Ketamine and haloperidol differentially influence auditory inhibitory gating, beta and gamma activity in rat medial prefrontal cortex

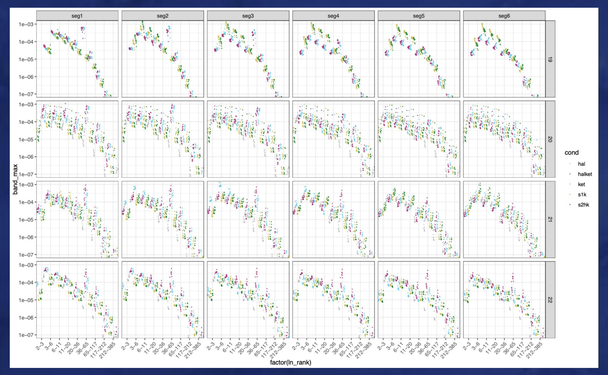
Ketamine is a novel rapid acting antidepressant undergoing clinical trials, and medial prefrontal cortex (mPFC) manifests an apparent locus of ketamine effects (Alexander, et al 2021). Acute ketamine disrupts transfer of information from MPFC with other long-distance brain networks involved in sensation, perception, & emotion.

METHODS

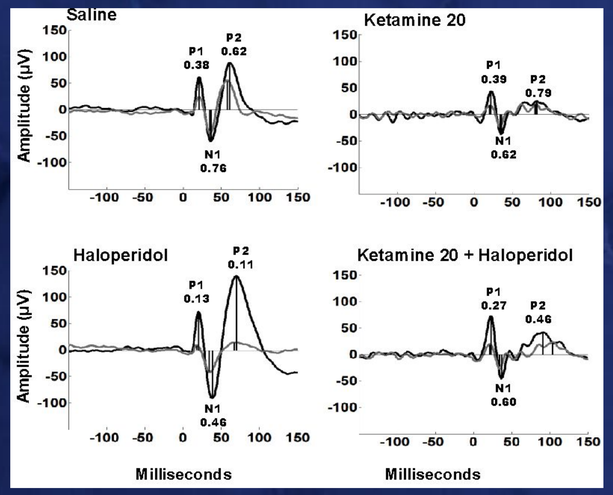
1. Collected three, 1 hr treatment sessions of 4 Sprague-Dawley rats.
2. Rats were treated in four conditions: Haldol (1 mg/kg), Ketamine (20mg/kg), Haldol+Ketamine, & control-saline.
3. Rats were presented with a series of paired clicks following treatment administration.
4. E-phys data was collected from the medial prefrontal cortex.

RESULTS

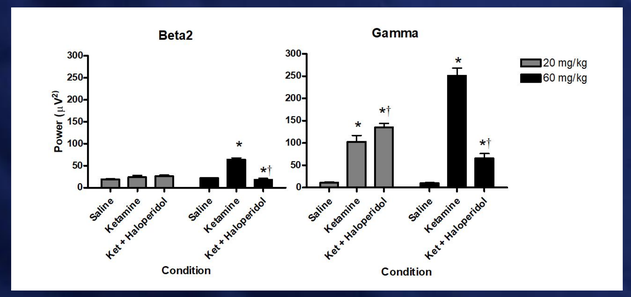
Ketamine had a dose-dependant impact on the degree of inhibitory gating in rats provided with the treatment, reducing inhibitory gating in the 60 mg/kg condition. The addition of haloperidol caused this effect to be reversed. Additionally, ketamine had a dose-dependent impact on beta2 and gamma wave levels. Beta2 levels were increased for the 60 mg/kg treatment, while gamma levels were increased in both treatments. Adding haloperidol reversed the changes in beta2 and attenuated the impact on gamma in the 60 mg/kg treatment group.



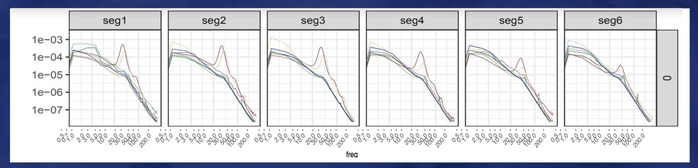
The relationship between MPFC spontaneous gamma and auditory evoked response. Ketamine dose-dependently increased power of spontaneous, non-stimulus elicited gamma rhythm. Each point represents a frequency band max value. The selected frequency bands are defined on a logarithmic scale.



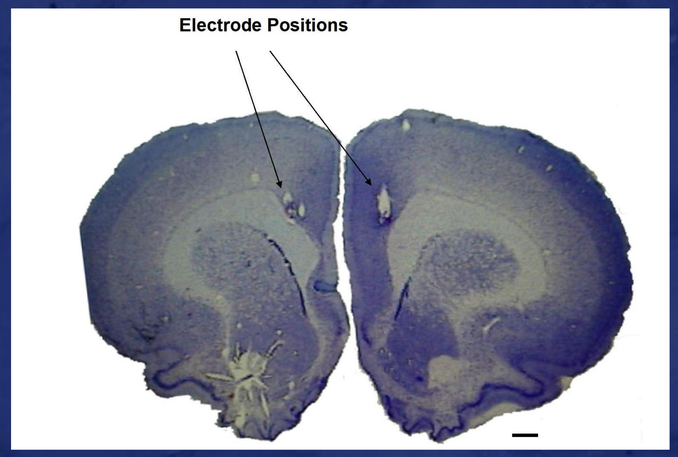
AEP waveforms are representative cases recorded from the same microelectrode for averages of all trials in each session. T/C ratios indicate the proportional relationships for each AEP component in response to Ctone (black trace) and Ttone (gray trace) in saline, ketamine (20 mg/kg), and haloperidol (1 mg/kg) with (20 mg/kg).



