Auditory steady state responses in a schizophrenia rat model probed by excitatory/inhibitory receptor manipulation

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Abstract

Alterations in neural synchrony and oscillations may contribute to the pathophysiology of schizophrenia and reflect aberrations in cortical glutamatergic and GABAergic neurotransmission. We tested the effects of a GABA agonist and a NMDA antagonist on auditory steady state responses (ASSRs) in awake rats with neonatal ventral hippocampal lesions (NVHLs) as a neurodevelopmental model of schizophrenia. NVHL vs. SHAM lesioned rats were injected with saline then either ketamine (NMDA antagonist) or muscimol (GABA$_A$ agonist). Time-frequency analyses examined alterations in phase locking (consistency) across trials and changes in total power (magnitude). ASSRs were compared at 5 stimulation frequencies (10, 20, 30, 40, and 50 Hz). In SHAM rats, phase locking and power generally increased with stimulation frequency. Both ketamine and muscimol also increased phase locking and power in SHAM rats, but mostly in the 20 to 40 Hz range. NVHL and ketamine altered the frequency dependence of phase locking, while only ketamine changed power frequency dependence. Muscimol affected power, but not phase locking, in the NVHL rats. NVHL and ketamine models of schizophrenia produce similar independent effects on ASSR, potentially representing similar forms of cortical network/glutamatergic dysfunction, albeit the effects of ketamine were more robust. Muscimol produced

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NVHL-dependent reductions in ASSR measures, suggesting that cortical networks in this model are intolerant to post-synaptic GABAergic stimulation. These findings suggest the utility of combining lesion, pharmacological, and ASSR approaches in understanding neural mechanisms underlying disturbed synchrony in schizophrenia.

Keywords

ASSRs; GABA; NMDA; NVHL; schizophrenia; synchronization

1. Introduction

Schizophrenia is a severe and chronic psychiatric disorder for which full understanding of the biobehavioral mechanisms remains elusive. Altered neural synchronization commonly measured via electroencephalographic (EEG) and magnetoencephalographic (MEG) recordings is thought to play a significant role in information and sensory processing abnormalities in schizophrenia (Ford & Mathalon, 2008; Uhlhaas & Singer, 2010; Whittington, 2008). Periodic auditory stimuli entrain the EEG to a specific phase and frequency, often referred to as a steady-state response (Brenner et al., 2009). Auditory steady-state responses (ASSRs) can test the functional integrity of neural circuits that support synchronization (Lins & Picton, 1995; Regan, 1989) across frequencies in both human and animal models.

Several EEG (Brenner et al, 2003; Krishnan et al., 2009; Kwon et al., 1999; Light et al., 2006; Spencer et al., 2008; Vierling-Claasen et al., 2008) and MEG (Teale et al., 2008) studies demonstrated reduced ASSR power (magnitude) and phase locking (phase consistency across trials) in schizophrenia particularly in the gamma range (30 to 80 Hz). ASSR reduction in schizophrenia patients may reflect neurophysiological abnormalities in auditory pathways or cortex (Brenner et al., 2009; Teale et al., 2008) and developmental alterations in neurotransmission of excitatory (glutamate) and inhibitory (Gamma-amino butyric acid: GABA) transmitter systems (Uhlhaas & Singer, 2010). Much of the evidence implicating glutamate and GABAergic transmission in disturbances of oscillatory activity in schizophrenia has been extrapolated from *in-vitro* studies, which support the role of N-methyl d-aspartate (NMDA) and GABA subtype A (GABA$_A$) receptors in synchronization (Bartos et al., 2007; Gonzales-Burgos & Lewis, 2008; Roopun et al., 2008; Whittington, 2008). It follows, therefore, that *in-vivo* manipulation of these receptors in animal models of schizophrenia provide a suitable translational assay for testing mechanisms underlying electrophysiological disturbances observed in patients and measurable across species (Brenner et al., 2009; Luck et al., 2011).

