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Original Article

Sex differences in propofol-induced loss of consciousness: a clinical study on effect-site concentration and electroencephalographic features

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Abstract: Objectives: Sex differences in propofol sensitivity have been reported, but their characterization remains inconsistent, particularly regarding their electroencephalographic (EEG) correlates. This study aims to elucidate sex-specific responses to propofol-induced loss of consciousness and to identify associated pharmacodynamic and EEG biomarkers for informing individualized clinical dosing. Methods: Fifty-four surgical patients (28 males/26 females) undergoing elective procedures were enrolled in this prospective cohort study. Using the Schnider pharmacokinetic model, we administered target-controlled infusion of propofol with precise effector compartment targeting. Synchronized recordings of effect-site concentration (Ce) and prefrontal EEG activity were obtained at loss of consciousness (LOC) thresholds. Results: Pharmacodynamic analysis revealed a significant reduction in Ce of propofol at LOC in females compared with males (3.1 vs 4.0 $\mu g \cdot ml^{-1}$). EEG analyses revealed sex-specific differences in neural oscillatory dynamics. Female participants exhibited enhanced alpha and delta oscillations. Sex-dependent coherence patterns were observed: male-predominant focal synchronization in the δ-θ band contrasting with female-biased distributed coherence across the θ-γ range. Both sexes exhibited comparable burst suppression indices ($P > 0.05$). Conclusion: Our findings demonstrate that females exhibit greater sensitivity to propofol-induced unconsciousness, as evidenced by a lower effect-site concentration, distinct enhancements in alpha and delta oscillations, and modified high-frequency coherence. These biomarkers offer robust evidence for sex-specific propofol dosing strategies, improving precision in anesthesia depth management and potentially mitigating overdose and awareness risks in female populations.

Keywords: Sex, individualized anesthesia, propofol, electroencephalogram, effect-site concentration

Introduction

General anesthesia achieves reversible unconsciousness by modulating the endogenous sleep-wake system. Notably, the important nuclei involved in this process exhibit significant sexual dimorphism in both structure and function [1, 2], and the GABAergic neurons that regulate anesthesia within these nuclei express estrogen receptors in large quantities [3], suggesting that anesthetic effects are likely sex-dependent. Clinical observations further support this idea: female patients show higher resistance to inhalational anesthetics and faster emergence from anesthesia [4], and have an increased risk of intraoperative awareness [5]. Basic research has also confirmed that testosterone can enhance sensitivity to inhalational anesthetics [6, 7]. Collectively, these lines of evidence indicate that sex plays a non-negligible role in the neurobiological mechanisms of anesthesia.

As one of the most commonly used intravenous anesthetics in clinical practice, the mechanism of action of propofol is fundamentally different from that of inhalational anesthetics [8]. Propofol exerts its hypnotic effect by binding with high affinity and stereoselectivity to GABA_A receptors containing the β3 sub-unit, significantly prolonging the open time of chloride channels and increasing their open probability in a dose-dependent manner [9, 10]. Clinical studies on sex differences in propofol

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sensitivity are currently limited, and the few existing reports show inconsistent conclusions without a clear consensus [11-13]. In anesthesia practice, the dosage of propofol is still generally standardized based on body weight, without systematically considering the possible neurophysiological differences brought about by sex. This knowledge gap may lead female patients to face the risk of insufficient or excessive depth of anesthesia. Therefore, it is of clear clinical necessity and urgency to thoroughly investigate the sex differences in propofol anesthesia sensitivity and the underlying neurodynamic mechanisms.

With the evolution of research paradigms, the study of anesthesia mechanisms has delved into the level of neural network dynamics, focusing on thalamocortical oscillations, cross-frequency synchronization, and large-scale brain network connectivity [14]. Electroencephalogram (EEG), with its millisecond-level temporal resolution and non-invasive monitoring characteristics [15, 16], can precisely capture the dynamic reconstruction process of brain states induced by propofol: from moderate sedation (weakening of occipital α activity, enhancement of spindle and β/γ band activities) to deep sedation (general enhancement of whole-brain θ, α, spindle, and β activities, concentrating in the frontal lobe) [17], until the emergence of the burst-suppression pattern that marks the decoupling of cortical-thalamic function. These EEG biomarkers with clear time-frequency characteristics provide a reliable window for quantitatively assessing sex differences at the level of neural oscillations.

