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Graph approaches for analysis of brain connectivity during dexmedetomidine sedation

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ABSTRACT

Sedation is commonly used to relieve fear and anxiety during procedures. Dexmedetomidine (DEX), approved by the US Food and Drug Administration in 1999 for short-term sedation, is a selective alpha2-adrenoreceptor agonist. The use of DEX is increasing due to minimal respiratory depression and easy and quick awakening from sedation. Its sedative mechanisms are suggested to be related to changes in the interaction between brain regions. In this study, we used graph theory to investigate whether the altered network connection is associated with sedation. Electroencephalogram (EEG) recordings of 32 channels were acquired during awake and DEX-induced sedation for 20 participants. We extracted EEG epochs from the awake and the DEX sedation state. Using the graph theory, we compared the changes in the network connection parameters with the awake state. We observed that the slopes in 1/f dynamics, which indicate overall brain network characteristics, were greater during DEX-induced sedation compared to the awake state, suggesting a transition towards a random network behavior. In addition, network connections from the perspective of information processing were significantly disturbed in the alpha frequency band, unlike other frequency bands augmenting network connections. The alpha frequency band plays a prominent role in the function and interaction of cognitive activities. These results collectively indicate that changes in the brain network critical to cognition during DEX administration may also be related to the mechanism of sedation.

1. Introduction

Dexmedetomidine (DEX), initially approved for sedation in the intensive care unit, has been widely adopted as a sedative in various clinical settings. The use of DEX has increased for dental sedation due to its minimal effect on respiration [1]. DEX is an alpha-2 adrenergic receptor agonists, which differs from most other sedatives that mainly act on the Gamma-Aminobutyric Acid (GABA) receptor. However, DEX sedative mechanism remains poorly understood unlike other sedatives.

The brain consists of a densely interconnected network of neurons. Consequently, the brain can be modeled as a complex network using a graph-theoretical approach. Graph theory utilizes a mathematical model that analyzes the neuronal network on a graph with a set of vertices connected by lines [2]. Given the tremendous interconnection among neurons in the brain, this approach enables an understanding of how the brain works by analyzing the patterns of interactions between nodes and edges [3]. The same analysis can also be applied to objectively evaluate information transfer efficiency within the brain.

Alterations in neuronal network patterns are observed for various neurological disorders such as schizophrenia [4,5], epilepsy [6], and stroke [7]. Since anesthesia affects brain function, it is not surprising that general anesthesia alters the topology of the brain network [8,9], Interestingly, altered network parameters are observed under sedation, not general anesthesia. Network alterations have been observed during

Abbreviations: DEX, Dexmedetomidine; GABA, Gamma-Aminobutyric Acid; EEG, Electroencephalogram; LOC, Loss of consciousness; BCT, Brain connectivity toolbox; fMRI, Functional magnetic resonance imaging; NREM, Non-rapid eye movement.

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sedation with propofol [10] and midazolam [11]. We have previously shown that the efficiency within the brain was significantly impaired under nitrous oxide sedation with a graph approach [12].

As shown by local and global studies, DEX impairs information efficiency within the brain [13]. A previous study have utilized graph theory to evaluate changes in information efficiency during DEX administration [13]. In this study, functional magnetic resonance imaging data with high spatial resolution were used. However, these neuroimaging techniques have limitations in capturing time changing conditions. In contrast, electroencephalography (EEG) has high temporal resolution, which is more suitable for clinical scenarios in which event occurrence is uncertain [14]. Also, analysis of multi-channel EEG data allows the identification of frequency-specific changes in network properties [12]. Hence, EEG enables study of DEX sedative mechanisms because frequency-specific implications are associated with various types of cognitive function [15]. However, the mechanisms of DEX focusing on frequency-specific network properties remains poorly understood. To address this knowledge gap, we studied to study how DEX affects network topology at specific frequency bands using a graph approach.

