

# Electroencephalogram Dynamics of Etomidate-Induced Loss of Consciousness

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## Research article

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# Abstract

## Background

Highly structured electroencephalography (EEG) oscillations can occur in adults during etomidate-induced general anesthesia, but the link between these two phenomena is poorly understood. Therefore, in the present study, we investigated the relationship between the neurological mechanism of etomidate-induced loss of consciousness (LOC) and electroencephalogram dynamics of etomidate-induced loss of consciousness.

## Methods

Etomidate-induced anesthesia was performed on eligible patients undergoing elective surgery. We analyzed EEG data from 20 patients who received etomidate for the induction of general anesthesia. We used power spectra and coherence methods to process and analyze the EEG data.

## Results

Compared with the baseline (awake period), etomidate induced an increase in power in each band during loss of consciousness. Compared with the awake period, the delta-wave (1–4 Hz) coherence increased significantly during loss of consciousness, while the slow-wave (<1Hz) coherence decreased.

## Conclusions

The neural circuit mechanism of etomidate-induced loss of consciousness is closely related to the induction of oscillation in each EEG band and is closely related to the enhancement of delta-wave, alpha-wave, and theta-wave coherence.

## Trial registration

ChiCTR1800017110.

# Introduction

Etomidate is a non-barbiturate intravenous anesthetic that has a rapid onset of action and induces a stable, quiet, comfortable, and non-excitatory transition during the induction period. Enhancement of  $\gamma$ -aminobutyric acid A receptor (GABAAR) activity is considered to be the primary mechanism mediating etomidate-induced anesthesia [1,2]. Etomidate has little effects on cardiovascular and respiratory systems. Based on these characteristics, etomidate is widely used in the induction of anesthesia in patients with impaired hemodynamics, such as in the elderly and those with cardiovascular disease or critical illness [3,4]. General anesthesia is a transient unconscious state [5]. General anesthetics are well described at the molecular level and cellular pharmacological level, but the neural circuit mechanisms that cause loss of consciousness remain unclear [6,7]. Electroencephalography (EEG) is considered to be

the most direct indicator of central nervous system activity [8,9]. The quantitative evaluation of the depth of anesthesia by EEG has made an important contribution to the practice of clinical anesthesia [8]. A recent study reported the effect of general anesthesia on neuronal data recorded in the frontal cortex, and found that frontal-lobe electrical activity is the precursor to a loss of consciousness [10].

Etomidate-induced general anesthesia produces dynamic changes in EEG data, but the characteristics of these changes have not been well elucidated. Furthermore, the relationship between etomidate-induced loss of consciousness and characteristic changes in EEG data is not well understood. Hence, the aim of our present study was to clarify the relationship between etomidate-induced loss of consciousness and electroencephalogram dynamics of etomidate-induced loss of consciousness.

## Methods

This study followed the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University. Standard monitoring techniques (noninvasive blood pressure, electrocardiography [ECG], and pulse oximetry) were applied. Hemodynamic variables were recorded every 60 sec. Written informed consent was obtained from the included patients, who were between 18 and 65 years old (ASA: I~II, No gender limit) and required general anesthesia. Exclusion criteria were as follows: pregnancy, hearing impairments, mental disorders, lack of coordination during induction of anesthesia, or taking drugs that may interfere with the accuracy of EEG recordings. Involuntary myoclonus often occurs during the induction of etomidate [11,12] anesthesia. If obvious myoclonus occurred in a patient, the patient's EEG data were not included in the data analysis. Case selection is shown in Figure 1. Table 1 presents the basic demographic and clinical characteristics of the included subjects.

<b>Table 1. Basic features information of case objects</b>	
	<b>Etomidate (n = 20)</b>
Sex (male/%)	8 (40)
Age (yr), mean ( $\pm$ SD)	36 (10)
Weight (kg), mean ( $\pm$ SD)	61 (9)
Height (cm), mean ( $\pm$ SD)	164 (7)
Time of LOC (min), mean ( $\pm$ SD)	168 (7)

\* LOC=Loss of consciousness

We used a four-channel Sedline brain function monitor (Masimo, Irvine, CA, USA) to record the frontal-lobe EEG data. EEG data were recorded in patients undergoing elective surgery (n = 20) during a baseline of 3 min (with awake periods of closed eyes), etomidate-induced loss of consciousness, and 3 min after the unconsciousness. Etomidate (0.06 mg/kg/min) was the only anesthetic used [13]. The EEG data were

recorded with a preamplifier bandwidth of 0.5–92 Hz, a sampling rate of 178 Hz, 16 bits, and a resolution of 29 nV. The standard Sedline-Sedtrace electrode array records were from electrodes located roughly at positions Fp1, Fp2, F7, and F8, with the ground electrode at Fpz and the reference electrode at roughly 1 cm above Fpz. The electrode impedance was less than 5 kΩ in each channel. The time record in the case report form was required to match the time on the EEG recorder in order to mark key events (e.g., induction start, loss of consciousness) during the analysis.

### **Criteria for the loss of consciousness**

At present, in the induction of clinical anesthesia, the determination of the loss of consciousness is assessed by aimless movements after harmful stimulation [14]. In the present study, the auditory stimulation assessment [15,16] was supplemented by the disappearance of the eyelash reflex to confirm the loss of consciousness. Before inducing anesthesia, we instructed patients not to open or move their eyes.

### **Data preprocessing**

A researcher with experience in reading electroencephalograms manually browsed the EEG data of each patient to manually remove artifacts. The investigator used the recorded information in the case report form to select the appropriately timed EEG data segment. For each case, the EEG segment representing 60 s of consciousness and closed eyes was carefully selected during the perioperative period, as was the EEG segment corresponding to 60 s after the loss of consciousness, for data analysis.

### **Spectral analysis**

The power spectrum quantifies the frequency distribution of power or energy within a signal. The spectrogram was computed using the multitaper method achieved in the Chronux toolbox in MATLAB[17]. And the group-level spectrogram computed by taking the median of all patients. The spectrum of the selected EEG epochs was also calculated by us. Then, for all epochs, the resulting power spectra were averaged, and by way of multitaper-based jackknife techniques [17], 95% confidence intervals (CIs) were computed. Parameters for spectral analysis are as follows: window length  $T = 2$  s with a 1.95 s overlap; time-bandwidth product of  $TW = 3$ ; number of tapers,  $K = 5$ ; and spectral resolution = 3 Hz. The time-frequency analysis is reflected in Figure 2.

