Published in final edited form as:

Neurobiol Dis. 2012 April ; 46(1): 93–100. doi:10.1016/j.nbd.2011.12.049.

NMDA Antagonists Recreate Signal-to-Noise Ratio and Timing Perturbations Present in Schizophrenia

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Abstract

Rationale—There is increasing evidence that functional deficits in schizophrenia may be driven by a reduction in the signal-to-noise ratio (SNR) and consistent timing of neural signals. This study examined the extent to which exposure to the NMDA receptor antagonists ketamine and MK801, frequently used pharmacological models of schizophrenia, recreate deficits in electrophysiological markers of disturbed brain circuits that are thought to underlie the illness. Furthermore, this study characterizes the specificity of these differences across the frequency spectrum so as to help identify the nature of selective circuit abnormalities that mediate each oscillatory response as relevant to schizophrenia.

Design—Mouse EEG was recorded during exposure to repeated auditory stimuli after injection of either vehicle or drug. The dose-response relationship for each electrophysiological measure was determined for ketamine and MK-801. Time-frequency analyses were performed to assess baseline, total, and evoked power and intertrial coherence (ITC) at low (5–10 Hz) and high (35–80 Hz)-frequencies.

Results—High frequency evoked and total power was decreased by MK-801 and ketamine in a dose-dependent fashion. High frequency baseline power was increased by MK-801 and ketamine in a dose-dependent fashion. Similar to evoked power, high frequency inter-trial coherence was dose-dependently decreased by both drugs. Low frequency ITC was only decreased by ketamine.

Conclusions—Both ketamine and MK-801 cause alterations in high-frequency baseline (noise), total (signal), and evoked (signal) power resulting in a loss of high frequency SNR that is thought to primarily reflect local circuit activity. These changes indicate an inappropriate increase in baseline activity, which can also be interpreted as non-task related activity. Ketamine induced a loss of intertrial coherence at low frequencies, indicating a loss of consistency in low-frequency

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Disclosures: All other authors report no biomedical financial interests or potential conflicts of interest.

circuit mechanisms. As a proportion of baseline power, both drugs had a relative shift from low to high frequencies, reflecting a change in the balance of brain activity from coordination of global regions to a pattern of discoordinated, autonomous local activity. These changes are consistent with a pattern of fragmented regional brain activity seen in schizophrenia.

Keywords

schizophrenia; electrophysiology; endophenotype; animal models; NMDA antagonist

Introduction

Schizophrenia is a disabling psychiatric illness that affects about 1% of the population. Currently, there are no effective treatments for the negative and cognitive symptoms associated with this disease. Developing novel therapeutics for treatment resistant symptoms requires appropriate neural biomarkers associated with these deficits and valid animal models that reflect underlying disease pathophysiology. This study examined two pharmacologically-induced models of schizophrenia based on the glutamate hypothesis of disease pathogenesis, which is based on the observation that NMDA-receptor antagonists, such as ketamine, PCP, and MK801, have been shown clinically to induce psychosis and cognitive deficits indistinguishable from that seen in schizophrenia (Javitt and Zukin, 1991). Additionally, administration of NMDA-receptor antagonists to model organisms has been demonstrated to recreate many of the cognitive, sensory, motor, and electrophysiological deficits seen in schizophrenia (Jackson et al., 2004; Javitt et al., 2000; Shiigi and Casey, 1999; Swerdlow et al., 2006). However, many of these preclinical studies have used ketamine to induce schizophrenia-like phenotypes, despite the fact that ketamine has many effects in addition to NMDA-receptor antagonism, such as activation of HCN1 channels, which make the causal interpretation of its effects more difficult (Chen et al., 2009). As such, this study investigated the effects of ketamine in addition to MK-801, a selective NMDA-receptor antagonist, to compare the effects of these two drugs. Finally, to our knowledge, no studies have investigate the effects of either drug on auditory-evoked gamma-frequency signal-to-noise, despite emerging evidence that this is an important biomarker for the treatment resistant symptoms of schizophrenia (Gandal et al.).