2. Materials and methods

2.1. Participant recruitment and DEX infusion scheme

The participant enrollment process and DEX infusion schemes were described in a previous study [16]. In brief, 20 healthy volunteers aged between 20 and 40 years old (Male:11, Female:9) were enrolled in this study after providing written informed consent after the approval of the Institutional Review Board. Those with any medical and laboratory abnormalities were excluded from the study. They fasted for at least 8 h before DEX infusion. All subjects were asked to close their eyes. A baseline EEG was acquired for 5 min. Then, a 0.5 μg/kg DEX bolus was administered over 10 min, followed by infusion at a rate of 0.5 μg/kg/hour until a loss of consciousness (LOC). We defined a loss of consciousness as the loss of any response to a verbal command to grasp the hand every 30 s. After the subjects lost consciousness, DEX infusion was stopped and time provided until they regained consciousness, defined as a positive response to a verbal command to grasp the hand or spontaneously eye opening. During the study, we also monitored the bispectral index (BIS) to evaluate sedation depth objectively. An EEG was recorded continuously until the subjects regained consciousness.

2.2. EEG signal collection

The EEG data were sampled with 32 channel EEG device (ActiveTwo, BioSemi, Amsterdam, the Netherlands) (Fp1, AF3, F7, F3, FC1, FC5, T7, C3, CP1, CP5, P7, P3, Pz, PO3, O1, Oz, O2, PO4, P4, P8, CP6, CP2, C4, T8, FC6, FC2, F4, F8, AF4, Fp2, Fz, Cz) in the standard 10/20 international placement [17]. In Biosemi software, a 2048-Hz sampling rate was used and a 417-Hz lowpass filter applied to the data. All data were analyzed offline. To analyze the changes in network properties during DEX sedation, the 3 min of EEG was selected 10 s before the loss of consciousness. The stored signal data were downsampled to 128 Hz, and a 60-Hz notch filter was applied. The data were manually reviewed to exclude signals corrupted by artifacts. The reference was obtained using a re-referenced method by averaging all EEG channels. Average Fourier cross-spectral matrices were obtained with the frequency bands of delta (1–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–44 Hz).

2.3. Data analysis

The following data analysis (1/f statistical behavior analysis, Lagged phase coherence, and Brain connectivity toolbox (BCT) analysis) has been described in our previous study [12]. The detailed description of the analysis is described as follows.

2.4. 1/f statistical behavior calculation

The power spectrum (PS) of EEG tends to have an inverse relationship between the amplitude of power and frequency. This inverse relationship can be expressed as: $PS(f) = \psi * f^{-\alpha}$ [18] α represents the rate at which the power spectrum decreases and ψ is the real component of the model coefficient as follows: $\log(PS(f)) = -\alpha * \log(f) + \log(\psi)$. α can be obtained with linear regression analysis between log(PS) and frequency f as follows: $\log(PS(f)) = -\alpha * \log(f) + \beta$ ($\beta = \log(\psi)$). α was calculated for each artifact-free 3 min epoch for frequencies between 1 and 44 Hz. The mean α in all epochs of all individuals was calculated for the awake and the dexmedetomidine-induced sedation states. All slopes for the two groups in each of the 32 sensor regions (Fig. 1) was calculated with linear regression analysis using the 'polyfit' function in MATLAB and compared using Wilcoxon Signed Rank Test.

2.5. Lagged phase coherence acquisition

Lagged phase coherence between two signals can be inferred from the amount of crosstalk between the signals of two source regions [19]. The lag of the sine waves can be decomposed by discrete Fourier transform and could be interpreted as a phase shift between two signals. The significance threshold for a lagged phase coherence value by the asymptotic results can be found as described by Pascual-Marqui et al. [20]. The lagged phase coherence was obtained between the 32 sensor pairs. Further analysis of the 32 × 32 functional connectivity matrix (excluding identical pairs) was performed for each frequency band in both groups. The functional connectivity values were compared to the Euclidean distance between sensors using Pearson's correlation. The Euclidean distance was calculated by the XYZ coordinates acquired by the sLORETA program (https://www.uzh.ch/keyinst/loreta.htm) [21]. The Pearson correlation values between the awake and the sedated conditions were compared using the z-score via the Fisher transform [22].