Focusing on propofol, this study uses effect-site concentration (Ce) at loss of consciousness (LOC) as the behavioral endpoint and combines EEG to systematically investigate sex differences in anesthetic sensitivity from the perspective of brain network dynamics. By integrating multidimensional EEG indices (e.g., multi-band power, cross-regional coherence, and network synchronization), we provide a multi-level analysis from pharmacodynamics to neural oscillation mechanisms, offering evidence that supports a shift from weight-based to sex- and neural function-guided precision anesthesia, ultimately aiming to improve perioperative safety.

Materials and methods

Study design and participants

This prospective observational study was approved by the Institutional Review Board of the First Affiliated Hospital of Anhui Medical University (Approval No.: ANMU LunShen-PJ2024-07-63) and prospectively registered at the Chinese Clinical Trial Registry (Registration No.: ChiCTR2400087614). After obtaining written informed consent, patients were grouped by sex (male/female). Inclusion criteria were defined as: (1) aged 18 to 60 years; (2) classified as American Society of Anesthesiologists (ASA) Physical Status I or II; and (3) patients scheduled for elective surgery under propofol-based anesthesia. Exclusion criteria: Extreme body mass index (BMI < 18 or > 33 kg/m^2); Endocrine or reproductive system diseases; Long-term or recent use of psychotropic medications; Propofol allergy; Impaired function of major organs; Neurological dysfunction; Scheduled for craniocerebral surgery; History of cerebrovascular disease; Communication difficulties due to hearing impairment.

Anesthesia procedure and data collection

Pre-induction preparation: Patients did not receive any pre-anesthetic medication or analgesics. Upon entering the operating room, an intravenous access was established and standard physiological monitoring included non-invasive blood pressure (measured every 3 minutes), 5-lead Electrocardiogram (ECG) with ST-segment analysis, and pulse oximetry (SpO_2) monitoring.

A 4-channel brain function monitor (Masimo Corp., Irvine, CA, USA) was used to collect prefrontal EEG signals. Electrodes were placed according to the international 10-20 System: recording electrodes at Fp1 (left frontal midline), Fp2 (right frontal midline), F7 (left anterior temporal region), and F8 (right anterior temporal region); ground electrode at the frontal pole midline (approximately Fpz); and reference electrode 1 cm above the ground electrode along the sagittal plane.

Skin preparation included degreasing with alcohol swabs and abrasion with exfoliating scrub (conductive paste) to ensure impedance below 5 kΩ. Signals were digitized at a sampling rate

of 178 Hz, with a preamplifier bandwidth of 0.5-89 Hz. Real-time artifact detection algorithms identified myoelectric interference (> 40 Hz) and motion artifacts, which were simultaneously verified by an electrophysiologist to ensure signal reliability.

Anesthesia induction: Propofol (Diprivan®, Fresenius Kabi, Brézins, France) was intravenously injected via TCI using the Base Primea® infusion system (Fresenius Kabi) based on the Schnider effect-site pharmacokinetic model. The target concentration in the effect chamber was initially set at 1.0 $\mu g \cdot mL^{-1}$, and then gradually increased in a gradient of 0.3 $\mu g \cdot mL^{-1}$. After each dose adjustment, we maintained a 1-minute equilibrium time to ensure that the concentration in the effect chamber stabilized at the current target level before continuing to increase. Titration continued until the patient entered a state of unconsciousness. The criterion was that the patient had no visible limb motor response to standardized auditory stimulation for 3 consecutive stimuli on the premise that the frontal lobe electroencephalogram signal showed continuous stability (no significant fluctuation). After 3 minutes of stabilization, the effect-site concentration displayed by the infusion pump at this time was recorded as the effect-site concentration at the time of loss of consciousness, along with vital signs and the patient state index (PSI).

Hemodynamic parameters (including arterial blood pressure and heart rate) were continuously monitored and strictly maintained within ± 20% of baseline values. Once hemodynamic instability developed, prespecified protocol-specified interventions (intravenous atropine if heart rate was < 50 beats per minute; phenylephrine/ephedrine if systolic blood pressure decreased > 20% from baseline) were initiated immediately. EEG monitoring was performed synchronously throughout the induction period to obtain neurodynamic data for subsequent analysis.

