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Esketamine-induced reduction of whole-brain alpha power tracks peak behavioral drug effect

STUDY RATIONALE

Background

- Esketamine was FDA-approved for treatment-resistant depression in 2019 and has been shown to exert rapid antidepressant effects^{1,2}
- Disinhibition hypothesis proposes that ketamine's fast-acting antidepressant actions may be due to preferential inhibition of NMDA receptors expressed on GABAergic interneurons, enhancing excitatory activity⁵
- Amplitude of alpha oscillations (8-12 Hz) recorded by EEG might reflect cortical activation³ and have been implicated in MDD⁴
- Understanding immediate effects may aid in treatment stratification and recruitment of other treatment modalities

Hypotheses

- (1) Behavior:** Increase in positive mood and subjective drug effect
- (2) Neurophysiology:**
 - Reduction in whole brain alpha power (8-12 Hz)
 - Increase in whole-brain gamma power (30-78 Hz)
- (3) Behavior / Neurophysiology Interaction:** Association between changes in oscillatory power and subjective measures

METHODS

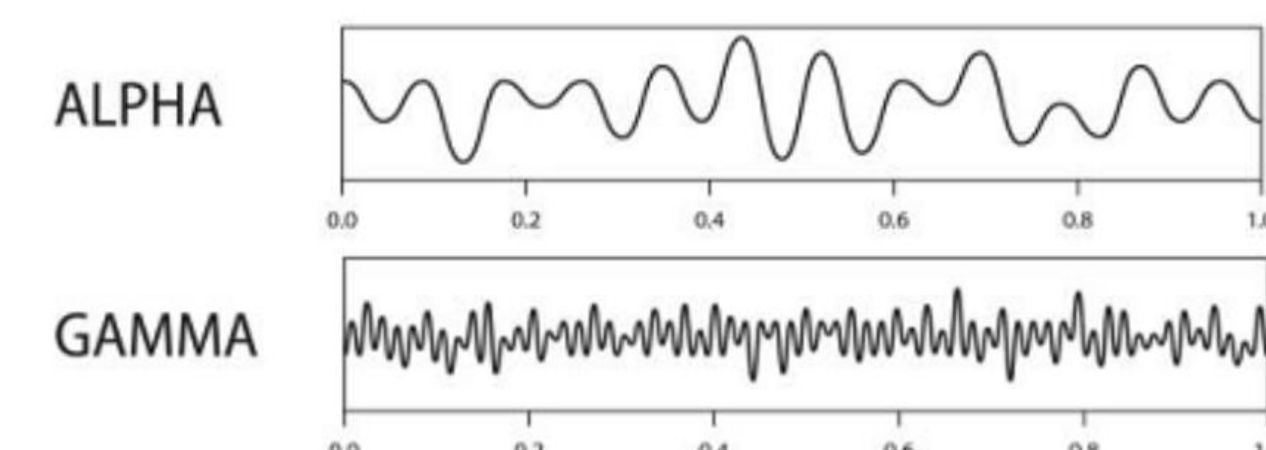
Study Design

- Observational study in participants with treatment-resistant depression
- N = 5, 3 female, Age: 44 ± 17.6 (M ± SD)
- No specific exclusion criteria
- 128-channel EEG before and after nasal Esketamine administration
- Resting state (2 minutes eyes-open)

