

The "FRAIL" scale scores do not predict frontal electroencephalographic features during awake baseline or remimazolam-induced loss of consciousness in elderly patients: a pre-planned secondary analysis of a prospective observational cohort study

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Abstract

Background

Frailty predicts adverse postoperative outcomes, but its association with electroencephalographic (EEG) features during remimazolam-induced loss of consciousness (LOC) in elderly patients is unknown. This pre-planned secondary analysis tested whether frailty, defined by the “FRAIL” (Fatigue, Resistance, Ambulation, Illness, Loss of weight) scale, is associated with frontal EEG features during awake baseline and at LOC.

Methods

We enrolled 49 elderly patients (≥ 65 years) undergoing surgery with remimazolam induction. Frailty was preoperatively assessed using the “FRAIL” scale; patients were categorized as non-frail ($n = 25$) or frailty-prone ($n = 24$). Frontal EEG was recorded during awake baseline and at LOC. We analyzed conventional band powers, quantitative EEG parameters, and aperiodic (offset and exponent) and periodic components via spectral decomposition. Mixed-design repeated-measures analysis of variance evaluated Group (frailty status) and State (awake/LOC) effects.

Results

No significant Group main effect or Group $\times$ State interaction was observed for any EEG metric (all $P > 0.05$). In contrast, significant State effects were found for most parameters ($P < 0.001$). Despite substantial differences in American Society of Anesthesiologists (ASA) physical status between the two groups ($P < 0.001$), their EEG characteristics remained indistinguishable.

Conclusions

Preoperative “FRAIL” scale scores did not predict differences in frontal EEG features between non-frail and frailty-prone elderly patients during awake baseline or remimazolam-induced LOC. These findings suggest that somatic frailty and brain vulnerability are dissociable. Thus, perioperative brain risk prediction should rely on direct indicators of brain reserve, such as cognitive assessments, resting-state EEG, or neuroimaging, rather than frailty scales alone.

Registration:

Chinese Clinical Trial Registry (ChiCTR2500113571; December 1, 2025).

Background

Frailty is a clinical condition characterized by diminished physiological reserves, compromised stress responses, and a heightened vulnerability to adverse health outcomes.[1] Frailty, though closely related to aging, is not the same as chronological age; rather, it is a measure of biological aging that accounts for individual differences in functional decline beyond what age alone predicts.[2]

Aging itself induces well-characterized alterations in the frontal electroencephalogram (EEG), encompassing reduced spectral power across multiple frequency bands, a lower alpha (8–13 Hz) peak frequency, a diminished spectral edge frequency (SEF), and changes in the aperiodic (1/f-like) background that include a flatter spectral slope and a reduced offset.[3, 4] Nevertheless, among older surgical patients, physiological reserve exhibits considerable interindividual variability: some individuals remain robust, whereas others meet the criteria for frailty or pre-frailty as defined by standardized instruments such as the “FRAIL” (Fatigue, Resistance, Ambulation, Illness, Loss of weight) scale or the Fried phenotype.[5] This heterogeneity has prompted investigations aimed at determining whether frailty is associated with EEG alterations under anesthesia that go beyond those attributable to age alone.

The existing evidence on this association remains inconclusive and, in some instances, contradictory. Fang and colleagues[6] and Windmann and colleagues,[7] employing propofol and volatile agents respectively, reported that frail patients displayed reduced intraoperative alpha power and SEF, thereby suggesting that the physiological exhaustion inherent to frailty may directly manifest as alterations in anesthetic-induced thalamocortical oscillations. Conversely, a recent prospective cohort study by Boncompagni and colleagues[8] found that intraoperative EEG features did not independently predict frailty after accounting for age and clinical covariates, leading the authors to propose a “brain–body dissociation” hypothesis. According to this hypothesis, traditional frailty scales predominantly capture somatic (physical) reserve, whereas frontal EEG is more closely linked to brain health.

It is noteworthy that this evidence derives almost exclusively from studies using propofol or sevoflurane, agents known to generate prominent frontal alpha oscillations and progressive slow-wave activity.[9] However, remimazolam, an ultra-short-acting benzodiazepine, possesses a distinct pharmacodynamic profile and produces an EEG signature different from that of propofol or sevoflurane.[10–12] Whether frailty-related EEG features observed under other anesthetics are also present during remimazolam anesthesia has not been investigated.

To address this gap, we performed a pre-planned secondary analysis of a prospective cohort study in which elderly surgical patients received remimazolam anesthesia. Frailty was preoperatively assessed using the “FRAIL” scale,[5] and patients were categorized as non-frail or frailty-prone. We analyzed frontal EEG recordings obtained during awake baseline and at loss of consciousness (LOC), examining conventional spectral measures, quantitative EEG (qEEG) parameters, and aperiodic and periodic components derived from spectral decomposition. We hypothesized that FRAIL scale-defined frailty would be associated with distinct frontal EEG features during awake baseline and remimazolam-induced LOC. The primary aim was to determine whether the “FRAIL” scale-defined frailty status[5] correlates

with distinct frontal EEG characteristics in the awake state and at remimazolam-induced LOC within an elderly surgical population.

Methods

Study design and ethics

This study represents a pre-planned secondary analysis of a prospective, observational, single-center cohort study conducted at Xiangya Hospital, Central South University. Patients were enrolled between December 2, 2025, and May 1, 2026. The parent study received approval from the Medical Ethics Committee of Xiangya Hospital (approval number: 2025071262; 23 July 2025) and was registered in the Chinese Clinical Trial Registry (ChiCTR2500113571; principal investigator: Tao Zhong; 1 December 2025) before patient enrollment. The current secondary analysis was covered by the original ethical approval and written informed consent. All procedures were conducted in accordance with the Declaration of Helsinki. This study followed the STROBE reporting guidelines for observational studies. A flow diagram of patient enrollment and analysis is provided as Supplemental Fig. 1.