Data collection and EEG signal preprocessing: The original EEG signals were standardized using EEGLAB (v2021.1, SCCN, San Diego, USA). A zero-phase linear finite impulse response (FIR) filter (0.5-50 Hz, roll-off 60 dB/octave) was applied to suppress low-frequency drift (< 0.5 Hz) and high-frequency noise (> 50 Hz) while preserving target neural oscillation signals. Artifact correction was accomplished through a three-stage process: (1) automatic detection using EEGLAB (threshold ± 100 μV); (2) visual verification by two researchers independently (sampling rate 1 second/frame), identifying residual electro-myographic artifacts (20-60 Hz), eye movement artifacts (characterized by slow, large-amplitude deflections and synchronous deflections across frontal channels, Fp1/Fp2), as well as amplifier noise such as signal saturation, abrupt baseline shifts, or persistent 50 Hz line noise; (3) the quality assessment required inter-rater agreement above 0.8 (Cohen's κ), and if there were disagreements, they were decided by a senior electrophysiologist (> 10 years of experience). For the included data, artifact removal was performed at the epoch level. Entire 2-second epochs were removed if any channel exhibited a clear artifact (as defined above) lasting > 0.5 s. Only epochs that were free of obvious artifacts across all channels were retained. To ensure high signal quality, we employed a strict inclusion criterion: each subject's EEG recording used for core analyses had to contain > 95% artifact-free (clean) data.

In the EEG recording protocol: t = 0 was defined as the start of propofol infusion; t = LOC was defined as the moment when both behavioral unresponsiveness and sustained EEG stability were observed. The analysis period extended from 60 seconds before propofol injection (t = -60 s) to 60 seconds after LOC confirmation (t = End + 60 s), including two key phases: baseline (t = -60 s → 0) and LOC transition (LOC 0 → LOC + 60 s). Periods with residual artifacts were excluded per predefined criteria, retaining only EEG segments with artifact proportions < 5%. The final processed data were analyzed using three methods - spectral power distribution, bicoherence analysis, and burst-suppression quantification - implemented via MATLAB-based scripts (R2022a, MathWorks).

Standard frequency bands were identified using an automated detection process: δ (1-4 Hz), θ (4-8 Hz), α (8-13 Hz), β (13-30 Hz), and γ (30-45 Hz). For each canonical frequency band, the peak power (the maximum power value within the band) was extracted and used in all subsequent band-specific analyses. Multidimensional EEG phenotyping integrated time-frequency decomposition, cross-frequency coupling, and burst-suppression patterns.

Bicoherence is a normalized bispectral measure that quantifies quadratic phase coupling between frequency components within a signal, independent of signal power. This nonlinear analysis detects whether the phase of an oscillation at a frequency f1 + f2 is consistently the sum of the phases at f1 and f2, revealing a specific form of phase synchronization that indicates nonlinear neural interactions. Crucially, high bicoherence values are theorized to reflect stable, reverberant activity within thalamocortical networks - a key neural substrate for conscious states [18, 19]. As such, bicoherence can capture the integrity of this re-entrant system even from a single EEG channel (e.g., over the prefrontal cortex), providing a unique window into brain-state dynamics that may not be evident in the power spectrum or linear coherence between regions [20, 21]. In this study, we employed a validated, standardized bispectral analysis method to assess the nonlinear phase coupling in the EEG signal, thereby evaluating the synchronization of neural oscillations within thalamocortical circuits. The detailed methodology follows below.

All bicoherence analyses were performed on single-channel EEG data derived from prefrontal electrodes (Fp1), reflecting within-region, cross-frequency coupling in the frontal cortex. A continuous 3-minute period of artifact-free EEG signal from the stable anesthetic phase was extracted for analysis. The signal was first band-pass filtered between 0.5 and 50 Hz. Subsequently, the 3-minute signal was segmented into a series of 2-second epochs with 75% overlap between consecutive epochs, resulting in a total of 360 epochs. A Blackman window function was applied to each epoch to minimize spectral leakage. A Fourier transform was performed on each epoch to obtain its complex spectral components $X_j(f)$, where j denotes the j-th epoch. The bicoherence value $BIC(f_1,f_2)$ for each frequency pair (f_1,f_2) was then computed across a range of 0.5 Hz to 20 Hz with a frequency resolution of 0.5 Hz. The calculation formulas are as follows: First, the Bispectrum was computed:

$$B(f_1, f_2) = \left| \sum_{j=1}^{L} X_j(f_1) \cdot X_j(f_2) \cdot X_j^*(f_1 + f_2) \right|$$

where:

- L is the total number of epochs (360),
- X_j^* denotes the complex conjugate of the Fourier coefficient X_j,
- $|\cdot|$ denotes the magnitude of the complex number.

Subsequently, the normalized bicoherence value, expressed as a percentage, was calculated:

$$BIC(f_1, f_2) = 100 \times \frac{B(f_1, f_2)}{\sqrt{\sum_{j=1}^{L} |X_j(f_1) \cdot X_j(f_2)|^2 \cdot \sum_{j=1}^{L} |X_j(f_1 + f_2)|^2}}$$

This normalization procedure ensures that $BIC(f_1,f_2)$ values range from 0% to 100%, representing the strength of phase coupling among frequencies f_1, f_2, and their sum frequency $f_1 + f_2$. This analysis focuses on the coupling between a specific frequency and its own second harmonic, which has been demonstrated in anesthesia research to be a sensitive indicator of the effects of GABAergic agents like propofol on the oscillatory stability of the cortical-thalamic network [22, 23].