### **Coherence analysis**

Coherence graphs are coherent time-varying versions, which are estimated using continuous windows of EEG data. Between two signals,  $x$  and  $y$ , the coherence  $C_{xy}(f)$  function, is determined as follows:

$$C_{xy}(f) = \frac{|S_{xy}(f)|}{\sqrt{S_{xx}(f)S_{yy}(f)'}}$$

$S_{xy}(f)$  is the cross-spectrum between the signals  $x(t)$  and  $y(t)$ ,  $S_{xx}(f)$  is the power spectrum of the signal  $x(t)$ , and  $S_{yy}(f)$  is the power spectrum of the signal  $y(t)$  [17]. In order to acquire the appraised coherence, based on the Chronux toolbox in MATLAB, the coherence was computed between F7 and F8, the two frontal electrodes[18]. The electrode position is shown in Figure 3. By taking the median across subjects, the group-level coherograms were computed. The coherence for selected EEG epochs was also calculated. The resulting coherence estimates were averaged for all epochs, and by way of multitaper-based jackknife techniques, 95% CIs were computed [17]. Parameters for the coherence analysis were similar to spectral analysis and spectral resolution of  $2W = 3$  Hz. The peak coherence and its frequency of the frontal alpha oscillation for each individual patient were estimated by us. Then, in order to acquire the group-level peak coherence and frequency for these oscillations, we averaged across subjects.

## Statistical analysis

So as to emulate spectral and coherence computes between groups, we utilized jackknife-based methods [17], the two-group test for spectra, and the two-group test for coherence, as performed in the Chronux toolbox routine [19]. This method takes into account the frequency spectrum and the basic spectral resolution of the coherence estimation, and only when the difference occurs at a continuous frequency on a frequency band wider than the spectral resolution of  $2W$ , the difference is considered significant. To be specific, for frequencies  $f > 2W$ , the negative assumption was rejected only if the test statistic surpassed the significance threshold over a contiguous frequency range  $\geq 2W$ . For frequencies  $0 \leq f \leq 2W$ , in order to illustrate the capabilities of multitaper spectral estimation when the frequency is near zero, the negative assumption was rejected only if the test statistic surpassed the significance threshold over a contiguous frequency range from 0 to  $\max(f, W) \leq 2W$ . A significance threshold of  $P < 0.001$  was confirmed for comparisons between groups.

## Results

We collected EEG data from 40 cases of etomidate-induced general anesthesia but excluded 12 patients due to the coordination of their EEG records in the awake period being poor. Ultimately, of the remaining 28 patients, 20 patients were considered fit for analysis. Subjects which with poor-quality data were excluded, most likely due to poor electrode contacts.

### Etomidate power-spectra analysis

We observed the EEG spectra during both the awake period before etomidate administration and during etomidate-induced loss of consciousness. The two time-frequency diagrams were continuous in time, and the EEG power changes changed significantly over time. The sober period was dominated by slow-wave (0.1–1.0 Hz) and delta-wave (1.0–4.0 Hz) oscillations; the period corresponding to the etomidate-induced loss of consciousness was dominated by slow-wave (0.1–1.0Hz) and delta-wave (1.0–4.0 Hz) oscillations. Theta-wave (4.0–8.0 Hz) and alpha-wave (8.0–13.0Hz) oscillations were relatively insignificant. Next, we performed time-frequency analysis of EEG data in the two periods and found that after etomidate-induced loss of consciousness, the oscillation in each band increased. We also observed

that the two periods were clearly different in time and frequency between 0–22.97 Hz and 27.28–40.00 Hz. The result of power-spectra analysis is shown in Figure 4.

### **Etomidate coherence analysis**

We next analyzed the similarities and differences in the correlation patterns between the awake period and the period during etomidate-induced loss of consciousness. We found that the awake-phase coherence map had a specific coherence in the theta wave and alpha wave. In contrast, the phase coherence map during the etomidate-induced loss of consciousness was significantly enhanced for the theta wave and alpha wave compared to that during the awake phase. Hence, some coherence was produced. We also observed that there was a significant difference in the coherence between the waking period and the period of etomidate-induced loss of consciousness in the 1.86–3.17 Hz band. The result of coherence analysis is shown in Figure 5.

## **Discussion**

In the present study, we analyzed the characteristic changes in the EEG bands before and during etomidate-induced anesthesia via spectral analysis and coherence analysis. From the awake period to the loss of consciousness period, etomidate general anesthesia induced an increase in oscillation in each frequency band within the EEG data. Additionally, when etomidate induced loss of consciousness, the coherence of the EEG signal in the theta wave and alpha wave was obviously enhanced, and the delta wave also showed obvious coherence.

Etomidate exerts its anesthetic actions through potentiation of GABAARs containing  $\beta 2$  and  $\beta 3$  subunits. It has recently been shown that the  $\beta 2$  subunit contributes to the sedative properties of etomidate, whereas the  $\beta 3$  subunit is responsible for its anesthetic properties [20,21]. In our present study, etomidate induced anesthesia and enhanced theta-wave oscillations. In our coherence analysis, etomidate produced strong coherence in the theta wave; interestingly,  $\beta 3$ -subunit-containing receptors play an important role in theta-wave oscillations. A previous study analyzed the effects of etomidate on rhythmic population activity by recording local field potentials (LFPs) [22]. In slices, which derived from wild-type mice, etomidate (200 nM) amplified the oscillatory population activity in the theta-frequency band, but this effect was not seen in slices, which derived from  $\beta 3$ -knockin mice, and this phenomenon was also observed in vivo [23]. These findings indicate that the neuronal mechanism of etomidate-induced loss of consciousness is closely related to the  $\beta 3$  subunit of GABAAR functional activity. Furthermore, previous evidence has shown that the overall effect of etomidate reflects a balance between enhancement and inhibition produced by GABAARs containing  $\beta 2$  and  $\beta 3$  subunits [22]. Etomidate enhances theta oscillations by acting on  $\beta 3$ -containing GABAA receptors but depresses these oscillations via  $\beta 2$ -subunit-containing receptors. In our present study of etomidate-induced loss of consciousness, we systematically observed the enhancement of EEG theta oscillations. However, inhibition of EEG theta oscillations and a balance of enhancement and inhibition of EEG theta oscillations was not reflected in our present study. Therefore, future studies should be conducted to investigate these additional phenomena.

In the present study, etomidate induced a loss of consciousness and changed the EEG theta rhythm. Some studies have indicated that hippocampal interactions with the prefrontal cortex, another significant memory-associated structure, are coordinated by theta-rhythm plasticity [24,25]. Amnesia is a significant symptom of general anesthesia. Several different brain areas participate in memory formation, including the prefrontal cortex, amygdala, and hippocampus. Anesthesia may be associated with memory impairment, as has been indicated by many studies in the hippocampus [26,27], and evidence suggests that different frequency oscillations are related to changes in information coding and synaptic weights [28]. Etomidate-induced amnesia arises by means of GABAAR modulation, which highly depends on  $\alpha$ -5 subunit modulation; this process likely occurs principally within the hippocampus [29,30]. Anesthetics may disturb the greatly organized rhythmic activity patterns that are thought to be indispensable for hippocampal learning [31]. For instance, changes in theta frequency and theta power may contribute to amnesia by means of anesthetic actions on a variety of molecular targets [32]. Theta rhythms act as internal clocks that synchronize large networks and serve as a reference mechanism for internal and external synchronization, which is greatly coherent throughout the medial temporal lobe. These findings suggest that etomidate-induced loss of consciousness and changes in hippocampal theta rhythms are closely related. Collectively, these potential associations have led us to hypothesize that etomidate-induced theta oscillations may be an indicator of a functional disconnection between the hippocampus and cerebral cortex.

