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Brain Connectivity Analysis in Anesthetized and Awake States: an ECoG Study in Monkeys

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Abstract— **Increasingly, studies have shown that changes in brain network topology accompany loss of consciousness such that the functional connectivity of the prefrontal-parietal network differs significantly in anesthetized and awake states. In this work, anesthetized and awake segments of electrocorticography were selected from two monkeys. Using phase lag index, functional connectivity matrices were built in multiple frequency bands. Quantifying topological changes in brain network through graph-theoretic properties revealed significant differences between the awake and anesthetized states. Compared to the awake state, there were distinct increases in overall and Delta prefrontal–frontal connectivity, and decreases in Alpha, Beta1 and Beta2 prefrontal–frontal connectivity during the anesthetized state, which indicate a change in the topology of the small-world network. Using functional connectivity features we achieved a satisfactory classification accuracy (93.68%). Our study demonstrates that functional connectivity features are of sufficient power to distinguish awake versus anesthetized state.**

Clinical Relevance— **This explores the brain network topology in awake and anesthetized states, and provides new ideas for clinical depth of anesthesia monitoring.**

I. Introduction

Scholars have explored the differences between the conscious and unconscious states of the brain before and after anesthesia induction. It has been proved that frequency-specific large-scale communication mode switching throughout the cortex accompanies change from conscious to unconscious state [1]. Previous studies also showed that the frontal-parietal interactions are of significance when experiencing conscious states [2]. During anesthesia, anesthetists need to monitor the patient's level of consciousness in real time. The EEG bispectral index (BIS), SedLine, auditory evoked potentials (AEP) index and anesthesia entropy are some of the most commonly used clinical techniques for monitoring the depth of anesthesia. However, the current anesthesia depth monitoring technologies still have some clinical shortcomings. For example, BIS is no more effective than monitoring a pharmacologic endpoint of end tidal volatile anesthetic concentration [3]. Some of these limitations may result from their need to be noninvasive, as EEG-based anesthesia depth monitoring technologies have relatively poor spatial resolution compared to ECoG [4].

Recently, functional connectivity has also been applied anesthesia, to analyze changes associated with loss of consciousness [5]. Previous studies also proved the potential of combining neurophysiological principles with brain network connectivity in the study of anesthesia [6].

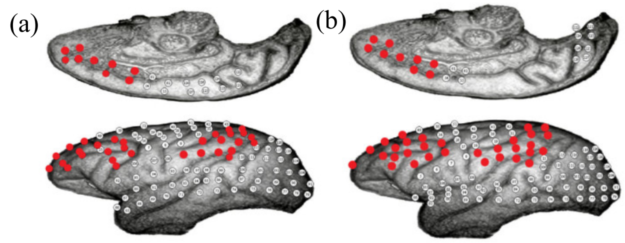

Figure 1. 40 channels covering the prefrontal-parietal were selected for analysis. The red dots represent the channels we selected. (a) shows Monkey Chibi's electrode distribution. (b) shows Monkey George's electrode distribution.

Loss of consciousness caused by anesthetics is as much due to the disruption of higher-order cortical information integration as to the interruption of cortical information transmission [7]. Losing consciousness is influenced by changes in brain network topology [8]. These studies have confirmed the feasibility of functional connectivity to be applied in the study of anesthesia awareness. However, probing the effects of anesthetics on the prefrontal-parietal functional connectivity network using high resolution ECoG signals has only just begun. In addition, few studies have applied functional connectivity to the classification of anesthetized and awake states, and no research has applied functional connectivity to monitoring the depth of anesthesia.

Based on the above research, this study uses data from two monkeys from the anesthesia experiments in the public repository Neurotycho (http://neurotycho.org/) to build a functional connectivity matrix based on ECoG signals in multiple frequency bands, and utilizes graph theory to analyze changes in prefrontal-parietal functional connectivity in the anesthetized and awake states, to explore the mechanism of anesthesia and to classify the two states.

II. Method And Material

A. Subjects and Data Acquisition

With the approval of the RIKEN Ethics Committee and the recommendations of the Weatherall report, "The use of non-human primates in research", the ECoG data of monkeys were collected according to the experimental protocols (No. H24-2-203(4)), at the Laboratory for Adaptive Intelligence, Brain

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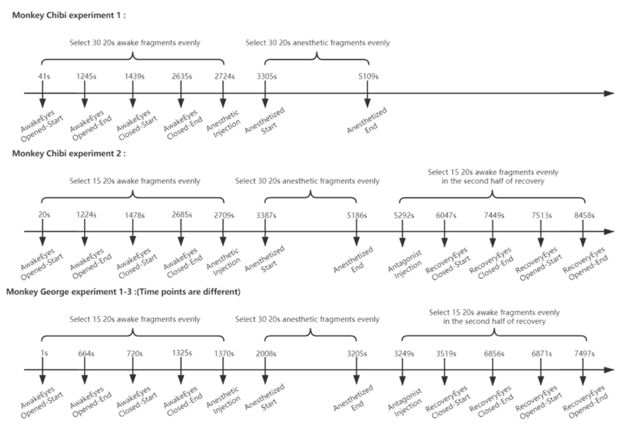

Figure 2. Timeline graph of relevant events, which shows significant events in five anesthetic experiments on two monkeys and the selection of anesthetized and awake segments.