Burst-suppression parameters in EEG recordings were quantified manually: burst phase: EEG segments with duration > 0.5 seconds and voltage fluctuation > 5 μV; Suppression phase: EEG segments with duration > 0.5 seconds and peak-to-peak amplitude within ± 5 Mv [23]; State transition point: Defined by instantaneous amplitude crossing the 5 μV threshold. Burst Suppression Ratio (BSR) was calculated as: (Total suppression time/Length of analysis period) × 100%. Cumulative suppression time was defined as the sum of all suppression phase durations from the start of propofol infusion (t = 0) to LOC (t = LOC).

Statistical analysis

The primary outcome was the propofol Ce at LOC predicted by the TCI system. Pilot data showed sex differences in Ce at LOC: males had a mean Ce of 3.4 (2.8, 4.0) $\mu g \cdot mL^{-1}$, while females had a mean Ce of 2.65 (2.5, 2.8) $\mu g \cdot mL^{-1}$. To achieve 80% statistical power with a two-tailed $\alpha = 0.05$ and power 80% ($\beta = 0.2$), each

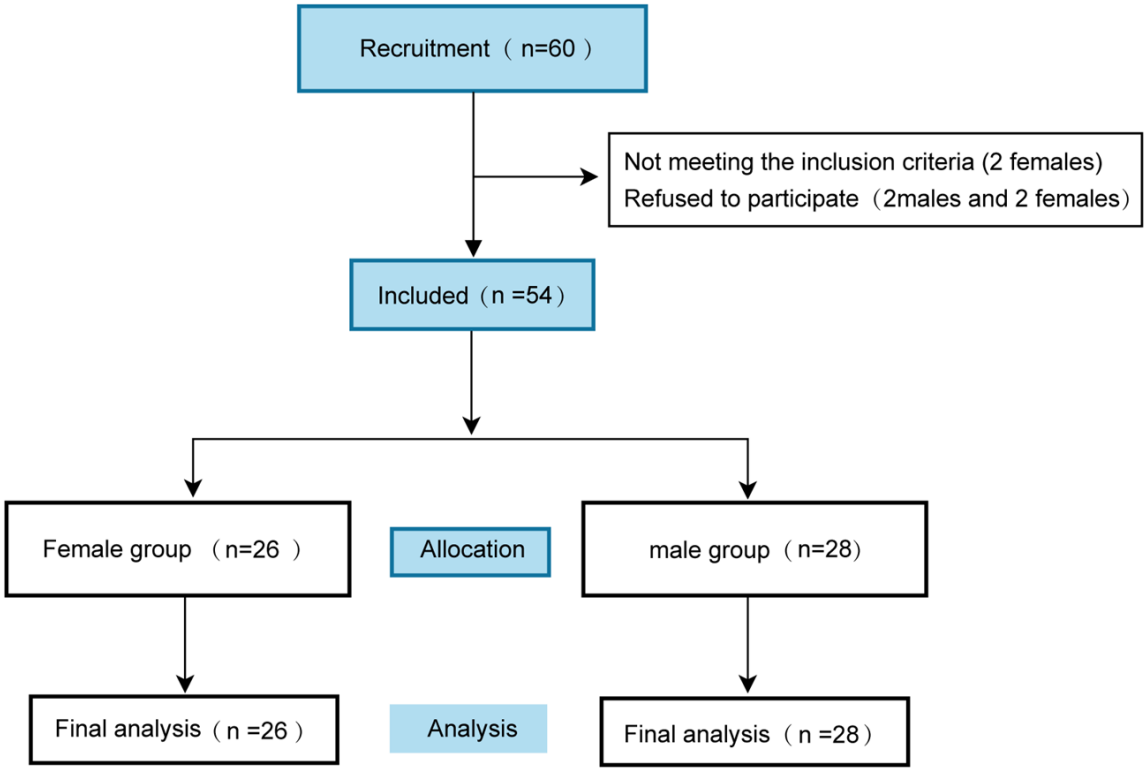

Figure 1. Flowchart of participant screening, enrollment, allocation, and analysis.

group required at least 17 participants. Accounting for a 20% potential dropout rate, the final sample size was expanded to 30 participants per sex.

Normality assessment: Continuous variables were tested for normality using the Lilliefors-corrected Kolmogorov-Smirnov test.

