INTRODUCTION
Quantitative EEG (qEEG) offers an opportunity to provide a pharmacodynamic, mechanistic and potentially translatable biomarker for various drug-induced and disease states. Changes in electrophysiologic (EEG) gamma band power, defined as frequencies ranging between 30 and 80 Hz, have been linked in humans to enhanced cognitive function, but also to pathological states such as schizophrenia, drug-induced hallucinations, epilepsy and Alzheimer’s disease. Thus, the ability to pharmacologically modulate gamma power may be of therapeutic interest. The EEG provides temporal resolution in the millisecond range, and the ability to detect both excitatory and inhibitory neuronal activity. Here we study effects of NMDA receptor blockers on mouse EEG, with an overall aim to develop a useful biomarker for this compound class, with a potential for forward and back-translation.

EXPERIMENTAL PROCEDURES
Surgical implantation of EEG electrodes. Male C3H/HeN mice were anesthetized and a head-mount with four screw electrode holes was placed on top of the skull and centered along the midline, with frontal screw positioned 1-1.5 mm anterior to Bregma. The head-mount assembly was cemented onto the skull with dental acrylic. Animals were allowed to recover from surgery for at least 10 days and were used for up to 4 months after surgery.

EEG recordings
Continuous EEG recordings were performed with a Pinnacle Technology system (Lawrence, Kansas). A baseline electrophysiologic response was recorded for a period of 30 min prior to drug administration. Test or reference compounds were administered intra-peritoneally, except Traxoprodil, which was administered sub-cutaneously. EEG data was collected for 90 minutes following drug administration. At the end of each experiment, plasma from blood was collected for bioanalysis. Fast Fourier analysis was applied to EEG data in MATLAB to generate time-frequency series. Z-score maps from individual animals were averaged to obtain average maps shown. The power specific to a band was averaged post-drug administration across 90 minutes to generate response curves.

PK/PD methods
Mouse plasma concentrations for Ketamine and Traxoprodil were determined by LC/MS. For the Ketamine PK/PD modeling, PK was fitted simultaneously across 30 and 120 mg/kg doses. Predicted concentrations were then used to fit EEG responses to a sigmoidal Emax link PK/PD model for determination of EC50, Emax and keo.

RESULTS
Heat maps showing power spectrum changes following administration of ketamine (left column, 30, 60 and 120 mg/kg), Remacemide (middle column, 30 and 100 mg/kg) or Traxoprodil (Right column, 30, 60 and 100 mg/kg).

Plots showing average fold-change in the γ frequency band power 90 minutes following drug administration as a function of C∞. (Left, ketamine; Right, traxoprodil)

Clinical ranges were simulated or quoted from listed references.

REFERENCES

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SUMMARY
Non-selective NMDA receptor open channel blockers, ketamine and remacemide increased β and γ-power in a dose- and exposure-dependent manner.

In contrast, traxoprodil, an NR2b specific allosteric antagonist showed a small decrease in γ-power.

Differences in the effects on EEG γ-power caused by the two types of NMDA receptor antagonists may be explained by differences in blocking mechanism (open-channel pore blocker vs allosteric antagonist) subtype-selective effects, and/or a yet unexplored polypharmacology.