PARTICIPANT INFORMATION AND INFORMED CONSENT FORM

Auditory Task-Based EEG Study

Mechanisms of General Anesthesia-Induced Altered Consciousness via Cortical-Thalamic Network Modulation and Development of a Precision Anesthesia Depth Monitoring Device

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Participant Identification Code	□□□□

Please read this form carefully before deciding whether to participate.

Dear Volunteer,

You are invited to take part in a clinical research study entitled "Mechanisms of General Anesthesia-Induced Altered Consciousness via Cortical-Thalamic Network Modulation and Development of a Precision Anesthesia Depth Monitoring Device." The study has been reviewed by the Ethics Committee of Beijing Chaoyang Hospital. Before deciding whether to participate, please read the information below carefully. It explains why the study is being conducted, what participation involves, and the potential benefits, risks, and discomforts. This process is called informed consent.

You may discuss the study with your relatives, friends, or doctor before making a decision. Participation is entirely voluntary. If anything is unclear, please ask the investigator who is explaining the study to you. If you understand the study and agree to participate, you will be asked to sign this form, and you will receive a signed copy for your records. You cannot participate in this study if you are currently taking part in another clinical research study.

1. Why is this study being conducted, and who may participate?

1.1 Study objectives

- To determine whether frontal-hub cortico-cortical and cortico-thalamic networks constitute core brain regions or circuits involved in changes in consciousness induced by general anesthetic drugs.
- To investigate the roles and mechanisms of cortico-cortical and cortico-thalamic circuits in anesthesia-induced alterations of consciousness.
- To evaluate the role and mechanisms of transcranial temporal interference stimulation (tTIS) during transitions in consciousness and to establish a clinical tTIS neuromodulation database.
- To establish a multimodal anesthesia-depth monitoring framework and develop a prototype device for precision monitoring of anesthetic depth.

1.2 Eligibility criteria

Inclusion criteria:

- American Society of Anesthesiologists (ASA) physical status I; ASA physical status II is permitted for older participants.
- Written informed consent must be provided by all healthy volunteers and surgical patients; for pediatric participants, consent must be provided by a legal guardian.

Exclusion criteria:

- A history of neurological or psychiatric disease, including epilepsy or dementia.
- Known hearing impairment or physical impairment that may interfere with study procedures or task performance.
- A history of allergy to propofol, benzodiazepines, or other anesthetic drugs used in the study.
- Long-term use of sedative or analgesic medications for more than 1 month.
- Disrupted sleep patterns during the 14 days before the study, including shift work or insomnia.
- Communication difficulties or inability to cooperate with EEG data acquisition.

2. What screening will be performed before enrollment?

If you decide to participate, the Principal Investigator or an authorized study doctor will first obtain your written informed consent and then perform laboratory tests and other screening assessments to confirm that you satisfy all inclusion criteria and none of the exclusion criteria. Study-related screening costs will be covered by the Beijing Natural Science Foundation - Capital Clinical Medical Innovation Joint Fund (Grant No. L2510005). You may enter the study only after the required screening assessments confirm your eligibility.

Screening may include the following:

- Collection of demographic information, including date of birth, sex, ethnicity, and contact information.
- Collection of past and current medical history, treatment history, medication history, vaccination history, blood-donation history, previous participation in clinical studies, and food or drug allergy history.
- Collection of personal-history information, including smoking, alcohol use, substance use, tea and coffee consumption, diet, and reproductive plans.
- Online or database screening, as applicable, together with height, weight, physical examination, vital signs, 12-lead electrocardiography, pulmonary function testing, chest radiography, and other screening assessments required by the study.

3. What will I be expected to do if I participate?

Signing this informed consent form does not guarantee enrollment. You may participate only after you have passed all screening requirements specified in the protocol. Once enrolled, you will be expected to comply with the study requirements below.

- Follow the study doctor's instructions, answer questions about your health truthfully, and cooperate with health examinations.
- Complete study procedures as instructed, including study-drug administration, physical examinations, sample collection, and requirements related to food and water intake. Do not leave the study center without permission. Follow study-center rules and investigator instructions. During screening, admission, hospitalization, and follow-up, comply with dietary restrictions and report all medications taken.
- Do not smoke or drink alcohol from the screening examination until study completion.
- Do not take any other prescription or nonprescription medication during the study unless the study doctor confirms that it is permitted.