2.6. Brain connectivity toolbox (BCT) analysis

Node strength, functional distance, characteristic path length, clustering coefficient, local efficiency, and cross-frequency correlations were acquired with the BCT (Version 2017-15-01) [23]. The input data were the awake and sedation functional connectivity matrices.

Node strength is the sum of the weights for all connections between the target node and the rest of the network. A network's *average node strength* is the arithmetic mean of the individual node strengths. *Functional distance* is defined as the length of the shortest path between a pair of nodes in the network. The *function distance matrix* was calculated from the connection length matrix using Dijkstra's algorithm [24]. The *characteristic path length* is the arithmetic mean of the network's shortest path length. It is calculated as the mean of the functional distance matrix. The *clustering coefficient* indicates the strength of a node's local connectivity with neighboring nodes. The clustering coefficient was considered by estimating the number of triangles around a node. The *local efficiency* is a parameter that summarizes the efficiency of information transfer between the neighbors of a particular node. The local efficiency is the average inverse shortest path length in the subnetwork constituted by the node adjacencies.

2.7. Statistical analysis

Paired t-tests were performed for each network connectivity measure in this study to analyze the differences between awake and sedation state with 95 % confidence intervals (CI) in different frequency bands. In slope comparison between the two states, Wilcoxon Rank Sum test was

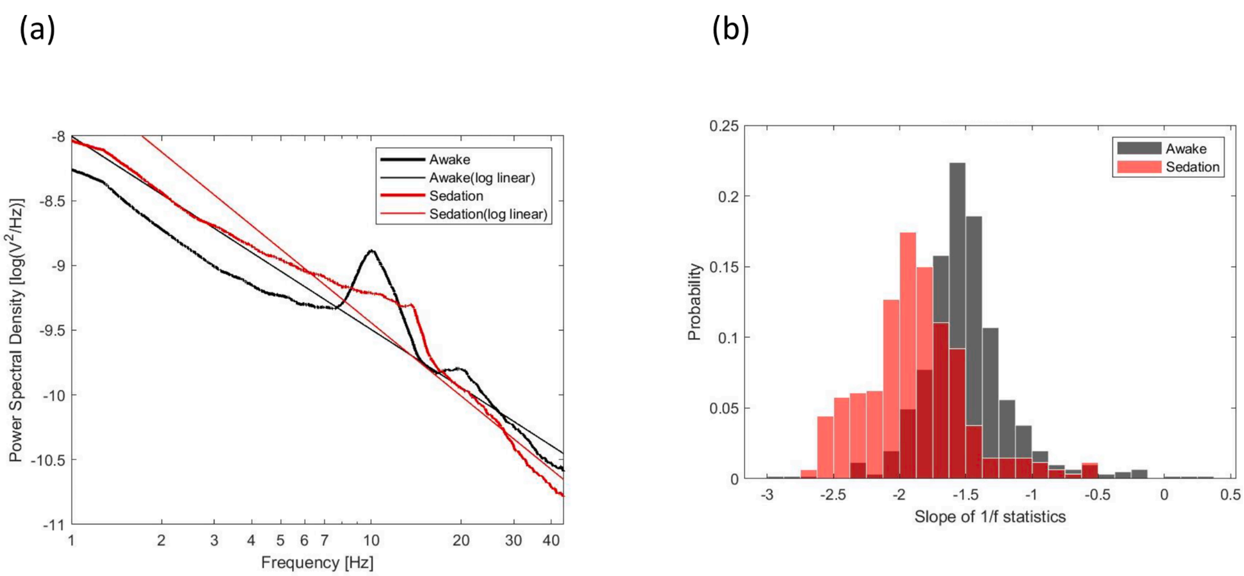

Fig. 1. (a) Representative log(1/f) dynamics for the awake (red) and sedation states (black). (b) The slope histogram of all the log(1/f) dynamics in baseline (red) and awake status (blue). The slopes of sedation states (black) were steeper than those of the awake states. The x-axis represents the value of slopes and the y-axis represents its density. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