The EEG data analyzed in this study were all derived from the frontal 4-channel pathway, so our analysis was unable to assess other reported cortical kinetic connectivity associated with anesthetic-induced loss of consciousness. Our observations need to be further validated in future high-density EEG studies<sup>[33]</sup>. At present, exploring the relationship between the neural circuit mechanism of etomidate-induced loss of consciousness and the characteristic changes of EEG can only be carried out on animal experimental models. Therefore, the clinical observed 'the connection' still needs to be verified by animal models.

According to our analysis and discussion, from the awake period to the loss of consciousness, the neural circuit mechanism of etomidate-induced loss of consciousness is closely related to the enhancement of delta-wave, alpha-wave, and theta-wave coherence. The characteristic transformation of the EEG that we described can be calculated and displayed in real time, providing a good reference for the monitoring of the depth of anesthesia and the evaluation of the level of sedation and consciousness by an anesthesiologist.

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## **Declarations**

### **Funding**

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### **Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

### **Authors' contributions**

Lei Zhang and Shunqin Fan contributed equally and share first authorship with manuscript editing, and modifying figures and Tables. Other authors contributed to the writing, review and editing of the manuscript. All authors read and approved the final manuscript.

### **Ethics approval and consent to participate**

No Applicable

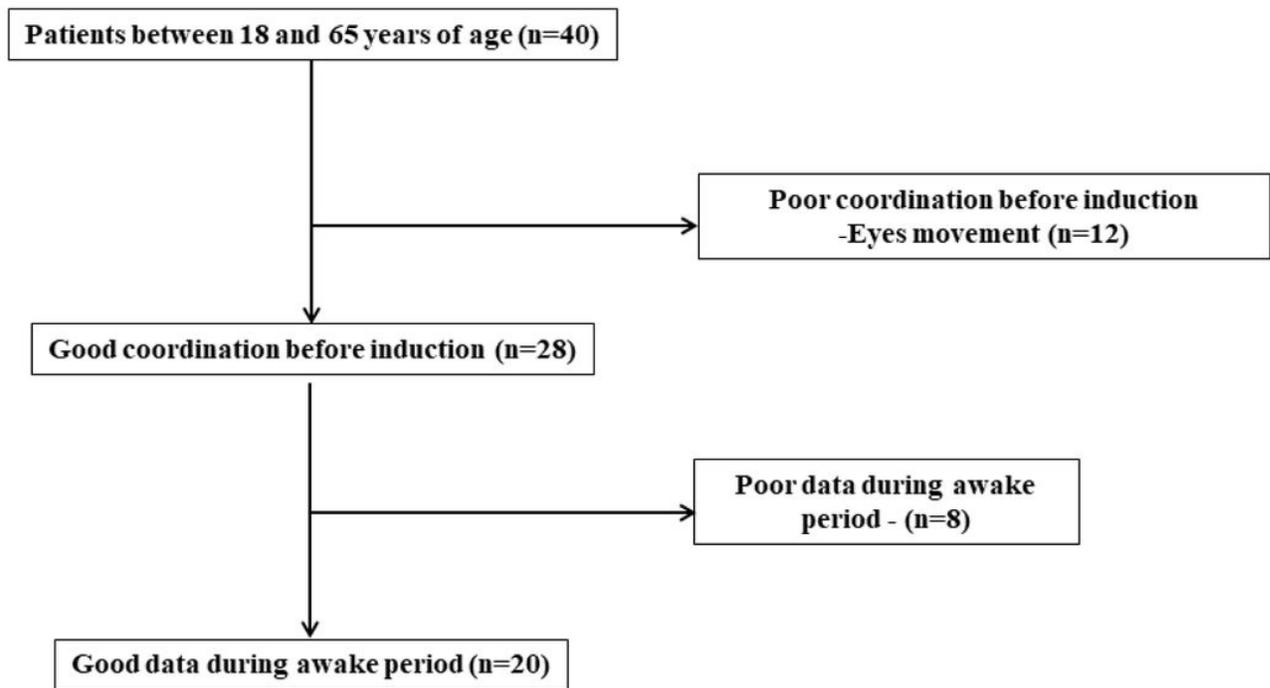
### **Consent for publication**

Not Applicable

### **Competing interests**

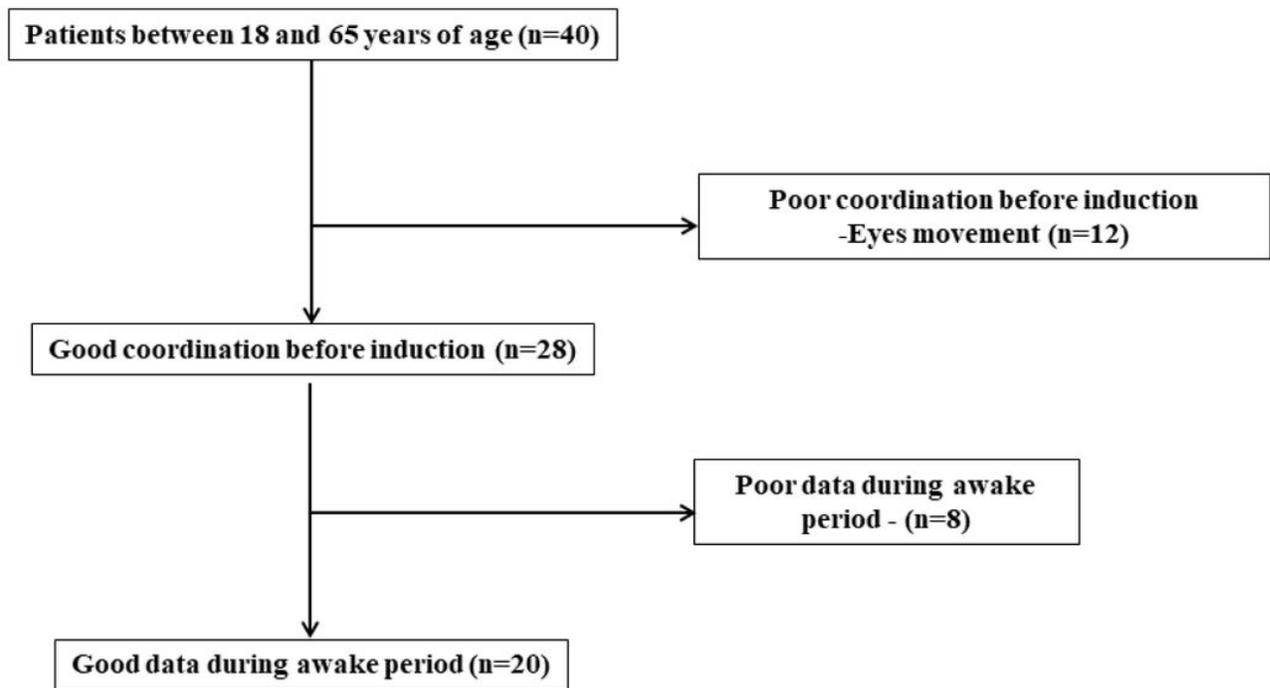
The authors declare that they have no competing interests.

