

Original Research

Effects of Transcranial Ultrasound Stimulation on Neural Electrical Activity in the Paraventricular Thalamus of Rats Under Etomidate Anesthesia

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Abstract

Background: Transcranial ultrasound stimulation (TUS) has been shown to modulate recovery from propofol anesthesia. Etomidate is also widely used as an anesthetic in clinical practice. Therefore, further investigation is needed to clarify whether TUS modulates thalamic neural electrical activity under etomidate anesthesia. **Methods:** In this study, we applied TUS to the paraventricular nucleus of the thalamus (PVT) in etomidate-anesthetized rats. Local field potentials (LFPs) from the PVT and electromyography (EMG) signals from cervical muscles were recorded to analyze anesthesia recovery time, time-frequency characteristics, power spectral density, and sample entropy (SampEn). **Results:** The recovery time from anesthesia was significantly shorter in the TUS group than in the sham group. TUS also induced significant changes in LFPs metrics during emergence, including: a significant decrease in mean absolute power (MAP) in the 4–8 Hz band and increases in the 30–60 Hz, 60–100 Hz, 100–140 Hz, and 140–200 Hz bands; a reduction in relative power (RP) in the 4–8 Hz band and elevations in the 30–60 Hz and 60–100 Hz bands; and a significant increase in SampEn across the 1–200 Hz frequency spectrum. **Conclusion:** TUS effectively modulated the relative power, mean absolute power, and SampEn of LFPs during the transition from anesthetized to awake states in etomidate-anesthetized rats.

Keywords: transcranial ultrasound stimulation; paraventricular thalamus; anesthesia; etomidate

1. Introduction

Emergence from anesthesia is a critical phase during which patients gradually regain consciousness. Delayed emergence poses significant challenges in clinical anesthesia management [1,2]. Therefore, identifying strategies to accelerate recovery from anesthesia remains a key research priority. The thalamus plays a crucial role in regulating transitions in consciousness during anesthesia [3,4]. Neuromodulation techniques such as deep brain stimulation [5] and optogenetic and chemogenetic approaches [6] have been shown to promote emergence from anesthesia in animal models. Transcranial ultrasound stimulation (TUS), a noninvasive neuromodulation technique, has recently gained attention for its deep penetration and high spatial resolution [7,8]. It does not cause significant thermal accumulation in brain tissue at low intensities [9]. TUS has been successfully used to modulate neural electrical activity in both animal models [10,11,12,13] and in human brain regions, including the thalamus [14], visual cortex [15], and motor cortex [16].

Previous studies have shown that TUS can modulate neural electrical activity across various anesthetic conditions, including ketamine [17], isoflurane [18], and propofol anesthesia [19]. Etomidate is widely used for anesthesia induction and short-term procedural sedation because

of its minimal effects on systemic blood pressure and its low respiratory depressant effects [20]. This study aimed to investigate whether TUS could modulate thalamic neural electrical activity and accelerate recovery in etomidate-anesthetized rats.

2. Materials and Methods

2.1 Animal Surgery

Twelve healthy male Sprague-Dawley rats (240–260 g) were obtained from Beijing Life River Experimental Animal Technology Co., Ltd (Beijing, China). Rats were housed under controlled temperature and humidity conditions with a 12 h light/12 h dark cycle and ad libitum access to food and water.

Rats were randomly assigned to the TUS group ($n = 6$) or the Sham group ($n = 6$). Randomisation was performed using a random-number table. Outcome assessment and data analysis were performed by investigators blinded to group allocation. Anesthesia was induced with 4% isoflurane, and the animals were secured in a stereotaxic apparatus (Models 68,002 and 68,030, RWD Life Science Co., Ltd., Shenzhen, China). Anesthesia was maintained with 1.5% isoflurane (2024082201, RWD Life Science Co., Ltd.) delivered via a face mask. The surgical site was cleaned with normal saline and then disinfected with