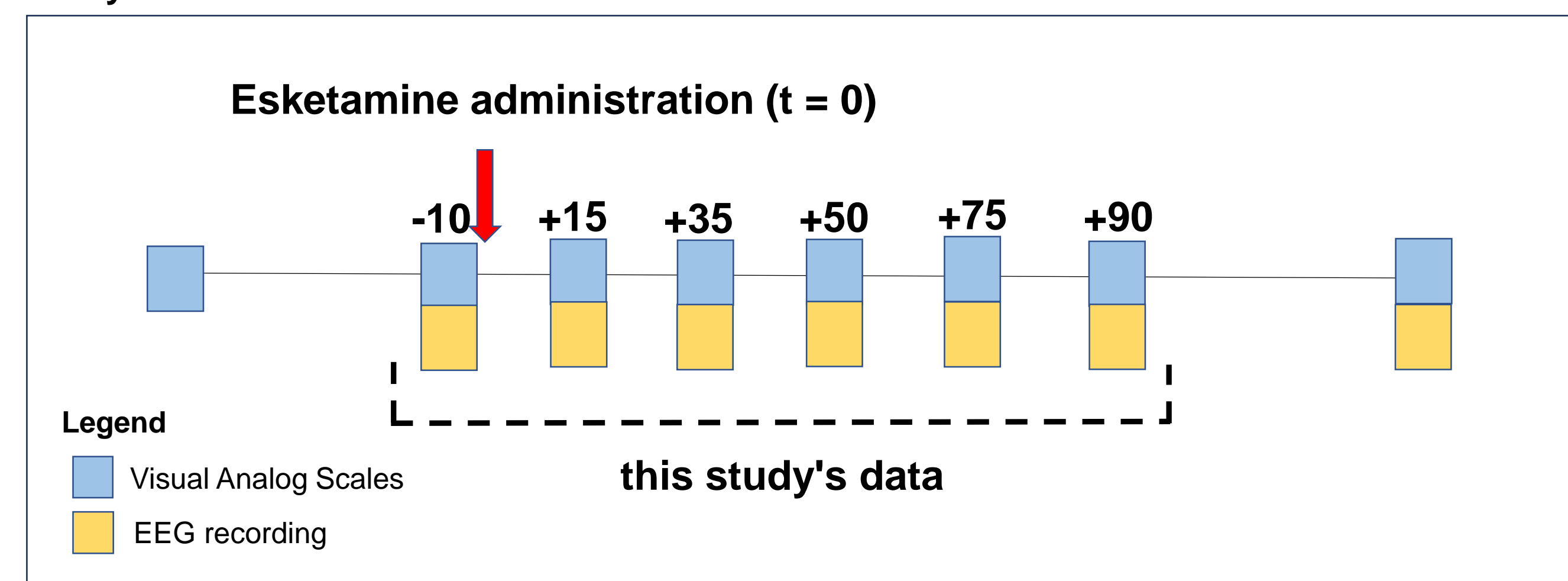
Neuropsychological Questionnaire Scores

	Assessment Score (Mean ± SD)
PHQ-9	16.20 ± 5.22
GAD-7	10.20 ± 7.73
SHAPS	38.40 ± 7.40
LOT-R	5.80 ± 1.48
Q-LES-Q-SF	34.20 ± 12.77