applied. Pearson correlation coefficient was calculated to assess the linear relationship between awake and sedation's functional distances. The p values <0.05 were considered statistically significant. If necessary to compensate for multiple comparisons, the Benjamini-Hochberg method was applied to adjust the p-value.

3. Results

3.1. 1/f dynamics

The slopes of 1/f dynamics during sedation was significantly steeper than that of the awake (Fig. 1a,b $p < 0.001$, with 95 % CI [0.367, 0.424]), indicating the power spectra have the characteristic of random noise during DEX sedation. Hence, with DEX sedation, a shift to a network dominated by random noise occurs (Fig. 1).

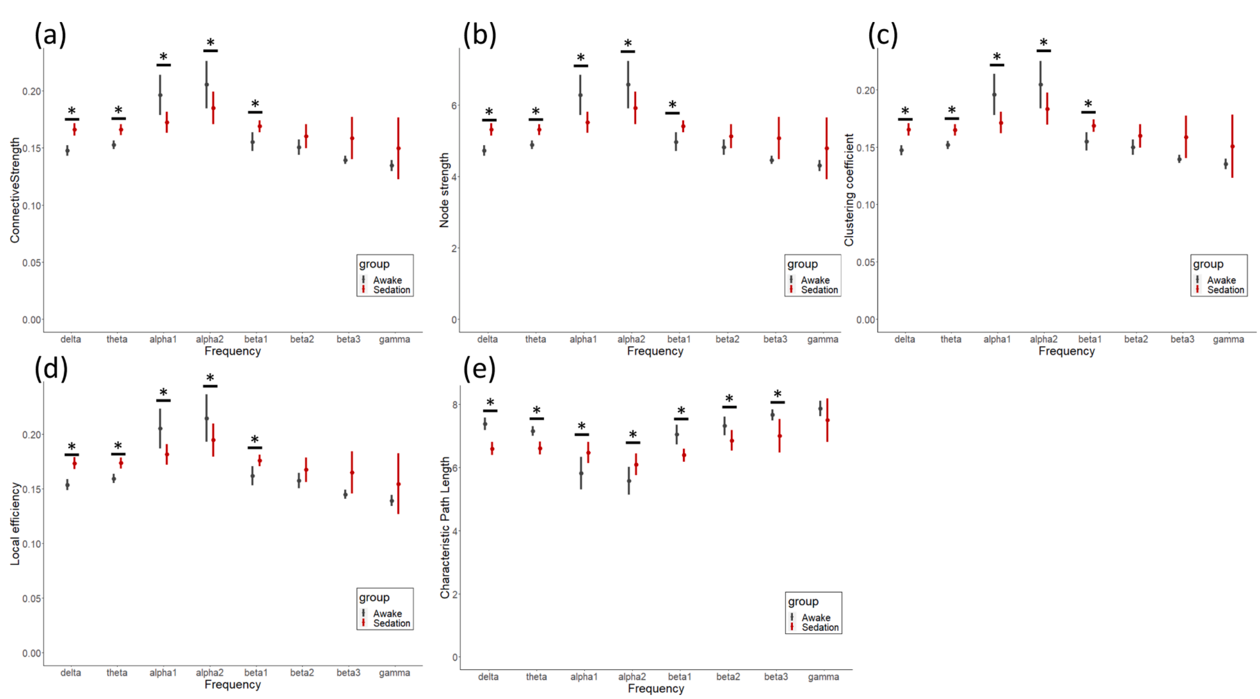

Fig. 2. Network connectivity parameters at awake (black) and during the sedation state (red) frequency bands. (a) Connectivity strength, (b) Node strength, (c) Local efficiency, (d) Clustering coefficient, and (e) Characteristic path length (*$p < 0.05$). Only in the alpha frequency band, connectivity strength, node strength, local efficiency, and clustering coefficient were decreased. However, characteristics pathlength was increased, suggesting a significant decrease in network efficiency. The bars indicate 95 % confidence intervals of the parameters, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.2. Network connectivity analysis