The Neonatal Ventral Hippocampal Lesion (NVHL) model is an established neurodevelopmental rat model of schizophrenia that has been shown to have endophenotypic similarities to patients, including behavioral and molecular changes, as well as a pharmacological response profiles (Lipska et al., 2004; Tseng et al., 2009). NVHL lesions affect both GABAergic (Francois et al, 2009; Tseng et al., 2008) neurotransmission and sensitivity to NMDA antagonists (Al-Amin et al, 2000; Tseng et al., 2007). Because anatomical studies have shown that the hippocampus CA1 field (Cenquizca & Swanson, 2007) and the entorhinal cortex (Insausti et al, 1997) project to the auditory cortex, it is plausible that neonatal ablation of the ventral hippocampus in rat pups would also developmentally alter projections to auditory cortex and excitatory and inhibitory neurotransmission relevant to both schizophrenia and ASSR generation.

The present investigation is among the first to utilize both a 'multifaceted' developmental and pharmacological rodent models of schizophrenia *in vivo* during ASSR elicitation and recording. ASSR's across a range of frequencies (10 – 50 Hz) were systematically examined in NVHL and SHAM rats. Further, the role of two major neurotransmitter systems involved in both schizophrenia phenomenology and ASSR generation, maintenance, and perturbation (Whittington, 2008) were tested via ketamine (NMDA antagonist) and muscimol (GABA$_A$ agonist) administration. We hypothesized that pharmacological manipulation of either GABAergic or glutamatergic receptor systems would alter ASSR generation and maintenance. Data from this study are expected to replicate our previous finding that GABA$_A$ agonism differentiates cortical and hence oscillatory responses in NVHL vs. SHAM (decrease and increase response, respectively) rats (Vohs et al., 2010) and characterize the impact of both NMDA antagonism and GABA$_A$ agonism across a range of frequencies.

2. Materials and Methods

2.1 Animals

All procedures complied with the Guide for the Care and Use of Laboratory Animals and were approved by the Indiana University Animal Care and Use Committee (IACUC). Six pregnant Sprague-Dawley rats were obtained from *Harlan* Labs (Indianapolis, IN) at the gestational age of 14–17 days and individually housed for 7–14 days until birth. At post-natal day (PND) 7, a subset of male pups were taken into a surgical room for 2–3 hours, where they were hypothermically anesthetized and received either an ibotenic acid excitotoxic lesion (N = 12) to the ventral hippocampi, or a SHAM lesion (N = 10), following the same procedure less the excitotoxin (see Vohs et al, 2010). Pups were monitored and warmed before being returned to their home cages.

Rats were weaned (PND 25) and at PND 49, paired (2 per cage) and moved to standard plastic cages. Three days prior to implantation of EEG electrodes, rats were moved to single-house plexiglass cages. Rats were kept in a temperature-controlled room, maintained on a 12:12 hr light/dark cycle (7am-7pm), with food and water available ad libitum. To reduce stress, rats were handled daily until implantation of electrodes and twice weekly thereafter.

2.2 EEG Electrode Implantation

Upon reaching 350 g (+/− 50 g; approximately PND 70), rats underwent surgery for EEG electrode implantation. Rats were anesthetized via isoflurane/air mixture and positioned in a stereotaxic frame. A midline incision exposed the dorsal surface of the skull and another incision reflected the right temporalis muscle, exposing the temporal bone. Stainless steel screw electrodes with wire leads were implanted epidurally over the vertex (AP −4.0 mm, ML −1.0 mm, VD 0.0 mm), temporal cortex (AP −4.5 mm, ML −7.5 mm, VD −4.0 mm), cerebellum (ground) and frontal sinus (reference). Stainless steel lead wires were connected to an Amphenol plug and the entire assembly was secured to the skull with dental cement. All ASSRs reported were recorded from the temporal electrode, as the vertex electrode was implanted for another study (Vohs et al., 2009). After surgery rats were allowed 14 days recovery. All SHAM rats (N = 10) used in the present investigation survived surgery without incident, however one NVHL rat (final N = 11) was lost during surgery, due to anesthetic complications.

