-Burgos, 2008). The NMDA receptor is thought to contribute to the generation of network oscillations via modulation of both interneuron to interneuron and interneuron to pyramidal neuron, cell connections. A recent in vitro study demonstrated that the effects of altering NMDA function via ketamine administration may be region specific. Roopun et al. (2008) used horizontal cortical slices to examine the effects of NMDA antagonism of beta2 (20–29 Hz) and gamma (30–80 Hz) range oscillations. This study showed that, following the administration of ketamine, beta2 power increased in association with prelimbic cortices, while gamma range power was decreased in slice recordings of several regions (medial entorhinal, perirhinal, insular, and medial orbital cortices). Of the areas studied, NMDA-induced increase in gamma power was only detected in auditory cortex. In an in vivo study involving rodents, Pinault (2008) showed that acute blockade of NMDA receptors (with ketamine and MK-801) increased gamma activity in a dose-dependent manner. It could, therefore, be speculated that blocking excitation of inhibitory interneurons decreased phasic inhibitory post-synaptic potentials onto pyramidal cells, resulting in a net excitatory effect on the neuronal network.

In summary, while NMDA antagonists cause an increase in in vitro gamma activity in several brain regions, the auditory cortex appears to show the opposite effect for acute blockade. *In vivo* studies have shown an increase in gamma activity after acute NMDA blockade. These variations in synchronization patterns may result from intrinsic differences in NMDA signaling in different regions, or interactions among regions that are evident in in vivo studies (Kuwada et al., 2002; Roopun et al., 2008).

6.2.2. Pharmacological effects on ASSRs

The anatomical and functional organization of auditory pathways in humans and other mammalian species is comparable, allowing for the use of animals such as rodents to study ASSR in cross-species studies of schizophrenia-related phenotypes. However, an important issue is whether a specific animal model demonstrates the same frequency response function as that observed in humans. For example, while the healthy human brain has an ASSR resonant frequency at 40 Hz (Kwon et al., 1999), rat ASSRs appear to be maximal at a bout 50 Hz (Fig. 3; (Vohs et al., 2010). It has been argued that this difference should not preclude the use of rodents in ASSR studies because the observed frequency shift is likely secondary to brain volume differences (see Leiser et al., 2011 for further information).

Because NMDA and GABAergic interneurons are thought to be the most likely candidate mechanisms for ASSR generation, studies examining pharmacological effects on this response have focused on these transmitter systems. However, few studies have utilized pharmacological manipulation on ASSRs. NMDA receptor antagonism via phencyclidine (PCP), MK-801, or ketamine administration induces schizophrenic-like symptoms in healthy individuals (Javitt and Zukin, 1991; Krystal et al., 1994) and exacerbates psychoses in patients with schizophrenia (Lahti et al., 1995; Malhotra et al., 1997). These effects likely reflect dysregulation of the glutamatergic system, and more specifically the NMDA receptor, in the disorder (Tsai et al., 1998). NMDA receptor antagonism not only induces positive (similar to amphetamine psychosis), but also mimics negative and cognitive symptoms associated with schizophrenia. As in patients with schizophrenia and healthy subjects (Plourde et al., 1997), NMDA antagonism (ketamine MK-801 PCP) produces an increase in baseline (unevoked) gamma power in vivo local field potentials (LFPs) and EEG in awake rodents (Pinault, 2008; Ehrlichman et al., 2009; Hakami et al., 2009; Lazarewicz et al., 2010). While these studies mostly examined baseline gamma magnitude and suggested that NMDA antagonism increased gamma, none specifically tested ASSRs. In humans, it has been demonstrated that ketamine increased the 40 Hz ASSR in healthy individuals (Plourde et al., 1997). Ehrlichman et al. (2009), however, examined both baseline and evoked gamma band responses. These investigators found that subanesthetic (20 mg/kg) doses of ketamine produced increased baseline, but not evoked gamma response. Interestingly, dopamine agonism (D-amphetamine) did not alter gamma band response, suggesting that dopamine may not play a direct role in the gamma deficits observed in patients with schizophrenia.