Alpha & Gamma Oscillations

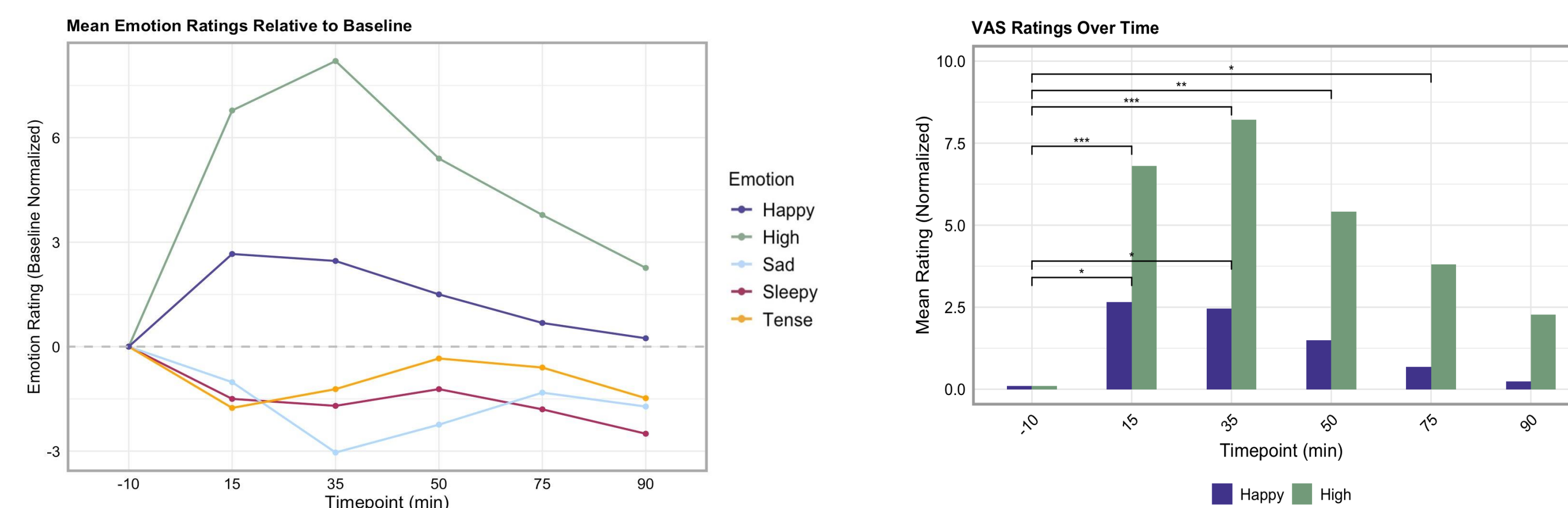


Study Session Outline



RESULTS

(1) BEHAVIOR

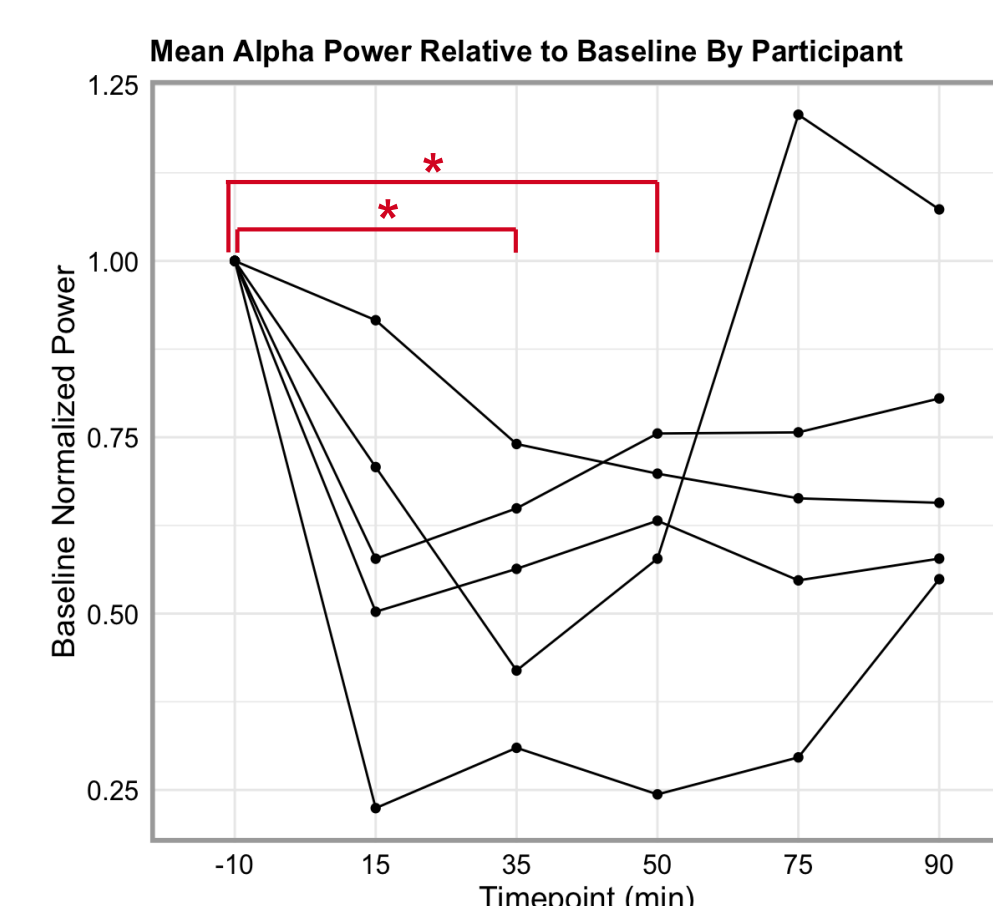


- "Highness" and "Happiness" increase throughout treatment
- Peaks of "Highness" (+31.73%) and "Happiness" (+22.75%) at 35 and 15 min, respectively, which align with known peak Esketamine plasma concentrations