Participants

The sample size for the parent study was determined based on pilot data: with a mean frontal α power difference of $0.27 \mu V^2$ at LOC and a pooled SD of 0.40, 48 participants per group were required ($\alpha = 0.05$, power = 0.9), and this was increased to 106 to allow for 10% attrition. Of the 106 enrolled, five were excluded because of inadequate EEG signal quality, resulting in 101 participants (52 non-elderly, 49 elderly). For the present analysis, only elderly participants (aged ≥ 65 years, $n = 49$) were included. Frailty was preoperatively evaluated using the “FRAIL” scale, a validated five-component questionnaire covering fatigue, resistance, ambulation, illness, and weight loss, which categorised patients into non-frail (score = 0) and frailty-prone (score ≥ 1) groups.[5] The primary endpoint of this secondary analysis was the difference in frontal EEG band powers across frailty groups at awake baseline and LOC.

Anesthesia, loss of consciousness, and EEG data extraction

Remimazolam was administered via target-controlled infusion (TCI) using a CONCERT CLE infusion pump (Veryark, Guangxi Weili Fangzhou Technology Co., Ltd., Nanning, China) that implements the Eleveld pharmacokinetic-pharmacodynamic model for remimazolam,[13] titrated until LOC, defined as the loss of response to loud verbal commands, accompanied by the loss of eyelid reflex,[14] For each participant, two 30-second artifact-free EEG segments were selected: a pre-induction awake baseline segment (the 30 seconds immediately preceding remimazolam infusion) and the LOC segment centered on the moment of LOC (15 seconds before and 15 seconds after the confirmed time point). All subsequent analyses were conducted separately on these two segments.

EEG recording and preprocessing

Frontal EEG was recorded continuously with a SEDLine monitor (Masimo Corporation, Irvine, CA, USA) at a sampling rate of 178 Hz, with electrodes placed according to the International 10-20 System (Fp1, Fp2, F7, F8; ground at Fpz; reference approximately 1 cm above Fpz) and impedances maintained below 5 k Ω . Only the Fp1 and Fp2 channels were used, and both were zero-phase bandpass filtered between 1 and 47 Hz.

Power spectral density and band power extraction

For each subject and each state (awake and LOC), the power spectral density (PSD) was computed from the respective 30-s segment by means of Welch's method (2-second Hamming window, 50% overlap, frequency resolution 0.5 Hz),^[15] after which the linear-scale spectra from Fp1 and Fp2 were arithmetically averaged to obtain a single PSD per subject and then converted to decibels ($10 \cdot \log_{10}$). Absolute band powers were extracted by averaging the dB values across the delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–47 Hz) frequency bands. In addition, several conventional quantitative EEG parameters were calculated from the PSD, including SEF95 (the frequency below which 95% of total power resides),^[16] beta ratio ($\log_{10}$ of the ratio between high beta [30–47 Hz] and low beta [11–20 Hz] power),^[17] permutation entropy (PeEn, with $m = 3$, lag = 1, normalized by $\log(\text{factorial}(m))$),^[18] and the alpha/delta ratio (α/δ , ratio of mean alpha power to mean delta power).^[19]

Aperiodic and periodic decomposition

For each PSD (awake and LOC separately), the aperiodic (1/f-like) component was modeled using the FOOOF algorithm (version 1.1.0)^[20] implemented in Python 3.9 and called from MATLAB R2024a, with parameters set according to previously validated settings for anesthesia research (fitting range 1.4–45 Hz, peak width limits 2–12 Hz, maximum number of peaks = 3, minimum peak height = 0.3, peak threshold = 2.0 standard deviations).^[21] From each fit, the aperiodic exponent α (the negative slope of the 1/f function) and the offset (the intercept at 1 Hz) were retained, and the aperiodic PSD model was reconstructed in linear space, converted to dB, and subtracted from the original dB-scaled PSD to obtain the periodic (oscillatory) power spectrum. Periodic band powers were then extracted for the same five frequency bands by averaging the periodic dB values within each band.

Statistical analysis

Continuous data were first tested for normality with the Shapiro–Wilk test. Normally distributed variables (age, body mass index, and remimazolam effect-site concentration at LOC) are presented as mean $\pm$ SD and were compared between the two groups using independent-samples t-test. Categorical variables (sex and American Society of Anesthesiologists (ASA)) were expressed as frequencies (percentages)

and analysed using the chi-square test, with Fisher's exact test applied when expected cell counts were < 5.

For band powers (original and periodic components), aperiodic parameters (exponent α and offset), and quantitative EEG parameters (SEF95, beta ratio, PeEn, and α/δ ratio), a 2×2 mixed-design repeated-measures ANOVA (rmANOVA) was performed, with Group (non-frail vs frailty-prone) as the between-subjects factor and State (awake vs LOC) as the within-subjects factor. To evaluate whether the inclusion of intermediate-risk (pre-frail) patients influenced the primary findings, we performed a supplementary analysis restricted to non-frail ($n = 25$) and high-risk frail ($n = 9$; FRAIL score ≥ 3) patients, excluding those with intermediate-risk status, using the same rmANOVA model. Effect sizes are reported as partial eta squared (η^2). All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA).