## **Figures**



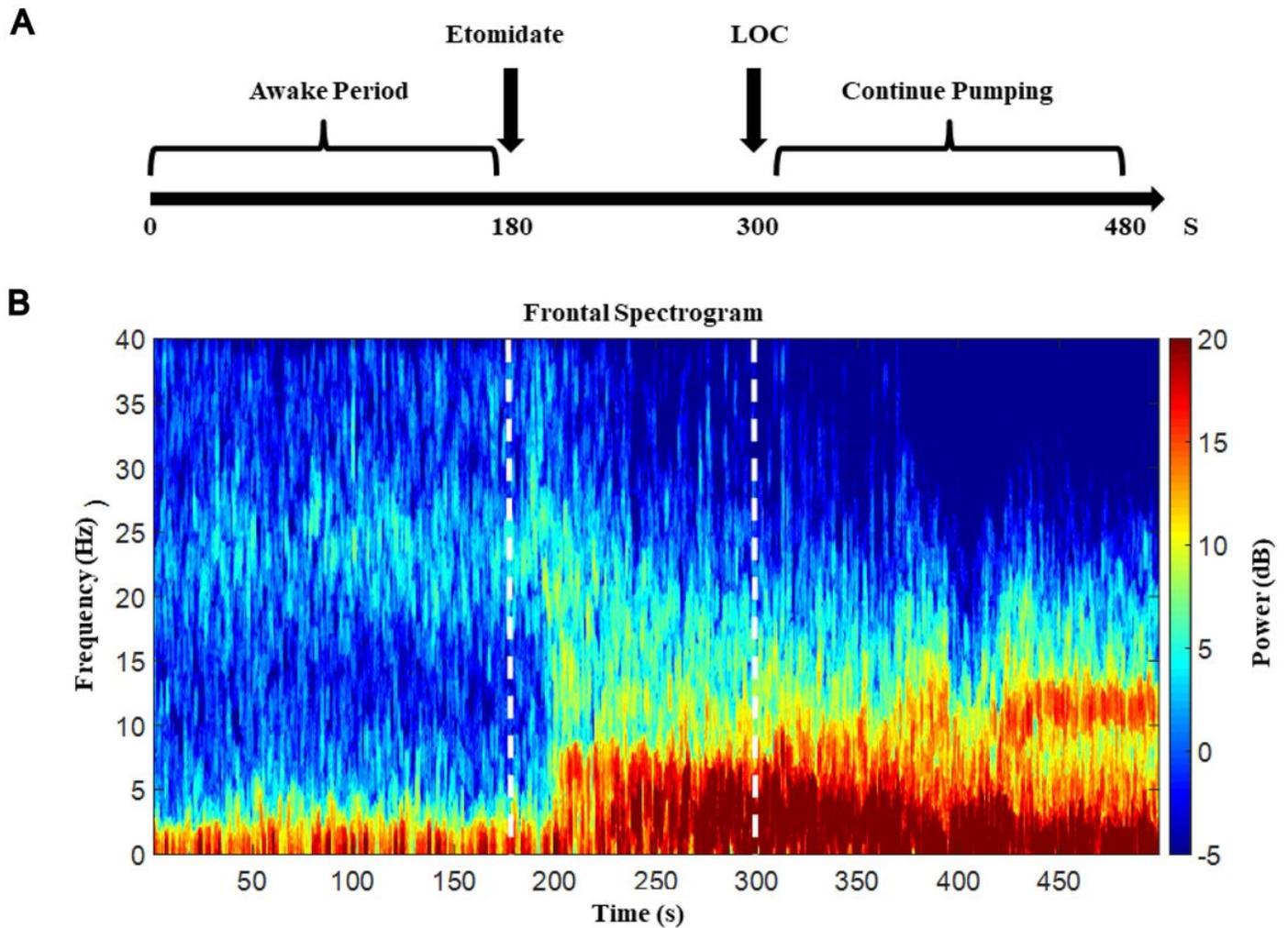
**Figure 1**

Patient selection. Our study initially included 40 individuals between 18 and 65 years old. We excluded 12 patients because of poor cooperation before anesthesia. We then examined the EEG data of the remaining 28 patients and excluded the data of eight of these patients due to poor data quality. Ultimately, we analyzed the EEG data from 20 patients.