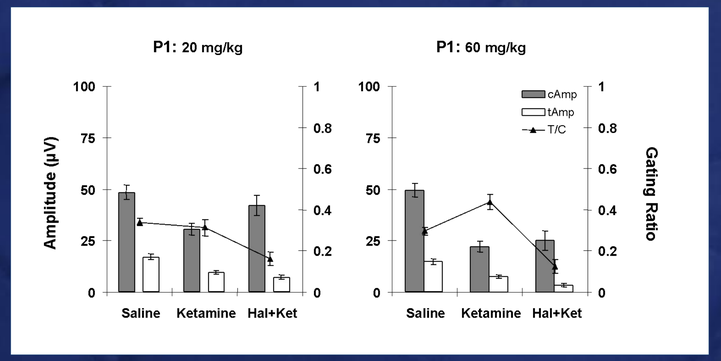
The results for maximum power of beta and gamma reveal effects of ketamine at the two doses investigated. Significant differences ($p < 0.001$) are indicated with asterisk * for ketamine versus saline and with hatched bar † for haloperidol with ketamine versus ketamine alone.



Spontaneous local field potentials during 10 sec inter-trial period for one electrode from a single subject (mpfc21). The spectral power for each condition are indicated on a log-log plot of frequency (Hz) and Power mV^2. Ketamine (gold) and ketamine+haloperidol (red) have peaks in the range of 30-50Hz. Over the course of the session the magnitude of the gamma peak steadily decreases. However, the gamma peak is present for both the ketamine alone and combined.



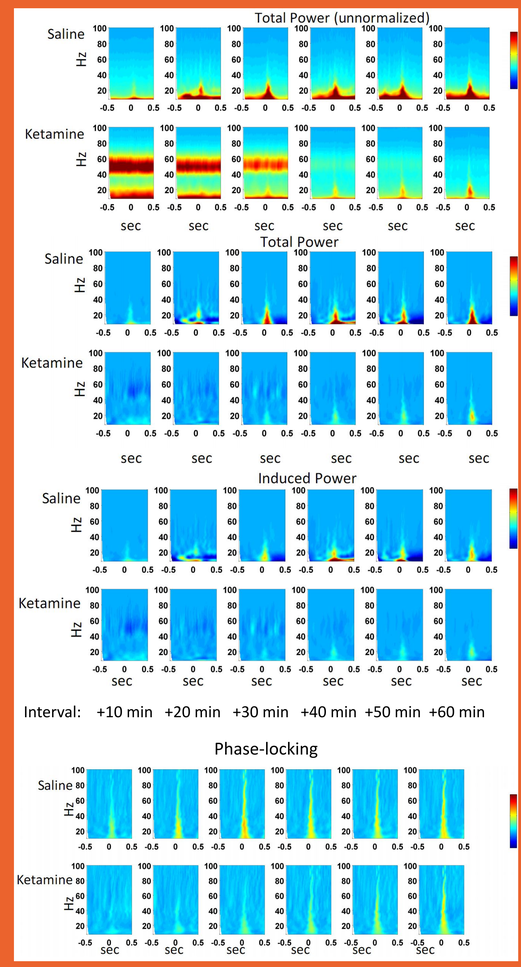
Anatomical mapping of (A) electrode lesions indicated that (B) microelectrode placements (n = 112) centered primarily in dorsal prelimbic mPFC. Horizontal bar below slices represents 1 mm.



Side-by-side presentation of session marginal means (with SE whiskers) for cAmp, tAmp (bars) and T/C (lines) clearly indicate that change of P1 tAmp brings about T/C change across sessions. P1 tAmp and T/C ratios increased for the high, but not lower, ketamine dose. Differences of cAmp and tAmp marginal means approximate the C-T difference decrease in gating for both doses of ketamine.

Neurophysiology: Ketamine 20 mg/kg, cAmp

Time-frequency plots were produced to evaluate spontaneous local field potentials and evoked potentials with the same analysis method. The spectral power for each condition are indicated with time (x-axis), frequency (Hz, y-axis), and Power mV^2 (z-axis). The ketamine has a spontaneous peak in a range of 30-50Hz before and after the first tone at time 0 s. Over the course of the session the magnitude of the gamma peak steadily decreases, and the amplitude in response to Ctone increases. This inverse relationship of evoked activity to spontaneous total power holds for total and induced power measures as well as phase locking.



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References:

Garcia S., Guarino D., Jaillet F., Jennings T.R., Pröpper R., Rautenberg P.L., Rodgers C., Sobolev A.,Wachtler T., Yger P. and Davison A.P. (2014) Neo: an object model for handling electrophysiology data in multiple formats. *Frontiers in Neuroinformatics 8*:10: doi:10.3389/fninf.2014.00010

Gramfort, A., Luessi, M., Larson, E., Engemann, D. A., Strohmeier, D., Brodbeck, C., Goj, R., Jas, M., Brooks, T., Parkkonen, L., & Hämäläinen, M. (2013). MEG and EEG data analysis with MNE-Python. *Frontiers in neuroscience, 7*, 267. https://doi.org/10.3389/fnins.2013.00267
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