6.2.2. ASSRs in rodent models of schizophrenia phenotypes

EEG synchronization has recently been studied in rodent models of schizophrenia (Pinault, 2008; Ehrlichman et al., 2009; Lazarewicz et al., 2010). However, limited data have been obtained using the ASSR protocol commonly employed in patients with schizophrenia in animal models. One such study (Vohs et al., 2010) elicited 40 Hz ASSRs from neonatal ventral hippocampal lesion (NVHL) model rats, an established rat model of schizophrenia. In addition, a pharmacological manipulation targeting the $GABA_A$ receptor was also performed to further elucidate this receptor's role in ASSR generation and its status in the NVHL model. The authors found that agonism of the $GABA_A$ receptor yielded a strong lesion by drug interaction, with ASSR magnitude and synchronization decreased in NVHL and increased in sham rats (Vohs et al., 2010). These data suggested an alteration in $GABA_A$

receptor function in NVHL rats and altered inhibitory transmission in the neuronal networks responsible for ASSR generation in NVHL rats.

6.2.4. Summary

A key question in the application of a translational biomarker is whether a comparable neural response can be obtained in human and in an animal model. The ASSR can be elicited from a wide range of species, although initial studies suggest the need for better characterization of the frequency response function to both click and AM tone stimuli in rodent models. in vitro studies suggest that gamma range oscillations in cortical circuits are entrained by $GABA_A$ neurons and are reduced by NMDA receptor antagonists. Importantly, the effect of NMDA antagonists on gamma activity may vary across cortical regions, and between in vitro and in vivo preparations. Thus, while the sensitivity of gamma range activity has been demonstrated by both types of preparation, study of local circuit activity and neural populations in vivo will be required to better characterize the basis of specific pharmacological effects. Several studies have examined ASSRs in rodent models of schizophrenia-related phenotypes and suggest that this approach may offer a flexible vehicle for cross-species studies of pathophysiological mechanisms and medication effects.

6.3. Discussion

ASSRs, particularly in the gamma frequency range (> 30 Hz), are reduced in power and phase synchronization in schizophrenia. Because synchronized neural activity appears to be critical for a wide range of perceptual, cognitive and motoric processes, oscillatory deficits may index a key mechanism for functional disconnection or integration in SZ (Basar et al., 2001; Whittington, 2008; Uhlhaas and Singer, 2010). ASSRs therefore appear to have the potential to serve as a translational, cross-species biomarker for schizophrenia and related disorders. However, the functional significance of the ASSR deficit and its implications regarding the pathophysiology of SZ must be better characterized for this response to be effectively utilized as an informative biomarker in studying etiological factors, mechanisms and intervention effects.

The ASSR represents only one of a variety of EEG and MEG paradigms which can capture disturbances of neural synchrony or oscillations in schizophrenia (Basar et al., 2001; Uhlhaas and Singer, 2010; Basar, 2011). Gamma activity, for example, may also be evoked by the onset of an auditory stimulus, or induced by working memory demands in patients with schizophrenia. Moreover, gamma activity deficits have been observed in other disorders as well, including attention deficit hyperactivity disorder and bipolar disorder (see Basar and Guntekin, 2008, for review), and therefore are not specific to schizophrenia. Given the dependence on gamma oscillations on interactions among GABAergic and glutamatergic neurons within cortical circuits, it is not surprising that oscillatory deficits would be sensitive to a range of neuropsychiatric disorders.

From a clinical perspective, the relationship of ASSRs to the development and course of the illness, treatment, and outcomes is incompletely characterized. While it has been established the motoric, cognitive and social behavior deficits are often present in children who develop schizophrenia later in life (O'Donnell, 2007), there are no studies of ASSRs in high-risk or

prodromal individuals who later develop the illness. A single study (Hong et al., 2004) has reported that the 40 Hz ASSR deficit occurs in non-psychotic relatives of patients with schizophrenia, consistent with an effect of familial or genetic risk factors. No longitudinal studies have been conducted, and long- term test–retest reliability of the measure in SZ has not been evaluated. The relationship of ASSR deficits to long-term outcomes or treatment response has not been studied. Hong et al. (2004) reported that patients receiving novel antipsychotic medication may show enhanced 40 Hz activity, but no studies have examined ASSRs in patients before and after receiving antipsychotic medications.

The ease of recording ASSRs in animal models of SZ phenotypes suggests that these measures could also be highly informative in testing neurophysiological models of the disorder, particularly with respect to glutamate and GABAergic interactions. ASSRs can test cellular mechanisms that are not accessible through non-invasive measures in humans and could provide a preclinical measure to test novel antipsychotic treatments. The potential of a combined human and animal model approach to treatment development is especially intriguing and merits exploration in future research.