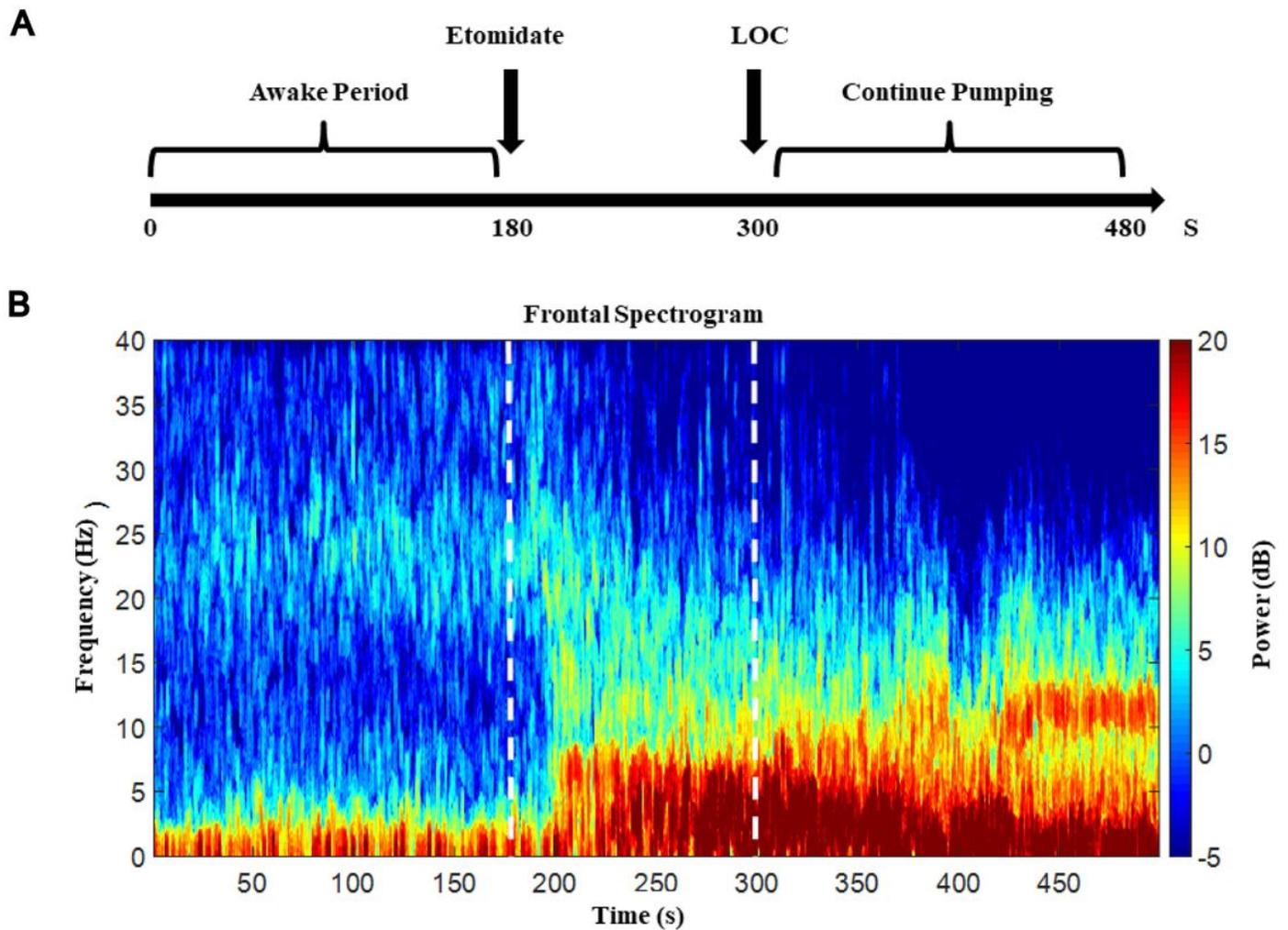
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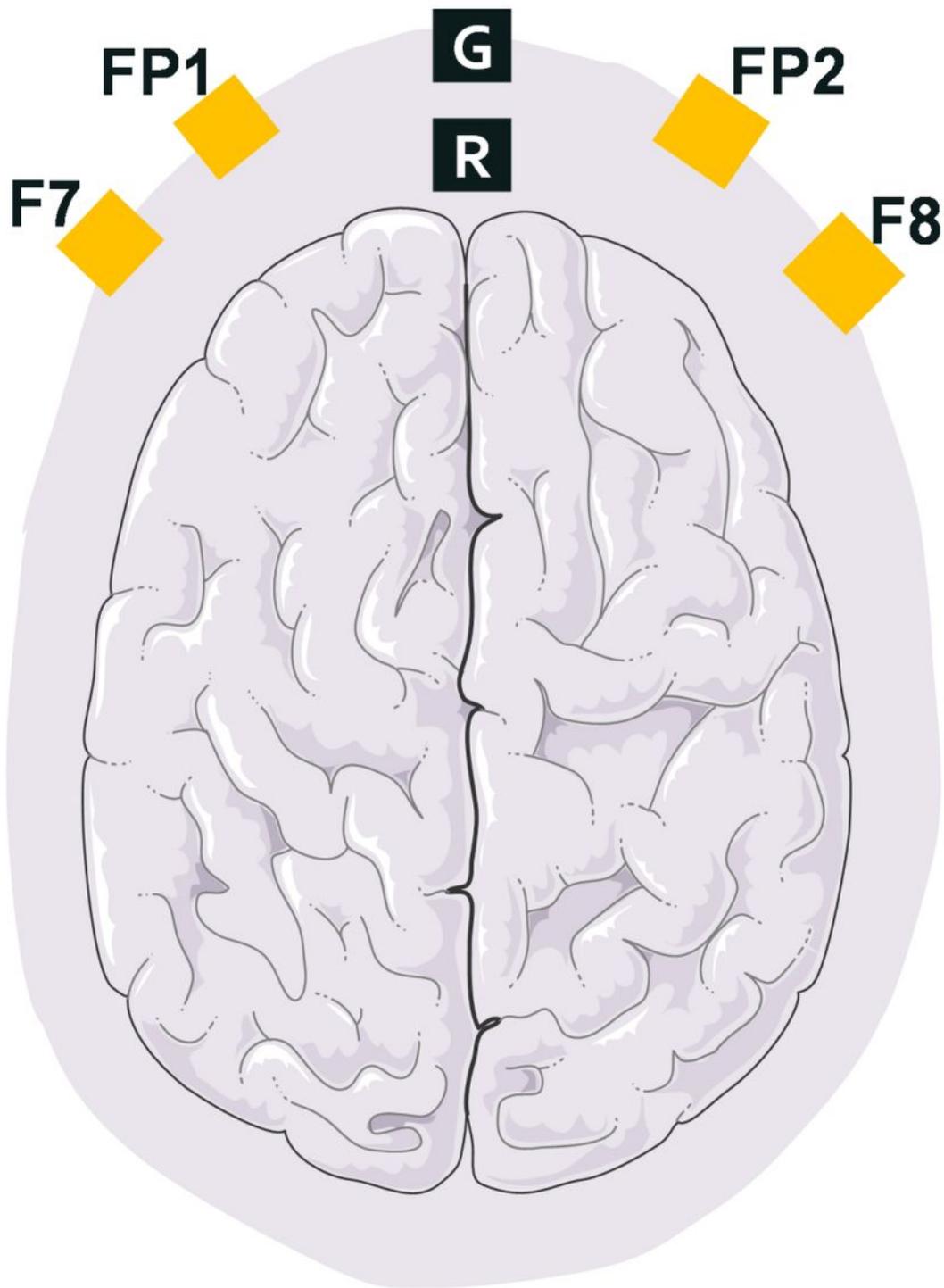
**Figure 2**

Frontal-lobe EEG spectrograms in the study of etomidate-induced loss of consciousness. (A) In the etomidate study, the main events are marked on the timeline. The “continue pumping” event denotes that etomidate was continuously pumped for 3 min after the loss of consciousness (LOC). (B) During the study, each patient was instructed to keep their eyes closed and without motion for a period of 3 min before etomidate was administered to induce general anesthesia. The spectrogram shows the frequency composition as a function of time. The frequency is plotted on the y-axis and time is plotted on the x-axis. The energy or power in the signal is represented by color. As the induction of etomidate began, the slow-wave, delta-wave, and theta-wave oscillations increased. After loss of consciousness, the alpha wave oscillation increased.



