Ketamine induces EEG oscillations that may aid anesthetic state but not dissociation monitoring

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Abstract

Objective: Ketamine is an anesthetic drug associated with dissociation. Decreased electroencephalogram alpha (8–13 Hz) and low-beta (13–20 Hz) oscillation power have been associated with ketamine-induced dissociation. We aimed to characterize surface electroencephalogram signatures that may serve as biomarkers for dissociation.

Methods: We analyzed data from a single-site, open-label, high-density surface electroencephalogram study of ketamine anesthesia (2 mg/kg, n = 15). We assessed dissociation longitudinally using the Clinician Administered Dissociation States Scale (CADSS) and administered midazolam to attenuate dissociation and enable causal inference. We analyzed electroencephalogram power and global coherence with multitaper spectral methods. Mixed effects models were used to assess whether power and global coherence signatures of ketamine could be developed into dissociation-specific biomarkers.

Results: Compared to baseline, ketamine unresponsiveness was associated with increased frontal power between 0.5 to 9.3 Hz, 12.2 to 16.6 Hz, and 24.4 to 50 Hz. As subjects transitioned into a responsive but dissociated state (mean CADSS ± SD, 22.1 ± 17), there was a decrease in power between 0.5 to 10.3 Hz and 11.7 to 50 Hz. Midazolam reduced dissociation scores (14.3 ± 11.6), decreased power between 4.4 to 11.7 Hz and increased power between 14.2 to 50 Hz. Our mixed-effects model demonstrated a quadratic relationship between time and CADSS scores. When models (frontal power, occipital power, global coherence) were reanalyzed with midazolam and electroencephalogram features as covariates, only midazolam was retained.

Conclusions: Ketamine is associated with structured electroencephalogram power and global coherence signatures that may enable principled anesthetic state but not dissociation monitoring.

Significance: A neurophysiological biomarker for dissociation may lead to a better understanding of neuropsychiatric disorders.

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1. Introduction

Ketamine is associated with altered arousal and awareness of self, environment, and reality, termed dissociation (Domino, 2010, Li and Vlisides, 2016, Nowacka and Borczyk, 2019). Ketamine is also associated with acute analgesia, antihyperalgesia, and modulation of opioid-mediated analgesia (Heifets, 2020, Persson,
In the United States, ketamine is typically administered as part of a balanced general anesthetic regimen to enhance postoperative analgesia. At high doses, ketamine is sometimes used to induce a state of general anesthesia (Akeju and Brown, 2017, Akeju et al., 2016b, Domino, 2010, Li and Vlisides, 2016). However, the dissociative properties of ketamine have largely limited its widespread use as an analgesic or general anesthetic medication (Gitlin et al., 2020).

Anesthetic drugs such as ketamine significantly modulate neural circuits to produce unconsciousness, amnesia, anti-nociception, and immobility (Akeju and Brown, 2017, Brown et al., 2011, Purdon et al., 2015). Drug modulation of anesthetic (Akeju and Brown, 2017, Akeju et al., 2016a, Akeju et al., 2016b, Akeju et al., 2014, Blain-Moraes et al., 2014, Chamadia et al., 2019, Duclos et al., 2021, Hayashi et al., 2007, Mashour et al., 2021, Pavone et al., 2017, Shortal et al., 2019), and potentially dissociation promoting neural circuits may be associated with unique electroencephalogram signatures. For example, the administration of ketamine as an anesthetic adjunct during steady-state general anesthesia maintained with a γ-amino butyric acid modulating general anesthetic has been associated with decreased alpha and low-beta oscillation power (~8 to 20 Hz) and increased high-frequency oscillation power (Akeju et al., 2016a, Chamadia et al., 2019, Hayashi et al., 2007). Decreased alpha and low-beta oscillation power have also been associated with the dissociative state induced by subanesthetic ketamine (de la Salle et al., 2021, de la Salle et al., 2016, Vlisides et al., 2018). However, it is not clear whether these ketamine-induced surface electroencephalogram findings are specific to dissociation.