Studies from our group and others have shown a high degree of similarity between human and mouse EEG measures and auditory event-related potentials (ERPs) in terms of waveform morphology, as well as physiological and pharmacological response properties. These measures offer greater translatability than behavioral phenotypes as they can be investigated using the same auditory paradigms in preclinical and clinical studies, while giving responses with analogous components such as the P20/P50 and N40/N100 between mouse/human (Connolly et al., 2003; Metzger et al., 2007; Umbricht et al., 2004). We have demonstrated that schizophrenia-like auditory-ERP deficits, such as reduced P1/N1 amplitude and habituation, can be recreated using pharmacological manipulations that disrupt neurotransmitter systems involved in schizophrenia pathophysiology, including dopamine, acetylcholine, and glutamate systems (Maxwell et al., 2006; Phillips et al., 2007; Siegel et al., 2005). Similar abnormalities have been demonstrated in transgenic mice with mutations in schizophrenia risk genes, including *DTNBPI*, *NRG1*, and *GRIN1*, which

regulate glutamatergic signaling (Carlson et al.; Ehrlichman et al., 2009b; Halene et al., 2009).

Recent work has indicated that high-frequency (e.g., gamma) oscillations are particularly important as a biomarker for the treatment-resistant symptoms of schizophrenia (Gandal et al.; Gonzalez-Burgos et al.; Sun et al.; Uhlhaas and Singer, 2010). Gamma oscillatory activity is known to be important for attention, working memory, sensory processing, and perceptual ‘feature binding’ – neurocognitive processes that are all disrupted in schizophrenia (Gandal et al.). Indeed, one study reported a disruption in the phase-locked auditory-evoked gamma band response in schizophrenia patients, which was correlated with reduced working memory capacity (Light 2006). Parvalbumin-expressing, fast-spiking interneurons – a sub-population of GABAergic cells disrupted in schizophrenia – have been shown to be necessary and sufficient to generate gamma rhythms *in vivo* (Cardin et al., 2009; Hashimoto et al., 2003; Sohal et al., 2009). There is preliminary evidence that pharmacologic reversal of gamma-band deficits in patients with schizophrenia is associated with clinical improvement in treatment-refractory domains (Lewis et al., 2008). Finally, there is a wealth of evidence that the properties of gamma rhythms -- including frequency range, cross-frequency coupling, circuit generators, cortical function, and cognitive correlates – are phylogenetically conserved across mammals (and even invertebrates), making this an attractive biomarker for translational investigation (Brosch et al., 2002; Buzsaki and Draguhn, 2004; Colgin et al., 2009; Gray and Singer, 1989; Hall et al., 2005; Kirschfeld, 1992; Sohal et al., 2009).

Since NMDA receptor antagonists have been able to recreate many of the cognitive, sensory, motor, and electrophysiological deficits of schizophrenia, these pharmacologic agents are among the leading methods for recreating schizophrenia-like deficits in animals (Jackson et al., 2004; Javitt et al., 2000; Shiigi and Casey, 1999; Swerdlow et al., 2006). However, the electrophysiological consequences of disrupted glutamate signaling have only been studied for a limited number of outcomes, P1, N1, P2, amplitude and latency as well as mismatch-negativity deficits following ketamine (Amann et al., 2009; Maxwell et al., 2006; Turetsky et al., 2007). Furthermore, the mechanism by which high-frequency oscillations are perturbed by NMDA disruption is less studied, even though evidence suggests these oscillations reflect deficits in higher order cognitive functioning in schizophrenia (Light et al., 2006). Therefore, it is important to understand how well these pharmacological models reflect the true endophenotypes of the disease in order to assess their face and predictive validity. This study examines how different NMDA antagonist agents influence low- and high-frequency oscillations to determine the extent to which they recreate the perturbations in SNR present in schizophrenia.

Methods

For calculating SNR, morlet wavelets were used to create a time and frequency resolved map of event related spectral perturbations (ERSP), as shown in Figure 1A. This method allows evoked, baseline, and total power changes to be observed as they change in both the time and frequency domains in contrast to the traditional ERP and FFT methods which only have resolution in one domain. This enables more comprehensive analysis of transient