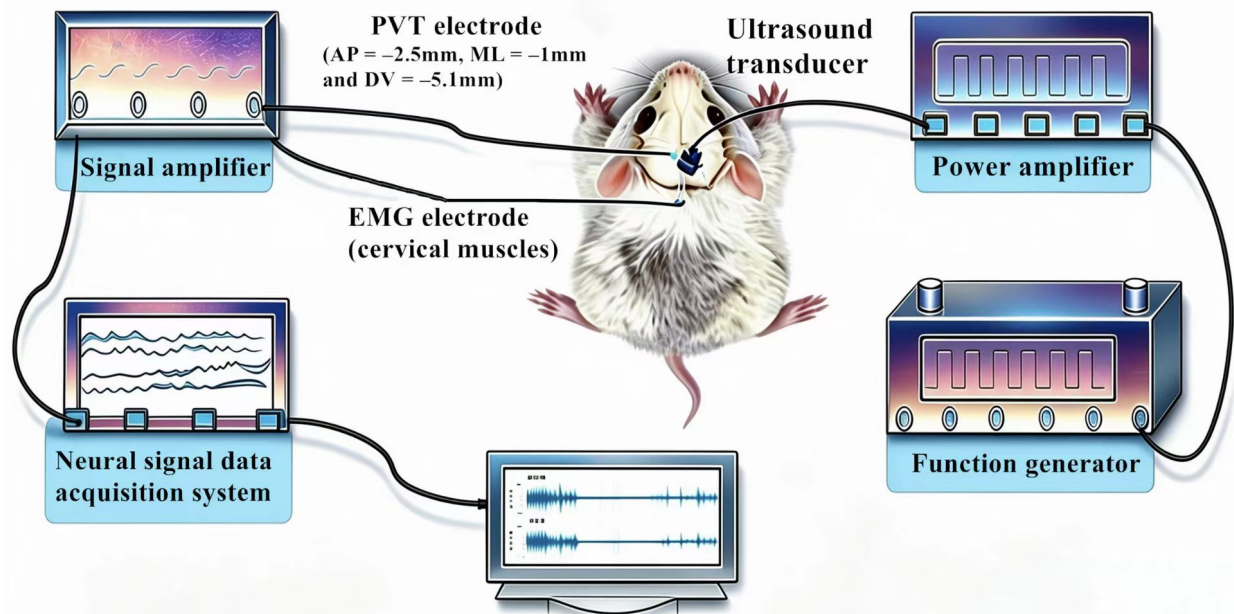


Fig. 1. The schematic representation of the experimental setup. The electromyography electrode was positioned on the neck and back muscle groups. PVT, paraventricular nucleus of the thalamus; EMG, electromyographic; AP, anteroposterior; ML, mediolateral; DV, dorsoventral. (AI-generated with doubao).

povidone-iodine solution (Guangdong Kelun Pharmaceutical Co., Ltd., Meizhou, Guangdong, China). After shaving the cephalocervical hair, sequential dissection was performed along the midline through the skin, subcutaneous tissue, muscle, and fascia to fully expose the cranial region, including the bregma, lambda, sagittal suture, and coronal suture, thereby providing optimal surgical access for subsequent electrode implantation and ultrasound intervention.

Surgical procedures were performed as follows: (1) Based on the rat's brain atlas, a 4-mm craniotomy was created over the thalamic target (AP = -2.5 mm, ML = -1 mm, DV = -5.1 mm) with a cranial drill (Model 78001, RWD Life Science Co., Ltd.) to implant single-channel tungsten electrodes. (2) Two burr holes were drilled near the nasal bone to accommodate intracranial screws for reference and ground electrode connections. (3) Custom-made wire electrodes (Tungsten wire: KD-SCR, KEDOU Brain-computer Technologies; Suzhou, Jiangsu, China) were inserted into the cervicodorsal muscle groups to monitor electromyographic signals during anesthesia-awakening transitions. (4) An ultrasound positioning ring was secured to the cranial surface. (5) Electrodes and the positioning ring were permanently fixed with cyanoacrylate adhesive (ergo 5800, Ergo, Switzerland) and dental cement (Super-Bond C&B, Sunmedical Co., Ltd., Moriyama, Shiga, Japan).

Seven days after surgery, anesthesia was induced with intraperitoneal etomidate at 15 mg/kg (2509262, Jiangsu Enhua Pharmaceutical Co., Ltd., Xuzhou, Jiangsu, China). Local field potentials (LFPs), widely accepted as a reliable measure of ensemble neuronal activity in localized brain regions (including the paraventricular nucleus of the thalamus (PVT)), were recorded during wakefulness and after loss of the pinch reflex, and used as an indicator of adequate anesthesia. Rats assigned to the TUS group received 5 minutes of low-intensity transcranial ultrasound stimulation, immediately followed by continuous LFPs monitoring until full recovery of consciousness. The interval between loss and recovery of the pinch reflex was defined as the duration of anesthesia. Rats in the Sham group underwent identical probe placement without energy output.