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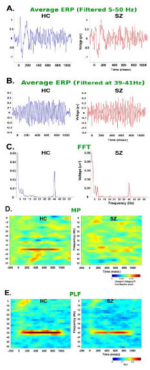

Fig. 1.

Auditory steady-state responses (ASSRs) to a 1-s, 40-Hz amplitude-modulated tone recorded at Cz in a healthy control group (HC; N = 21) and in patients with schizophrenia (SZ; N = 21). (A) The ERP in the time domain averaged across subjects, showing both a large onset response as well as the 40-Hz oscillation. In (B), the averaged wave form has been filtered between 39 and 41 Hz. (C) A power spectrum obtained by applying a Fast Fourier Transform on the ERPs in the two groups, showing the 40-Hz response in the HC group which is reduced in magnitude in the SZ group. (D) Mean power (MP) across the epoch which indicates the average change in power at a given frequency from the mean baseline power. The x-axis represents time in milliseconds, the y-axis represents frequency in Hertz, and the colors represent the magnitude of power. (E) The phase-locking factor (PLF) across trials. The x-axis indicates time in milliseconds, they-axis indicates frequency, and the colors represent phase reproducibility across trials ranging from 0 (absence of synchronization) to 1 (perfect synchronization). (For color figures, please refer to the color figures in last section of the book.)

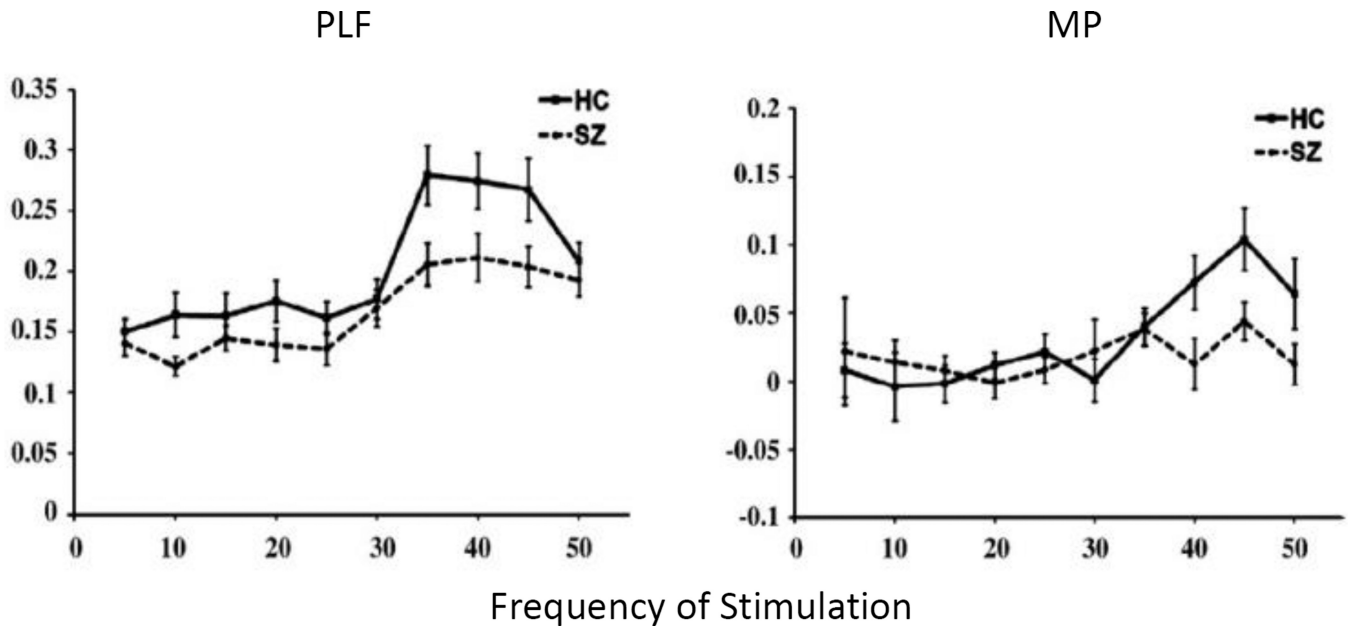

Fig. 2.

The modulation transfer function (MTF) for the ASSR recorded at Cz from healthy control (HC; N = 21) and schizophrenia (SZ; N = 21) groups. The MTFs for the each stimulus frequency are displayed. Each data point is the mean value across the entire stimulus period averaged across subjects within the group. The error bars indicate standard errors. Note the large decrement in schizophrenia for both PLF and MP between 35 and 50 Hz.