stimulus related responses and by extension, understanding of neural circuit response. This method has been previously established in clinical studies of schizophrenia and autism and to examine power changes in those disorders. To evaluate the state of SNR in this model, baseline, evoked and total power were examined in high and low frequency ranges to determine if these two well established pharmacological models cause perturbations in the noise or stimulus-related signal similar to those found in schizophrenia (Behrendt, 2003; Behrendt and Young, 2004; Brenner et al., 2009; Canive et al., 1998; Dierks et al., 1995; Doheny et al., 2000; Ford et al., 2008; Fujisawa et al., 2004; Gaspar et al., 2009; Hall et al.; Hall et al., 2009; Hong et al., 2004; Jensen and Lisman, 1996; Kessler and Kling, 1991; Kirino and Inoue, 1999; Kissler et al., 2000; Koukkou et al., 2000; Krause et al., 2003; Krishnan et al., 2009; Kwon et al., 1999; Leicht et al.; Lifshitz et al., 1987; Light et al., 2006; Reinhart et al.; Schellenberg and Schwarz, 1993; Spencer et al., 2004; Teale et al., 2008; Yamamoto, 1997). Additionally, inter-trial coherence, a measure for determining the trial to trial response consistency, was examined was analyzed in low and high frequency regions to determine whether or not a loss of response consistency is associated with changes in power. This measure has also been used in clinical studies to examine deficits in circuit response timing in schizophrenia clinical trials. These measures will give a better understanding of the circuit disruptions driven by the NMDA system and how they match those found in schizophrenia.

Subjects

Forty-five male C57BL/6Hsd (B6) mice were obtained at 7–8 weeks of age from Jackson Labs (Bar Harbor, ME, USA). All testing was conducted between 10 and 18 weeks of age. Mice were acclimated to the animal facility for 7 days before experimentation began and were housed four to five per cage until surgical implantation of the recording electrode, after which they were single-housed for the remainder of the study. All subjects were maintained in a standard 12-h light/dark cycle with free access to food and water. Experiments were performed during the light phase between 9:00 AM and 4:00 PM. All protocols were conducted in accordance with University Laboratory Animal Resources (ULAR) guidelines and were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Pennsylvania. All efforts were undertaken to minimize the number of animals used in the experiment and their suffering.

Electrode Implantation

At 12 weeks of age, animals underwent stereotaxic implantation of electrode assemblies (PlasticsOne Inc., Roanoke, VA, USA) for non-anesthetized recording of auditory ERPs as previously reported (Connolly et al., 2004; Connolly et al., 2003; Maxwell et al., 2004; Siegel et al., 2003). Animals were anesthetized with isoflurane and unipolar recording electrodes were placed in the CA3 hippocampal region (1.8 mm posterior, 2.65 mm lateral and 2.75 mm deep relative to bregma) and referenced to the ipsilateral frontal sinus to reflect whole brain electrical activity. ERPs recorded from this electrode configuration are characteristically similar to human recordings from the Cz scalp location as illustrated in a prior publication by our group (Siegel et al., 2003). The electrode pedestal was secured to the skull using ethyl cyanoacrylate (Loctite, Henkel, Germany) and dental cement (Ortho Jet, Lang Dental, Wheeling, Illinois). EEG was recorded 1 week later, as described below.

Electrophysiological Recordings

EEG was recorded with Power1401 hardware and Spike6 software (CED, Cambridge, UK) as published previously (Ehrlichman et al., 2009a). A total of 1000 white noise clicks were presented with a 1000 ms interstimulus interval at 85 dB.

Pharmacology

MK801 was obtained from Sigma-Aldrich (St. Louis, MO) and ketamine was obtained from Hospira (Lake Forest, IL). MK801 was dissolved in saline at doses of 0.1, 0.4, 0.7, and 1 mg/kg prior to recording. Ketamine was dissolved in saline at doses of 5, 10, 20, 40 mg/kg. All drugs and saline controls were administered via i.p. injection 5–10 minutes prior to initiation of recording.

Electrophysiology Analysis

Intertrial coherence (ITC), evoked (total stimulus-related activity minus induced and baseline), baseline (pre-stimulus power), and event-related spectral perturbation (ERSP also known as baseline corrected total power) values were calculated with Morlet wavelet decomposition using EEGLab (Delorme and Makeig, 2004). Single-trial epochs –250 and 750 ms relative to the auditory stimulus were extracted from the continuous data. For each epoch (trial), the ITC, baseline power, evoked power, and baseline corrected total power were calculated at 75 linearly spaced frequencies from 5 to 80 Hz, with wavelet cycles increasing from 2 (at low frequencies) to 10 (at high frequencies). ITC is expressed as a unitless ratio between 0 and 1, where 1 represents complete phase synchrony at a given frequency and time across trials. Baseline, evoked, and total power were expressed in dB ($10 * \log_{10} V^2$). For each subject, high-frequency ITC and the power measures were calculated in a window around the peak evoked response, defined as the region from 0–60 ms poststimulus and from 35–80 Hz. The 0–60 ms range was also examined for perturbations in low frequency (5–10 Hz) activity. N40 amplitude was calculated from the ERPs as the difference between the lowest point between 30 and 80 ms and the average of the baseline amplitude 50 ms pre-stimulus.