Continuous variables: Normally distributed data were presented as mean ± standard deviation (SD), with between-group comparisons using two-tailed independent samples t-tests and 95% Confidence Intervals (CI) for mean differences. Non-normally distributed data were presented as median (Q1, Q3), with between-group comparisons using the Mann-Whitney U test and 95% CIs for group differences calculated via the Hodges-Lehmann estimator.

Categorical variables: Presented as counts and percentages [n (%)], with between-group differences analyzed using Pearson's χ^2 test or Fisher's exact test (when expected frequency < 5).

All statistical analyses were performed using IBM SPSS Statistics (v26.0, Armonk, NY, USA), and figures were generated using GraphPad Prism (v8.4.3, San Diego, CA, USA). Statistical significance was defined as $P < 0.05$.

Results

Baseline characteristics of participants

This observational study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to develop a flowchart (**Figure 1**). This flowchart describes participant enrollment and allocation across different study phases. Among 60 consecutive participants, 54 eligible patients (28 males and 26 females) were ultimately included and divided into two groups according to sex. Two females were excluded due to failure to meet the inclusion criteria, and 4 participants (2 males and 2 females) declined participation. The two groups were comparable in all key baseline indicators (**Table 1**).

Sex differences in propofol-induced hypnotic effects: enhanced sensitivity in females

The Ce of propofol at LOC in female patients was 22.5% lower than that in male patients

Table 1. Baseline characteristics of the patients

Variable	Male Group (n = 28)	Female Group (n = 26)	Test Statistic (U/χ^2)	*P* Value	95% CI
Age (years)	39.5 (33.5, 56.0)	42.0 (35.8, 54.0)	334.5	0.62	1.5 (-8 to 5)
BMI (kg/m^2)	24.45 (21.37, 26.12)	23.44 (22.19, 25.53)	348	0.79	-1.01 (-2.32 to 1.51)
ASA Classification			0.8	0.41	-
Grade I, n (%)	2 (7.1%)	4 (15.3%)			-
Grade II, n (%)	26 (92.9%)	22 (91.7%)			-
Surgical Type			0.42	-	-
Orthopedics	9 (32.14%)	3 (11.54%)			-
Urology	3 (10.71%)	1 (3.85%)			-
Spinal Surgery	3 (10.71%)	3 (11.54%)			-
Joint Surgery	1 (3.57%)	2 (7.69%)			-
Oral Surgery	3 (10.71%)	3 (11.54%)			-
Otorhinolaryngology	2 (7.14%)	2 (7.69%)			-
Hepatobiliary Surgery	2 (7.14%)	2 (7.69%)			-
Thyroid Surgery	2 (7.14%)	6 (23.08%)			-
Gastrointestinal Surgery	1 (3.57%)	3 (11.54%)			-
General Surgery	2 (7.14%)	0			-
Gynecology	0	1 (3.85%)			-

Data are presented as median (Q1, Q3) or n (%). Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; CI, confidence interval.

Table 2. Effect-site concentration of propofol and physical parameters at loss of consciousness

Indicator	Male Group (n = 28)	Female Group (n = 26)	Test Statistic (t/U)	*P* Value	95% CI
Effect chamber concentration (μg/ml)	4.0 (3.4, 4.6)	3.1 (2.5, 3.4)	96.5	< 0.001	-0.94 (-1.47 to -0.71)
MAP (mmHg)	68 (65.17, 81.58)	74.67 (67.42, 84.17)	300	0.27	6.67 (-3.33 to 9.33)
HR (bpm)	65 ± 9.8	68.23 ± 12.68	1.05	0.3	-3.23 (-2.93 to 9.39)
PSI	47 (41, 66)	49.5 (37, 63)	345	0.75	2.5 (-12 to 8)

Abbreviations: MAP, mean arterial pressure; HR, heart rate; PSI, the patient state index.

[3.1 (2.5, 3.4) vs 4.0 (3.4, 4.6) $\mu g \cdot mL^{-1}$; $P < 0.001$, 95% CI: -1.473 to -0.7103; **Table 2**], and there were no statistically significant differences in mean arterial pressure, heart rate and PSI values between the two groups (**Table 2**).

Sex-specific multi-band power spectrum analysis during propofol-induced consciousness transition

EEG spectral analysis revealed no statistically significant sex differences in EEG power across all frequency bands prior to anesthesia induction (**Figure 2**; **Table 3**). However, distinct sex-specific patterns emerged during propofol-induced loss of consciousness (LOC). At the moment of LOC, females displayed significantly higher α band power than males [2.42 (1.24, 3.59) vs 1.8 (1.2, 2.06), $P = 0.009$]. Additionally, females demonstrated a significantly greater increase in δ band power compared to males [3.93 (3.68, 4.16) vs 3.32 (2.78, 3.96), $P < 0.001$]. No statistically significant sex differences were detected in other clinically relevant frequency bands (γ, θ, and β rhythms) (**Figure 2**; **Table 3**).