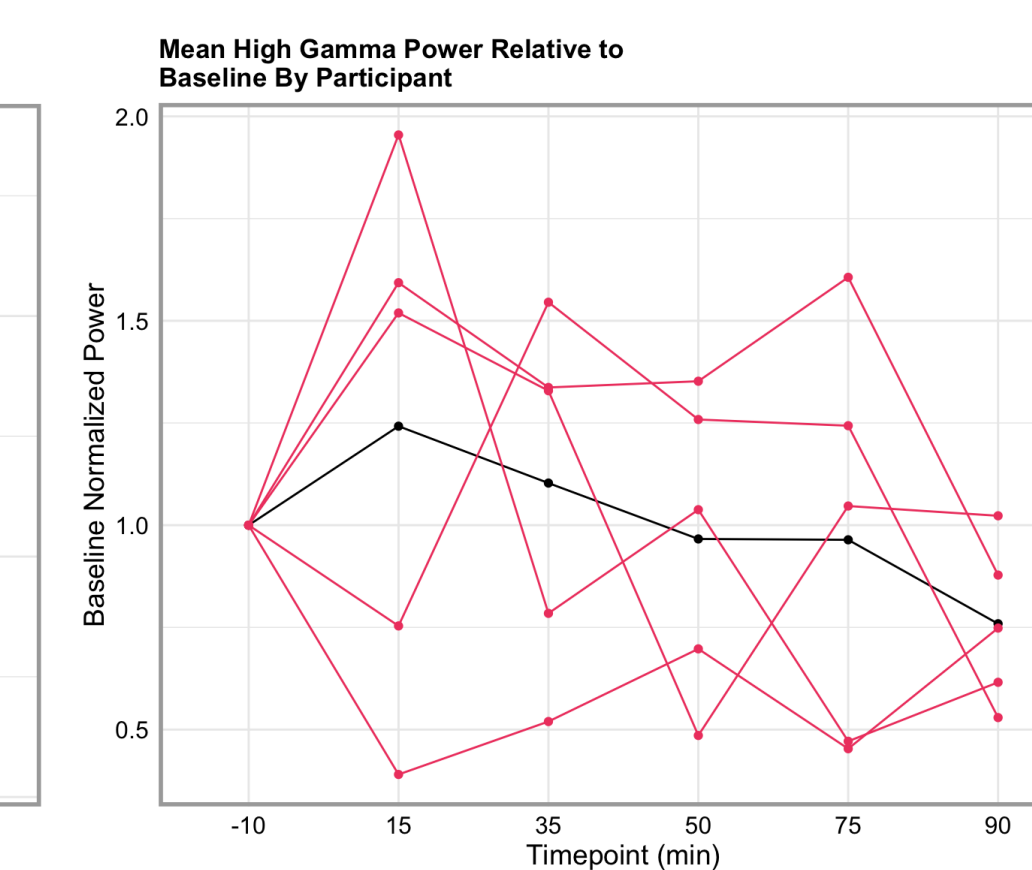
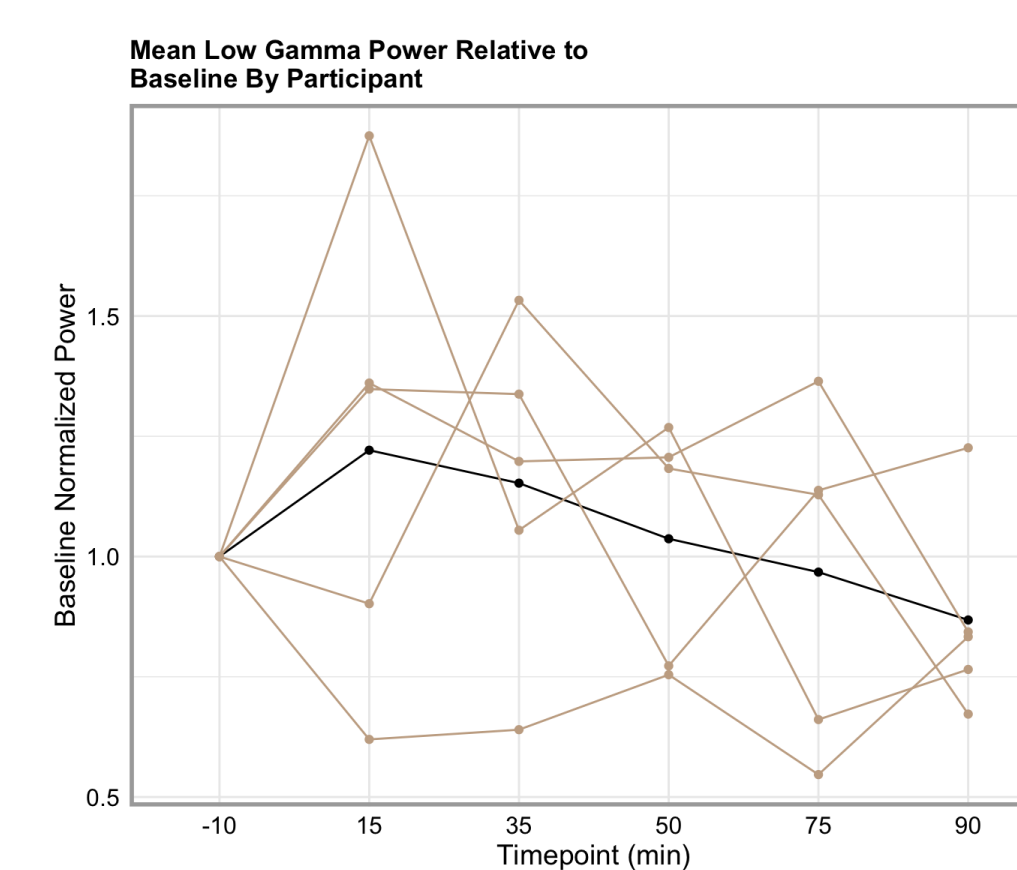
- ✓ **(1) Behavior:** Increase in "Happiness" and "Highness" throughout treatment
- ✓ **(2) Neurophysiology:** Reduction of alpha power which aligns with peak plasma concentrations
- ✓ **(3) Behavior / Neurophysiology Interaction:** Alpha power had a significant effect on "Highness"

