Broadband Coupling to Slow-Wave Phase Acts as a Biomarker for Brain State in Ketamine-Induced Unconsciousness

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Introduction

- Ketamine is a widely used general hypnotic anesthetic for surgical procedures
- There is no reliable, brain-related biomarker that is clinically used for accurate dosing of anesthetics
- Previous ketamine research has shown that there is a characteristic but inconsistent pattern between slow-wave and high-frequency activity during unconsciousness (Sleigh et al. 2019)
- Slow-wave coupling to broadband activity from propofol **electroencephalography** (**EEG**) data has been shown to indicate states of unconsciousness (Stephen et al., 2020)
  - **EEG:** a technique to measure brain electrical activity from the scalp
  - **Slow-wave activity:** an electrophysiological signature across states of unconsciousness found at 0.1-4 Hz
  - **Broadband:** a measure of overall local network firing rates
  - Slow-wave coupling to broadband serves as a biomarker of propofol-induced unconsciousness
- We hypothesize that analysis of brain wave data of ketamine-induced unconsciousness will reveal similar broadband coupling to slow-wave phase as a function of brain state

Methods

Data:

- Analyzed **electrocorticography (ECoG) data** from a **male monkey** treated with **ketamine** (Yanagawa et al., 2013)
  - 128 total electrode channels
  - 4.3 mg/kg of ketamine
- Observed channels 45 and 114 to measure activity in the frontal and posterior regions (highlighted in red)

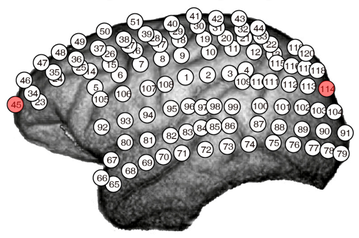

Fig 1. Spatial distribution of electrodes on monkey brain

Processing:

- Applied a **multitaper** using the Spectral Connectivity library to reduce noise in raw ECoG data
- Produced spectrogram representations of overall broadband activity
  - Applied **Butterworth bandpass** filters to the data at 4 Hz bands up to 100 Hz
  - Applied **Hilbert transform** to each filtered band to find the instantaneous amplitude
- Compared visual representations of slow wave and broadband activity across three different 30-second epochs: before anesthetization, during anesthetization, and during emergence
- Computed **phase-amplitude coupling (PAC)** analysis of each epoch
  - Created a phase-amplitude plot to assess the relation between the phase of the slow wave (in radians) and the broadband amplitude

Results

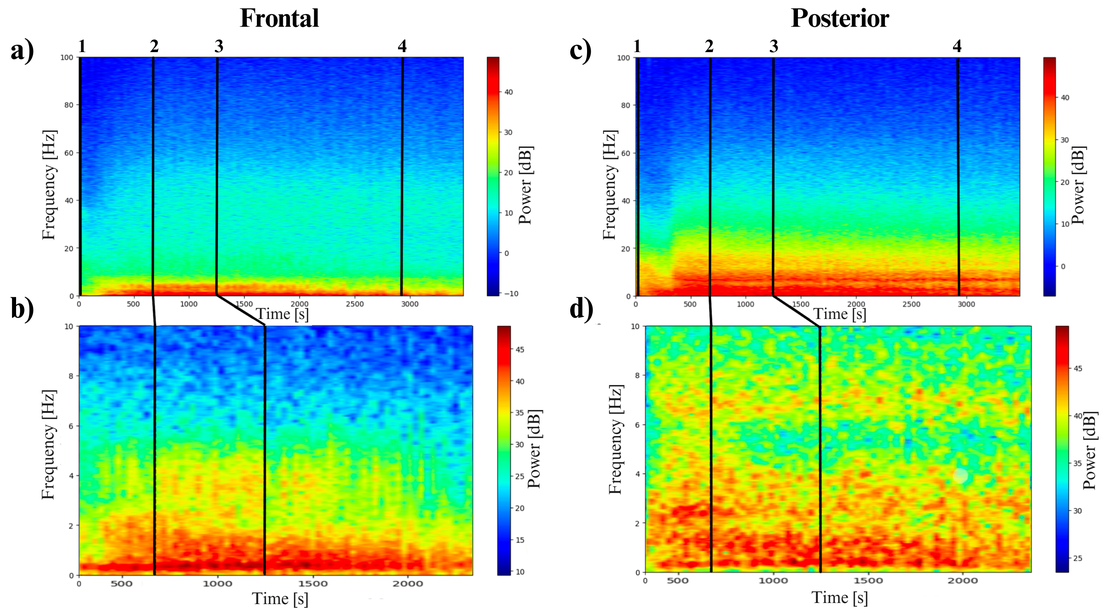

Fig 2. Spectrograms of entire 3532s study in channels 45 and 114 with multi-taper applied. Time of anesthetic injection marked with line 1 (21.82s). Start of anesthetized state marked with line 2 (676.11s). Start of emergence marked with line 3 (1250.12s). Start of recovery marked with line 4 (2931.97s). **a)** Channel 45 over frequencies 0-100 Hz. **b)** Channel 45 over frequencies 0-10 Hz. **c)** Channel 114 over frequencies 0-100. **d)** Channel 114 over frequencies 0-10.