2.3 Drugs

The GABA$_A$ agonist muscimol hydrobromide (Sigma, St. Louis, MO) and NMDA receptor antagonist ketamine (Sigma, St. Louis, MO) were dissolved in physiological saline for

subcutaneous injection. Physiological saline, with an altered pH of 3.5 to match the lower pH drug (muscimol), was used as a control condition at a volume of 0.3 ml per injection. Drug dosages were calculated based on animal weight and adjusted to dosages of 10 mg/kg for ketamine and 1mg/kg for muscimol. The subanesthetic ketamine dose was selected because it was previously demonstrated to increase cortical glutamate release up to 60 minutes post-injection (Moghaddam et al., 1999), while the muscimol dose was selected based on previous investigations showing behavioral alterations (Houston et al., 2002).

2.4 Stimuli and EEG Recording Procedure

Rats were placed in a 5-sided plastic mesh cage within an electrically shielded chamber. A flexible, insulated plug connector was attached to the Amphenol plug. Rats were allowed a 20 minute acclimation period, which was immediately followed by an injection of saline, NMDA antagonist (ketamine), or $GABA_A$ agonist (muscimol). ASSRs were elicited from all rats, with 3 sessions of data collection (at least 24 hours apart): 1) saline control; 2) ketamine (10 mg/kg); and 3) muscimol (1 mg/kg). Based on literature review (Houston et al., 2002; Moghaddam et al, 1997) and behavioral observations, a 20 minute drug absorption period was observed after muscimol administration, while a 3 minute drug absorption period was observed for saline and ketamine. While saline was always the first condition, drug type (ketamine/muscimol) was randomly assigned to balance against order effects.

ASSRs were elicited via the presentation of auditory stimuli (80 dB) through a small speaker mounted on the ceiling of the recording chamber. Stimuli consisted of ten 10 second trains of clicks, presented at a range of frequencies (10, 20, 30, 40, and 50 Hz), with an inter-trial-interval (ITI) of 1000 ms. EEG data were collected (band pass .1 – 300 Hz) and digitized (1,000 Hz). Test-retest reliability of ASSRs in lesion and SHAM rats has been demonstrated (Vohs et al., 2010).

2.5 Histology

Following completion of recordings, NVHL and SHAM rats were sacrificed (deep isoflurane anesthesia and decapitation) and brains were sectioned on a cryostat into coronal slices 40 micrometers thick spaced 400 micrometers apart. Once mounted and fixed with chloroform, each section was Nissl stained with .05% thionin. The extent of the lesions was determined by microscopic assessment from approximately 3.30 to 5.80 mm posterior to bregma, by a collaborator (R.A.C.) blind to electrophysiological results. Four NVHL rats did not meet criteria for successful hippocampal lesions and two SHAM rats with needle damage to the hippocampi or surrounding regions were excluded. A figure showing acceptable lesion size and placement for the NVHL rats used in this study has been previously published (Vohs et al., 2009) in an investigation during which all rats underwent EEG electrode implantation and recording, but no pharmacological manipulations were performed. Data from each of the remaining rats (SHAM, N = 8; NVHL, N = 7) were analyzed.

2.6 Data Analysis

ASSR data analysis was performed using specialized code for MatLab® (R2007a). ASSRs at each frequency of stimulation (+/− 1.9 Hz) were segmented to include the time period when the stimulus was presented (10 seconds). Data from each 10 second segment was then further segmented into 1 second epochs. Each epoch was baseline corrected to control for waveform polarity drift away from 0 mV and submitted to a 100% Hanning window, to reduce bias in estimation of both power and phase. The taper was applied to the windowed EEG segments before performing FFT. A time-frequency spectrogram, using the short time sliding ~ window (128 ms) FFT was then obtained. The FFT returns a complex number

output ($\tilde{R}(f,t)$) for each frequency (f) and time step (t) in each trial. The sliding window FFT was then moved with 10 ms time steps to perform the spectrogram analysis.