(2) NEUROPHYSIOLOGY

ALPHA OSCILLATIONS



GAMMA OSCILLATIONS



OTHER FREQUENCY BANDS

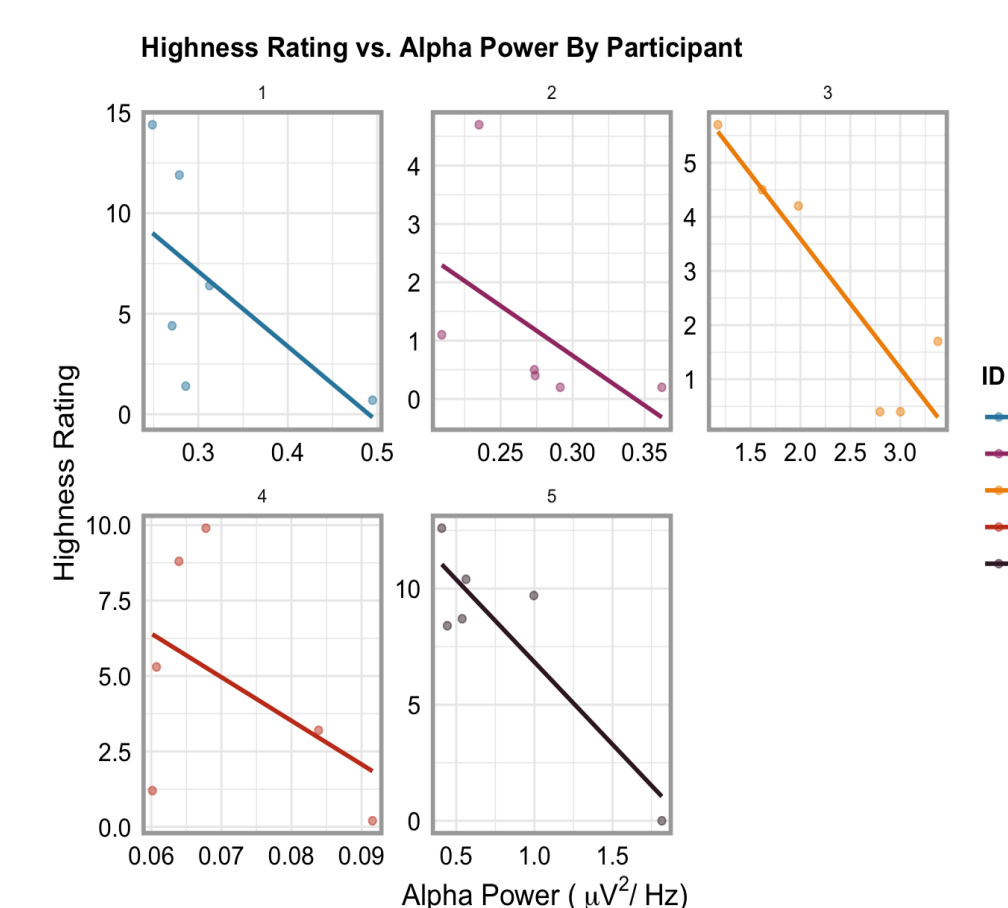
Percent Change in Power from Baseline to "On-Treatment" (15-90 min) per Participant for All Six Frequency Bands

ID	Frequency Band					
	Delta	Theta	Alpha	Beta	Low Gamma	High Gamma
1	-24.36	-33.88	-43.54	-11.53	16.44	8.07
2	20.76	18.45	-29.11	-15.37	8.37	6.60
3	-27.59	-4.05	-20.29	-16.50	12.48	-2.72
4	-30.22	-22.45	-26.49	-10.89	19.45	35.33
5	-23.81	-43.34	-67.55	-49.75	-32.12	-43.82
M	-17.05	-17.05	-37.40	-20.81	4.93	0.69

Red indicates increase; blue indicates decrease

- Alpha oscillations:** Reduction in power peaked at 35 min post administration (-46.36%) and maintained up to 50 min (all $p < .05$), aligning with known peak plasma concentrations
- Gamma oscillations:** Power was not significantly different from baseline at any timepoint. Expected numerical increase between 15-35 min
- Other frequency bands:** Low frequency oscillations (delta, theta) in addition to beta show a numerical decrease among most participants post-Esketamine