Analysis of sex difference in bicoherence in the unconscious state induced by propofol

Dissociation of prefrontal coherence provides a quantifiable neural indicator of the disruption of cortical integration during unconsciousness. By analyzing phase coupling between different

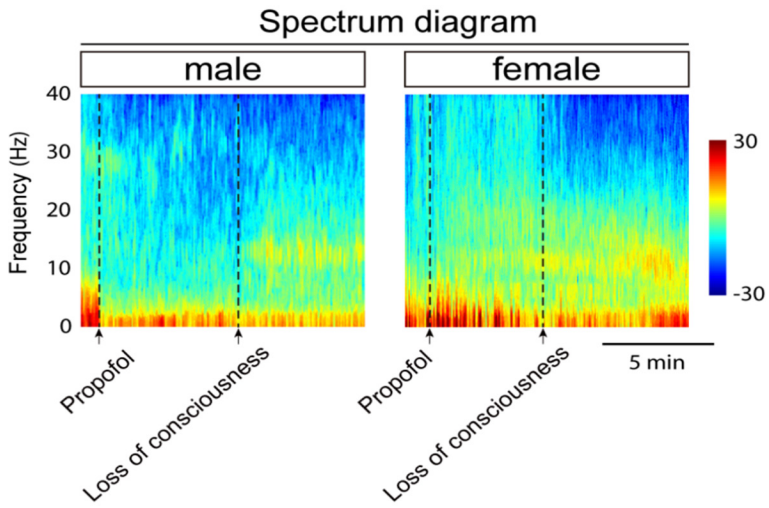

Figure 2. Sex differences in prefrontal EEG spectral power during propofol-induced loss of consciousness. Female participants demonstrated significantly higher α-band power ($P = 0.009$) and δ-band power ($P < 0.001$) at LOC compared with male participants. Statistical comparisons between groups are summarized in **Table 3**.

frequency pairs, bicoherence analysis quantifies non-linear interactions within the cerebral cortex.

Our bicoherence connectivity maps identified sex-specific network reorganization patterns during propofol-induced hypnosis: The male-dominated low-frequency rhythm enhancement was manifested as the strengthening of phase-amplitude coupling in the δ-θ frequency band (1-8 Hz), while the female cross-frequency decoding showed an increase in the specific α-γ frequency band (8-45 Hz) bicoherence clusters (**Figure 3**; **Table 4**).

Analysis of sex-based inhibition events

Four key electrophysiological parameters of burst-suppression patterns during propofol induction were quantified: burst suppression ratio, percentage of suppression time, maximum duration of suppression periods (minutes), and transition frequency between burst/suppression states. No statistically significant differences were found in any of the burst-suppression indicators between the two groups (**Table 5**). In conclusion, from a neurophysiological perspective, propofol-induced cortical suppression dynamics show significant sex independence when quantified using standardized burst-suppression indicators.

Discussion

To explore the pharmacodynamic basis of sex-specific responses to propofol, this work innovatively combined synchronized monitoring of propofol Ce with multi-dimensional EEG analysis. This approach was chosen because Ce more directly reflects central drug activity, while high-resolution EEG reveals mechanisms at the level of neural oscillations.

The study is the first to confirm that female patients require a significantly lower propofol Ce (22.5% lower on average) to achieve LOC compared to male patients. This finding provides key pharmacodynamic evidence for clinical phenomena such as increased blood pressure fluctuations during induction and a relatively higher risk of intraoperative awareness in females.

In-depth analysis of the electroencephalogram data revealed that during propofol anesthesia, female patients exhibited sex-specific neural activity patterns: enhanced oscillatory activity in the low-frequency bands (δ and α) and disintegration of coherence in the high-frequency bands (β/γ). This finding suggests that the regulatory effect of propofol on the brain has sex-dependent neural dynamic characteristics. It is generally believed that enhanced low-frequency oscillations reflect an increase in cortical inhibition, while changes in high-frequency coherence dissociation may involve the reconfiguration of functional connections between distant brain regions [24-26]. This result indicates that in the female population, the inhibition of the GABAergic system by propofol further induces a synchronous disruption or weakening of the high-frequency rhythms responsible for advanced information integration among different functional regions of the brain, thereby forming a unique neural state of “increased inhibition and enhanced dissociation”. This provides a new physiological perspective for understanding the clinical phenomenon of “high sensitivity” (requiring less anesthesia)