2.2 TUS Protocol

Ultrasound was generated by a function generator (Model AFG3022C, Tektronix, Beaverton, OR, USA) and amplified to the target intensity using a power amplifier. A 3D-printed conical collimator filled with ultrasound coupling gel ensured efficient transmission. Based on rat brain stereotaxic coordinates, the transducer's spatial position was calibrated to cover the thalamic target region. The stimulation protocol was configured with the following param-

eters: 50 ms pulse duration, 1 Hz pulse repetition rate, 5% duty cycle, and 5 minutes of stimulation. Under these parameters, the system produced a peak negative pressure of 0.51 MPa, measured in free water, corresponding to a spatial peak pulse-average intensity ($I_{\text{sp}}^{\text{pa}}$) of 8.67 W/cm² and a peak temporal-average intensity ($I_{\text{sp}}^{\text{ta}}$) of 0.43 W/cm²

2.3 Data Acquisition

LFPs from the paraventricular thalamus and electromyographic (EMG) signals were amplified using a preamplifier (Model 63, 386, A-M Systems Inc., Sequim, WA, USA) and then converted to digital format via a multi-channel data acquisition system (Apollo, Bio-Signal Technologies, McKinney, TX, USA) for transmission and storage on a computer workstation. Subsequent data analysis was performed in MATLAB R2023b (MathWorks, Natick, MA, USA) using the EEGLAB toolbox (Swartz Center for Computational Neuroscience, University of California San Diego, San Diego, CA, USA) for signal processing. A schematic of this process is shown in Fig. 1.

2.4 The Relative Changes in Mean Absolute Power and Relative Power

Data were categorized into the following experimental epochs: Pre-Anes (mean values from the middle 6-minute segment of the 10-minute pre-anesthesia awake period) and Post-TUS-01/05/10/15/20/25 (1/5/10/15/20/25 minutes post-transcranial ultrasound stimulation, immediately). In MATLAB, the EEGLAB toolbox was used to process LFPs data with a 1–200 Hz bandpass filter and to remove 50 Hz line noise and its harmonics (48–52 Hz, 98–102 Hz, 148–152 Hz, 198–202 Hz). EMG signals were processed with a 0–500 Hz bandpass filter. Power spectral density (PSD) of LFPs was computed using the Welch method, and mean absolute power (MAP) and relative power (RP) were calculated across the following frequency bands: 1–4 Hz, 4–8 Hz, 8–13 Hz, 13–30 Hz, 30–60 Hz, 60–100 Hz, 100–140 Hz, and 140–200 Hz. Total absolute power was defined as the sum of all sub-band powers within the 1–200 Hz range. Relative power for each band was obtained by dividing its absolute power by the total absolute power. To mitigate inter-individual variability, both relative power and mean absolute power were normalized to the pre-drug administration period as the reference, yielding relative changes in these measures. The mathematical formulation is expressed as follows Eqn. 1 and Eqn. 2:

$$\text{Relative change of mean absolute power} = \frac{\text{mean absolute power}_n}{\text{mean absolute power}_{\text{Pre-Anes}}}, n = 1, 2, 3, 4, 5, 6 \quad (1)$$

Mean absolute power_{*n*} represents the mean absolute power of the six time periods; Mean absolute power_{Pre-Anes} represents the mean absolute power value for the 6th min before any administration.

$$\text{Relative change of relative power} = \frac{\text{mean absolute power}_n}{\text{mean absolute power}_{\text{Pre-Anes}}}, n = 1, 2, 3, 4, 5, 6 \quad (2)$$

Relative power_{*n*} represents the relative power for the six time periods; Relative power_{Pre-Anes} represents the relative power value for the 6th min before any administration.

2.5 Time-frequency Diagram

Time-frequency analysis of LFPs within the 140–200 Hz frequency band was performed using the short-time Fourier transform (STFT), yielding a time-frequency diagram.

2.6 Sample Entropy

Sample entropy (SampEn) was computed for the [1–200 Hz] frequency band using the established Eqn. 3:

$$\text{SampEn}(m, r, N) = -\ln \left[\frac{C^{m+1}(r)}{C^m(r)} \right] \quad (3)$$

N denotes the data length; *m* denotes the embedding dimension; *r* denotes the tolerance threshold.

2.7 The Euthanasia of Rats

After data collection was completed, the experimental rats were euthanized with an intraperitoneal overdose (150–200 mg/kg) of sodium pentobarbital (Catalog No. BD081201-10g, Bide Pharmatech Ltd., Shanghai, China). This agent induces a rapid, painless deep coma by profoundly depressing the central nervous system, followed by cessation of spontaneous respiration and cardiac activity, thereby ensuring that the rats are treated in accordance with humane endpoint principles throughout the experiment.

