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Research article

Suppressed neural complexity during ketamine- and propofol-induced unconsciousness

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HIGHLIGHTS

- A reduction of complexity may be a common feature of unconscious state.
- Complexity-randomness analysis was performed on the electroencephalogram.
- Ketamine (propofol) increased (decreased) the randomness of neural dynamics.
- Complexity decreased in both ketamine- and propofol-induced unconsciousness.

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ABSTRACT

Ketamine and propofol have distinctively different molecular mechanisms of action and neurophysiological features, although both induce loss of consciousness. Therefore, identifying a common feature of ketamine- and propofol-induced unconsciousness would provide insight into the underlying mechanism of losing consciousness. In this study we search for a common feature by applying the concept of type-II complexity, and argue that neural complexity is essential for a brain to maintain consciousness. To test this hypothesis, we show that complexity is suppressed during loss of consciousness induced by ketamine or propofol. We analyzed the randomness (type-I complexity) and complexity (type-II complexity) of electroencephalogram (EEG) signals before and after bolus injection of ketamine or propofol. For the analysis, we use Mean Information Gain (MIG) and Fluctuation Complexity (FC), which are information-theory-based measures that quantify disorder and complexity of dynamics respectively. Both ketamine and propofol reduced the complexity of the EEG signal, but ketamine increased the randomness of the signal and propofol decreased it. The finding supports our claim and suggests EEG complexity as a candidate for a consciousness indicator.

1. Introduction

Identifying a universal feature of brain dynamics during anesthetic-induced unconsciousness is important because it both advances the understanding of the mechanisms of anesthetic-induced unconsciousness and facilitates the development of reliable depth-of-anesthesia (DOA) monitors. However, this task is also challenging because different anesthetic agents have varied mechanism of actions which cause distinct neurophysiological characteristics (Table 1).

One way to evaluate the state of consciousness on EEG is a complexity analysis that uses measures of entropy or complexity to assess the unpredictability or randomness of the signal [1]. Hypnotic agents like propofol or isoflurane that promote γ-aminobutyric acid-ergic (GABAergic) inhibitory neurotransmission, cause the EEG signal to slow down, oscillate synchronously, and decrease in power in the high-frequency band [2–5]; i.e., the entropy, or randomness of the signal decreases. Various entropy/complexity measures [6], such as approximate entropy [7],

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Table 1
Effects of Propofol and Ketamine.

Characteristic	Anesthetic	
	Propofol	Ketamine
Mechanism of action	Agonist on $GABA_A$ receptor	Antagonist on NMDA receptor
EEG feature(Neurophysiological feature)	Increased coherence Increased rhythmic α oscillation (anteriorization) Suppressed γ power	Decreased coherence Decreased α power Increased γ activity
Physiological/Behavioral feature	Depressant effect Hypotension, Bradycardia, Cardiac arrest, Apnea, Sedation, Atonia, Seizure-like phenomena	Antidepressant effect Hypertension Hallucination, Dissociative state, Analgesia

Lempel–Ziv complexity [8,9], and permutation entropy [10], have been used for analysis.

Most complexity measures in previous consciousness studies are categorized as type-I. The limitation of type-I complexity is that it regards a random signal as the most complex, though it is simple in the context of dynamical system [11]. Meanwhile, ketamine acts as a N-methyl-D-aspartate (NMDA) antagonist on inhibitory interneurons, promoting aberrant excitatory activity and high frequency power in EEG [12]. Therefore, type-I based complexity measures are not applicable to ketamine anesthesia. In this study, we intuitively consider a system complex when it is neither regular nor random, but at an intermediate state between these two extremes governed by deterministic rules to preserve diverse repertoire (Fig. 1**A**) [13]. To estimate this type of complexity, we apply a type-II complexity measure to the EEG signal.