Parameters that differed between the awake and sedation states include connectivity strength, node strength, clustering coefficient, local efficiency, and characteristic path length. During the sedation state, the delta, theta, and beta frequency bands had a significantly higher connective strength, node strength, clustering coefficient, and local efficiency than awake. In addition, characteristic path length was significantly shorter in the sedation state than in the awake state (Fig. 2a,b,d,e). In contrast, for alpha frequency bands, the results were reversed: the alpha frequency bands had significantly lower connective strength, node strength, clustering coefficient, and local efficiency than awake, while characteristic path length was significantly longer than awake (Fig. 2c). Collectively, our data suggest that a bimodal, frequency-dependent pattern of network parameters exists during DEX-induced sedation.

3.3. Distributions of functional distance correlations

The functional distance measured during DEX sedation was greater than in the awake state only in the alpha frequency band across most brain channel pairs (Fig. 3c,d). However, unlike the alpha frequency band, the functional distance during DEX sedation was shorter than the awake state in the delta, theta, beta, and gamma frequency bands in most of brain channel pairs (Fig. 3a,b,e,f,g,h). The pairs with significant functional distance increases in the awake state were greater in delta and theta frequency bands. Taken together, this suggests that the increases in functional distances occur in the alpha frequency band during DEX sedation, which indicates impaired network efficiency. In topoplot of the log-ratio sedation relative power divided by awake relative power, higher power was observed only in delta, theta and beta1 frequency bands (Fig. 4a,b,e). However, the power was decreased in other frequency bands although only alpha frequency band showed a difference in functional distance for these frequency bands (Fig. 4c,d,f,g,h). The slope of correlation between physical distance and functional distance was only increased in the alpha frequency bands, indicating that DEX significantly increases functional distance (Fig. 5c,d). Unlike alpha frequency band, the slope of correlation between physical distance and functional distance significantly decreased in other frequency bands (Fig. 5a,b,e,f,g,h). When functional distances were compared between channels, statistically significances were observed for all frequencies (Fig. 5a,b,c,d,e,f,g,h).

4. Discussion

In this study, we showed that DEX alters the topology of the brain network system. DEX induces changes of global brain network pattern. The multichannel EEG analysis allows us to investigate the effects of DEX in specific frequency bands, which has been rarely attempted in a previous study with DEX [13]. Interestingly, with this approach, we found unexpectedly that DEX's effects on network topology are frequency-dependent. DEX suppress the efficiency of the network system in the alpha frequency band while augmenting the efficiency in low (delta, theta) and high (beta, gamma) frequency bands.

1/f dynamics have been used to decipher the general pattern of complex network systems [25]. In this study, the 1/f slope became steeper during DEX administration, indicating that the brain network system converts from pink noise to Brownian noise. More specifically, the brain is characterized as having a small-world topology, which is associated with a higher clustering coefficient and small path length. This topology suggests that the existence of a hub primarily connected with a subnetwork facilitates effective information transfer, enabling the brain to adapt to the outside world by manipulating varying outside stimuli, which resembles pink noise structure. However, in this study, DEX breaks down small-world topology and favors the transition to Brownian noise structures. The brownian noise structure represents more randomness where hubs break down and random connections rather increase, leading to deteriorate the overall network performance