Science Institute, RIKEN. 128 electrodes were placed on the monkey's cerebral cortex, covering the prefrontal, parietal, visual, and other cortices of the brain. More details can be found in the previous research [1].

B. Data Preprocessing

The sampling rate of the ECoG signals is 1 kHZ. Before the functional connectivity analysis, common rereference, line noise filter and detrending were applied on the ECoG signals. The 50Hz electrical line noise was removed by a noncausal filter, and a 4th order bandpass Butterworth filter of 0.5-100HZ was used. Then ECoG signals were down-sampled to 200 Hz. The above processing was done in MATLAB2016b.

40 channels covering the prefrontal-parietal cortices were selected for research, as shown in the Figure.1.Then the data of these 40 channels are decomposed into 5 frequency bands by wavelet packet decomposition, Delta (1-4HZ), Theta (4-7HZ), Alpha (8-12HZ), Beta1 (13 -19HZ), Beta2 (20-30HZ). Here, a 6-layer decomposition tree is built to obtain a 1HZ range of node spans, and then the nodes are reconstructed and the processed signals are superimposed.

In the graph theory analysis experiment, we evenly selected 30 time slots with 20s of anesthetized data and 20s of awake data in each experiment (Figure.2 and TABLE I).

In the classification experiment, all the anesthetized and awake data of two monkeys were intercepted for classification, the fragment time was 20s (TABLE II).

C. Functional Connectivity Network Construction

PLI was used to calculate the functional connectivity between channels. Considering the signal sequences of two channels are $s_1(t)$ and $s_2(t)$, Hilbert transform for the instantaneous phase $z_i(t)$ can be computed as [9]:

$$z_i(t) = s_i(t) + jHT(s_i(t)) \tag{1}$$

$HT(s_i(t))$ means the Hilbert transform of $s_i(t)$, computed by:

$$HT(s_i(t)) = \frac{1}{\pi} P.V. \int_{-\infty}^{\infty} \frac{s_i(t)}{t-\tau} d\tau \tag{2}$$

In the above equation, P.V. is the Cauchy principal value. After we calculate the phase of each channel signal, the relative phase locking between two channels can be calculated as:

$$\Delta\varphi(t) = \arg\left(\frac{z_1(t) z_2^*(t)}{|z_1(t)||z_2(t)|}\right) \tag{3}$$

The range of PLI is between 0 and 1, 0 means no phase locking and 1 means perfect phase locking. The PLI value is calculated as:

$$PLI = \left|\left\langle \sin\varphi(t) \right\rangle\right| \tag{4}$$

D. Graph Theoretical Analysis

By using PLI, the adjacency matrices (N = 40 in this work) were computed to build prefrontal-parietal functional connectivity networks.

The established network contains some redundant information, so the adjacency matrices need to be converted into binary matrices. It was found that the PLI values of all frequency bands are mostly distributed in the range of 0-0.3, but the PLI values of some frequency bands are mainly distributed in the range of 0-0.1. In order to avoid the situation of all 0 or all 1 in the binary matrix, we determine the range from 0 to 0.1, with 0.005 as the step size, find 20 binary matrices, and finally take the average.

In this study, the Brain Connectivity Toolbox was used to quantitatively calculate the topological characteristics of the brain network [10]. Some representative network parameters based on the binary matrices were calculated: node strength, clustering coefficient, local efficiency, characteristic path length and global efficiency.

E. Statistical Analysis

After calculating the network graph feature parameters, Wilcoxon signed-rank test was used to measure significant differences in different states.

TABLE I. DATA FOR COMPLEX NETWORK ANALYSIS

	Anesthetized	**Awake**
Chibi	60*20s	60*20s
George	90*20s	90*20s

a. Anesthetized fragments and awake fragments of two monkeys were selected to analyze complex network parameters.

TABLE II. DATA FOR SVM CLASSIFICATION

	Anesthetized	**Awake**
Chibi	179*20s	350*20s
George	182*20s	523*20s

b. For SVM classification, all experimental data of two monkeys were selected and divided into multiple 20-second fragments.