We hypothesize that the complexity of neural dynamics is essential to maintain consciousness, and that anesthetics, regardless of their molecular action, induce loss of consciousness by disrupting complexity. On the other hand, an unconscious brain during anesthesia should tend towards the extremes, either over-regularized or randomized dynamics with reduced complexity. Our hypothesis emerged from observing that NMDA antagonist ketamine causes diverse patterns in an EEG, whereas GABAergic propofol induces a regularized EEG (Table 1). These opposite changes in the regularization of the EEG signal would also correspond with opposite changes in type-I measures. In effect, the randomness value that indicates type-I complexity decreases during anesthesia induced by propofol [6], but increases when ketamine is administered [14].

We expected that these two opposite changes caused by ketamine and propofol can be interpreted as one common change, a reduction of type-II complexity. In this study, we performed complexity analysis on EEG data in humans during consciousness and unconsciousness induced by ketamine or propofol. Here type-II complexity is denoted as complexity, whereas type-I complexity indicates randomness or unpredictability. Mean Information Gain (MIG) [15] and Fluctuation Complexity (FC) [16], which are respectively a type-I and type-II complexity measure based on information theory, were used to track the degree of randomness and complexity of the EEG time series. We observed that the complexity of the signal is reduced during loss of consciousness induced by ketamine and by propofol; this finding supports our hypothesis.

2. Materials and methods

For both ketamine and propofol experiments, the Institutional review board of Asan Medical Center (Seoul, Korea) approved the study and written informed consent was also acquired.

2.1. Ketamine experiments

Thirty patients scheduled for elective stomach, colorectal, thyroid, or breast surgery were studied (15 male, 15 female, American Society Anesthesiologists Physical Status I or II, aged: 22–64 years). One dataset was lost after recording and three data sets were excluded from the analysis due to severe noise contamination; thus, total 26 subjects were analyzed in this study. Data were obtained using an 8-channel EEG (10–20 system for electrode position Fp1, Fp2, F3, F4, T3, T4, P3, and P4) and have been analyzed twice for previous studies [17,18].

Ketamine (2 mg/kg diluted in 10 ml of 0.9% normal saline) was injected for 20 s (Baxter infusion pump AS40A; Baxter Healthcare Corporation, Deerfield, IL); no premedication was applied before the general anesthesia. Electrocardiography (ECG), pulse oximetry, end-tidal carbon dioxide concentration, and noninvasive blood pressure were also monitored. Systolic blood pressure was assessed every 30 s; when it increased 30% over baseline blood pressure, 5–10 mg Labetalol was administered. LOC time was determined by the loss of response to verbal command, "squeeze your right hand twice", which was repeated every 10 s. EEG signals were recorded until 5 min after LOC. At the end of the study, an effect-site target concentration (2.5 μg/ml) of propofol combined with an effect-site target concentration (5 ng/ml) of remifentanil were administered.

2.2. Propofol experiments

We studied 10 healthy male subjects aged 20–28 years old with identical protocols. They participated on two separate days one week apart. Data were recorded for about 20–30 min using a 21-channel EEG (10–20 system, Fp1, Fp2, F3, F4, F5, F6, F7, F8, Fz, C3, C4, Cz, T7, T8, P3, P4, P5, P6, P7, P8, Pz). Propofol (2 mg/kg) was injected for 11.4–36 s, about 4 min after recording started. LOC and Recovery of consciousness (ROC) were determined by the loss and recovery of responsiveness to verbal command. To be consistent with ketamine experiments which have no recorded recovery states, only wakeful and anesthetized states were investigated. These data have been analyzed twice with different hypotheses and analyses [19,20].

2.3. Data acquisition and preprocessing

Data were obtained at 256 Hz referenced to the A2 channel by using a WEEG-32 (LXE3232-RF; Laxtha Inc., Daejeon, Korea). To exclude ocular artifacts and electromyography contamination, a band-pass filter that admits 0.1–45 Hz was written using "filtfilt.m" in Matlab Signal Processing Toolbox (MathWorks, Natick, MA). Epochs containing spectral power (>60 Hz) > 0.3 μV^2 were also excluded in the analysis. In all calculations, window size was 10 s and overlap size was 5 s. The window size of 10 s was assumed to be short enough to obtain a stationary signal for analysis. We representatively analyzed Fp2 channel data.