Results

Participant characteristics

A total of 49 elderly patients were included and, on the basis of the "FRAIL" scale, assigned to non-frail (score 0, $n = 25$) and frailty-prone (score ≥ 1 , $n = 24$) groups. The two groups did not differ significantly in age, body mass index, remimazolam effect-site concentration at LOC, or sex distribution (all $P > 0.05$). In contrast, ASA physical status showed significant intergroup differences ($P < 0.001$), with a markedly higher proportion of ASA III patients in the frailty-prone group (45.8%) than in the non-frail group (4.0%) (Table 1).

Table 1
Baseline demographic and clinical characteristics of the non-frail and frailty-prone elderly patients.

Characteristic	Non-frail (n = 25)	Frailty-prone (n = 24)	P value
Age (years)	71.04 ± 4.53	73.71 ± 5.43	0.064
BMI (kg/m ²)	24.10 ± 2.80	23.85 ± 3.22	0.771
Remimazolam Ce at LOC (ng/mL)	264.00 ± 95.22	300.00 ± 157.24	0.336
Sex, n (%)			0.607
Male	16 (64.0)	17 (70.8)	
Female	9 (36.0)	7 (29.2)	
ASA physical status, n (%)			0.001
II	24 (96.0)	13 (54.2)	
III	1 (4.0)	11 (45.8)	
Data are presented as mean ± SD or n (%).			

Grand-average PSD and time-frequency representations

No discernible differences in spectral morphology or time-frequency characteristics were observed between the two frailty subgroups from the grand-average PSD curves (original and after decomposition) and the corresponding time-frequency representations in either state (Fig. 1).

Traditional absolute band power

The mixed ANOVA revealed no significant Group main effect for any of the five frequency bands: δ ($F(1,47) = 0.343$, $P = 0.561$, $\eta^2 = 0.007$), θ ($F(1,47) = 0.574$, $P = 0.453$, $\eta^2 = 0.012$), α ($F(1,47) = 0.701$, $P = 0.407$, $\eta^2 = 0.015$), β ($F(1,47) = 0.446$, $P = 0.507$, $\eta^2 = 0.009$), and γ ($F(1,47) = 0.547$, $P = 0.463$, $\eta^2 = 0.011$). For the State main effect, δ ($F(1,47) = 72.448$, $P < 0.001$, $\eta^2 = 0.607$), θ ($F(1,47) = 47.275$, $P < 0.001$, $\eta^2 = 0.501$), and γ ($F(1,47) = 49.084$, $P < 0.001$, $\eta^2 = 0.511$) were significant, whereas α ($F(1,47) = 1.019$, $P = 0.318$, $\eta^2 = 0.021$) and β ($F(1,47) = 0.018$, $P = 0.894$, $\eta^2 < 0.001$) were not. The Group $\times$ State interaction did not reach statistical significance for all bands: δ ($F(1,47) = 0.586$, $P = 0.448$, $\eta^2 = 0.012$), θ ($F(1,47) = 0.408$, $P = 0.526$, $\eta^2 = 0.009$), α ($F(1,47) = 0.006$, $P = 0.939$, $\eta^2 < 0.001$), β ($F(1,47) = 0.195$, $P = 0.661$, $\eta^2 = 0.004$), and γ ($F(1,47) = 0.017$, $P = 0.897$, $\eta^2 < 0.001$) (Fig. 2A, 2C, 2E, 2G, 2I).

Periodic band power

After removal of the aperiodic component, the Group main effect for periodic power was not significant for any band: δ ($F(1,47) = 0.155$, $P = 0.696$, $\eta^2 = 0.003$), θ ($F(1,47) = 0.159$, $P = 0.692$, $\eta^2 = 0.003$), α ($F(1,47) = 0.155$, $P = 0.695$, $\eta^2 = 0.003$), β ($F(1,47) = 0.001$, $P = 0.981$, $\eta^2 < 0.001$), and γ ($F(1,47) = 0.099$,

$P = 0.754$, $\eta^2 = 0.002$). For the State main effect, periodic δ ($F(1,47) = 4.345$, $P = 0.043$, $\eta^2 = 0.085$) was significant, whereas periodic θ ($F(1,47) = 0.078$, $P = 0.782$, $\eta^2 = 0.002$) was not; periodic α ($F(1,47) = 70.431$, $P < 0.001$, $\eta^2 = 0.600$), β ($F(1,47) = 158.475$, $P < 0.001$, $\eta^2 = 0.771$), and γ ($F(1,47) = 71.540$, $P < 0.001$, $\eta^2 = 0.604$) were significant. All interactions did not reach statistical significance: δ ($F(1,47) = 0.396$, $P = 0.532$, $\eta^2 = 0.008$), θ ($F(1,47) = 0.026$, $P = 0.873$, $\eta^2 = 0.001$), α ($F(1,47) = 0.318$, $P = 0.575$, $\eta^2 = 0.007$), β ($F(1,47) = 0.733$, $P = 0.396$, $\eta^2 = 0.015$), and γ ($F(1,47) = 0.032$, $P = 0.859$, $\eta^2 = 0.001$) (Fig. 2B, 2D, 2F, 2H, 2J).