A neurophysiological biomarker for dissociation is expected to be of widespread clinical benefit. For example, it may be used to detect the onset of neuropsychiatric disorders like schizophrenia (O’Driscoll et al., 2014), panic disorders (Ball et al., 1997), and obsessive-compulsive disorder (Watson et al., 2004). Further, the association between ketamine-induced dissociation assessed using the Clinician Administered Dissociative States Scale (CADSS) and ketamine’s antidepressant response remains of interest (Ballard and Zarate, 2020). Therefore, we performed a single-site, open-label electroencephalogram study of ketamine anesthesia (n = 15). We assessed for dissociation longitudinally using the CADSS. The initial version of the CADSS consisted of 27 clinician-administered and observed items scored on a 0–4 Likert scale (Bremner et al., 1998, van Schalkwyk et al., 2018). Although objective cut points for dissociation were not defined per se, the CADSS enabled measurement of present-state dissociative symptoms, e.g., patients with post-traumatic distress syndrome had a mean CADSS of 21.9, which significantly increased to 35 after exposure to trauma-related complications, suspected history of drug abuse, and neuropsychiatric diagnoses. We also performed a 12-lead electrocardiogram and the following screening laboratory tests: complete blood count, liver function, basic metabolic panel, urine toxicology, and urine pregnancy for females.

### 2.2. Dissociation assessments

We assessed dissociation using the CADSS, which was developed to measure perceptual, behavioral, and attentional alterations during dissociative experiences (Bremner et al., 1998). The CADSS questionnaire was administered by a trained clinical research coordinator (JG). As previously reported (Gitlin et al., 2020) the first CADSS assessment (baseline) occurred before the administration of ketamine. The second assessment occurred approximately 60 min after the administration of ketamine. After the second assessment, we administered 2 mg of midazolam to attenuate ketamine-associated dissociation. The third assessment occurred approximately 75 min after the administration of ketamine (approximately 5 min post midazolam). The fourth assessment occurred approximately 120 min after the administration of ketamine. One subject did not perform assessments after recovery of responsiveness.

### 2.3. EEG acquisition and processing

We recorded eyes-closed high-density EEG signals using the Waveguard system with a standard EEG cap (64 channels, ANT Neuro, Netherlands) and electrode impedances of < 5 kΩ. We acquired the EEG data at 512 Hz, down-sampled to 250 Hz for analysis, and remountaged using the nearest neighbor Laplacian referencing scheme. We averaged data from three channels to approximate frontal (Fz) and occipital (Pz) channel locations. Anesthetic drugs are associated with a transition from occipitally dominant awake-alpha oscillations to frontally dominant alpha and beta oscillations termed anteriorization. Therefore, we selected frontal and occipital channel locations to place our findings in context with anteriorization and previous neurophysiological studies. Five 2-min periods of interest were extracted: baseline (2 minutes before ketamine administration), ketamine unresponsiveness (4
minutes post ketamine), ketamine responsiveness (2 minutes before midazolam administration), midazolam (3 minutes post midazolam administration), and post midazolam (45 minutes post midazolam administration). We instructed all subjects to close their eyes throughout the data acquisition period to reduce blink and muscle artifacts.

We used the Chronux toolbox in MATLAB (MathWorks) to compute the multitaper spectral estimates. The spectral parameters were: TW or time-bandwidth product = 3, K or number of tapers = 5, and T or window size = 2 s with no overlapping windows for statistical inference. For visualization, spectrograms with overlapping windows were computed. We obtained a frequency vector for each subject by computing the median baseline spectral estimates for each frequency bin across time. We divided the spectral estimates obtained from the ketamine and midazolam states by this frequency vector to obtain our baseline normalized estimates. We computed the median of the spectral estimate across all subjects for group-level visualization. We summed the spectral estimates across frequency and weighted them by the frequency difference to obtain point estimates of spectral power in frequency bands of interest. We next obtained the median estimates across time. The topoplot function in EEGLab was used to generate spatial head plots. Global coherence was estimated using methods previously described (Chamadia et al., 2019). Briefly, we computed the cross-spectral matrix for every subject over every non-overlapping moving window using multitaper methods. Next, we computed the median of the imaginary and real components of overlapping moving window using multitaper methods. Next, we computed a median of the bootstrapped estimates at the subject level and then computed the group median. We computed the 99% confidence interval bounds. (f) Baseline-normalized power spectral-spatial plots. dB = decibel; Hz = Hertz; CADSS = Clinician Administered Dissociative States Scale; unresp. = unresponsiveness; resp. = responsiveness; mins = minutes; Norm. = normalized.