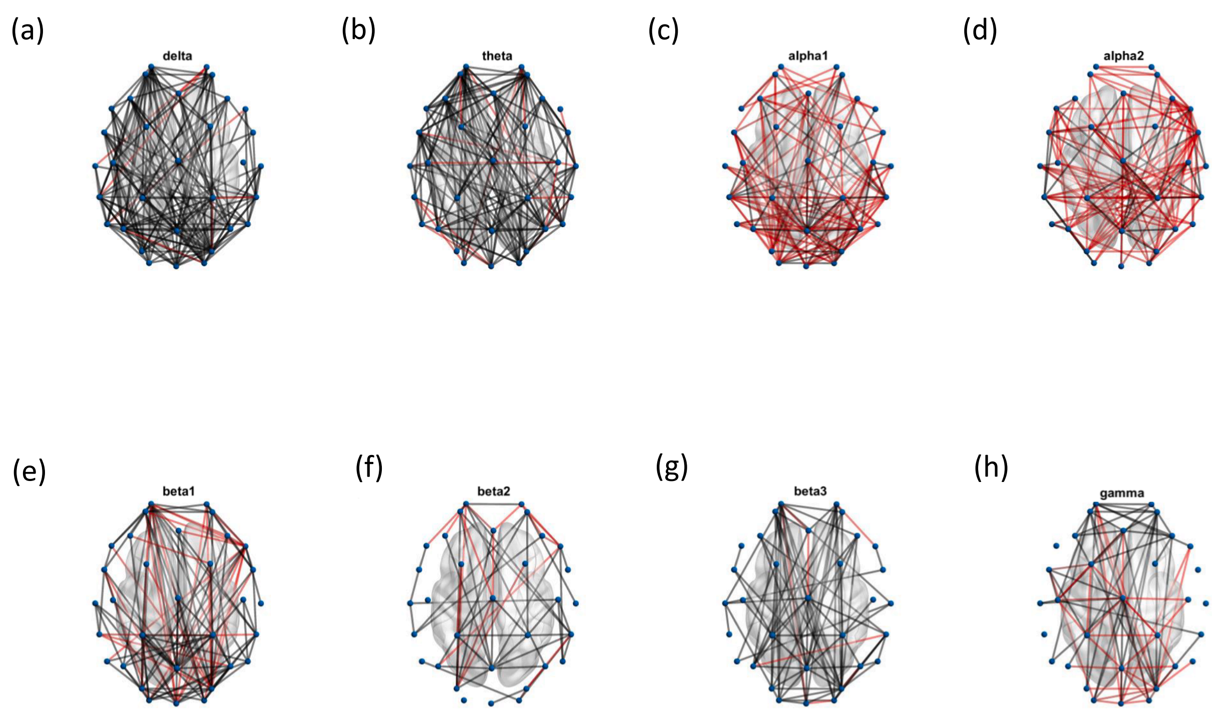

Fig. 3. Correlation plot of the functional distances for (a) delta, (b) theta, (c) alpha1, (d) alpha2 (e) beta1, (f) beta2, (g) beta3, and (h) gamma bands. In the plot, the black lines indicate a longer functional distance in the awake state. Red lines indicate a longer functional distance in the sedation state. Unlike other frequency bands, the red lines were prominent in alpha frequency band. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