Quantitative EEG parameters

None of the four conventional qEEG metrics showed a significant Group main effect: beta ratio ($F(1,47) = 0.061$, $P = 0.806$, $\eta^2 = 0.001$), SEF95 ($F(1,47) = 0.012$, $P = 0.914$, $\eta^2 < 0.001$), α/δ ratio ($F(1,47) < 0.001$, $P = 0.990$, $\eta^2 < 0.001$), and PeEn ($F(1,47) = 0.066$, $P = 0.799$, $\eta^2 = 0.001$). The State main effect was significant for beta ratio ($F(1,47) = 94.160$, $P < 0.001$, $\eta^2 = 0.667$), α/δ ratio ($F(1,47) = 31.609$, $P < 0.001$, $\eta^2 = 0.402$), and PeEn ($F(1,47) = 85.146$, $P < 0.001$, $\eta^2 = 0.644$), but not for SEF95 ($F(1,47) = 3.772$, $P = 0.058$, $\eta^2 = 0.074$). All interactions did not reach statistical significance: beta ratio ($F(1,47) = 0.068$, $P = 0.796$, $\eta^2 = 0.001$), SEF95 ($F(1,47) = 0.065$, $P = 0.800$, $\eta^2 = 0.001$), α/δ ratio ($F(1,47) = 0.655$, $P = 0.422$, $\eta^2 = 0.014$), and PeEn ($F(1,47) = 0.011$, $P = 0.915$, $\eta^2 < 0.001$) (Fig. 3).

Aperiodic parameters

For the aperiodic parameters, the Group main effect was not significant for offset ($F(1,47) = 0.112$, $P = 0.739$, $\eta^2 = 0.002$) or exponent ($F(1,47) = 0.043$, $P = 0.837$, $\eta^2 = 0.001$). The State main effect was significant for offset ($F(1,47) = 39.677$, $P < 0.001$, $\eta^2 = 0.458$), but not for exponent ($F(1,47) = 1.757$, $P = 0.191$, $\eta^2 = 0.036$). The Group $\times$ State interaction did not reach statistical significance for offset ($F(1,47) = 1.066$, $P = 0.307$, $\eta^2 = 0.022$) or exponent ($F(1,47) = 0.800$, $P = 0.376$, $\eta^2 = 0.017$) (Fig. 4).

Supplementary analysis

Results of the supplementary analysis comparing non-frail and high-risk frail patients (excluding intermediate-risk status) are presented in Supplemental Fig. 2.

Discussion

The aging process is highly heterogeneous, and frailty can be conceptualized as a branch on the continuum of aging that leads to faster functional decline and elevated health risks.[22] Several clinical tools exist for frailty assessment, but two approaches have predominated. The first views frailty as a phenotype or syndrome, emphasizing physical decline, with specific indicators including low grip strength, slow gait speed, weight loss, reduced activity, and exhaustion (the Fried phenotype).[23] The second, the deficit accumulation model, treats frailty as a graded health state proportional to the number of age-related deficits accumulated over time.[24] The “FRAIL” scale used in the present study represents a popular self-reported variant of the frailty phenotype model, which quantifies five components via a simple questionnaire.[5, 25] Although originally developed in African-American

populations,[5] it has since been validated across diverse ethnic groups, supporting its utility as a universal screening tool.[26]

In this study, we focused specifically on conventional band powers, aperiodic parameters, and quantitative EEG metrics such as SEF95 and entropy measures, because these parameters can characterize EEG alterations from multiple dimensions, encompassing oscillatory rhythms, neurodynamic balance, and signal complexity, and have shown potential value in perioperative identification of the “vulnerable brain” and prediction of cognitive decline.[27–34] However, contrary to our expectations, we found no significant group main effect between the non-frail and frailty-prone groups for any of the conventional band power, quantitative EEG, or aperiodic parameters, nor any significant group-by-state interaction. A supplementary analysis restricted to non-frail and high-risk frail patients yielded consistent results, with no significant Group main effects or Group × State interactions for any EEG metric. Of note, the state main effect was highly significant for the vast majority of measures, indicating that the anesthesia-induced transition in consciousness did evoke marked EEG changes, yet the magnitude of these changes did not differ between frailty groups. Moreover, given that traditional broadband power spectral analysis cannot effectively distinguish periodic oscillations from the aperiodic background, and that contamination by aperiodic components may seriously distort the characterization of true neural oscillations,[34] we further applied parametric spectral fitting to isolate the aperiodic-corrected periodic power after removing the aperiodic component. After this removal, the results for periodic power were largely consistent with those of conventional band power in terms of group differences and Group × State interactions: no significant group main effect or interaction was found for any periodic band. Notably, the State effects of conventional and periodic band powers differed across multiple frequency bands. Conventional delta and theta power decreased significantly from awake to LOC, whereas after aperiodic removal, the periodic theta component no longer exhibited a significant state effect. Conversely, conventional alpha and beta power showed no significant State effects, while their periodic counterparts increased significantly. These findings suggest that the removal of the aperiodic component may differentially affect the sensitivity of distinct frequency bands to anesthetic-induced state changes.

Our results indicate that preoperative the “FRAIL” scale scores do not correlate significantly with EEG features during remimazolam-induced LOC. However, this null finding should not be simplistically interpreted as “frailty does not affect EEG,” but rather as a reflection of the inherent complexity of the frailty–EEG relationship. This complexity is manifested in at least three interconnected dimensions.