- Inform the study doctor or study staff of any change in your health, whether favorable or unfavorable.
- Do not participate in any other drug clinical trial during this study.
- You or your spouse must use effective contraception throughout the study and for 3 months after study completion and must have no pregnancy plans during this period.
- Report all symptoms or discomfort, regardless of whether you believe they are related to the study drug.
- Tell the study doctor at any time if you wish to stop participation.

3.1 Circumstances in which the study doctor may stop your participation

The study doctor may discontinue your participation at any time if any of the following occurs:

- An adverse event or serious adverse event occurs and the investigator considers that it may affect study results or make continued participation inappropriate.
- You use other medications that the investigator believes may affect study results or make continued participation inappropriate.
- An abnormal admission or screening examination result is identified and the investigator believes it may affect the study or make continued participation inappropriate.
- Poor compliance, including failure to take study medication or undergo required examinations as instructed; smoking, alcohol consumption, or consumption of food that may affect drug absorption, distribution, metabolism, or excretion; or failure to use one or more non-drug contraceptive methods such as complete abstinence, an intrauterine device, or partner sterilization.
- Other behavior may affect safety assessments or pharmacokinetic study results and the investigator considers continued participation inappropriate.
- The investigator determines that withdrawal is in your best interest or that continuation is otherwise inappropriate.

4. How is the auditory task-based EEG study designed?

4.1 Study groups and planned enrollment

Participants are grouped according to anesthetic drug: propofol, remimazolam, esketamine, or dexmedetomidine. Each drug group includes three prespecified age subgroups: children aged 6-12 years, young adults aged 20-40 years, and older adults aged 65-80 years. Twenty participants are planned for each prespecified subgroup, with an overall target of 320 participant-visits across the clinical study components.

For pediatric participants, who are surgical patients, only resting-state high-density EEG will be collected in the operating room. Young-adult and older-adult participants are healthy volunteers monitored with 64-channel EEG. Across the clinical study, EEG data are collected under different anesthetic drugs and during different states of consciousness, including wakefulness, loss of consciousness, and recovery. The auditory task-based procedure described below is specified for the young-adult group in the source protocol.

4.2 Auditory task-based procedure for young-adult healthy volunteers

Preparation:

You will fast from food and water for 8 hours before the study. After entering the observation room, you will be connected to monitoring equipment for continuous noninvasive blood pressure, heart rate, and oxygen-saturation monitoring. EEG will be acquired in a recording environment designed to minimize electromagnetic interference.

Continuous auditory-task paradigm:

Auditory stimuli will be presented continuously throughout the experiment in a pseudorandom sequence. Stimulus categories include pure tones, white noise, Chinese characters, words, sentences, another person's name, and your own name. The stimulus onset asynchrony (SOA) will be pseudorandomized between 3 and 8 seconds.

Stage 1 - Awake baseline (10 minutes): You will rest with your eyes closed while the continuous auditory sequence begins immediately. You will be instructed: "Please close your eyes and rest. You do not need to make any response. Sounds will continue to play through the headphones; simply listen naturally. Sounds will be presented throughout the entire experiment. When I ask you through the intercom to make a fist, please squeeze your hand immediately." The source protocol states that behavioral responsiveness is checked with hand-squeeze commands and that an additional confirmation command is issued during the final minute of this baseline stage.

Stage 2 - Anesthetic induction: Auditory stimulation continues without interruption. Anesthetic administration follows the same stepwise dosing approach specified by the study protocol and is continued

until loss of consciousness (LOC). Once every minute, the investigator gives a command such as "Squeeze your right hand" or "Squeeze your left hand" and records whether the response is correct, incorrect, or absent. LOC is defined as no correct response to two consecutive commands (two consecutive minutes). The LOC time is assigned to the first nonresponsive command, provided the subsequent command confirms the loss of responsiveness. Once LOC is reached, dose escalation is stopped and the current concentration is maintained.

Stage 3 - LOC maintenance: Auditory stimulation continues without interruption. The anesthetic concentration present at LOC is maintained. The protocol specifies collection of at least 10 minutes of LOC-state EEG-fMRI data. A hand-squeeze command is given once every minute to confirm that LOC is maintained.