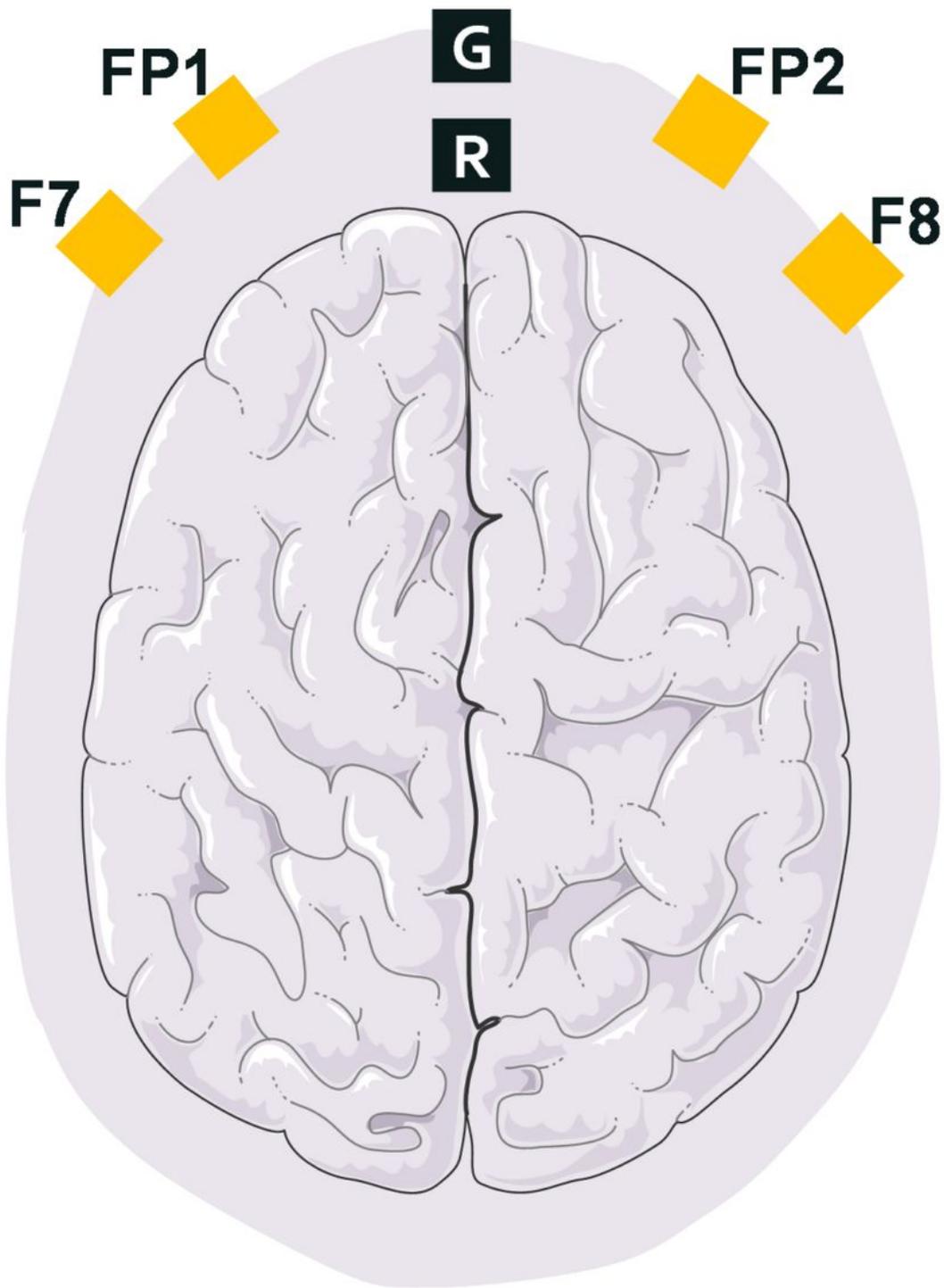
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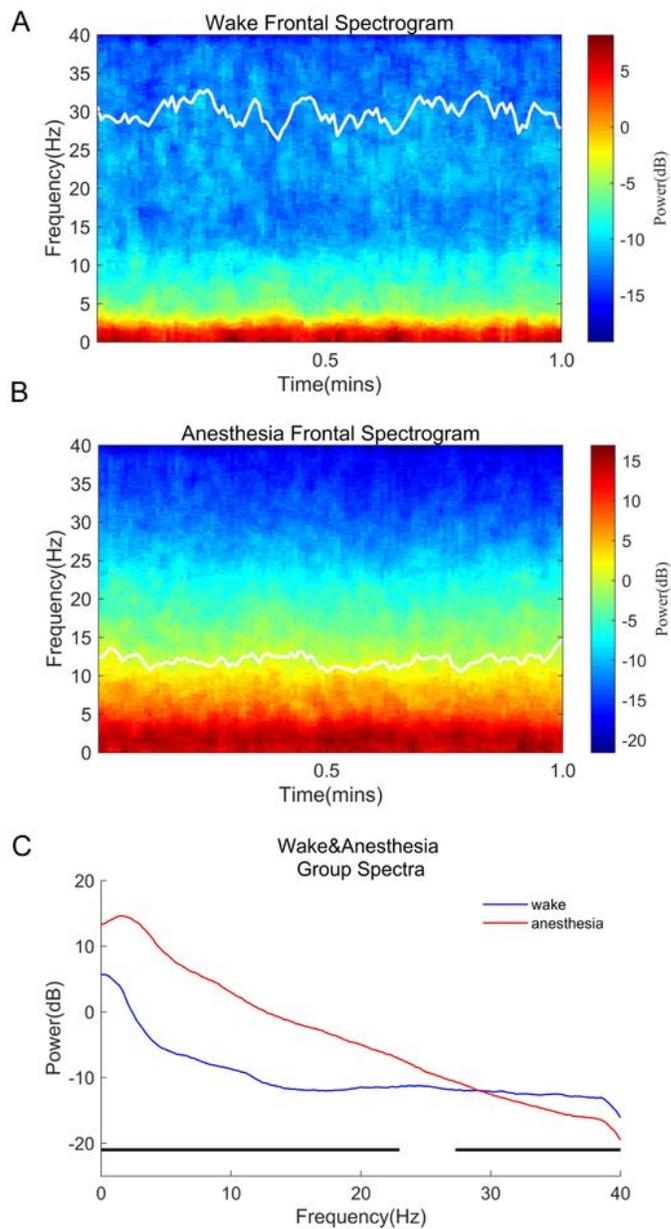
**Figure 3**

The channel position and the two bipolar frontal channels: F7 and F8, which we used for coherence analysis.