First, the multidimensional heterogeneity of frailty phenotypes merits attention. Frailty spans somatic, cognitive, nutritional, and other domains, each with distinct neurobiological underpinnings; broad categorization may obscure subtype-specific associations, such as cognitive frailty. Indeed, frailty is linked to adverse brain health outcomes, including cognitive decline, structural gray and white matter atrophy, altered connectivity, reduced neuropathological resilience, and systemic inflammation,[35] as well as to postoperative cognitive disorders in surgical patients.[36] However, the “FRAIL” scale used in this study focuses exclusively on the somatic domain, assessing peripheral musculoskeletal integrity,

nutritional status, and metabolic reserve,[5] without incorporating any cognitive or neurological indicators. It therefore cannot evaluate cognition, brain function, or central nervous system integrity, and is incapable of probing the thalamocortical circuits that generate EEG oscillations.[8] This "brain–body dissociation" is supported by our observation that, although the "FRAIL" scale identified patients with greater somatic burden (reflected by significantly higher ASA class in the frailty-prone group), these patients did not show corresponding EEG differences. Thus, somatic frailty is not equivalent to brain frailty, a dimension insufficiently captured by current phenotype models [8]

Second, there is the dependence on selected EEG metrics. The conventional qEEG parameters employed in this study are widely used tools for perioperative brain function monitoring and anesthetic depth assessment. However, frailty-related neural alterations may not be fully captured by these conventional metrics. Recent studies have demonstrated that EEG complexity metrics, such as multiscale entropy and Lempel-Ziv complexity, exhibit characteristic alterations in physiological aging and neurodegenerative diseases, with sensitivity that may surpass conventional spectral measures.[29, 37] Similarly, functional connectivity and network analyses, including graph theory and coherence, have revealed that normal aging is accompanied by reduced connectivity within the default mode and frontoparietal networks, and that frailty may further accelerate this network dedifferentiation.[38] Microstate analysis captures the spatiotemporal dynamics of large-scale brain networks at millisecond timescales, offering unique information on neural network integrity that is not reflected by spectral averaging.[39] These emerging analytical approaches, though not yet widely implemented in routine perioperative monitoring, may provide complementary insights into brain functional integrity beyond the conventional parameters used in this study, and warrant further investigation in future research.

Third, the anesthetic agent itself may serve as a critical contextual factor that modulates the detectability of frailty-related EEG signatures. Different anesthetics produce distinct oscillatory profiles. Propofol and sevoflurane generate prominent frontal alpha and delta oscillations at LOC,[9] whereas remimazolam induces a predominant surge in beta oscillations at LOC, with alpha and delta activity emerging only at deeper anesthetic levels.[10, 11] This distinction suggests that different agents may differentially expose or mask frailty-related EEG features. Furthermore, remimazolam is rarely associated with burst suppression, even in elderly patients, in contrast to propofol.[40] Our findings are consistent with this observation: no burst suppression was detected in either the non-frail or frailty-prone group. This not only reflects the unique EEG phenotype and pharmacodynamic profile of remimazolam, but also suggests that the type of anesthetic agent may influence whether frailty-related EEG features become manifest.

This study has several limitations. First, we analyzed only the awake baseline and the moment of loss of consciousness; whether frailty-related EEG differences emerge during the maintenance or emergence phases of remimazolam anesthesia remains to be determined. Second, because postoperative delirium data were not collected, we could not directly evaluate the clinical relevance of the observed EEG metrics. In addition, as a single-center study, the generalizability of our findings to other populations or different anesthetic regimens requires confirmation through larger multicenter investigations.

Conclusions

In summary, preoperative "FRAIL" scale scores did not predict differences in frontal EEG features between non-frail and frailty-prone elderly patients during either awake baseline or remimazolam-induced LOC. This suggests that somatic frailty and brain vulnerability are separate constructs. Therefore, perioperative brain risk prediction should rely on direct measures of brain reserve, such as cognitive assessment, resting-state EEG, or neuroimaging, rather than on frailty scales alone.

Abbreviations

ASA	American Society of Anesthesiologists
BMI	body mass index
Ce	effect-site concentration
EEG	electroencephalography
FRAIL	Fatigue, Resistance, Ambulation, Illness, Loss of weight
LOC	loss of consciousness
PeEn	permutation entropy
PSD	power spectral density
qEEG	quantitative electroencephalography
rmANOVA	repeated-measures analysis of variance
SEF95	spectral edge frequency at 95%
TCI	target-controlled infusion

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Xiangya Hospital, Central South University (approval number: 2025071262; 23 July 2025). Written informed consent was obtained from all

participants. All procedures were conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to patient privacy but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TZ conceptualized the study. JW, HL, and JX conducted the investigation. JW performed the formal analysis and wrote the original draft. TZ reviewed and edited the manuscript. All authors read and approved the final manuscript. TZ is the guarantor.