Statistical Analysis

One way ANOVAs were performed to investigate the effect of each pharmacologic agent on EEG measures. Significant effects were followed by Tukey's post-tests where appropriate. Factor analysis was performed using principle component analysis (PCA) on the individual subject data, examining the relationship between different measures across all drug and saline conditions.

Results

Baseline EEG

Baseline, pre-stimulus auditory-evoked EEG power was calculated at low and high frequencies using EEGLab. Both MK801 and ketamine dose-dependently increased baseline high-frequency power (MK801: $F(1,4)=6.523$, $P=0.0001$, ketamine: $F(1,4)=11.92$,

$P < 0.0001$) (Fig 2). MK801 and ketamine had no significant effects on baseline low frequency power.

Post-stimulus Total Power

Total power (e.g., event-related spectral perturbation, ERSP) was measured from 0–60 ms following auditory stimuli using Morlet wavelet decomposition in EEGLab. MK-801 dose-dependently decreased total power at high frequencies (35–80 Hz) (Fig 2A; $F(1,4)=15.15$, $P < 0.0001$). Ketamine had a similar effect, reducing high frequency total power (Fig 2B; $F(1,4)=18.48$, $p < 0.0001$). MK801 and ketamine had no effect on low frequency total power.

Post-Stimulus Evoked Power

Evoked (e.g., phase-locked) power was calculated within the same time and frequency ranges. MK801 and ketamine reduced high-frequency evoked power (Fig 3; MK801: $F(1,4)=7.533$, $P < 0.0001$, ketamine: $F(1,4)=6.727$, $P < 0.0001$).

Intertrial coherence (ITC) and evoked power are related measures that reflect the degree of phase-locking of an oscillation with a repeated external stimulus. ITC is thought to be a more pure measure of neural synchrony, however, as it is not biased by the amplitude of an oscillation (CITE). Ketamine reduced low and high frequency ITC (low frequency ITC: $F(1,4)=4.417$, $P=0.002$, high frequency ITC: $F(1,4)=7.573$, $P < 0.0001$). MK-801 did not change low frequency ITC but did reduce high-frequency ITC (Fig 4; $F(1,4)=6.99$, $p < 0.0001$).

N1 Amplitude

Patients with schizophrenia have reduced auditory-evoked response amplitudes, especially for the N1 component, which is thought to reflect glutamatergic signaling (Dias et al., 2011). Validating that this effect was also present in our mouse models, MK801 and ketamine dose-dependently reduced N1/N40 amplitude. An ANOVA for the effects of each drug on N40 amplitude revealed that MK801 and ketamine significantly lowered N40 amplitude (Fig ; MK801: $F(1,4)=10.36$, $p < 0.0001$, ketamine: $F(1,4)=15.01$, $p < 0.0001$).

Signal-to-Noise Ratio (SNR)

A change in SNR can be driven (1) a decrease in signal, (2) an increase in noise, or (3) both. In this study, decreased evoked and total power can be thought of as a reduction in signal, whereas increased baseline power likely reflects an increase in noise. To more explicitly calculate SNR, we divided post-stimulus evoked power by the preceding baseline levels in the same frequency range. As expect, both pharmacologic agents significantly reduced high frequency SNR, consistent with deficient sensory encoding (Fig 5; MK-801: $F(1,4)=7.564$, $P < 0.0001$; ketamine: $F(1,4)=7.57$, $P < 0.0001$). (Table 1)

Factor analysis is used to understand the relationships between different variables within a dataset. Variables that concurrently have high loadings on the same factor indicate that they are related or depend on common causes. We separated the measures for all saline and drug conditions on to different factors using a threshold of 0.5 for each factor loading, meaning half the variance of each EEG measure can be accounted for by the factor. Using this

process high-frequency evoked power, baseline power, and SNR grouped on factor 1. High-frequency and low-frequency coherence, high-frequency baseline-corrected total power, and N40 amplitude grouped together, on factor 2.