Stage 4 - Recovery from anesthesia: Auditory stimulation continues without interruption. Anesthetic administration is stopped, and a behavioral command is given once every minute. Recovery of consciousness (ROC) is defined as correct responses to two consecutive commands (two consecutive minutes). The ROC time is assigned to the first correct response, provided it is confirmed by the subsequent command. This stage ends when the ROC definition has been met.

Stage 5 - Post-recovery period: Auditory stimulation continues without interruption. EEG recording continues for at least 10 minutes after ROC. A command is given once every minute to confirm that responsiveness remains stable. After the 10-minute recording is complete, auditory stimulation is stopped and the experimental session ends.

4.3 Outcome measures and planned EEG analyses

Primary outcome measure:

- Task-specific analysis of auditory-evoked EEG responses across states of consciousness.

Secondary outcome measures:

- LOC and ROC times.
- Slope of the anesthetic dose-response relationship.
- Incidence of adverse reactions.

Analysis strategy:

Outcomes will be compared hierarchically across anesthetic-drug groups and age subgroups, as specified in the source protocol.

4.4 Detailed auditory-task EEG analyses

Event-related potential (ERP) analysis:

For each state of consciousness (awake baseline, LOC maintenance, and post-ROC), ERPs will be averaged separately for each stimulus category: pure tones, white noise, characters, words, sentences, another person's name, and the participant's own name. Key components include:

- N100: sensitive to sounds in general and used to reflect early auditory processing.
- Mismatch negativity (MMN): reflects pre-attentive detection of auditory change and requires comparison of standard and deviant stimuli.
- N400: sensitive to semantic incongruity and semantic processing, with particular emphasis on comparisons of words/sentences with pure tones.
- P300: sensitive to target stimuli and the participant's own name, with particular emphasis on comparison of the participant's own name with another person's name.

A key question is whether ERP components present during wakefulness, such as N400 and P300, disappear after LOC and, if they do, whether the change is abrupt or gradual. Sliding-window analysis will be used to track changes in ERP amplitude over time.

Time-frequency analysis:

Wavelet-based time-frequency analysis will be performed for each stimulus category. Event-related spectral perturbation and inter-trial phase coherence will be calculated. Particular attention will be paid to theta-band activity (4-8 Hz), which is related to semantic processing, and alpha-band activity (8-12 Hz), which is related to attention and inhibition.

Source-space ERP imaging:

ERP components will be projected to cortical source space to localize the sources of N400, P300, and other components. Key questions include whether expected N400 sources, such as the left temporal lobe and

inferior frontal gyrus, become inactive after LOC, and how expected P300 sources, such as temporoparietal and prefrontal regions, change after LOC.

Single-trial analysis and association with level of consciousness:

Single-trial linear regression will be used to estimate the evoked-potential amplitude for each trial. Single-trial amplitudes will be associated with behavioral responsiveness measured at the corresponding time point, coded from the minute-by-minute command results as 1 = responsive and 0 = unresponsive. A key question is whether the P300 response to the participant's own name declines gradually during the transition to LOC or disappears abruptly after a threshold, directly addressing continuous versus all-or-none accounts of conscious processing.

Content-gradient parametric modulation analysis:

Stimulus type will be encoded as a continuous semantic-load variable using the values specified in the source protocol: pure tone = 0, white noise = 0.5, character = 2, word = 3, sentence = 4, another person's name = 3.5, and own name = 5. A parametric modulation model will be built in EEG source space to estimate, for each region of interest (ROI), the relationship between evoked-response amplitude and semantic load. During wakefulness, ROIs positively associated with semantic load will be identified as candidate semantic-processing regions. During LOC, the analysis will assess whether semantic modulation in these ROIs disappears. The planned output is the trajectory of a semantic modulation index, defined as the regression coefficient for semantic load, across states of consciousness.

5. What are the possible risks, and how will my safety be protected?

The study team's primary goal is to protect your safety. Anesthetic drugs can cause side effects, including rare or currently unknown reactions. During the study, your vital signs and electrocardiogram will be monitored closely. If your health worsens or you experience any unexpected or unusual symptom, please contact the study team immediately, even if you do not believe the problem is related to the study procedures or study drug.