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Figures

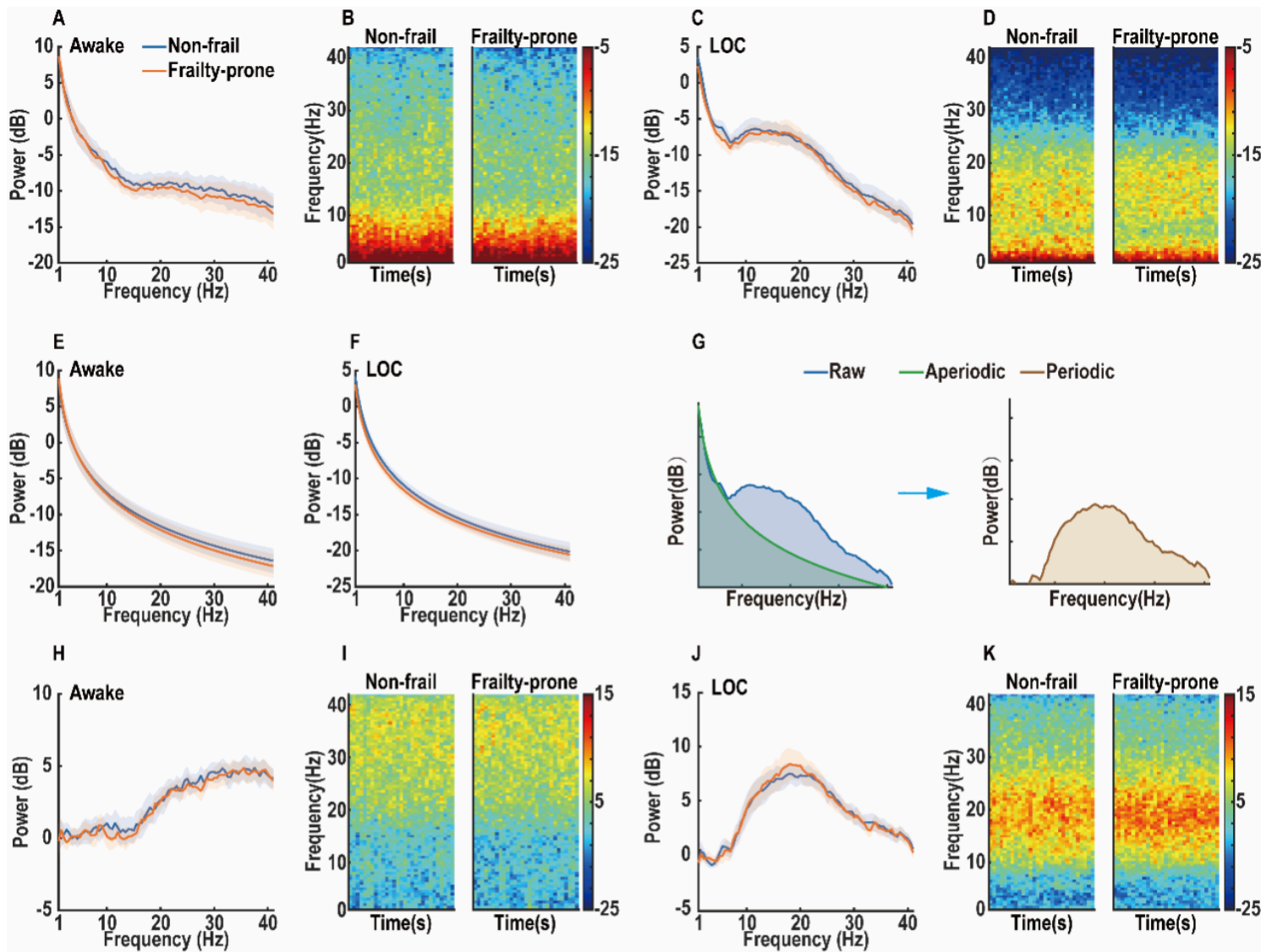


Figure 1

Electroencephalographic spectral and time-frequency characteristics in non-frail and frailty-prone older adults during awake and remimazolam-induced loss of consciousness (LOC). (A) Original power spectral density (PSD) in the awake state. (B) Original time-frequency spectrogram in the awake state. (C) Original PSD at remimazolam-induced LOC. (D) Original time-frequency spectrogram at LOC. (E) Aperiodic (1/f-like) PSD in the awake state. (F) Aperiodic PSD at LOC. (G) Schematic diagram illustrating the extraction of periodic (oscillatory) parameters from the original PSD via removal of the aperiodic component. (H) Periodic (oscillatory) PSD in the awake state. (I) Periodic time-frequency spectrogram in the awake state. (J) Periodic PSD at LOC. (K) Periodic time-frequency spectrogram at LOC. In all PSD panels (A, C, E, F, H, J), blue and orange lines denote the non-frail and frailty-prone groups, respectively, with shaded regions indicating 95% confidence intervals. Group sizes: $n = 25$ (non-frail) and $n = 24$ (frailty-prone). Statistical analysis was performed using repeated-measures analysis of variance (ANOVA) with Group (non-frail vs frailty-prone) and State (awake, LOC) as factors.