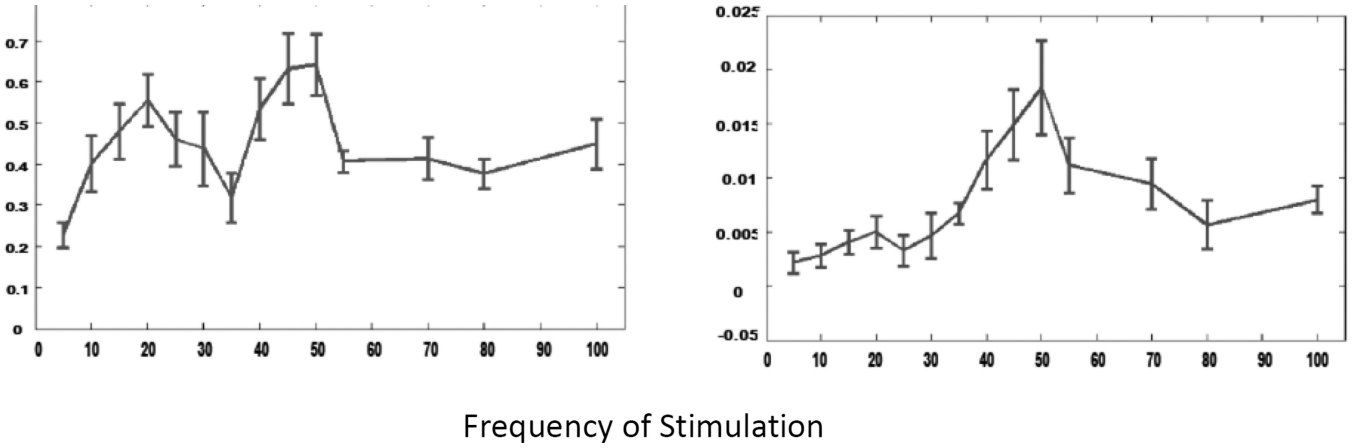

Fig. 3.

Modulation transfer function of phase locking factor (PLF, left panel) and mean power (MP, right panel) to 10-s click trains in eight male rats, with frequency of stimulation on the x-axis. The peak frequency of response for hoth phase locking and mean power is at a slightly higher frequency in rats than in humans (hetween 45 and 50 Hz).

Table 1

Studies of Auditory Steady State Responses (ASSRs) in Schizophrenia and Related Disorders)

Author	Stimuli Frequency	Stimuli Type	Group	Results (Power, MP or PLF)
Kwon et al., 1999	20, 30, 40 Hz	Clicks	SZ	Reduced 40 Hz
Brenner et al., 2003	11, 22, 31, 42, 51, 62, 82 Hz	AM Tones	SZ	Reduced across multiple frequencies
Brenner et al., 2003	11, 22, 31, 42 51, 62, 82 Hz	AM Tones	SPD	No reduction at any frequency
Hong et al., 2004	20, 30, 40 Hz	Clicks	SZ	No reduction at 40 Hz
Hong et al., 2004	20, 30, 40 Hz	Clicks	First-degree relatives	Reduced 40 Hz
Light et al., 2006	20, 30, 40 Hz	Clicks	SZ	Reduced 40 Hz
Spencer et al., 2008	20, 30, 40 Hz	Clicks	First-episode Psychosis: SZ	Reduced 30, 40 Hz, reduced PLF of 40 Hz harmonic of 20 HZ ASSR
Teale et al., 2008	40 Hz	AM Tones	SZ	Reduced 40 Hz
Vierling-Classen et al., 2008	20, 30, 40 Hz	Clicks	SZ	Reduced 40 Hz, but increased 20 Hz
Wilson et al., 2008	40 Hz	Clicks	adolescent psychosis: SZ, BP	Reduced 40 Hz
Krishnan et al., 2009	5 to 50 Hz	AM tones	SZ	Broadband reduction
Spencer et al., 2009	40 Hz	Clicks	SZ	Reduced 40 Hz
Mulert et al, 2011	40 Hz	Clicks	SZ	Reduced 40 Hz
Hamm et al., 2011	5, 20, 40, 80 160 Hz	Broadband Noise Bursts	SZ	Reduced 5 Hz and 80 Hz, reduced 40 Hz in right hemisphere

Abbreviations: Schizophrenia (SZ), schizotypal personality disorders (SPD), mean power (MP), phase locking factor (PLF)