Two independent measures of ASSR activity, mean trial power (MTP) and phase locking factor (PLF), were obtained from the spectrogram by averaging across trials for the normalized complex output for every time period and frequency (Makeig et al., 2004). MTP was computed by determining the power, or squared amplitude, of individual trials, then subtracting the mean power of the baseline period (260 ms before stimulus onset) from the power of each trial. MTP scores were then log scored, as appropriate, to normalize the distribution. PFL measures phase synchronization of EEG activity across trials at particular time intervals and frequencies. To illustrate these measures, Figure 1 shows the average time-frequency spectrograms for NVHL and SHAM rats at 50 Hz stimulation, which was the frequency that best illustrated differential group responses.

Statistical analysis was performed using SPSS for Windows (18.0, 2010. Chicago: SPSS, Inc.). Effect size, as measured by partial eta squared (η_p^2) was calculated to reflect strength of association. Partial Eta squared is the proportion of the effect variance to the effect plus error variance ($\eta_p^2 = SS_{factor}/(SS_{factor} + SS_{error})$), with higher η_p^2 values reflecting stronger effects. Statistical significance was determined at $p < 0.05$. Repeated measures analyses of variance (ANOVAs) were performed on the dependent measures of phase locking and power in separate analyses. Focusing exclusively on lesion effects, repeated measure ANOVAs with the within subject factor frequency and between subjects factor of lesion status were performed on data collected after saline administration. Additional repeated measures ANOVAs examined lesion by drug by frequency effects in which ketamine and muscimol were examined separately.

3. Results

3.1 NVHL vs. SHAM rats after saline

Phase locking increased with increases in stimulation frequency as shown in Figure 2 (**upper panel**) (F(4,52) = 10.28, η_p^2 = .44, $p < .001$). This frequency dependence was altered by NVHL as indicated by a frequency × lesion interaction (F(5, 52) = 3.06, η_p^2 = .19, $p < .05$) associated with a flattening of the phase locking frequency response curve in NVHL rats. Power did not show significant frequency dependent variation or a main lesion effect or frequency × lesion interaction (Figure 2, **lower panels**).

3.2 NVHL vs. SHAMs: ketamine effects

The dependence of phase locking on frequency (F(4,52) = 10.86, η_p^2 = .46, $p < .001$) again interacted significantly with NVHLs (lesion × frequency: (F(4,52) = 2.91, η_p^2 = .18, $p < .05$). Ketamine also significantly disrupted the frequency dependence of phase locking as indicated by drug × frequency interaction (F(4,52) = 4.86, η_p^2 = .27, $p < .01$). As shown in Figure 3 (**upper**), phase locking values generally increased from low to high frequencies across all rats (albeit most robustly in SHAMs), while ketamine blunted phase locking magnitude at 50 Hz.

Power showed significant main effects of frequency (F(4, 52) = 4.51, η_p^2 = .27, $p < 0.01$), ketamine (F(1, 12) = 5.11, η_p^2 = .30, $p < 0.05$), and a frequency × drug interaction (F(4, 52) = 3.86, η_p^2 = .24, $p < .01$). As shown in Figure 3 (**lower**), ketamine-induced elevations were most pronounced at 30 and 40 Hz.