III. RESULTS

A. Functional Connectivity Networks

In Figure 3, the dynamic curves of the all data and Delta band data show stronger functional connectivity in Anesthetized states, with a step increase after anesthetic injection. Meanwhile, the curves of Alpha, Beta1 and Beta2 bands show the opposite trend.

The network topology of the two monkeys in different states was analyzed and the specific data is shown Figure 4. The characteristic path length in delta decreases from the awake to the anaesthetized state, while other network properties increase. In Theta, Alpha, Beta1, and Beta2, the characteristic path length increases, and other network properties decrease, which is contrary to Delta.

B. Classification

The classification accuracy is shown in Table III. We use the mean value of the PLI matrix as feature, to distinguish two states, using SVM (linear kernel) for classification, and implement the 5-fold cross validation, and the classification accuracy rate is 93.68%. At the same time, this feature is also used for classification in Delta, Theta, Alpha, Beta1 and Beta2, and a classification accuracy rate of 74.96% is also obtained in the Delta domain. Other frequency bands are inferior.

IV. DISCUSSION

Generally, the reduction of functional connectivity will be accompanied by decreasing node strength, clustering coefficient, local efficiency, global efficiency, and increasing characteristic path length. Local efficiency can be used as an indicator of local information transmission efficiency, global efficiency measures global information exchange efficiency, local efficiency and clustering coefficient characterize graphs locally, while characteristic path length and global efficiency characterize graphs globally [10]. Usually a larger clustering coefficient corresponds to a smaller characteristic path length.

A. Topological Alterations of Functional Connectivity Networks

Many studies based on EEG signals or fMRI in humans have shown that from the awake to anesthetized state, the brain's functional connectivity is reduced [7], with greater representation in the prefrontal-parietal region. While some studies have also found enhanced functional connectivity in humans [11]. In this study, the overall functional connectivity showed an increasing trend in anesthetized state. This corroborates results in a few previous studies based on EEG signals or fMRI in humans. However, it has been demonstrated, by using phase-amplitude coupling to build functional connectivity, that propofol-induced anesthesia enhances frontal and parietal interactions in monkeys [5].

In Delta, the functional connectivity in anesthetized state is stronger than that in the awake state, and the characteristic path length is decreased with the other four properties all increased. Delta band power is weak in conscious states, and will increase in unconscious states [12]. In Theta, differences in functional connectivity between the two states also were observed. Specific mental tasks and working memory can induce significant Theta band oscillatory activity [13]. The reduced functional connectivity of this band suggests there might be some impairing of cognitive processes. A significant reduction in functional connectivity can be observed in Alpha. Alpha oscillation is related to body sensorimotor processing [14]. In Beta1 and Beta2, the functional connectivity of monkeys during sedation was reduced. Beta oscillations are often related to cognitive activities such as stimulus evaluation and decision making, so they can be regulated by related cognitive tasks [15].

As with studies of ECoG in monkeys [5] and studies in humans [11], we found increased functional connectivity in anesthetized state, which is inconsistent with theories that posit unconsciousness is due to disruption of functional connectivity.

B. Awake and Anesthetized States Classification

Few experiments have been conducted to classify conscious and unconscious states based on functional connectivity. In [16], after establishing functional network， the authors used GCN to achieve motor imagery quadruple classification and the classification efficiency could reach 88.397%. GCN performs well in the classification of networks. Inspired by this, better results may be obtained if more appropriate classification methods are used.

C. Experimental Limitation

The main limitation of this work is the small number of subjects. Also, we only used one feature, the mean PLI, for classification. Future research can turn to looking for fusion features or more detailed features.

V. CONCLUSION

In this study, the network structure of the prefrontal-parietal of two monkeys in the anesthetized and awake states was explored. The data were divided into five frequency bands for research. Topological changes in functional connectivity were measured quantitatively through graph-theoretic properties, and valid features were selected for state classification. In Delta, the functional connectivity in the awake state is weaker than that in anesthetized state, while in Alpha, Beta1, and Beta2, the functional connectivity is stronger. The increasing functional connectivity and its reduction show significant overall integration and local isolation. This study has demonstrated that the prefrontal-parietal network in different states has significantly different topologies and anesthetics induce changes in brain networks. Our research may facilitate a new approach to distinguishing consciousness from unconsciousness.

ACKNOWLEDGMENT

Thanks to my teachers for their patience and help during my research.