**Figure 3**

The channel position and the two bipolar frontal channels: F7 and F8, which we used for coherence analysis.



**Figure 4**

Time-frequency analysis of EEG data between the pre-anesthesia awake period and etomidate-induced loss of consciousness. (A) During the awake period before induction of etomidate (n = 20), slow-wave (<1.0 Hz) and delta-wave (1.0–4.0 Hz) oscillations were mainly present. (B) Etomidate-induced loss of consciousness (n = 20) yielded an increase in the power of slow waves (<1.0 Hz), delta waves (1.0–4.0 Hz), theta waves (4.0–8.0 Hz), and alpha waves (8.0–13.0 Hz). (C) Spectrograms of the pre-anesthesia

awake period. Compared with those during the awake period, the powers of the slow wave (<1.0 Hz), delta wave (1.0–4.0 Hz), theta wave (4.0–8.0 Hz), and alpha wave (8.0–13.0 Hz) during the etomidate-induced loss of consciousness were significantly increased (C: 0–22.97 Hz, 27.28–40.00 Hz;  $P < 0.001$ , two-group test for spectra). Median spectra presented with 95% jackknife CIs. Horizontal solid black lines represent the frequency ranges at which there were significant differences.

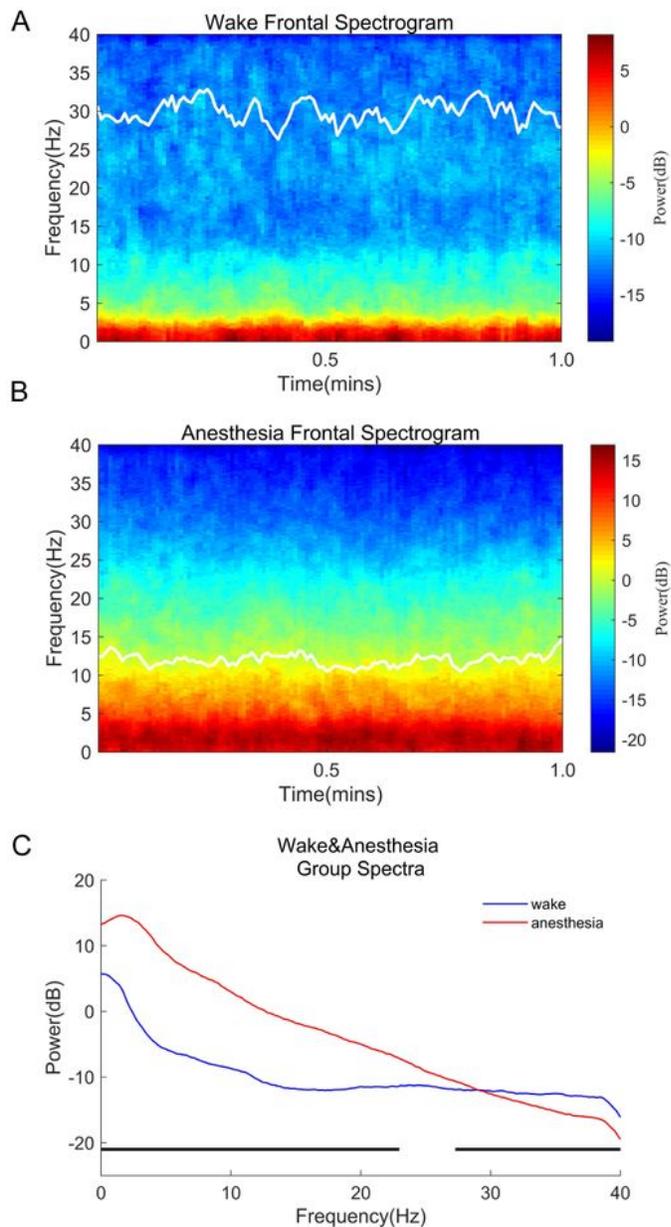
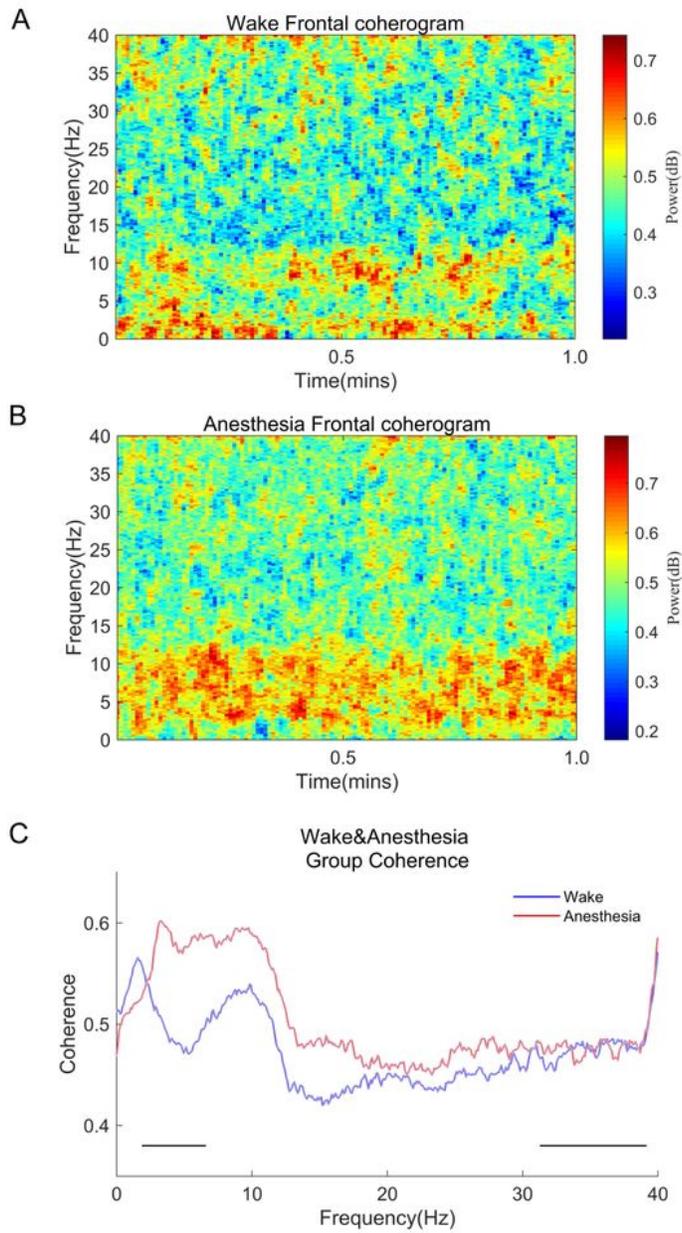


