COVER PAGE Study protocol

Changes in Information Integration and Brain Networks During Unresponsiveness Induced by Propofol, Dexmedetomidine, and Esketamine

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Investigator-Initiated Clinical Study Protocol

Changes in Information Integration and Brain Networks During Unresponsiveness Induced by Propofol, Dexmedetomidine, and Esketamine

Study Drugs: Propofol / Dexmedetomidine / Esketamine
Indication: Elective non-cardiac surgery
Study Type: Investigational study
Version No.: 01
Version Date: March 20, 2026
Sponsor: Fudan University Shanghai Cancer Center
Principal Investigator: Jun Zhang
Study Team: Xiaoge Liu, Shumei Cao, Yali Chen
Statistical Design and Analysis Unit: School of Electrical Engineering, Yanshan University
Statistician: Zhenhu Liang

Investigator’s Statement

I have carefully read and understood this study protocol. I confirm that the protocol contains all necessary elements to conduct the study properly. I will conduct this clinical study in compliance with the protocol and Good Clinical Practice (GCP) principles.
I will provide this protocol and relevant study documents to all personnel involved in the study and ensure they fully understand study methods, procedures, and responsibilities.

Principal Investigator: Jun Zhang
Date: March 20, 2026

List of Abbreviations

- EEG: Electroencephalogram
- LOR: Loss of responsiveness
- LOC: Loss of consciousness
- BIS: Bispectral index
- ASA: American Society of Anesthesiologists
- BMI: Body mass index
- PAC: Phase-amplitude coupling

1. Study Background

General anesthesia is a drug-induced, reversible state of unconsciousness. The nature of consciousness is a major topic in neuroscience. Consciousness is often judged by behavioral responses; however, behavioral signs alone are often insufficient to assess consciousness levels, especially under general anesthesia. In recent years, with the rise of neural network research, electroencephalography (EEG)-based neurodynamics has become a focus in anesthesia mechanism research. EEG is a non-invasive method with high temporal resolution for monitoring brain activity. EEG-based monitors such as the Bispectral Index (BIS) and entropy were widely used clinically, but many studies have confirmed they do not reliably reflect consciousness levels induced by anesthetics such as ketamine, with large inter-individual variability. This may be because these devices only analyze the frequency spectrum.

Commonly used anesthetics act on different molecular targets, including gamma-aminobutyric acid type A (GABAA) receptor agonists, N-methyl-D-aspartate (NMDA) receptor antagonists, and alpha2-adrenoceptor agonists. These drugs induce loss of responsiveness (LOR) to external stimuli (e.g., auditory and visual input). Previous studies indicate that anesthetics induce loss of consciousness (LOC) by disrupting large-scale brain networks, but the mechanisms by which they alter neurodynamics to interfere with information processing remain unclear. Updated EEG-based algorithms, including analyses of functional and effective connectivity, allow more precise assessment of consciousness levels, which motivated the present study. Recent studies using non-invasive multi-channel EEG across different states of consciousness have revealed spatiotemporal characteristics of neural oscillations. Propofol (a GABAA agonist)-induced LOC is characterized by anteriorization of alpha oscillations. Our group previously used high-density EEG to characterize functional brain network connectivity during propofol sedation and anesthesia at different doses. Dexmedetomidine, a highly selective alpha2-adrenoceptor agonist, induces sedation resembling non-rapid eye movement (NREM) sleep, with EEG features of spindle oscillations (12–16 Hz) and alpha coherence. Slow-wave oscillations are observed during both propofol- and dexmedetomidine-induced sedation. EEG-based connectivity analysis shows that frontopolar–frontal alpha connectivity is specifically associated with LOR during drug administration. Furthermore, propofol infusion induces frontal alpha dominance and phase-amplitude coupling (PAC), which are absent during dexmedetomidine infusion, indicating state-dependent and drug-dependent effects. In contrast, the NMDA receptor antagonist ketamine induces “gamma bursts” and markedly increases theta power and functional connectivity. Thus, these intravenous anesthetics with distinct molecular targets but a common endpoint (LOR or LOC) provide tools to track neurodynamics associated with brain states.

At the macro level, theories of consciousness include Higher-Order Theory, Global Workspace Theory, Integrated Information Theory, and Brain Network Theory. These theories interpret consciousness from different perspectives and link it to distinct brain regions. The core of Global Workspace Theory is that mental states are consciously broadcast in a global workspace. The brain is viewed as a modular system performing

multiple functions, with information transmitted and shared across modules via long-distance neural connections, giving rise to consciousness. Integrated Information Theory posits that consciousness arises from the integration of diverse information sources in the brain. The posterior cortical regions (parietal, temporal, and occipital) are identified as “hot zones” of consciousness.