Table 3. Sex-related EEG spectral characteristics at propofol-induced loss of consciousness

Spectral Parameter	Male Group (n = 28)	Female Group (n = 26)	Test Statistic (t/U)	*P* Value	95% CI
β Power					
Baseline	0.7 ± 0.2	0.62 ± 0.18	1.54	0.13	-0.08 (-0.18 to 0.02)
At LOC	1.96 ± 0.88	2.39 ± 1.15	1.55	0.13	0.43 (-0.13 to 0.98)
θ Power					
Baseline	0.47 (0.36, 0.56)	0.44 (0.25, 0.73)	348	0.77	-0.03 (-0.16 to 0.13)
At LOC	0.97 ± 0.25	0.91 ± 0.28	1.77	0.45	-0.06 (-0.2 to 0.09)
α Power					
Baseline	0.73 (0.65, 0.77)	0.8 (0.64, 0.94)	267	0.09	0.07 (-0.02 to 0.16)
At LOC	1.8 (1.2, 2.06)	2.42 (1.24, 3.59)	2.72	0.009	0.84 (0.22 to 1.46)
γ Power					
Baseline	0.23 ± 0.11	0.22 ± 0.13	0.34	0.7	-0.01 (-0.08 to 0.05)
At LOC	0.23 ± 0.11	0.22 ± 0.12	0.67	0.5	-0.02 (-0.08 to 0.04)
δ Power					
Baseline	3.47 (2.98, 3.86)	3.98 (2.4, 2.99)	302	0.29	-0.49 (-0.69 to 0.24)
At LOC	3.32 (2.78, 3.96)	3.93 (3.68, 4.16)	3.67	< 0.001	-0.66 (-0.97 to 0.35)

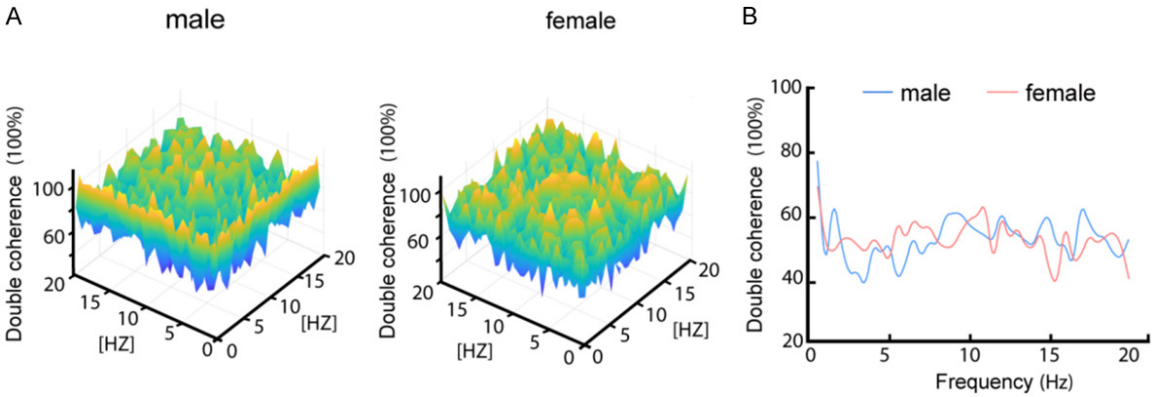

Figure 3. Sex differences in EEG bicoherence patterns during propofol-induced unconsciousness. Female participants exhibited significantly increased α- and γ-band bicoherence, whereas males showed stronger δ- and θ-band coupling (all $P < 0.001$). Quantitative statistical comparisons are summarized in **Table 4**.

Table 4. Sex differences in bicoherence during propofol anesthesia

Parameter	Male Group (n = 28)	Female Group (n = 20)	Test Statistic (t/U)	*P* Value	95% CI
β-Bicoherence Peak	28.65 (27.55, 30.35)	32.2 (30.33, 33.58)	84.5	< 0.001	3.55 (2.1 to 4.1)
δ-Bicoherence Peak	46.5 ± 2.11	31.98 ± 1.87	26.36	< 0.001	-14.33 (-15.42 to -13.24)
θ-Bicoherence Peak	45.2 (43.5, 47.18)	34.55 (33.13, 36.28)	0	< 0.001	-10.65 (-11.8 to -9.6)
α-Bicoherence Peak	24.7 (23.55, 25.88)	29.6 (28.35, 30.93)	0	< 0.001	4.9 (4.1 to 5.8)
γ-Bicoherence Peak	32.5 ± 2.35	56.05 ± 1.98	39.63	< 0.001	23.55 (22.35 to 24.74)

and "high risk" (increased risk of intraoperative awareness).