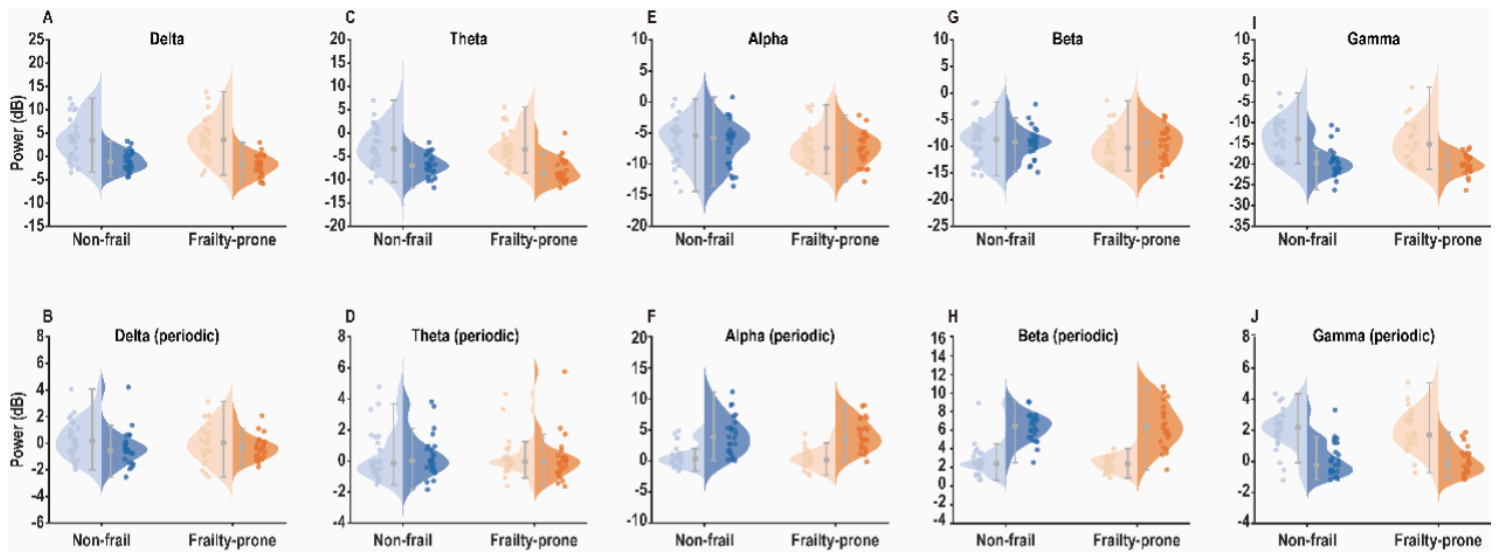


Figure 2

Split-violin plots of frontal electroencephalogram (EEG) band powers in non-frail and frailty-prone older adults during awake and remimazolam-induced loss of consciousness (LOC). (A) Original absolute band power for delta. (B) Periodic band power for delta after removal of the aperiodic component. (C) Original absolute band power for theta. (D) Periodic band power for theta after removal of the aperiodic component. (E) Original absolute band power for alpha. (F) Periodic band power for alpha after removal of the aperiodic component. (G) Original absolute band power for beta. (H) Periodic band power for beta after removal of the aperiodic component. (I) Original absolute band power for gamma. (J) Periodic band power for gamma after removal of the aperiodic component. In each panel, the left half of the violin represents the awake state, and the right half represents the LOC state. Blue and orange correspond to the non-frail and frailty-prone groups, respectively. Gray lines and dots embedded in each half-violin indicate the median (circle) and interquartile range (IQR; whiskers extending to $1.5 \times \text{IQR}$). Group sizes: $n = 25$ (non-frail) and $n = 24$ (frailty-prone). Differences between states and between groups were assessed using repeated-measures ANOVA.