TABLE III. CLASSIFICATION ACCURACY IN DIFFERENT FREQUENCY BANDS

	All	Delta	Theta	Alpha	Beta1	Beta2
Acc (%)	93.68	74.96	70.75	70.75	70.75	70.75
AUC	0.9977	0.9321	0.6857	0.8406	0.9388	0.7274

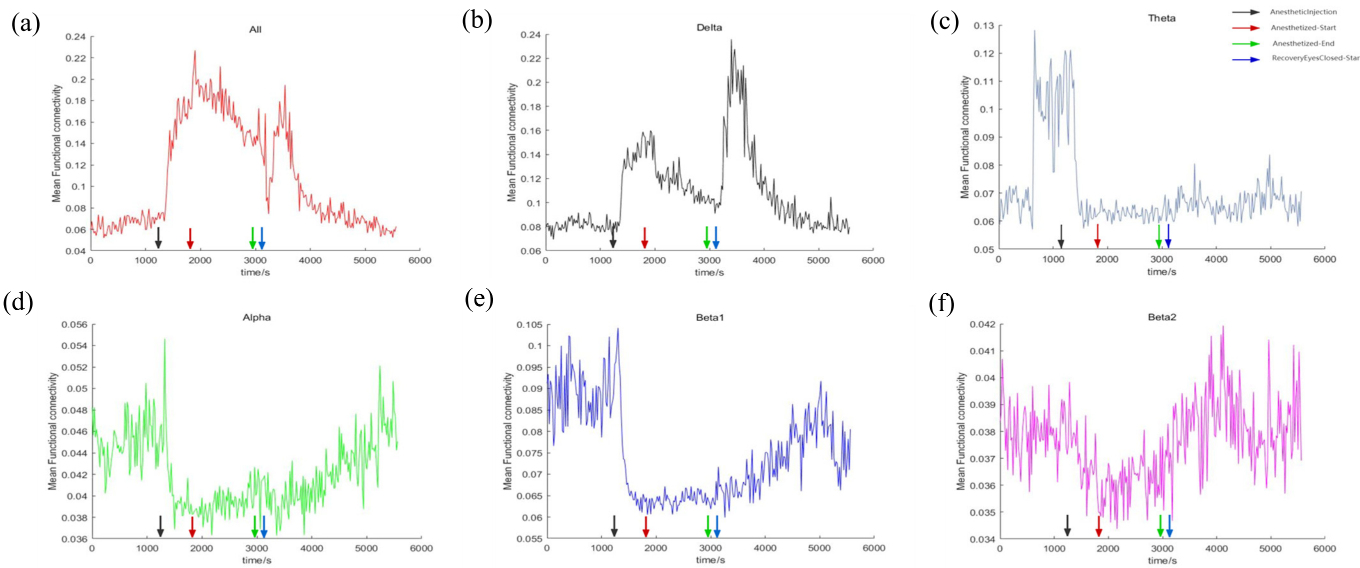

Figure 3. Dynamic curves of mean functional connectivity in all data, Delta, Theta, Alpha,Beta1,and Beta2. (a) All; (b) Delta; (c) Theta; (d) Alpha; (e) Beta1; (f) Beta2. Mean functional connectivity is the average of the PLI matrix. All dynamic curves were averaged from 5 experiments of two monkeys. Special moments have been marked with arrows in the diagram. (1) AnestheticInjection: the moment of ketamine-medetomidine cocktail injection. (2)Anesthetized-Start/End: start/end of anesthetized condition. (3)RecoveryEyesClosed-Start: the point when the slow wave oscillation in the neural signal disappeared.

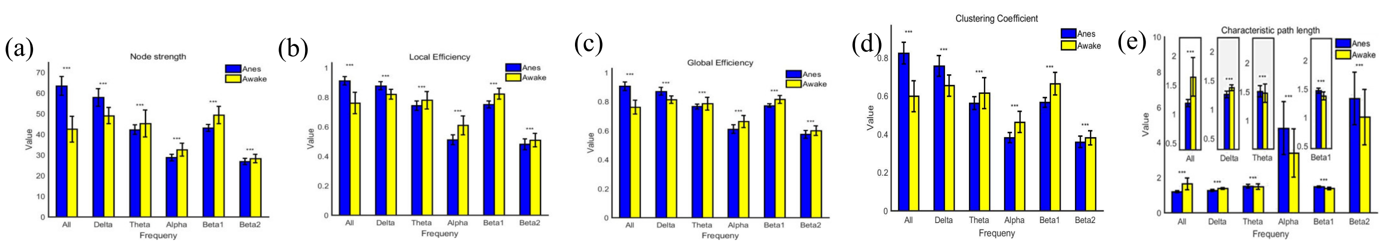

Figure 4. Graph theoretical properties in anesthetized states and awake states in all data and different frequency bands. *** means significant difference(p<0.05) and the error bars indicate standard error (a) Node strength, (b) Local efficiency, (c) Global efficiency, (d) Clustering coefficient, (e) Characteristic path length.

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