This neurophysiological difference likely stems from inherent sex differences in the brain. Critical nuclei regulating sleep-wake cycles and consciousness, as well as the GABAergic system, have structures and functions modulated by sex hormones. It has been proposed that estrogen may alter the excitation-inhibition bal-

Table 5. Burst suppression patterns during propofol anesthesia

Parameter	Male Group (n = 28)	Female Group (n = 26)	Test Statistic (t/U)	*P* Value	95% CI
Burst Suppression Ratio	0 (0, 0.008)	0 (0, 0.01)	356	0.86	0 (0 to 0)
Suppression Time (%)	0 (0, 0.008)	0 (0, 0.06)	358.5	0.91	0 (0 to 0)
Max Suppression Duration (min)	0 (0, 0.04)	0 (0, 0.06)	356	0.86	0 (0 to 0)
Burst/Suppression Transition Frequency	0 (0, 0.008)	0 (0, 0.01)	347	0.71	0 (0 to 0)

ance and synchronization of neural circuits by influencing the expression and function of specific GABA_A receptor subunits [27], raising the possibility that hormonal factors contribute to the observed sex differences. Direct testing of this hypothesis, however, requires future studies that include serum hormone measurements. This forms the biological basis for different brain responses to the same drug concentration across sexes [28, 29]. Although hormone levels fluctuate cyclically, the present study and previous evidence show that sex-driven patterns remain relatively stable, further supporting sex as an independent factor in anesthetic practice [30].

Focusing on LOC is methodologically and clinically justified. LOC defines the fundamental pharmacodynamic threshold of propofol sensitivity - a prerequisite for any dynamic analysis of maintenance or emergence [31]. Our key metric, bicoherence, requires stationary EEG, which the stable LOC state provides; transition phases introduce non-stationary artifacts. Within this endpoint, we integrated effect-site concentration, multi-band power, bicoherence, and burst suppression - a novel multidimensional approach. We found that females require 22.5% lower Ce, exhibit enhanced alpha/delta oscillations, and display sex-divergent bicoherence (male δ-θ vs. female α-γ coupling) - the first multi-level mechanistic evidence for heightened female sensitivity, directly challenging one-dose-fits-all practice [32]. Dynamic characterization across induction, maintenance, and emergence remains an important next step, but it depends on first establishing the threshold. Our study fills that gap and provides a rigorous foundation for sex-individualized propofol anesthesia.

This study has several limitations: First, although powered for the primary endpoint (Ce at LOC), our sample size remains modest for detecting sex differences with smaller effect sizes or subgroup effects. The lack of significant differences in some measures (e.g., beta/gamma power, burst suppression) may reflect either true absence or insufficient power. Cohort restrictions limit generalizability. Larger multi-center prospective studies with broader criteria are needed to validate and extend our findings. Second, the study focused primarily on the single time point of LOC during induction; the complete dynamic profile of anesthesia maintenance and emergence remains to be characterized. Third, further prospective clinical trials are needed to verify whether the identified EEG biomarkers can be translated into real-time bedside monitoring indicators. Fourth, sex hormone levels were not measured, so direct correlation with propofol sensitivity is unavailable. Fifth, no correlation was established between EEG biomarkers and clinical outcomes (e.g., intraoperative awareness, emergence time, postoperative cognition), as our study was powered for the pharmacodynamic endpoint (Ce at LOC), not for these confounder-prone outcomes. Despite these limitations, our study provides robust evidence for sex differences in propofol pharmacodynamics and neural oscillations, underscoring the need for future studies with hormone assays, animal models, and adequate power to test whether our sex-specific EEG signatures predict or guide interventions to improve clinical outcomes. Our study does not provide a ready-to-use sex-specific dosing algorithm. Nevertheless, the observed 22.5% lower Ce requirement in women (median 3.1 vs. 4.0 μg/ml) serves as a quantitative benchmark for future prospective trials to develop and validate sex-adjusted dosing strategies.

Conclusion

In conclusion, this multimodal study reveals significant sex differences in propofol pharmacodynamics and neural activities, challenging the traditional weight-based dosing paradigm.

Future research should validate sex-specific EEG biomarkers for clinical outcomes and closed-loop dosing strategies, paving the way for intelligent, real-time EEG-guided systems that integrate sex as a key factor to improve safety and recovery, particularly for female patients.

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Disclosure of conflict of interest

None.

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