2.8 Statistical Analysis

GraphPad Prism 8.0 (GraphPad Software, Inc., Boston, MA, USA) and MATLAB R2023b were used for data analysis and visualization. Continuous variables were expressed as mean ± standard error of the mean (SEM). Data normality and homogeneity of variance were assessed before parametric testing. For comparisons of recovery time between groups, two independent-samples *t*-tests were used when the assumptions of normality and homogeneity of variance were met; otherwise, Mann-Whitney U tests were used. Relative changes in relative power, mean absolute power, and SampEn of LFPs across different time intervals were assessed using a two-way analysis of variance (ANOVA) with least significant difference (LSD) post hoc multiple comparisons.

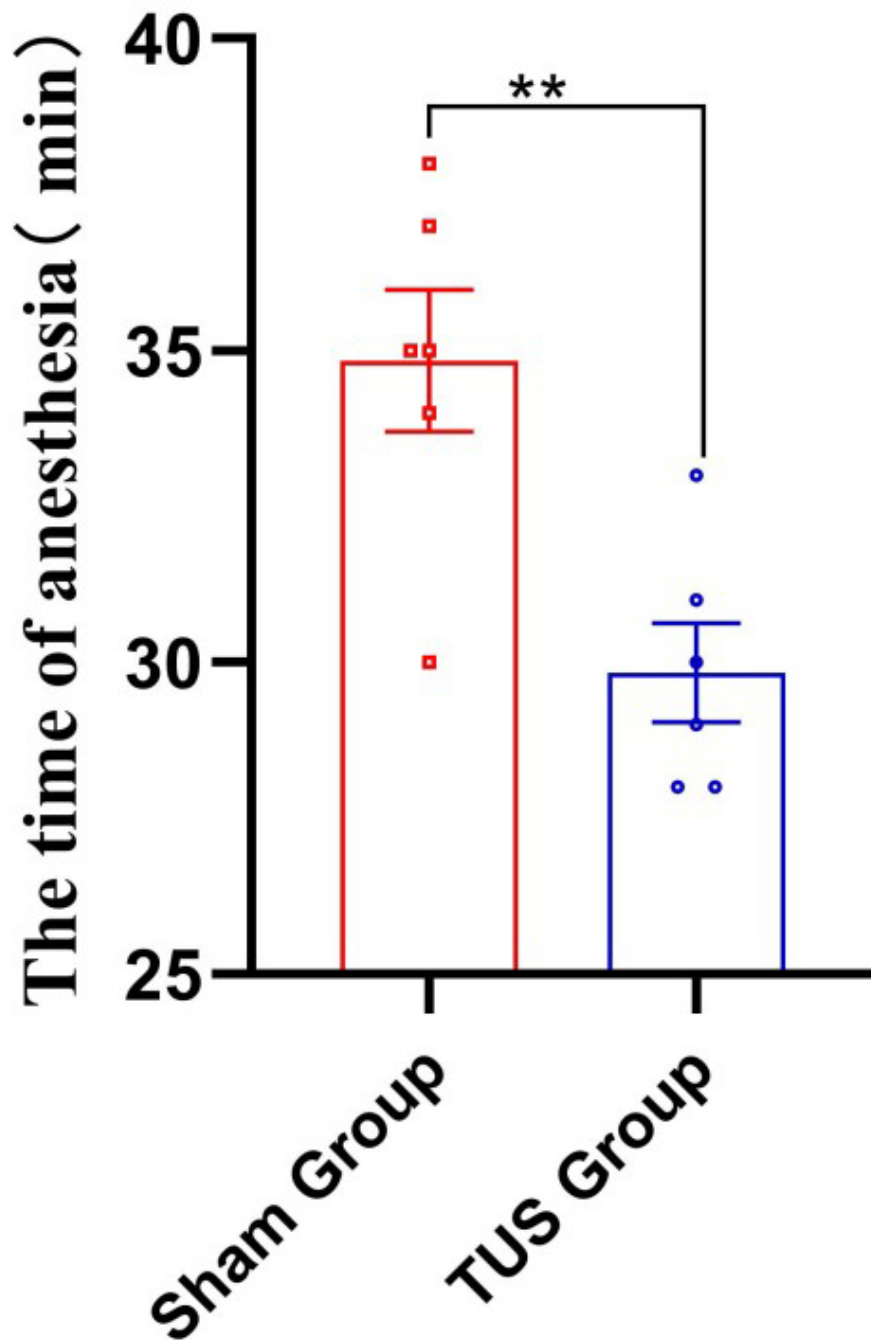


Fig. 2. Time to emergence from anesthesia in the TUS group and the Sham group (** $p < 0.01$). TUS, transcranial ultrasound stimulation.