3. Results

No serious adverse events were reported during this study.

3.1. Spectral analysis

Group-average frontal spectrograms, occipital spectrograms, baseline-normalized frontal spectra, and baseline-normalized spatial head plots are presented in Fig. 1.

3.2. Frontal

We first directly compared ketamine responsiveness (dissociated) and midazolam (dissociation treated) states to baseline. Ketamine responsiveness was associated with decreased power between 13.7 to 23 Hz. Midazolam was associated with decreased power between 3.4 to 12.2 Hz and increased power between 17.6 to 50 Hz. These data are summarized in Supplementary Fig. 1a-d.

Next, to enable inferences on the temporal evolution of electroencephalogram signatures, we compared electroencephalogram spectra across consecutive behavioral states: baseline versus ketamine unresponsiveness, ketamine unresponsiveness versus ketamine responsiveness, ketamine responsiveness versus midazolam, and midazolam versus post midazolam. Compared to baseline, ketamine unresponsiveness was associated with increased power between 0.5 to 9.3 Hz, 12.2 to 16.6 Hz, and 24.4 to 50 Hz. As subjects transitioned into being responsive, there was a decrease in power between 0.5 to 10.3 Hz and 11.7 to 50 Hz. Midazolam resulted in a further decrease in power between 4.4 to 11.7 Hz and an increase in power between 14.2 to 50 Hz. Approximately 45 minutes later, the effects of midazolam had begun to dissipate such that there was an increase in power between 7.8 to 11.7 Hz and a decrease in power between 15.6 to 45.4 Hz. These data are summarized in Fig. 2a-d.

3.3. Occipital

Compared to baseline, ketamine responsiveness was associated with decreased power between 2.4 to 5.4 Hz and 7.3 to 26.4 Hz. Midazolam decreased power between 4.9 to 18.6 Hz and increased power between 23.4 to 50 Hz. These data are summarized in Supplementary Fig. 1e-h.

Fig. 1. Schematic of the study protocol, spectrograms, spectral analyses, and spatial plots. (a) We acquired data using an open-label and single-site study design in (n = 15) healthy subjects. Subjects were induced to lose responsiveness with 2 mg/kg of intravenous ketamine. We also administered 2 mg of intravenous midazolam to attenuate ketamine-induced dissociation. We assessed dissociative symptoms using the Clinician Administered Dissociative States Scale (CADSS). Visual representation of group-level (b) frontal and (c) occipital spectrogram computed from 2 minutes EEG segments illustrates that ketamine induces structured electroencephalogram oscillations that may be used to monitor the anesthetic state. Baseline-normalized group-level spectral comparison of (d) frontal and (e) occipital channel with shaded regions representing 99% confidence interval bounds. (f) Baseline-normalized power spectral-spatial plots. dB = decibel; Hz = Hertz; CADSS = Clinician Administered Dissociative States Scale; unresp. = unresponsiveness; resp. = responsiveness; mins = minutes; Norm. = normalized.
Analysis of consecutive behavioral states showed that compared to baseline, ketamine unresponsiveness was associated with increased power between 0.5 to 8.3 Hz and 27.3 to 50 Hz and decreased power between 18.6 to 21.5 Hz. As subjects transitioned into being responsive, there was a decrease in power between 0.5 to 8.9 Hz, 13.2 to 19 Hz, and 24.4 to 50 Hz. Midazolam resulted in a further decrease in power between 5.9 to 13.2 Hz and an increase in power between 17.1 to 50 Hz. Approximately 45 minutes later, the effects of midazolam had begun to dissipate such that there was an increase in power between 7.3 to 14.2 Hz and a decrease in power between 23.4 to 34.2 Hz, 37.1 to 40 Hz, and 42.5 to 46.4 Hz. These data are summarized in Fig. 2 e-h.