3.3 NVHL vs. SHAMs: muscimol effects

Phase locking was sensitive to muscimol administration and lesion status, and these two manipulations interacted to disrupt the frequency response function. These effects were revealed by a main effect of frequency ($F(4,52) = 14.39$, $\eta_p^2 = .53$, $p < .001$); a frequency × lesion interaction ($F(4, 52) = 4.13$, $\eta_p^2 = .24$, $p < .01$), a muscimol × lesion interaction ($F(1, 13) = 9.25$, $\eta_p^2 = .42$, $p < .01$) and as 3-way interaction (muscimol × lesion × frequency interaction ($F(4, 52) = 2.49$, $\eta_p^2 = .16$, $p = .05$). As indicated in Figure 4 **(upper)** these results indicate that muscimol increases 30 and 40 Hz phase locking in SHAM rats, but lacks a systematic effect on the frequency response function in NVHL rats.

Power was also affected by muscimol administration, as indicated by frequency dependent variation ($F(4, 52) = 5.03$, $\eta_p^2 = .28$, $p < .01$) that was altered by drug effects (frequency × muscimol: ($F(4, 52) = 4.22$, $\eta_p^2 = .25$, $p < .01$) and a muscimol × lesion interaction ($F(1, 13) = 4.54$, $\eta_p^2 = .26$, $p < .05$). As shown in Figure 4 **(lower)** these interactions suggested that muscimol increased power, especially at 30 and 40 Hz, in SHAM rats, while decreasing overall power in NVHLs.

4. Discussion

ASSRs are usually abnormal in schizophrenia, with reductions consistently found in the gamma frequency range. This study showed that the frequency response function of ASSRs in rats was sensitive to NVHL developmental perturbation and pharmacological manipulation of neurotransmitter systems implicated in the generation of neural oscillations and the pathophysiology of schizophrenia. Ketamine resembled, and muscimol interacted with the NVHL model, suggesting actions on common neural systems in auditory cortical pathways. These findings build on previous work identifying EEG markers of auditory information processing abnormalities in the NVHL model (Vohs et al., 2009, 2010) that are analogous to those identified in schizophrenia.

In examining responses over a wide range of frequencies, NVHLs were shown for the first time to produce alterations in the frequency dependence of the ASSR. This effect manifested qualitatively as a failure of NVHL rats to demonstrate increasing phase locking with increasing stimulation frequency, analogous to schizophrenia-related ASSR abnormalities that occur predominantly in the gamma range (Brenner et al, 2003, 2009; Krishnan et al., 2009; Kwon et al., 1999; Spencer et al., 2008). These findings may reflect altered network dysfunction with greater stimulation frequencies, due to increased demand for temporal coordination of neural firing (Ford et al., 2007; Ford & Mathalon, 2008) hypothesized to be modulated by excitatory and inhibitory neurotransmission (Bartos et al., 2007; Lazarewicz et al., 2010; Vierling-Claasen et al., 2008; Whittington et al., 2010). Developmental disruption, inherent to the NVHL model (Tseng et al., 2007, 2008), of connections from the hippocampal regions to the temporal (Cenquizca et al, 2007; Insausti et al, 1997) and prefrontal cortex (Goto & Grace, 2008; Jay & Witter, 1991) and possibly other cortical areas, may underlie network dysfunction which affects both GABAergic and NMDA transmission. This interpretation is consistent with hypotheses and supporting data suggesting that cortical networks in schizophrenia (Benes & Beretta, 2001; Carlsson et al., 2001; Javitt, 2008; Javitt et al., 2007; Krystal et al., 2003) and NVHL rats (Endo et al., 2007; Lipska et al., 2004; Tseng et al., 2009) show subtle yet pervasive abnormalities of both glutamatergic and GABAergic organization and function. While there is a paucity of data regarding auditory cortex abnormalities and dysfunction in the NVHL model, it is notable that the lesion does result in acoustic hypersensitivity in adult rats (Macedo et al., 2010) and altered event-related potentials to paired click stimuli (Vohs et al., 2009).