3. Results

3.1 The Time of Emergence From Anesthesia Under TUS

We quantified the time to emergence from anesthesia in both groups. The results showed that rats in the TUS group regained consciousness more quickly than those in the Sham group ($p < 0.01$). These findings indicate that TUS can substantially shorten the duration of anesthetic emergence in rats (Fig. 2).

3.2 Relative Changes in Mean Absolute Power Over Time for the Two Groups

Compared with the pre-anesthesia baseline, etomidate anesthesia induced a significant increase in the relative change in mean absolute power within the 4–8 Hz frequency band (Fig. 3b). As the anesthetic was metabolized, both groups showed a decline in the relative change in mean absolute power in the 4–8 Hz band, with the TUS group demonstrating a more pronounced reduction than the

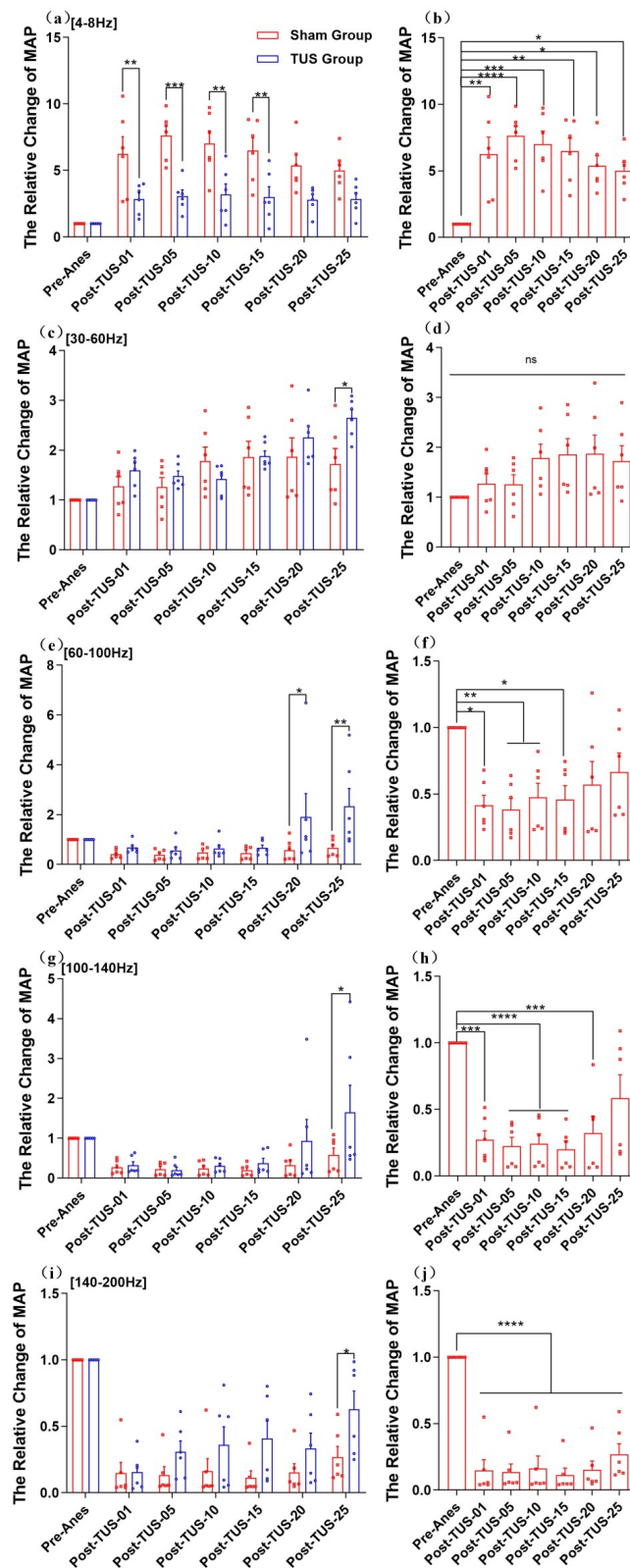


Fig. 3. Relative changes in mean absolute power for each frequency band. (a), (c), (e), (g), and (i): Relative changes in mean absolute power in the [4–8 Hz], [30–60 Hz], [60–100 Hz], [100–140 Hz], and [140–200 Hz] frequency bands of the TUS and Sham groups; (b), (d), (f), (h), and (j): Relative changes in mean absolute power in the [4–8 Hz], [30–60 Hz], [60–100 Hz], [100–140 Hz], and [140–200 Hz] frequency bands of the Sham group. (TUS group: $n = 6$; Sham group: $n = 6$; means $\pm$ SEMs; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$, ns, not significant).