5.1 Procedure-related risks

- Intravenous puncture or infusion may cause discomfort, pain, bruising, or, rarely, fainting or infection at the puncture site.
- Metal electrodes used for 12-lead electrocardiography may cause discomfort or an allergic reaction.

5.2 Other possible risks

- Unexpected events related to participation may include currently unknown drug-related risks, traffic accidents, or other unforeseen events.
- EEG conductive paste is applied to the scalp. In rare cases, a localized allergic reaction to the conductive gel may occur, including papular skin eruptions.

5.3 Safety measures and management of study-related injury

The operating rooms at Beijing Chaoyang Hospital are equipped with emergency medical equipment and rescue medications. Experienced clinical staff will monitor you during the study and will carefully assess potential adverse events. If study-related injury occurs, Beijing Chaoyang Hospital will provide prompt and appropriate treatment, cover treatment and examination costs, and provide appropriate compensation or indemnification according to the circumstances and applicable requirements.

You may withdraw from the study at any time without affecting your future medical care. Any adverse event occurring during hospitalization or follow-up will be observed or followed until it has resolved, improved, or stabilized. If important new study findings or risks arise that may affect your decision to continue, you will be informed promptly. You may discuss this information with a doctor you trust, study staff, friends, or family members.

If you experience any adverse reaction or believe that you may be experiencing one, please inform your study doctor promptly. For further questions or emergencies, you may contact the Principal Investigator. The investigators will follow any side effects or other health problems that occur during the study.

6. What are the potential benefits, costs, and compensation?

6.1 Potential benefits

You may receive no direct medical benefit from participation. However, your study results may provide new scientific information that could help others receive safer and more effective treatment in the future.

6.2 Costs and compensation

As a volunteer, you will receive compensation for time away from work and other burdens associated with participation. If you meet the study requirements and complete all study procedures, you will receive a total of RMB 3,000, including transportation and nutrition allowances, subject to applicable tax treatment. If you are enrolled and begin the study but do not complete all procedures, compensation may be provided in proportion to the study activities completed. If you are required to withdraw because of deliberate noncompliance with study requirements, the research team may withhold part or all of the compensation in accordance with the International Ethical Guidelines for Health-related Research Involving Humans (2016).

The study plans to purchase research-related injury insurance for participants, or implement equivalent protective measures, before formal recruitment begins. The insurance provider and specific policy details have not yet been finalized. Once available, this information will be updated and submitted for Ethics Committee review or filing as required. No formal recruitment or enrollment will occur before the insurance or equivalent protection becomes effective.

7. Under what circumstances may the study be terminated?

The clinical study may be terminated if any of the following occurs:

- Participants show a clearly intolerable response after study-drug administration.
- A major error is identified in the clinical study protocol that makes drug evaluation difficult or unreliable.
- The sponsor requests termination after appropriate protection of participant rights and safety has been ensured.
- The National Medical Products Administration or the Ethics Committee orders termination for any reason.
- Other circumstances make continuation of the clinical study impossible.

8. How will my personal information be protected?

Information about your participation will be recorded in your medical record as required. Authorized persons or organizations that may review your medical record and information collected in this study include the investigators, the data and safety monitoring committee, the National Medical Products Administration, government authorities in other countries to which study data may be submitted for review, an Institutional Review Board (IRB) or Independent Ethics Committee (EC), and the study sponsor or its authorized representatives.

Your personal information and any study information that identifies you will be kept strictly confidential and will not be made public. If study results are published, your identity will remain confidential. By signing this consent form, you authorize relevant researchers and oversight bodies to review confidential study records as permitted by applicable requirements.

By signing this form, you authorize the study doctor and study-center personnel to collect and process personal information including your date of birth, sex, age, physical and psychological status, information obtained during your participation, and results of follow-up or examinations. Authorized investigators may use this information for study management, implementation, research, and statistical analysis. Study data may be shared with the study sponsor and its authorized representatives. Only authorized researchers will be able to link your study data to your identity.

Authorized personal data may be reviewed at the study site by the sponsor or its representatives, regulatory authorities, the Ethics Committee, the data and safety monitoring committee, and other competent authorities to confirm that the study is being conducted correctly and that data quality is adequate. The authorization for use of study data has no stated expiration date. You may withdraw consent at any time orally or in writing. After withdrawal, authorized investigators will stop using or sharing your study data except when continued use is necessary to preserve the validity of the study data. Information already shared with the sponsor before withdrawal may continue to be used. Withdrawal of consent for use of study data means that you cannot continue to participate in the study.