Network science is considered critical for uncovering fundamental mechanisms of anesthesia-induced unconsciousness and building theoretical frameworks of consciousness. However, these theories explain only specific aspects of consciousness and often lack methodologies for quantifying conscious states. Consciousness may arise from complex spatiotemporal interactions among distributed brain functions. Multiple studies show that anesthesia-induced unconsciousness is associated with disrupted functional connectivity, reduced network efficiency, and constrained functional states. Since information integration and brain network theory are two major frameworks for exploring consciousness, we analyze three different anesthetic-induced unresponsive states from these two perspectives. Although multiple theories attempt to explain consciousness, findings from different anesthetics are conflicting. Distinguishing drug-specific from state-specific effects is therefore critical for evaluating competing theories of consciousness.

This study uses spatial and frequency-domain EEG analysis to investigate the macroscale neural correlates of anesthesia-induced unresponsiveness (used as a surrogate for unconsciousness). High-density EEG will be recorded during administration of propofol, dexmedetomidine, or esketamine, and changes in EEG power- and spectrum-based brain networks will be analyzed from wakefulness through unresponsiveness to recovery.

2. Study Objectives

Primary Objective

To investigate the neural correlates of unresponsiveness by analyzing EEG power spectra and functional connectivity during sedation and unconsciousness induced by propofol, dexmedetomidine, and esketamine.

Secondary Objective

To identify neurophysiological markers for monitoring the actual consciousness level during general anesthesia.

3. Study Design and Methods

3.1 Overall Design

This is a single-center, randomized, parallel-group exploratory clinical study. The study aims to identify neural correlates of unconsciousness by analyzing EEG power spectra and connectivity during unresponsiveness induced by propofol, esketamine, and dexmedetomidine.

Patients scheduled for elective non-cardiac surgery under general anesthesia will be

randomly assigned to three parallel groups. Each group will receive a constant infusion of one study drug until loss of consciousness. High-density EEG will be recorded and analyzed.

3.2 Outcomes

Primary Outcome

Group-specific EEG power spectrum and functional connectivity patterns.

Secondary Outcomes

- Perioperative vital signs (HR, BP, SpO2)
- Time to loss of responsiveness

3.3 Inclusion Criteria

1. Patients scheduled for elective non-cardiac surgery
2. ASA Class I–II
3. Age 18–65 years
4. BMI 18–31 kg/m²
5. Signed written informed consent

3.4 Exclusion Criteria

Patients meeting any of the following will be excluded:

- Severe cardiovascular, hepatic, or renal dysfunction
- Hearing impairment
- Psychiatric disorders or communication barriers
- Expected difficult airway
- Pregnancy or lactation
- Hypersensitivity to study drugs
- Participation in another clinical trial within 3 months

3.5 Patient Withdrawal or Termination Criteria

Subjects will be withdrawn or terminated if:

Informed consent is withdrawn.

The patient is noncompliant with the protocol.

The investigator judges continuation to be unfavorable (including occurrence of serious adverse events: cardiovascular/cerebrovascular events, anaphylactic shock, hypoxemia, cardiac arrest, etc.).

3.6 Randomization & Blinding

A random sequence is generated via R statistical software before subject enrollment. The Central sealed opaque envelope method is adopted for allocation concealment to avoid assignment bias. This is an open-label clinical trial; neither participants nor clinical investigators are blinded to the assigned study medication due to distinct clinical sedation manifestations of three investigational anesthetics. No interim analysis is planned during subject enrollment.

3.7 Study Procedures

Eligible patients will be randomly assigned to three groups (n = 40 each):
Group P: Propofol
Group D: Dexmedetomidine
Group K: Esketamine

All patients will fast for 6–8 hours preoperatively. On arrival in the operating room, standard monitoring (ECG, SpO2, non-invasive blood pressure) will be applied. A peripheral intravenous line will be established. Supplemental oxygen will be administered via a facemask at 5 mL/min. A 128-channel EEG electrode cap will be applied.

Group P (Propofol)
Concentration: 10 mg/mL
Dosage: 1 mg/kg infused over 5 minutes
EEG will be recorded from wakefulness through unresponsiveness to recovery of responsiveness.