3.4. Global coherence analysis

Group-average global coherograms, coherence spectra, and spatial head plots are presented in Fig. 3.

Similar to the spectral analysis, we first directly compared ketamine responsiveness and midazolam states to baseline. Ketamine responsiveness was associated with decreased coherence between 13.2 to 23 Hz and increased coherence between 27.3 to 31.7 Hz, 34.7 to 41 Hz, and 44.4 to 50 Hz. Midazolam was associated with decreased coherence between 6 to 14.2 Hz (occipital alpha) and increased coherence between 18.1 to 50 Hz (frontal). These data are summarized in Supplementary Fig. 2.

Finally, to assess the temporal evolution of coherence, we compared electroencephalogram coherence across consecutive behavioral states. Compared to baseline, ketamine unresponsiveness was associated with decreased coherence between 8.8 to 12.7 Hz (occipital alpha) and increased coherence between 0.5 to 8.3 Hz, 13.2 to 19 Hz, and 25.4 to 50 Hz. As subjects became responsive to verbal cues, there was decreased coherence between 0.5 to 8.3 Hz, 13.2 to 19 Hz, and 25.4 to 50 Hz, and increased coherence between 9.8 to 12.7 Hz (occipital alpha). Midazolam decreased coherence between 4.9 to 13.2 Hz (including loss of occipital alpha).
Fig. 4. Mean CADSS scores. (a) baseline, (b) ketamine responsiveness, (c) midazolam, and (d) post midazolam behavioral states. Horizontal error bars represent standard deviation in CADSS subscale across subjects. 0 = not at all, 2 = moderately, 3 = considerably, and 4 = extremely. CADSS = Clinician Administered Dissociative States Scale.
and increased coherence between 15.1 to 36.1 Hz and 38.1 to 45.4 Hz. The effect of dissipating midazolam was evident by increased coherence between 6.8 to 13.7 Hz (occipital alpha) with a decreased coherence between 15.1 to 24.4 Hz and 29.8 to 34.7 Hz. These data are summarized in Fig. 3.

3.5. Ketamine-induced electroencephalogram signatures were not dissociation-specific

CADSS scores are presented in Fig. 4. During the ketamine responsive (dissociated state), we did not find any significant correlations between CADSS and frontal alpha power (Spearman rho = 0.30, p = 0.294), frontal low-beta (Spearman rho = −0.14, p = 0.63) occipital alpha (Spearman rho = 0.33, p = 0.25), or occipital low beta (Spearman rho = 0.01, p = 0.958). Also, we did not find any significant correlations between CADSS and alpha global coherence (Spearman rho = 0.1, p = 0.730) or low beta global coherence (Spearman rho = 0.25, p = 0.399). The final backward elimination models for frontal power, occipital power, and global coherence all converged to a previously reported model that demonstrated a quadratic relationship between time and dissociation affected by midazolam. Specifically, and as previously reported (Gitlin et al., 2020), midazolam resulted in a 10.3 (95% CI: 3.4–17.1, p = 0.005) point reduction in CADSS adjusted means. Residuals from this model did not differ markedly from normality.

4. Discussion

In this investigation, we studied the spectral and global coherence electroencephalogram signatures of ketamine anesthesia. Similar to previous studies and compared to baseline, we found that ketamine unresponsiveness was associated with loss of occipital alpha and increased power in slow-delta, theta, beta, and gamma frequency bands (Akeju et al., 2016a, Blain-Moraes et al., 2014). Theta oscillations were coherent and widespread across the scalp. The ketamine responsive yet dissociated state was associated with decreased alpha and low-beta power. Treating dissociation with midazolam resulted in frontally dominant coherent beta oscillations. However, our primary finding was that CADSS scores had no strong correlation with ketamine-induced power or global coherence signature.