Figure 4

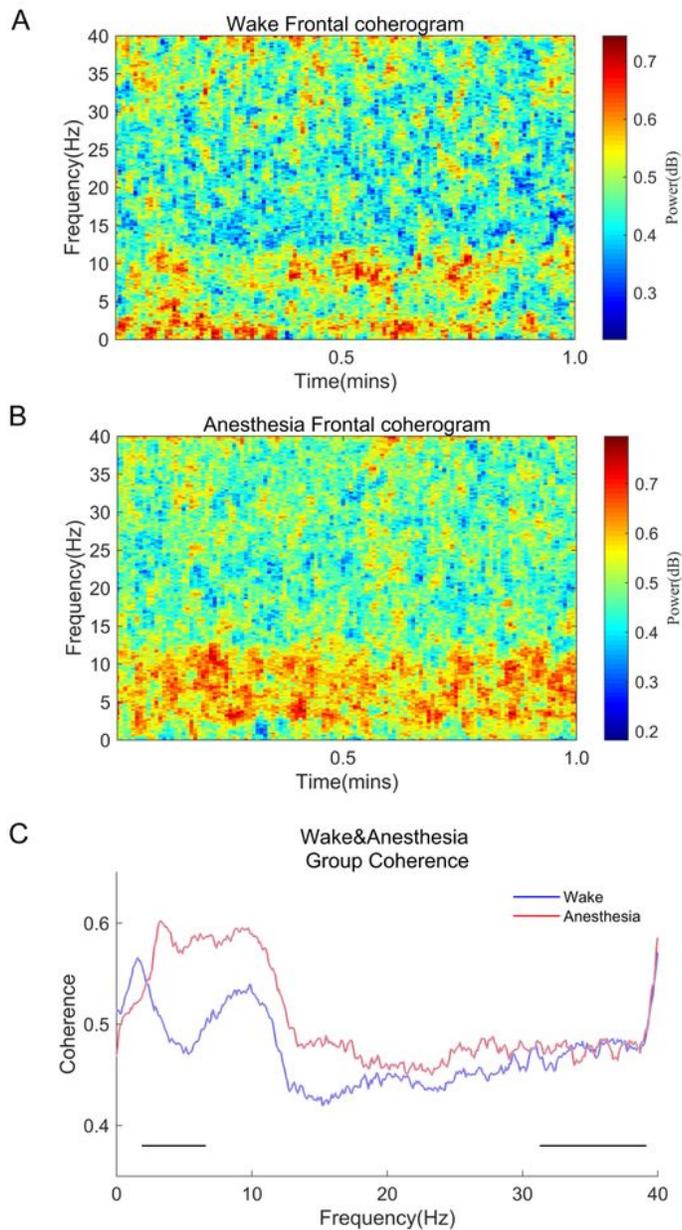
Time-frequency analysis of EEG data between the pre-anesthesia awake period and etomidate-induced loss of consciousness. (A) During the awake period before induction of etomidate (n = 20), slow-wave (<1.0 Hz) and delta-wave (1.0–4.0 Hz) oscillations were mainly present. (B) Etomidate-induced loss of consciousness (n = 20) yielded an increase in the power of slow waves (<1.0 Hz), delta waves (1.0–4.0 Hz), theta waves (4.0–8.0 Hz), and alpha waves (8.0–13.0 Hz). (C) Spectrograms of the pre-anesthesia awake period. Compared with those during the awake period, the powers of the slow wave (<1.0 Hz), delta wave (1.0–4.0 Hz), theta wave (4.0–8.0 Hz), and alpha wave (8.0–13.0 Hz) during the etomidate-induced loss of consciousness were significantly increased (C: 0–22.97 Hz, 27.28–40.00 Hz;  $P < 0.001$ , two-group test for spectra). Median spectra presented with 95% jackknife CIs. Horizontal solid black lines represent the frequency ranges at which there were significant differences.



**Figure 5**

Coherence analysis between the pre-anesthesia awake period and the period during etomidate-induced loss of consciousness. (A) The coherence analysis of the awake phase of etomidate general anesthesia (n = 20) showed the coherence spectrum in terms of the slow wave (<1.0 Hz), delta wave (1.0–4.0 Hz), and alpha wave (8.0–13.0 Hz). (B) The coherence analysis during etomidate-induced loss of consciousness (n = 20) shows the coherence spectra in terms of the delta wave (1.0–4.0 Hz), theta wave

(4.0–8.0 Hz), and the alpha wave (8.0–13.0 Hz) During the awake period, the coherence of slow waves (<1.0 Hz) was decreased. (C) The coherence spectra of the pre-anesthesia awake period and the period during induced consciousness loss. The alpha wave (8.0–13.0 Hz) coherence is similar in both periods. However, the delta wave (1.0–4.0 Hz) during etomidate-induced loss of consciousness was more coherent than during the conscious period (1.86–3.17 Hz, two-group test for coherence,  $P < 0.001$ ). Median coherence is presented with 95% jackknife CIs. Horizontal solid black lines represent frequency ranges at which there was significant difference. The bandpass filter allows frequency components to pass within a certain frequency range but attenuates the frequency components in other ranges to a very low level rather than cutting off frequencies outside the range at a certain frequency point; therefore, at 40 Hz, the graph shows that the coherence is uniform and rising.



**Figure 5**

Coherence analysis between the pre-anesthesia awake period and the period during etomidate-induced loss of consciousness. (A) The coherence analysis of the awake phase of etomidate general anesthesia (n = 20) showed the coherence spectrum in terms of the slow wave (<1.0 Hz), delta wave (1.0–4.0 Hz), and alpha wave (8.0–13.0 Hz). (B) The coherence analysis during etomidate-induced loss of consciousness (n = 20) shows the coherence spectra in terms of the delta wave (1.0–4.0 Hz), theta wave

(4.0–8.0 Hz), and the alpha wave (8.0–13.0 Hz) During the awake period, the coherence of slow waves (<1.0 Hz) was decreased. (C) The coherence spectra of the pre-anesthesia awake period and the period during induced consciousness loss. The alpha wave (8.0–13.0 Hz) coherence is similar in both periods. However, the delta wave (1.0–4.0 Hz) during etomidate-induced loss of consciousness was more coherent than during the conscious period (1.86–3.17 Hz, two-group test for coherence,  $P < 0.001$ ). Median coherence is presented with 95% jackknife CIs. Horizontal solid black lines represent frequency ranges at which there was significant difference. The bandpass filter allows frequency components to pass within a certain frequency range but attenuates the frequency components in other ranges to a very low level rather than cutting off frequencies outside the range at a certain frequency point; therefore, at 40 Hz, the graph shows that the coherence is uniform and rising.