Group D (Dexmedetomidine)
Concentration: 10 μg/mL
Loading dose: 1.0 μg/kg infused over 10 minutes
EEG will be recorded from wakefulness through unresponsiveness to recovery of responsiveness.

Group K (Esketamine)
Concentration: 5 mg/mL
Dosage: 0.5 mg/kg infused over 10 minutes
EEG will be recorded from wakefulness through unresponsiveness to recovery of responsiveness.

Intraoperative vital sign management and monitoring will follow the standard clinical practice of the Department of Anesthesiology, Fudan University Shanghai Cancer Center.

Study Drug Management
All three study drugs (propofol, dexmedetomidine, and esketamine) are sourced from qualified domestic pharmaceutical manufacturers and stored in the hospital pharmacy under the recommended storage temperature as per official drug specifications. Drug preparation, dispensing and residual drug recovery are implemented following institutional pharmacy SOP. Concomitant routine perioperative medicines allowed in this trial follow standard anesthesia practice of Fudan University Shanghai Cancer Center; no prohibited concomitant medication is administered during the study-related drug infusion period.

3.8 Data Collection

- Demographics, baseline characteristics
- Perioperative vital signs

- EEG signals (power spectrum, functional connectivity)
- Adverse events
- Postoperative follow-up

3.9 Detailed Statistical Methods & SAP

Sample Size

A priori power analysis was performed to guide sample size determination (Schmidt et al., 2018). To achieve 80% statistical power at a significance level of 0.05 in mixed-model ANOVA, the total sample size should be at least 100 patients. Allowing for a 20% dropout rate, we plan to enroll 40 patients per group, for a total of 120 patients.

All statistical analyses are performed using R Project software (Version 4.1.2, R Foundation, Vienna, Austria; http://www.r-project.org). Bayesian statistical analysis is applied for subject age, height and weight; the Chi-square test is used for gender comparison, and nonparametric factorial ANOVA based on aligned rank transform is conducted for all EEG parameters. Missing data of baseline and outcome variables will be handled via multiple imputation method. Multiplicity adjustment is not required in this exploratory trial. Primary endpoint analysis follows pre-defined statistical hypotheses specified in this protocol.

4. Study Flow and Timeline

Study Procedures

1. Protocol development and ethical approval
2. Patient screening
3. Informed consent
4. Randomization
5. Data collection
6. Statistical analysis and manuscript preparation

Timeline

- March 2026: Protocol finalization
- April 2026: Ethics approval & study initiation
- April–August 2026: Patient enrollment & data collection
- August–December 2026: Analysis, manuscript submission, and study completion

5. Ethical Considerations

The study will be conducted in accordance with the Declaration of Helsinki and GCP. Written informed consent is required before enrollment. Subjects may withdraw at any time without penalty. All personal data will be kept confidential.

This study obtained formal ethical approval from Fudan University Shanghai Cancer Center Institutional Review Board (SCCIRB), approval number: 2604-Exp427, approval date: April 27, 2026. No approved protocol amendments have been generated before current document submission. The written informed consent form describes study purpose, study-related examination procedure, predictable risks and potential clinical

benefits, available alternative anesthesia schemes, personal information confidentiality protection and voluntary withdrawal right for participants. The matching ICF Version 01 dated March 20, 2026 has been reviewed and formally approved together with the study protocol by the above IRB.

6. Safety and Adverse Events

Definitions

- Adverse Event (AE): Any unfavorable medical occurrence
- Serious Adverse Event (SAE): Life-threatening event, death, disability, prolonged hospitalization, or congenital anomaly
- Adverse Drug Reaction (ADR): AE related to the study drug

Assessment

AEs are graded by CTCAE v4.0.

Causality is assessed as related or not related.

SAE Reporting & Follow-up Rules

SAEs will be reported to the sponsor, IEC, and regulatory authorities within 24 hours after identification. All adverse events are continuously followed up until complete clinical resolution or stable medical status after surgery. An emergency unblinding procedure is not required for this open-label study. The overall trial will be prematurely terminated if serious unexpected safety incidents occur in more than 10% of enrolled participants or major protocol violations affecting trial integrity happen. Subjects lost to follow-up will be contacted via inpatient/outpatient hospital contact information for supplementary data collection as far as possible.

7. Data Management and Quality Assurance

- CRFs completed by authorized personnel
- Source documents stored for at least 5 years
- Protocol deviations documented
- Data quality controlled throughout the study