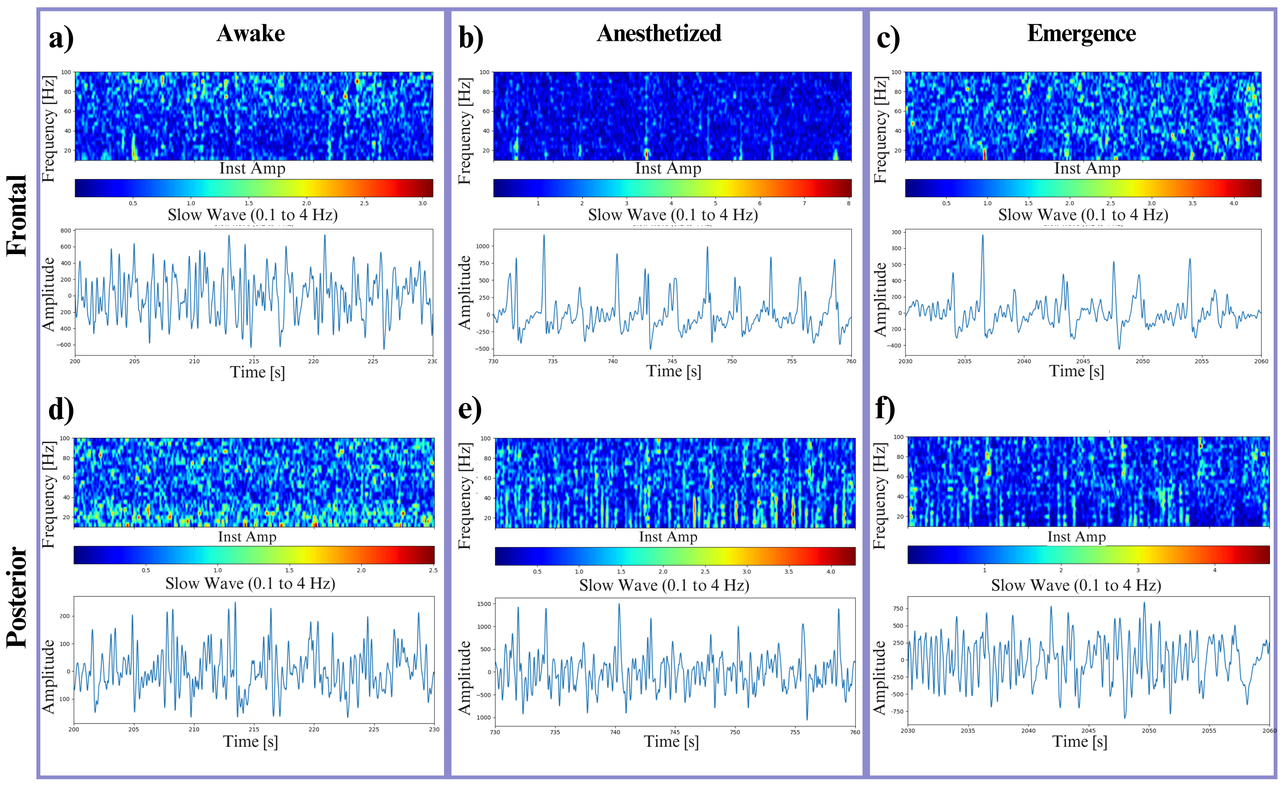

Fig 3. Broadband spectrograms over 0-100 Hz and corresponding slow-wave activity over 30 second epochs in channels 45 and 114. **a)** Awake, channel 45 (200-230s). **b)** Anesthetized, channel 45 (730-760s). **c)** Emergence, channel 45 (2030-2060s). **d)** Awake, channel 114 (200-230s). **e)** Anesthetized, channel 114 (730-760s). **f)** Emergence, channel 114 (2030-2060s).