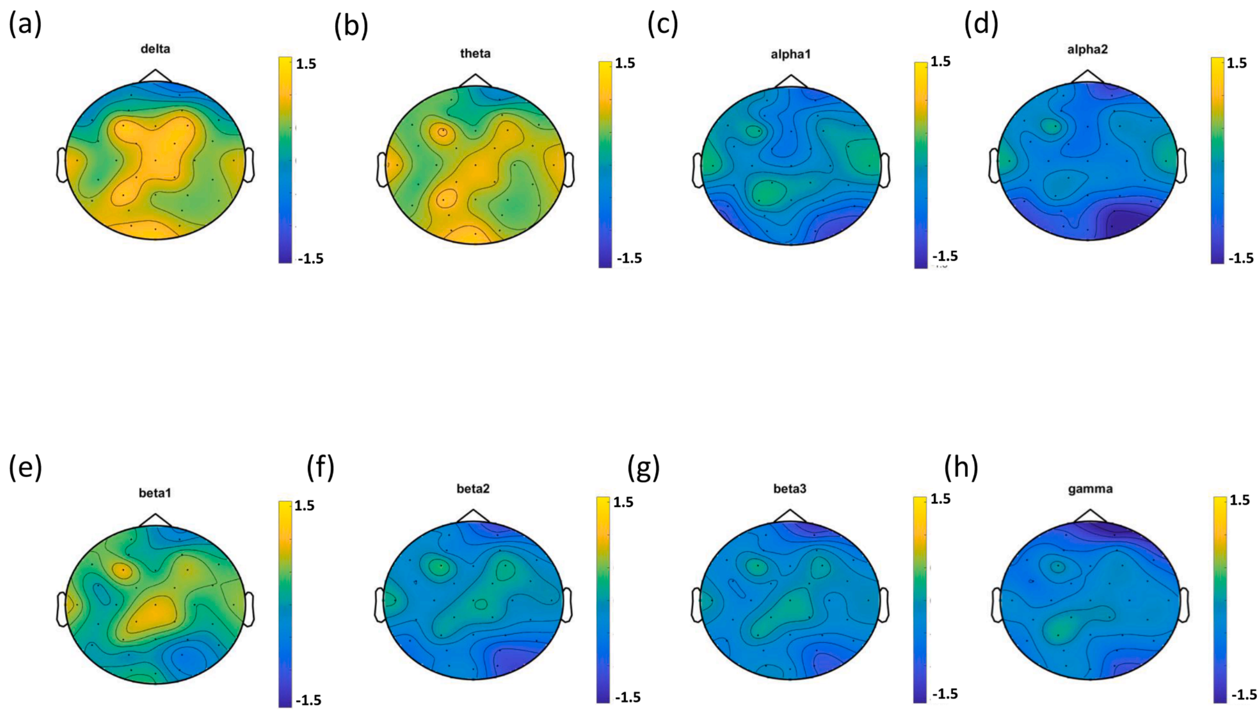

Fig. 4. Log-ratio sedation power density over awake power density for (a) delta, (b) theta, (c) alpha1, (d) alpha2 (e) beta1, (f) beta2, (g) beta3, and (h) gamma bands. The yellow color represents the increase in power while the blue color represents the decrease in power compared to the awake state. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