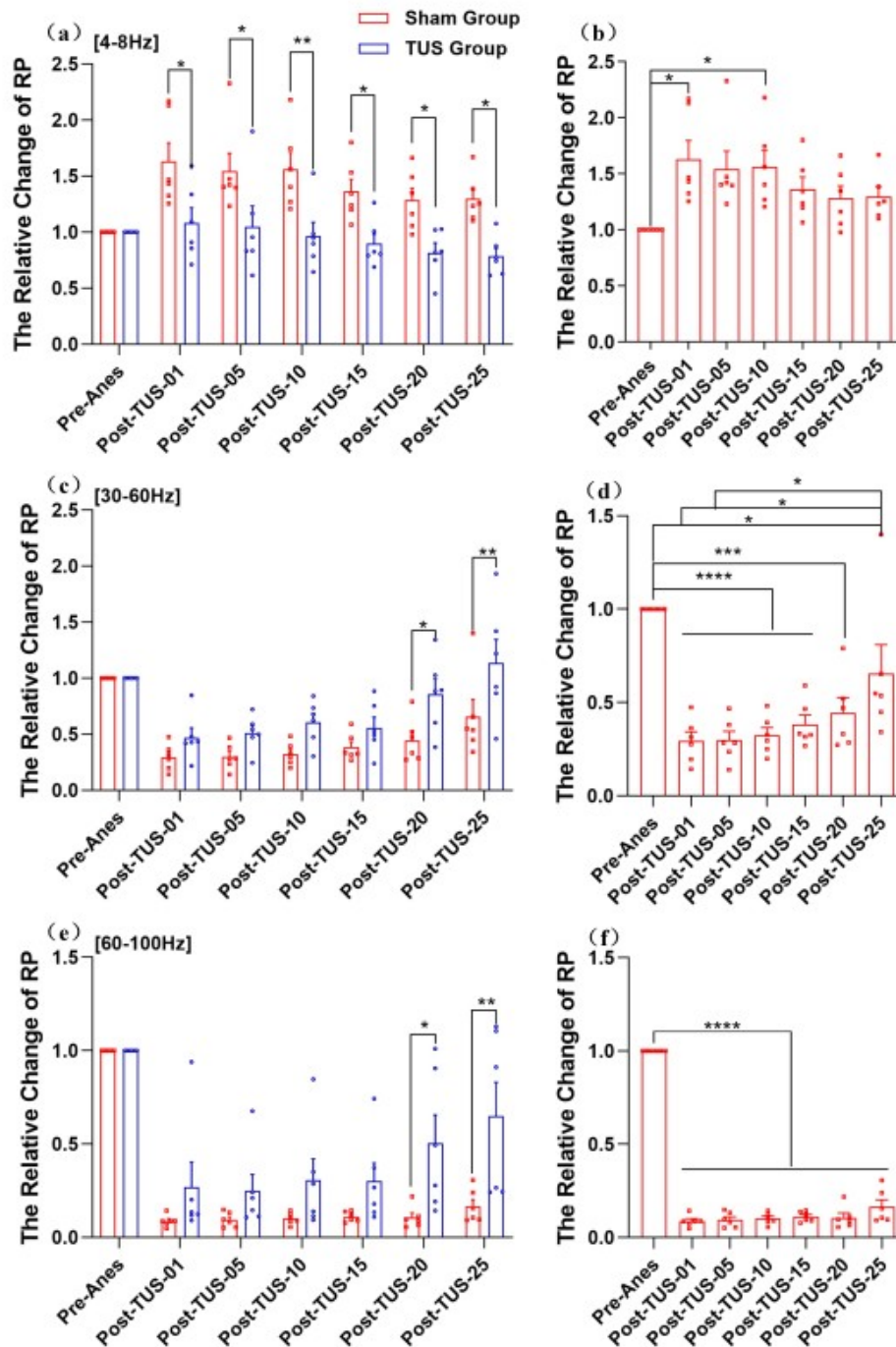


Fig. 4. Relative changes in relative power across different frequency bands. (a), (c), and (e): Relative changes in relative power in the [4–8 Hz], [30–60 Hz], and [60–100 Hz] frequency bands for the TUS group and the Sham group. (b), (d), and (f): Relative changes in relative power in the [4–8 Hz], [30–60 Hz], and [60–100 Hz] frequency bands for the Sham group. (TUS group: $n = 6$; Sham group: $n = 6$; means $\pm$ SEMs; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$).