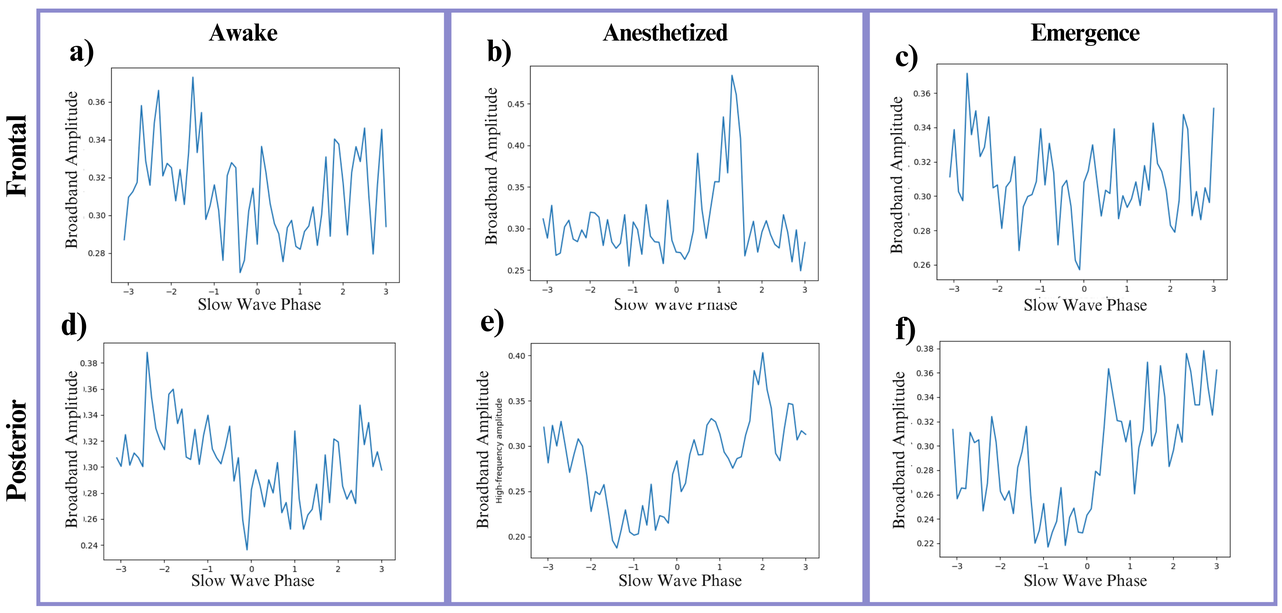

Fig 4. Cross-frequency-coupling analysis of each 30 second epoch in channels 45 and 114. **a)** Awake, channel 45. Corresponds to 3a. **b)** Anesthetized, channel 45. Corresponds to 3b. **c)** Emergence, channel 45. Corresponds to 3c. **d)** Awake, channel 114. Corresponds to 3d. **e)** Anesthetized, channel 114. Corresponds to 3e. **f)** Emergence, channel 114. Corresponds to 3f.

Analysis:

- Awake (3a, 3d): **slow-wave activity shows no association with broadband**
  - Broadband spectrograms from both channels 45 and 114 have no discernible pattern
- Anesthetized (3b, 3e): **slow-wave coupling to broadband is present**
  - Posterior lobe (channel 114) reveals prominent vertical bands of higher amplitude broadband activity associated with slow wave events; similar pattern in frontal lobe (channel 45) but to a lesser extent
- Emergence (3c, 3f): **phase-preference present in the posterior lobe, but not the frontal lobe**
  - Posterior lobe (channel 114) shows broadband continuing to align with slow wave activity, though less prominently than during anesthetization, while frontal lobe (channel 45) spectrogram shows no discernible pattern

Discussion

Conclusions:

- Slow-wave coupling to broadband has the potential to act as a region-specific biomarker of ketamine-induced unconsciousness
- The presence of slow-wave broadband coupling in only the posterior cortex during emergence supports existing research that suggests coupling propagates to the frontal lobe only in deeper states of unconsciousness (Stephen et al. 2020)
- PAC plots confirm that the mean amplitude of the broadband signal depends on the slow wave phase during anesthetization
  - PAC plots of the awake and emergence states show no coupling with the exception of the posterior region (channel 114) during emergence
- Implications could include utilization of real-time analysis of brain-wave activity to improve patient safety

Limitations:

- Conclusions drawn from this research are based off ECoG data from monkeys under ketamine and may not scale directly to humans
- This data only includes the brain waves of a single monkey, limiting the generalizability of the results

Future work:

- Analyzing electrode activity from multiple electrodes and averaging data for each region of the brain
- Collecting and conducting the same signal analysis on EEG data of humans under ketamine

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