Study findings may be presented in medical journals or at scientific meetings, but your personal information will not be disclosed. To protect participant rights and ensure standardized study management, the study process may be monitored continuously. Monitoring data from key study procedures, participant disputes, or abnormal study events may be retained until project verification is complete or for 5 years after approval of the study drug or termination of the clinical study, as applicable. Such data will be available only for on-site review by authorized researchers, the sponsor or its representatives, the Ethics Committee, drug-regulatory

authorities, and other competent authorities for the purpose of confirming proper study conduct and data quality.

9. What are my rights as a participant?

The decision whether to participate is entirely yours, and participation remains voluntary throughout the study. If you decide not to participate, this will not affect any treatment or medical observation that you would otherwise receive. If you decide to participate, you will be asked to sign this written informed consent form, but you may still withdraw freely at any stage without affecting future treatment.

The study doctor may also withdraw you if continued participation is not in your best interest. Participation may need to stop if a female participant becomes pregnant, an unacceptable adverse event occurs, the study is not conducted according to the protocol, enrollment was inappropriate, or informed consent is withdrawn. The sponsor or regulatory authorities may also terminate the study without your prior agreement. If the study is stopped early, you will be informed promptly and the study doctor will advise you about the next steps in your care.

If you withdraw, the study doctor may ask you to undergo withdrawal assessments for safety, including vital signs, physical examination, and laboratory testing, and to report any discomfort or concomitant medication used during the study.

10. What are my responsibilities?

As a volunteer, you are expected to:

- Provide truthful information about your medical history, current health, and lifestyle habits.
- Tell the study doctor whether you have recently participated in, or are currently participating in, any other research study.
- Report any discomfort that you notice during this study.
- Do not take any prescription or nonprescription medication other than permitted study medication unless approved by the study doctor.
- Follow the rules of the Beijing Chaoyang Hospital clinical research unit and the requirements of the study protocol.
- Take study medication and undergo blood collection and related examinations as required by the protocol.
- When no study-related safety risk is involved, do not disclose confidential study information to others.

11. Ethics review and who to contact

- The study doctor will explain the study in detail so that you can understand the information above and will give you sufficient time to decide whether to participate.
- If new information becomes available during the study that may affect your willingness to continue, you or your legal guardian will be informed promptly. If necessary, new written informed consent will be obtained.
- This study has been approved by the Medical Ethics Committee of Beijing Chaoyang Hospital. If the protocol is violated or you believe your rights have been affected, you may submit a complaint to the hospital Ethics Committee.

Medical Ethics Office, Beijing Chaoyang Hospital

Address	8 Gongti South Road, Chaoyang District, Beijing 100020, China
Telephone	010-85231484 (weekdays 08:00-11:30 and 13:00-17:00)
Email	cyylunli2019@163.com
Fax	010-85231484

PART II. INFORMED CONSENT SIGNATURES

Participant Statement

I have carefully read the Participant Information section of this informed consent form. The study doctor has explained the study to me in detail and answered my questions. I understand the purpose and procedures of the study, as well as my rights and the possible risks. I voluntarily agree to participate and agree to cooperate with the study doctor in treatment, follow-up, and completion of the study procedures described in this consent form.

Participant name (print)	Participant signature	Date
_____	_____	_____

Legal representative / guardian name (print)	Relationship to participant	Date
_____	_____	_____

Legal representative / guardian signature
_____

If the participant is unable to sign the informed consent form because of lack of legal capacity or another applicable reason, the participant's legal representative should sign the form.

Investigator Statement

I, or a member of my research team, have fully explained the purpose and procedures of this study, the possible risks, and the potential benefits to the participant, and I have answered all questions raised by the participant to the participant's satisfaction.

Name of investigator / person obtaining consent (print)	Signature	Date
_____	_____	_____

The participant and the investigator should sign two identical copies of this informed consent form. One copy will be retained by the participant and one by the study team.

Principal Investigator Confirmation

Principal Investigator Signature	_____
Date	____ / ____ / _____