Discussion

Comparison of Pharmacological Models to Schizophrenia

Mice treated with MK-801 showed reductions in high-frequency evoked power, total power and intertrial coherence, similar to the deficits observed in schizophrenia (Hall et al., 2009; Koukkou et al., 2000; Krishnan et al., 2009; Roach and Mathalon, 2008). There was also an increase in high frequency baseline power similar to schizophrenia (Hong et al., 2008). Unlike schizophrenia, there were no decreases in low-frequency evoked power, intertrial coherence, or increases in low-frequency baseline power (Canive et al., 1998; Ford et al., 2008; Kessler and Kling, 1991; Schellenberg and Schwarz, 1993). Similarly, ketamine administration caused reductions in high-frequency intertrial coherence, evoked, and total power, along with decreased low frequency intertrial coherence, similar to findings reported in schizophrenia (Hall et al., 2009; Koukkou et al., 2000; Krishnan et al., 2009; Roach and Mathalon, 2008). Across drugs, we observed an increase in high frequency baseline power similar to schizophrenia (Hong et al., 2008). In contrast, ketamine did not mimic the schizophrenia-like EEG signatures of reduced total low-frequency power, decreased low-frequency evoked power, and increased low-frequency baseline power (Canive et al., 1998; Ford et al., 2008; Kessler and Kling, 1991; Nakagawa et al., 1991; Schellenberg and Schwarz, 1993).

Ketamine decreased low frequency intertrial coherence across trials, indicating reduced global consistency of response. Neither agent significantly changed baseline low frequency activity. With both agents, there was a reduction in high-frequency SNR caused by both a reduction of stimulus response signal and an increase in baseline noise. The relative increase in high compared to low frequency baseline activity reflects the shift from low to high frequencies reported in patients with schizophrenia. Taken together, these data suggest that disruption of NMDA-receptor mediated neurotransmission caused schizophrenia-like deficits in global coordination and consistency of responses.

Factor analysis demonstrated the expected relationship between SNR and its constituent measures (factor 1). Factor analysis also indicated a pattern of disruptions in intertrial coherence, N40 amplitude reductions, and baseline-corrected total power (factor 2) which could be hypothesized as a deficit in ability to mount a timely response to a salient stimulus. Furthermore, this analysis indicates that the SNR component parts vary independently of the timing measures. This could be thought of as two separate patterns of system disruption, one in the strength of the signal over noise, factor 1, and one in the timing of the response, factor 2.

Potential Mechanisms for Specificity of Drug Effects

The NMDA-receptor is a cation channel that produces excitatory postsynaptic potentials when activated and is important for learning and synaptic plasticity. Although both NMDA-

receptor antagonists are non-competitive inhibitors, MK801 has a much lower reversibility than ketamine. Additionally, MK801 has 161 times the affinity of ketamine, necessitating higher ketamine doses for similar drug effect (Wong et al., 1986). Unlike MK801, ketamine also has activity at mu opioid receptors, the targets of morphine and codeine among other opiates, as well as at HCN channels which are thought to mediate its anesthetic effect. Furthermore, administration of mu-opioid receptor targeting drugs alters low frequency EEG (Greenwald and Roehrs, 2005). Therefore, high doses of ketamine may be altering low frequency oscillations via the mu-opioid receptor, while MK-801 may provide more specific activity at NMDA-receptors.

Limitations and Future Directions

The current study employed acute MK-801 and ketamine administration. Alternatively, chronic administration may have resulted in a different pattern of deficits. This is relevant as schizophrenia is thought to be a chronic developmental disease, in which both reduced NMDA-receptor function and compensatory changes likely contribute to observed phenotypes. This limitation is more applicable to ketamine where repeated administration is required for PV interneuron disruption as opposed to MK801 where only a single dose is required (Behrens and Sejnowski, 2009; Romon et al.).

This study limited its EEG analysis to the region 60 ms post-stimulus. While there are relevant changes outside this range reported, this study focused its analysis to the obligatory ERP region and EEG changes related to that range (Gallinat et al., 2004). This allowed for more cohesive analysis of a constellation of related features, and an examination of the relationship between these early related features.

In addition, it would be preferable to know the relative disruption of interneurons and pyramidal cells following NMDA-receptor blockade, however it is not possible to quantify that distribution using the systemic administration drug model. Some have suggested that there are brain region specific differences in high-frequency activity when treated with NMDA antagonists (Roopun et al., 2008). Although this has been noted in slices, *in-vivo* data suggests that the disruption is generalized (Hakami et al., 2009). There are many possible reasons for these apparently disparate results, many likely arising from the confounds inherent in slice work where physiologic conditions and connections are difficult to replicate. In addition, while similar results were recently published in human subjects following ketamine exposure, we believe this strengthens the current work by showing consistency across species after administration of similar drugs (Hong et al., 2010). We have also extended previous work by performing multi-factor analysis between the different disruptions of neural circuit operations and additionally used a more specific NMDA antagonist, MK-801, to confirm that the cause of the disruptions is primarily glutamate related.