Decreased alpha and low-beta oscillation power have previously been associated with the ketamine-induced dissociative state (de la Salle et al., 2021, de la Salle et al., 2016, Vilisides et al., 2018). However, it has been unclear whether this finding is a biomarker of dissociation as measured by CADSS. Consistent with our findings, Vesuna et al. recently showed that a 1–3 Hz rhythm in layer five neurons of the retrosplenial cortex underlies dissociation-like behavior in mice (Solt and Akeju, 2020, Vesuna et al., 2020). The authors further confirmed that this deep brain rhythm was associated with dissociation in a patient with epilepsy by eliciting this rhythm from electrodes located in deep, but not superficial, posteromedial cortex locations (Solt and Akeju, 2020, Vesuna et al., 2020). Thus, deep brain recordings may be necessary to elicit putative neurophysiological biomarkers that directly underly dissociation.

A transient gamma-burst electroencephalogram pattern was previously associated with a bolus administration of ketamine (Akeju et al., 2016a). However, a theta predominant oscillatory pattern was associated with the state we defined as ketamine unresponsive. Because this oscillatory dynamic was not spatially restricted, we speculate that ketamine-induced theta oscillations may underly the large-scale network disruption necessary to maintain the ketamine unresponsive state. We note that inhaled anesthetic vapors in common clinical use (desflurane, isoflurane, sevoflurane) are also associated with theta oscillations at high doses (Akeju et al., 2016a, Akeju et al., 2014, Chamadia et al., 2019, Shortal et al., 2019). However, anesthetic vapor theta oscillations are spatially restricted to frontal electrode locations, which suggests that the neural circuit mechanisms underlying ketamine theta are different from anesthetic vapor theta.

The 23-item CADSS has been used to assess dissociation in numerous clinical trials that have studied ketamine as a treatment for depression (Ballard and Zarate, 2020, Fava et al., 2020, van Schalkwyk et al., 2018). In these studies, sub-anesthetic ketamine has been typically dosed at 0.5 mg/kg infused intravenously over approximately 40 minutes (Ballard and Zarate, 2020). In a recent study, the median CADSS score measured at the 40-minute infusion point of ketamine was 13.6 (van Schalkwyk et al., 2018). Using the same dosing paradigm, Fava et al. (Fava et al., 2020) demonstrated a dose-response curve with respect to the dissociative symptoms elicited by ketamine at the 40-minute infusion point: 0.1 mg/kg (mean CADSS ~ 3), 0.2 mg/kg (mean CADSS ~ 4), 0.5 mg/kg (mean CADSS ~ 14), and 1 mg/kg (mean CADSS ~ 24). These findings are consistent with the median CADSS score of 22 we reported approximately 60 minutes after administering an anesthetic dose of ketamine. Taken together, these dose-dependent findings suggest that the CADSS measures ketamine-induced dissociation. However, it is unclear if all aspects of ketamine-induced dissociation are captured by the items on the CADSS (Singh et al., 2016, van Schalkwyk et al., 2018).

A major strength of our study is that we longitudinally conducted structured dissociation assessments. However, our study has several important limitations. First, although CADSS is a widely used instrument to measure ketamine-induced dissociation, it was initially introduced into clinical practice to discriminate patients with dissociative disorders from patients with other psychiatric disorders and healthy patients. Second, midazolam may reduce dissociation through neural circuits distinct from those necessary for inducing or maintaining dissociation. However, electroencephalogram features extracted during the dissociated state did not correlate with CADSS. Third, to obtain point estimates of power and global coherence, studies such as ours reduce the complexity of the electroencephalogram. Thus, future studies in various patient populations that couple machine learning techniques to an expansive set of electroencephalogram features may be necessary to predict the presence and severity of dissociation.

We conclude that ketamine is associated with structured electroencephalogram power and global coherence signatures that may enable principled anesthetic state but not dissociation monitoring.

Declarations of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: OA has received speaker’s honoraria from Masimo Corporation and is an inventor on EEG monitoring patents assigned to Massachusetts General Hospital. All other authors declare that no competing interests exist. NIH NIA RO1AG053582 to OA; and, Innovation funds from the Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital to OA.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.08.021.
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