Sham group (Fig. 3a). Conversely, the relative changes in mean absolute power across the 60–100 Hz, 100–140 Hz, and 140–200 Hz bands showed significant decreases during etomidate anesthesia relative to pre-anesthesia values (Fig. 3d,f,h,j). During drug metabolism, an ascending trend was observed in the relative changes in mean absolute

power within the 30–60 Hz, 60–100 Hz, 100–140 Hz, and 140–200 Hz frequency bands across both groups, with the TUS group exhibiting significantly greater increases than the Sham group (Fig. 3c,e,g,i).

Compared with the pre-anesthesia baseline, etomidate anesthesia resulted in a significant increase in relative

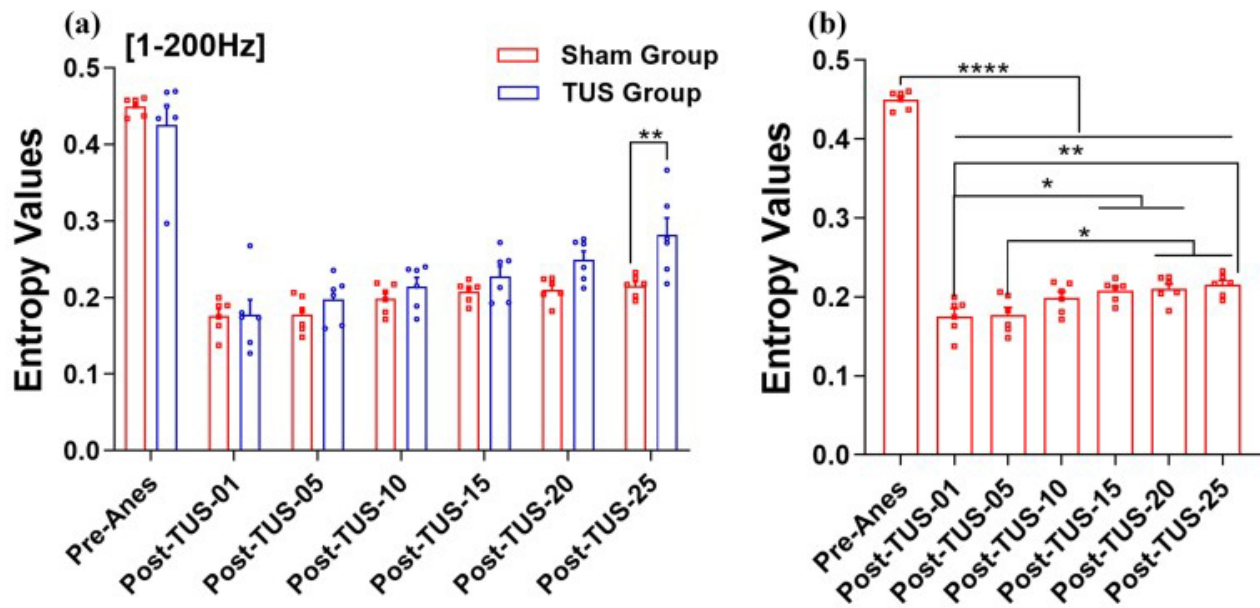


Fig. 5. Entropy values of LFPs [1–200 Hz] measured in the Sham and TUS groups. (a) Changes in entropy between the Sham and TUS groups after etomidate anesthesia. (b) Changes in entropy in the Sham group after etomidate anesthesia. (TUS group: $n = 6$; Sham group: $n = 6$; means $\pm$ SEMs; * $p < 0.05$; ** $p < 0.01$; **** $p < 0.0001$).

power in the 4–8 Hz band (Fig. 4b). During anesthetic metabolism, both groups showed a decreasing trend in the relative change in 4–8 Hz power, with the TUS group exhibiting a more pronounced reduction than the Sham group (Fig. 4a). Concurrently, the relative changes in power across the 30–60 Hz and 60–100 Hz bands showed significant decreases during etomidate anesthesia compared with pre-anesthesia values (Fig. 4d,f). As the drug was metabolized, both groups showed an increasing trend in relative power in the 30–60 Hz and 60–100 Hz frequency ranges, with the TUS group showing significantly greater increases than the Sham group (Fig. 4c,e).