In order to further explore the nature of the observed cortical dysfunction and its relationship to the model, we examined ASSRs after acute administration of ketamine. This and other non-competitive NMDA antagonists (PCP, MK-801) have long been appreciated as pharmacological models of the putative glutamatergic disturbance in schizophrenia (Carlsson & Svensson, 1990; Krystal et al., 1994). Like NVHLs, ketamine changed the frequency dependence of ASSR phase locking, tempering the trend for increased phase locking in the gamma range. This consistency between NVHL and ketamine ASSR response profiles may be indicative of similarities in their cortical network effects. It has been hypothesized that NMDA antagonists may acutely produce a functional state where NMDA blockade (on GABAergic interneurons) weakens inhibitory control of principal glutamatergic neurons (Coyle, 2004; Grunze et al., 1996; Homayoun & Moghaddam, 2007; Krystal et al., 2003; Moghaddam et al., 1997), which could manifest as altered phase locking at some frequencies. Similarly, NVHL rats show cellular and physiological markers of cortical GABAergic hypofunctionality (Endo et al., 2007; Francois et al., 2009; Tseng et al., 2008), and dysfunctional glutamatergic transmission associated with stimulus-dependent dis-coordination and/or hyper-active firing of cortical neurons (Chambers et al., 2010; O'Donnell et al., 2002; Tseng et al., 2007). These themes mirror histopathological and physiological evidence suggesting that GABAergic hypofunction and disorganization of excitatory transmission are themes characteristic of the schizophrenic cortex (Aghajanian, 2009; Coyle, 2004; Lewis & Moghaddam, 2006). Notably, we also observed a robust effect of ketamine on ASSR power, which was not observed as an independent NVHL effect. This difference may reflect the capacity of acute ketamine challenge to produce a more potent, uncompensated effect in altering cortical connectivity and network activity compared to NVHL, where developmental compensatory mechanisms may have minimized network dysfunction severity.

Analysis of the effects of the GABA$_A$ agonist muscimol provided an alternative perspective on the neurotransmitter basis of ASSR profiles and their derangements in NVHL rats. Consistent with our expectation to replicate previous findings (Vohs et al., 2010), GABA$_A$ agonism decreased gamma range activity in NVHL relative to the increased response observed in SHAM rats. The degradation of both phase locking and power that occurred only as a combined result of both muscimol and NVHL suggests that the low GABAergic functionality associated with the NVHL model could represent a compensatory adaptation to, or secondary consequences of other primary network aberrations. Then, GABAergic provocation in a NVHL cortical network that requires, or is inflexibly limited to, GABAergic hypoactivity may produce disruptions in cortical synchronization. Considering that muscimol and ketamine produce acute network effects that are to some extent in opposition (i.e. mucimol increases inhibitory/decreases excitatory activity; ketamine decreases inhibitory/increases excitatory activity), we posit that their differential effects on NVHL ASSRs could be further illustrative of the altered cortical dysfunction, particularly in auditory cortex, that is yet to be explored in this model.

Taking our results and interpretations in perspective, it is clear that follow-up investigations are needed to further explore network and neurotransmission alterations in the auditory cortex of NVHL rats. Further, additional data on ASSR measures in rats is needed to characterize dose-response relationships, cellular mechanisms, and predictive validity for anti-psychotic agents. This study is the first to characterize ASSRs in SHAM and NVHL rats across and range of frequencies and implement pharamacological manipulations to test the role of excitatory and inhibitory transmission, which could ultimately further understanding of this complex issue in patients with schizophrenia. Finally, this study highlights an experimental approach and rationale for using NVHLs and additional schizophrenia models, and alternative pharmacological challenges involving other dosing regimens and drug types. Providing a way to test mechanistic hypotheses that are not

feasible in humans, or for generating new clinically relevant hypotheses, ASSR studies in rat models are potentially highly complementary to, and synergistic with parallel human studies.

