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Research Article

Subanaesthetic ketamine and altered states of consciousness in humans

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Abstract

Background: Despite its designation as a 'dissociative anaesthetic,' the dissociative and psychoactive effects of ketamine remain incompletely understood. The goal of this study was to characterise the subjective experiences and accompanying EEG changes with subanaesthetic doses of ketamine.
Methods: High-density EEG was recorded in 15 human volunteers before, during, and after subanaesthetic ketamine infusion (0.5 mg kg^{-1} over 40 min), with self-reported measures of altered states of consciousness obtained after ketamine exposure. Sensor- and source-level EEG changes were analysed with a focus on spectral power and regional changes.
Results: Ketamine-induced altered states were characterised predominantly by dissociative experiences such as disembodiment and ego transcendence; sensory disturbances were also common. Ketamine broadly decreased low-frequency power, with mean reductions largest at alpha (8–12 Hz) in parietal (−0.94 dB, $P<0.001$) and occipital (−1.8 dB, $P<0.001$) channel clusters. Significant decreases in alpha were identified in the precuneus and temporal-parietal junction.
Conclusions: Ketamine induces altered states of consciousness during periods of reduced alpha power in the precuneus and temporal-parietal junction. Modulation of these temporal-parietal loci are candidate mechanisms of the psychoactive effects of ketamine, given that this region is involved in multisensory integration, body representation, and consciousness.

Keywords: consciousness; dissociative anaesthetics; ketamine

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Editor's key points

- The dissociative and psychogenic effects of ketamine are poorly understood.
- The effects of a subanaesthetic dose of racemic ketamine to produce altered states of consciousness were assessed using a validated questionnaire in 15 healthy volunteers monitored with high-density EEG.
- Ketamine-induced altered states were characterised by dissociative experiences such as disembodiment and ego transcendence.
- Ketamine decreased low-frequency EEG power, with significant decreases in alpha identified in the precuneus and temporal-parietal junction.
- Modulation of these temporal-parietal loci are candidate mechanisms for the psychoactive effects of ketamine.

Ketamine has anaesthetic,[1,2] analgesic,[1,2] antidepressant,[3] and psychoactive[4] properties, including perceptual distortions, cognitive impairment, and feelings of disconnection from the body and environment.[5] Given the phenomenology and behavioural features associated with ketamine, it was originally called a 'dissociative anaesthetic.'[1,6] Although ketamine use has remained popular in a variety of clinical settings,[7] the dissociative nature of ketamine remains incompletely understood. Studying validated, self-reported measures of altered states of consciousness and accompanying neurophysiologic changes may provide more precise characterisation of dissociative states related to ketamine and advance understanding of the neural mechanisms of ketamine's dissociative properties.

Recent data have provided mechanistic insights into pharmacologically induced dissociative experiences and other altered states of consciousness. In particular, alpha power correlates inversely with the experience of ego-dissolution during exposure to psilocybin and lysergic acid diethylamide.[8–10] This correlation might account for changes in ego integrity as synchronised alpha rhythms have been posited to contribute to self-awareness during normal, waking consciousness.[8,10–12] Furthermore, alpha rhythms have been suggested to play a central role in conscious orientation to space and time via coordinated, oscillatory activity that subserves neural information processing.[13] Clinically, disrupted alpha rhythms have been observed in association with postoperative delirium[14] and hepatic encephalopathy.[15,16] Ketamine also suppresses alpha rhythms,[17–19] suggesting the possibility that a reduction in alpha power is a neural mechanism by which ketamine induces dissociative states.

To test this hypothesis, we conducted a study of subanaesthetic doses of ketamine in healthy volunteers with high-density EEG and validated measures of altered states of consciousness.[20] We hypothesised that ketamine-induced dissociative states, characterised by validated altered states of consciousness scales, occur concurrently with reduced EEG alpha power. Although we previously examined dose-dependent effects of ketamine during subanaesthetic, anaesthetic, and recovery states,[17] we did not report altered states of consciousness data or source-level neuroanatomical findings, as the purpose of our prior work was to investigate anaesthetic-specific effects.

Methods

This study was approved by the University of Michigan Medical School Institutional Review Board (HUM00061087), and written informed consent was obtained from all participants. Study procedures were conducted at the University of Michigan Medical School. Healthy volunteers (seven males, eight females, age 20–35 yr) were recruited using flyers posted throughout the medical school and main hospital. We published a distinct EEG analysis for 10 of these participants that examined dose-dependent effects of ketamine on oscillatory and connectivity patterns, with particular focus on anaesthetic dosing.[17] This previous publication included neither EEG source analysis nor self-reported altered states of consciousness scales, which were reserved for the current manuscript.

Study population

Participants were eligible if they were ASA physical status 1, aged 20–40 yr, with BMI <30 kg m^{-2} and had no predictors of a difficult airway. Exclusion criteria included cardiovascular disease, cardiac abnormalities, hypertension, obstructive sleep apnoea, asthma, respiratory illness, gastro-oesophageal reflux, history of drug use (or positive drug screen before experiment), family history of problems with anaesthesia, neurologic disorders, psychiatric disorders, or current pregnancy.

Sample size justification

This was an exploratory study investigating neurophysiologic changes accompanying ketamine-induced self-reported altered states. The sample size of 15 subjects is similar to or larger than related studies investigating neurophysiologic and neuroanatomical associations with ketamine.[21,22]

Experimental protocol

Participants fasted from food and drink for 8 h before the experiment. A complete medical history and physical examination were conducted at the start of the study protocol. A minimum of two anaesthesiologists and two researchers were present throughout each experiment. Standard monitors were applied and i.v. catheters inserted before EEG recording. Procedures occurred in a well-lit operating room with participants lying supine. The first period (baseline) was 5 min of rest with eyes open and 5 min of rest with eyes closed. The second period was 40 min with eyes closed during continuous infusion of subanaesthetic (0.5 mg kg^{-1} total) racemic ketamine (Ketamine Hydrochloride, Hospira, Inc., Lake Forest, IL USA), followed by a brief physical examination and ondansetron (8 mg i.v.) for nausea prophylaxis. We chose this dosing regimen because of its common use in psychiatry. This was followed by 5 min of rest with eyes open and 8–10 min for completion of the altered states of consciousness questionnaire (Fig. 1). Within 48 h of the study period, participants completed online questionnaires assessing altered states of consciousness experiences.

Altered states of consciousness psychometrics

A 71-item altered states of consciousness questionnaire was used with 62 questions indexing 11 altered states of consciousness subscales[20] including the following: experiences of unity, spiritual experience, blissful state, insightfulness,