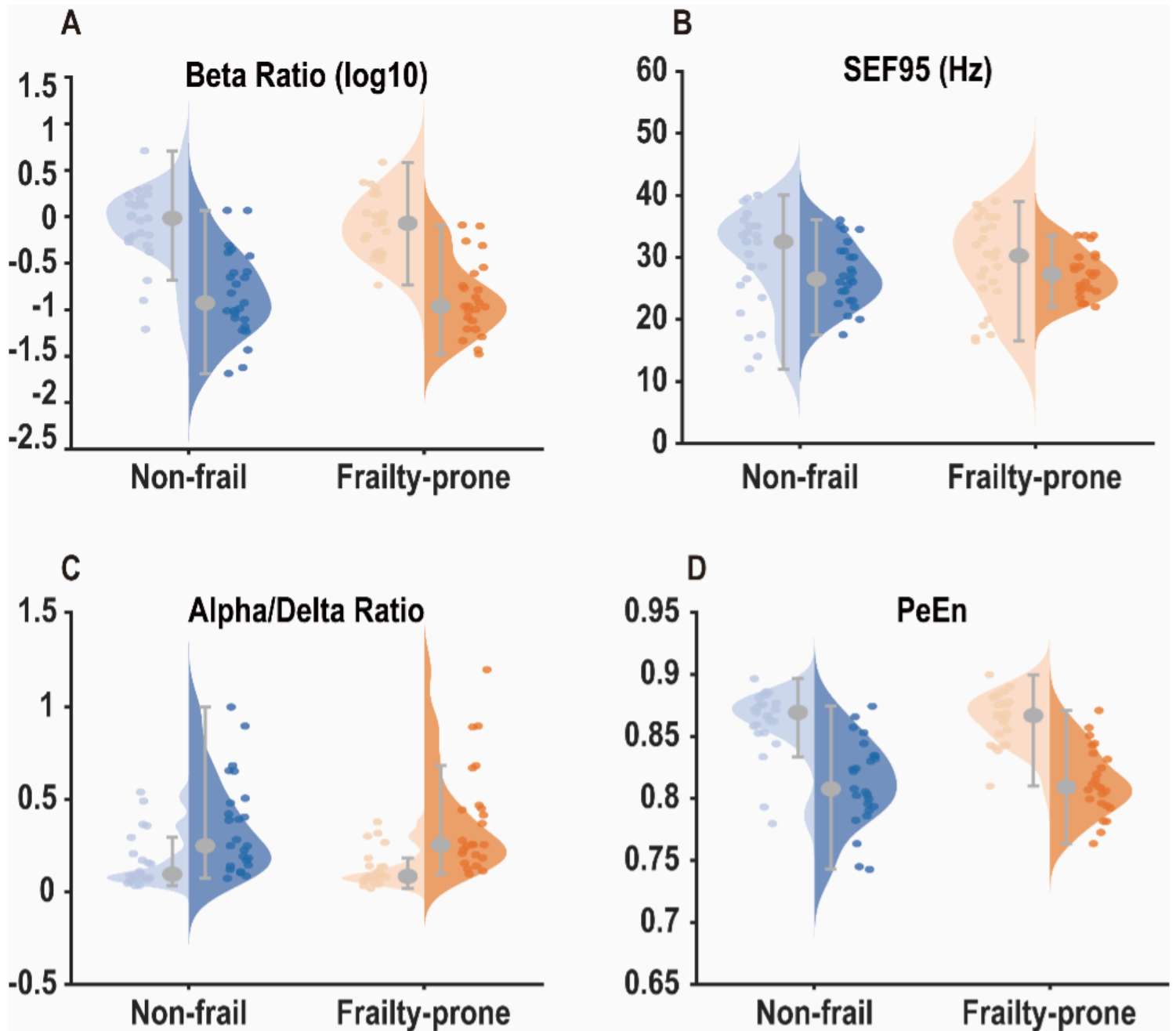


Figure 3

Split-violin plots of quantitative electroencephalogram (qEEG) parameters in non-frail and frailty-prone older adults during awake and remimazolam-induced loss of consciousness (LOC). (A) Beta ratio. (B) Spectral edge frequency at 95% (SEF95). (C) Alpha/delta ratio. (D) Permutation entropy (PeEn). In each panel, the left half of the violin represents the awake state, and the right half represents the LOC state. Blue and orange correspond to the non-frail and frailty-prone groups, respectively. Gray lines and dots embedded in each half-violin indicate the median (circle) and interquartile range (IQR; whiskers extending to $1.5 \times \text{IQR}$). Group sizes: $n = 25$ (non-frail) and $n = 24$ (frailty-prone). Statistical analysis used repeated-measures ANOVA with Group (non-frail vs frailty-prone) and State (awake, LOC) as factors.

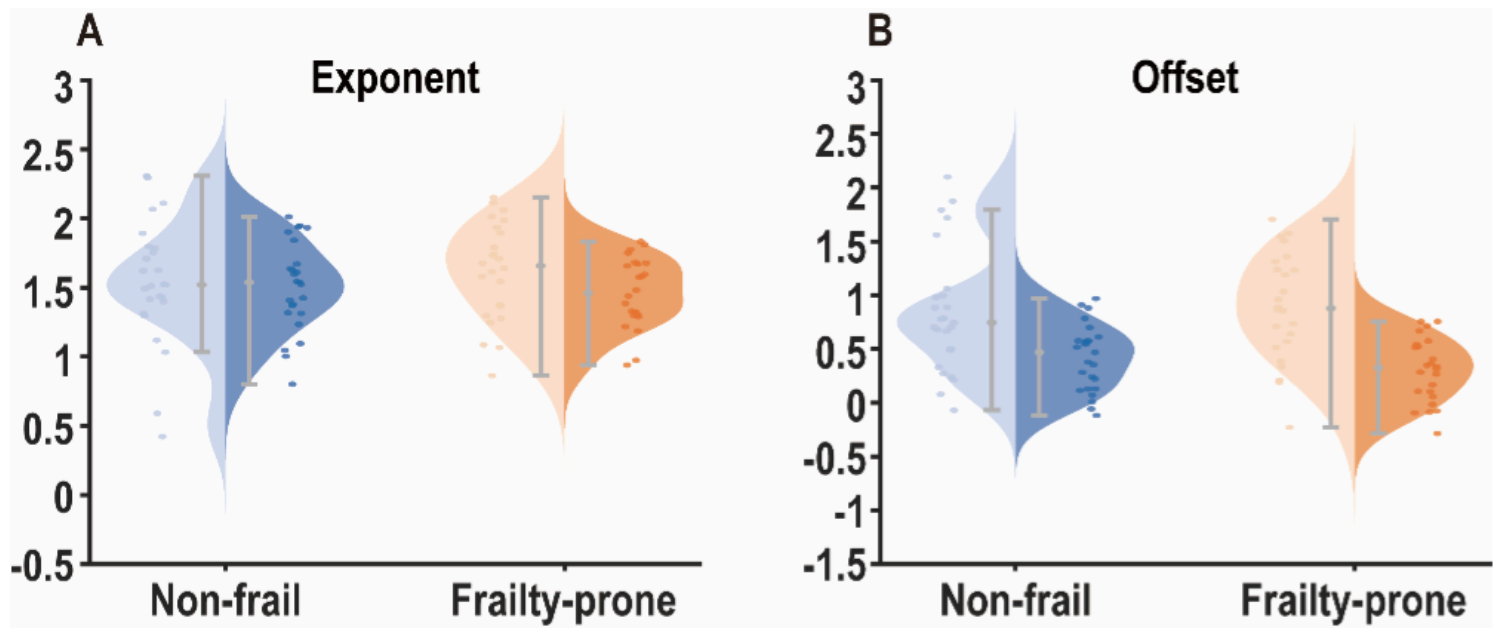


Figure 4

Split-violin plots of aperiodic electroencephalogram (EEG) parameters in non-frail and frailty-prone older adults during awake and remimazolam-induced loss of consciousness (LOC). (A) Exponent (α). (B) Offset. In each panel, the left half of the violin represents the awake state, and the right half represents the LOC state. Blue and orange correspond to the non-frail and frailty-prone groups, respectively. Gray lines and dots embedded in each half-violin indicate the median (circle) and interquartile range (IQR; whiskers extending to $1.5 \times \text{IQR}$). Group sizes: $n = 25$ (non-frail) and $n = 24$ (frailty-prone). Differences were analyzed using repeated-measures ANOVA with Group (non-frail vs frailty-prone) and State (awake, LOC) as factors.

Supplementary Files

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