Acknowledgments

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## Highlights

- NVHL, ketamine, and muscimol altered ASSRs frequency dependence

- Results sometimes differ depending on measure used (power vs. phase locking)

- Data may support receptor alterations in schizophrenia and ASSR generation

- Data suggest utility of combining lesion, pharmacological, and ASSR approaches

- Further study needed for mechanisms underlying disturbed ASSR in schizophrenia
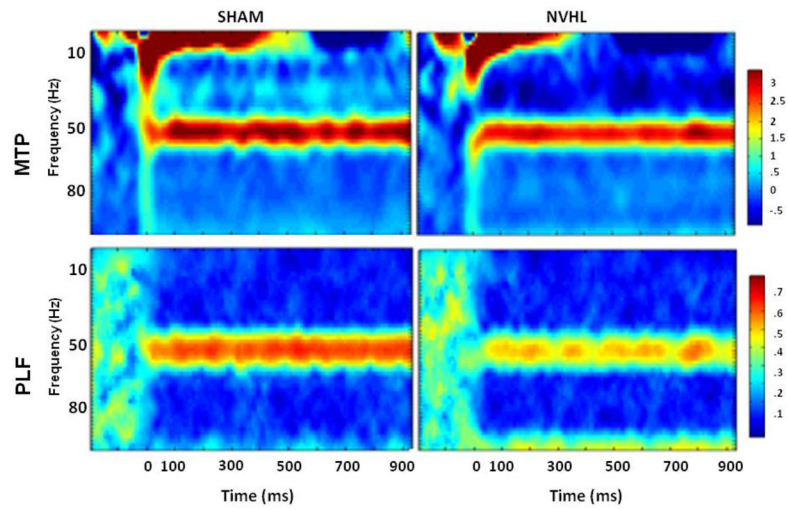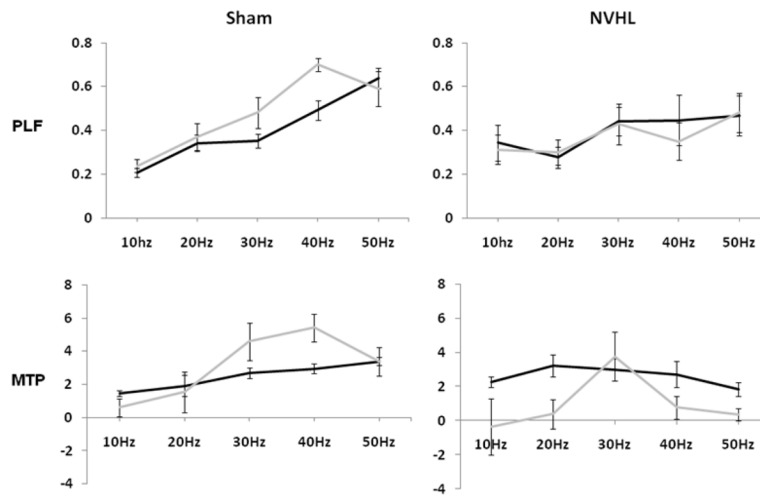
Figure 1.
PLF = phase locking factor (consistency across trials); MTP = mean trial power (magnitude of response). This figure shows time-frequency plots of ASSRs at 50 Hz stimulation, which most robustly illustrated the responses of NVHL vs. SHAM rats.
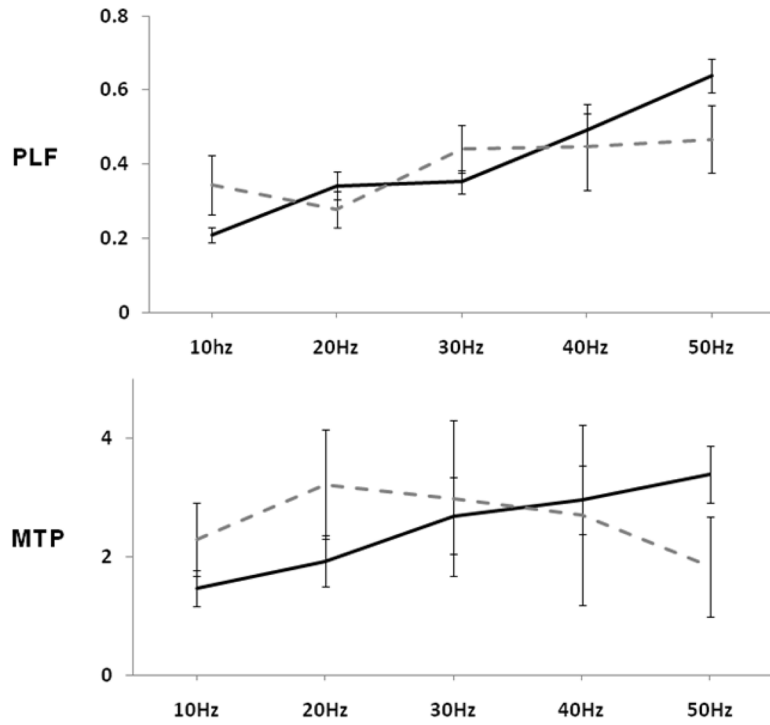
Figure 2.
PLF = phase locking factor (consistency across trials); MTP = mean trial power (magnitude of response). Data from each panel was used separately in repeated measure ANOVA. A frequency by lesion interaction ($p < .05$) was detected with PLF (upper panel). Error bars represent the standard error of the mean.
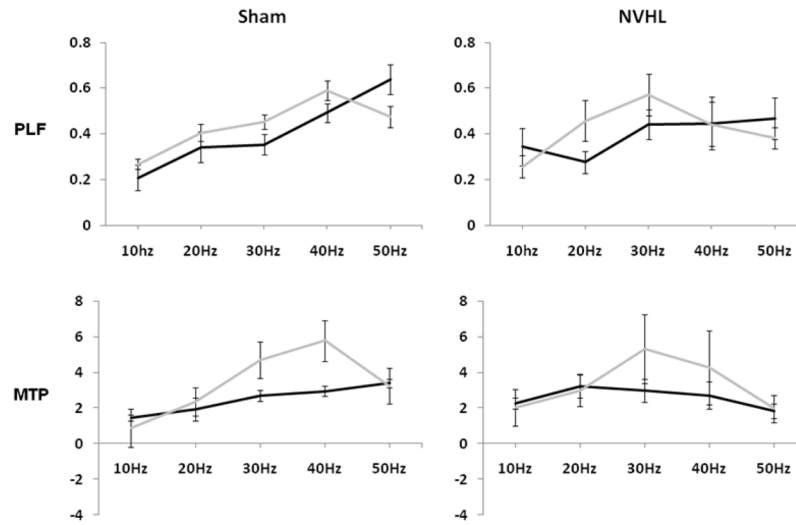
Figure 3.
PLF = phase locking factor (consistency across trials); MTP = mean trial power (magnitude of response). Data from the upper two and then lower two panels were each used in a repeated measure ANOVA to test for lesion and/or drug effects and interaction using PLF and MTP, respectively. Both lesion by frequency and drug (ketamine) by frequency interactions were detected using PLF, while main effects of frequency and drug, as well as a frequency by drug interaction were detected using the MTP measure. Effects and interactions were considered significant at $p<.05$. Error bars represent the standard error of the mean.

Figure 4.

PLF = phase locking factor (consistency across trials); MTP = mean trial power (magnitude of response). Data from the upper two and then lower two panels was used in a repeated measure ANOVA to test for lesion and/or drug (muscimol) effects and interaction using PLF and MTP, respectively. PLF data revealed a frequency by lesion, drug by lesion, and three way drug, frequency, lesion interaction (p < .05). Using MTP frequency by drug and drug by lesion interactions were detected. Effects and interactions were considered significant at $p <$. 05. Error bars represent the standard error of the mean.