(3) BEHAVIOR / NEUROPHYSIOLOGY INTERACTION



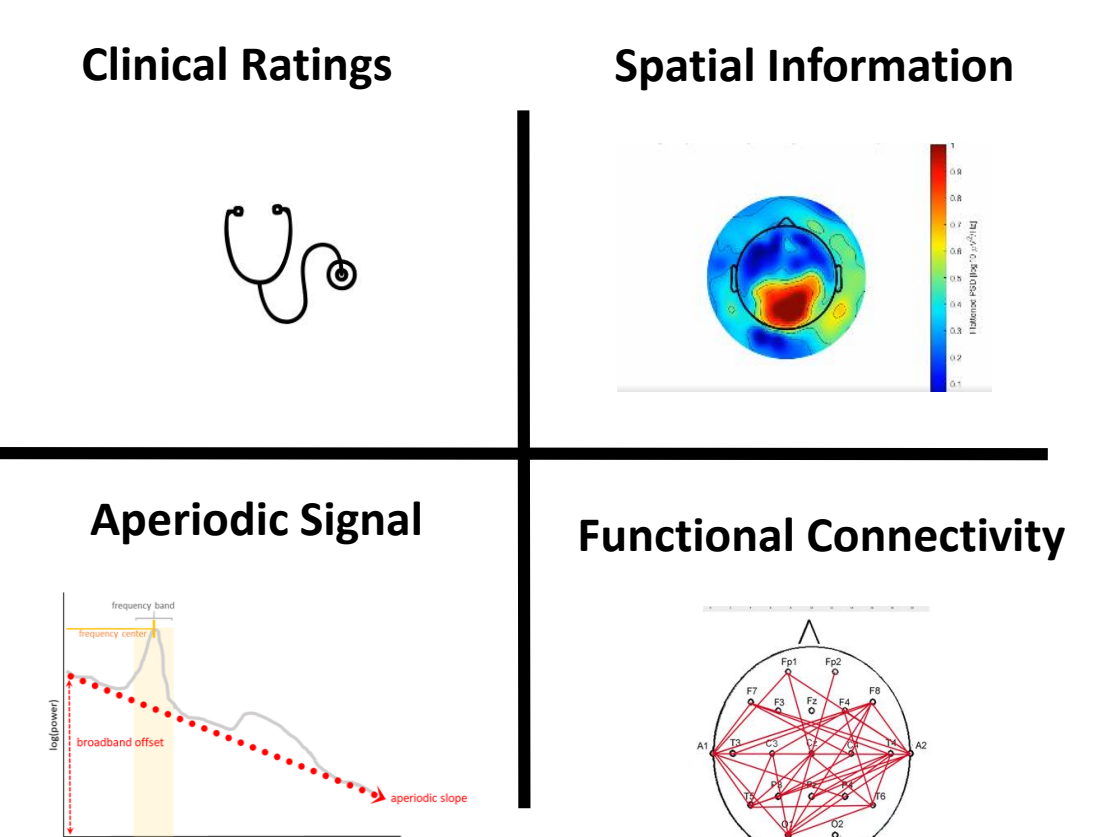
- Alpha oscillations:** Power had a significant effect on "Highness" $\beta = -2.760, SE = 1.20, p = .034$
- Gamma oscillations:** Power had no significant effect on "Highness" $p = 0.90$ and $p = 0.91$ for low and high gamma, respectively
- Individual with highest alpha power reduction corresponds with largest increase in "Highness"

DISCUSSION

- (1) Behavior:** Esketamine induces an increase in positive mood that aligns with peak plasma concentrations
- (2) Neurophysiology:** Reduction in alpha power may suggest an increase in cortical activation that aligns with the disinhibition hypothesis of ketamine's mechanism of action
- (3) Behavior / Neurophysiology Interaction:** Effect of alpha power on "Highness" suggests a potential link between neurophysiological alternations and subjective experiences

Limitations: N is low and the observational nature of this study within a clinical population limits control over confounds contributing to data noise. Results should be interpreted with caution, especially gamma findings.

Future Directions



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