Despite these potential limitations, the current study suggests that a reduction of NMDA-receptor signaling contributes to the pattern of reduced high-frequency SNR observed in schizophrenia, as well as the shift from low frequency to high frequency activity in schizophrenia. These changes are consistent with the hypothesis that schizophrenia is

characterized by a functional disconnection of distant brain regions, with a coincident increase in autonomous, local activity (Schmitt et al.).

Acknowledgments

Funding provided by 5R01DA023210.

Steven Siegel reports having received grant support from Eli Lilly, AstraZeneca, NuPathe, and Pfizer that is unrelated to the content of this paper and consulting payments from NuPathe, Merck, Sanofi, and Wyeth that are unrelated to this work.

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Highlights

- Evaluate extent to which NMDA antagonists reduce signal-to-noise ratio (SNR)
- Evaluates extent to which ketamine and MK801 reduce evoked gamma power (signal)
- Evaluates extent to which ketamine/MK801 reduce baseline gamma power (noise)
- Discusses how signal and noise perturbations recreate reduced SNR in schizophrenia

Figure 1. Grand-Average Time-Frequency Plots of 0.7 mg/kg MK801

The effect of MK801 on auditory-evoked power and intertrial coherence (ITC) is shown. A) Event-related spectral perturbation (e.g., ERSP, in dB relative to pre-stimulus-baseline) is demonstrated for saline and MK-801 (0.7 mg/kg) conditions. The right panel shows statistically different time-frequency regions ($P < 0.05$). B) Intertrial coherence (e.g., ITC) is plotted across time and frequency for saline and MK-801 conditions. The right plot highlights statistically different regions ($P < 0.05$).

Figure 2. Effects on total and baseline power in the high frequency range following ketamine and MK-801

A) Total high-frequency power 0–60 ms post-stimulus was dose-dependently reduced following both ketamine and MK-801. B) Both agents dose-dependently increased high-frequency baseline power, which can be thought of as non-task related activity or noise if it was increased over the reference state. Figures show mean + S.E.M. (***) $P < 0.001$

Figure 3. Effects on high-frequency evoked power following ketamine and MK-801 administration

Both agents dose-dependently reduced high-frequency evoked power 0–60 ms post-stimulus, which can be thought of as the specific signal response to an external stimulus.

Figures show mean + S.E.M. (** $P < 0.01$, *** $P < 0.001$)

Figure 4. Effects of ketamine and MK-801 on low and high-frequency intertrial coherence
 Both ketamine and MK-801 dose-dependently reduced high and low-frequency ITC 0–60 ms post stimulus which measures the precision of response timing in the brain. Figures show mean + S.E.M. (** $P < 0.01$, *** $P < 0.001$)

Figure 5. Signal-to-noise ratio (SNR) as calculated by evoked power divided by baseline activity
 Both ketamine and MK-801 dose-dependently decreased high-frequency SNR as defined by the ratio of evoked power divided by prestimulus baseline power. Figures show mean + S.E.M. (** $P < 0.01$, *** $P < 0.001$)

Figure 6. Effects on N40 amplitude following ketamine and MK-801 administration
 Both agents dose-dependently reduced N40 amplitude, replicating previous studies of NMDA-receptor antagonists and consistent with EEG results observed in schizophrenia patients. Grand average saline ERP shown on left. Figures show mean + S.E.M. (** $P < 0.01$, *** $P < 0.001$)

Table 1**Factor Analysis**

Factor analysis was used to understand the relationships between different variables within a dataset. Variables that concurrently have high loadings on the same factor indicate that they are related or depend on common causes. Using this process high-frequency evoked power, baseline power, and SNR grouped on factor 1. High-frequency and low-frequency coherence, high-frequency baseline-corrected total power, and N40 amplitude grouped together, on factor 2

Factor	1	2
High-frequency evoked power:	0.95	0.12
High-frequency ITC:	0.35	0.60
High-frequency baseline:	-0.60	-0.11
High-frequency baseline-corrected total power:	0.24	0.77
Low-frequency ITC	0.13	0.77
High-frequency SNR evoked:	0.96	0.12
N40 amplitude from baseline:	-0.01	-0.79