3.3 Sample Entropy Values From Anesthesia to Wakefulness in Both Groups

Compared with the pre-anesthesia baseline, etomidate anesthesia significantly reduced SampEn (Fig. 5b). During anesthesia, both groups showed an upward trend in SampEn, with the TUS group exhibiting a more pronounced increase than the Sham group (Fig. 5a). These findings indicate that TUS facilitates the transition of LFPs from an anesthetized to an awake state, as evidenced by the accelerated recovery of SampEn.

4. Discussion

General anesthesia is a standard procedure before surgery. However, delayed emergence from anesthesia can lead to various complications. To address this, researchers have explored transcranial ultrasound stimulation to promote cognitive recovery after anesthesia. The results indicate that ultrasound intervention significantly reduced re-

covery time in etomidate-anesthetized rats. From a molecular perspective, potentiation of GABA_A receptor function, the primary inhibitory receptor in the mammalian central nervous system [21], is a pivotal mechanism by which intravenous anesthetics such as propofol and etomidate induce loss of consciousness [22]. Consequently, TUS may facilitate arousal by modulating GABAergic neurotransmitter systems. This finding opens new avenues for research into the neuromodulatory mechanisms of TUS.

Furthermore, this study demonstrates that TUS significantly enhances SampEn. As a quantitative measure of the rate of new information generation in nonlinear dynamical systems [23], entropy is a valuable tool for investigating biological systems. Nonlinear dynamical analysis is an effective method for assessing the complexity and regularity of clinical and experimental time-series data [24]. Neural signals encapsulate complex information about underlying brain dynamics [25]. Empirical studies indicate that reduced SampEn correlates with increased self-similarity in local field potential signals, whereas elevated SampEn reflects greater complexity of electrophysiological activity [26]. Consequently, the attenuation of SampEn during anesthetic states signifies a decline in the complexity of neural information processing. As anesthetic agents are metabolized, the gradual restoration of SampEn reveals the dynamic reconfiguration of neural complexity during the recovery of consciousness. Experimental results demonstrate that TUS facilitates the transition of LFPs from anesthetic to awake states, as evidenced by a significant acceleration in the recovery rate of SampEn. This finding suggests that TUS may accelerate arousal by increasing the dynamic

complexity of neural networks, providing experimental evidence for further investigation into the neural mechanisms of consciousness regulation.

More importantly, the TUS group exhibited significant changes in electroencephalographic spectral characteristics. We observed a marked increase in spectral power in the gamma band (30–60 Hz) and higher-frequency bands during the late anesthetic phase in TUS-treated rats. Previous studies have demonstrated that enhanced gamma-band connectivity is associated with the recovery of consciousness after anesthesia [27]. Consequently, spectral analysis of electroencephalographic bands provides a viable method for characterizing anesthetic recovery.

Limitations

Analysis of SampEn, power spectrum, and time-frequency diagram indicates that TUS significantly facilitates recovery of consciousness during anesthetic states. However, this study has several limitations: First, to minimize unnecessary mortality during experimental procedures (e.g., electrode implantation, TUS intervention, and prolonged anesthesia), the investigation was confined to a single anesthetic agent, a specific brain region, and only male rats; second, the findings primarily rely on electrophysiological signal analysis without mechanistic validation at the level of inhibitory neurotransmitters. If necessary, we may design a series of experiments in the future with different anesthetics, brain regions, and genders.

5. Conclusion

In summary, TUS effectively modulated the relative power, mean absolute power, and entropy of LFPs during the transition from anesthesia to awakening, thereby demonstrating a facilitatory effect on recovery in etomidate-anesthetized rats.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

ZL: Conceptualization, Project administration, Supervision, Writing-review and editing; LZ: Data curation, Investigation, Software, Writing-original draft; YY: Methodology, Funding acquisition, Project administration, Supervision, Writing-review and editing; GC: Investigation, Software; CC: Investigation, Data curation; MQ: Investigation, Project administration. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All experimental procedures and study protocols were approved by the Animal Ethics and Management Committee of Yanshan University (The ethics ID: 2022018) and all procedures were performed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised 1996 or the UK Animals (Scientific Procedures) Act 1986 and associated guidelines, the European Communities Council Directive of 24 November 1986 (86/609/EEC), and ARRIVE 2.0 guidelines (see **Supplementary Material**). All efforts were made to minimize the number of animals used and their suffering.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

Figure created with Doubao (Doubao.com), an AI image generation tool developed by ByteDance.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/JIN49895>.

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