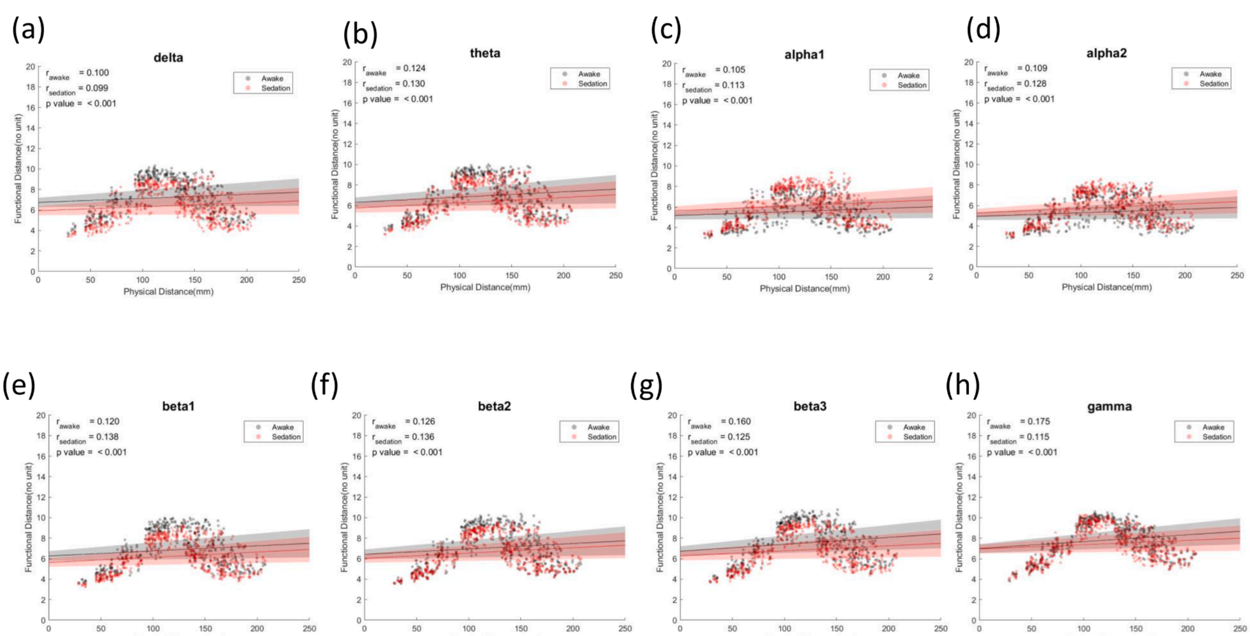

Fig. 5. Regression figures between physical distance and functional distance Regression plot between the physical and functional distance of (a) delta, (b) theta, (c) alpha1, (d) alpha2 (e) beta1 (f) beta2 (g) beta3 (h) gamma. The slope of correlation was only increased in alpha frequency bands during DEX sedation, indicating that DEX increases functional distances compared to its actual distances. The shaded areas in red and gray represent the 95% confidence intervals of the slopes in the sedative and awake state, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[26] Given that deviation from pink noise impairs the network's performance [27], this alteration may decrease the ability to integrate information, especially for rapidly changing stimuli, leading to a sedative effect.

Our data suggest that DEX inhibits the overall efficiency of the network system only in the alpha frequency band. Functional distance increased statistically compared to the physical distance during DEX sedation in the alpha frequency band. DEX increased functional connections between most brain regions. Our observations are consistent with previous findings. Brain synchronization in this band is implicated in maintaining consciousness. Many studies suggest that alpha oscillation is closely related to anesthesia-induced LOC [28–31]. This suggests the importance of the alpha frequency band in maintaining consciousness. It has been reported that functional connections implicated in consciousness are disrupted during the transitions into unconsciousness. DEX impairs frontal and thalamocortical connectivity [32], the latter playing a critical role in consciousness [33]. Thalamocortical connections are mainly mediated through alpha oscillations. During DEX-induced sedation, thalamocortical connections are impaired [32]. The disruption of thalamocortical functional connectivity in the alpha frequency band is related to impaired consciousness [34]. A functional magnetic resonance imaging (fMRI) study shows that the connections between the thalamus and higher-order cortical networks are impaired during moderate sedation with DEX [32]. Previous DEX studies suggest that DEX may impair functional connections between brain areas. In this study, we used a graph analysis approach to investigate the effect of DEX on the alpha frequency band, critical in consciousnesss. Consistent with our expectation, alterations in brain network efficiency were only observed in alpha frequency band. Collectively, the results from our study support the notion that DEX-induced alpha frequency alteration leads to DEX pharmacologic effects.

Meanwhile, the effect of DEX on network efficiency at other frequency bands (low and high-frequency bands) is quite surprising. Except for the alpha frequency bands, DEX rather enhance network efficiency and functional connections in other frequency bands. Unlike our results, previous studies suggest that reducing connections between cortico-cortical or subcortical regions during DEX administration can be intriguingly interpreted as impairing network efficiency [35,36], which is similar to our result in alpha frequency band. However, these studies did not investigate DEX effect after subdividing time series signals into specific brain frequency bands. In addition to differences in analytic methods, this difference between our result and previous findings can be also understood from the standpoint of network topology reorganization. Higher frequencies are associated with local synchrony and lower frequencies with long-range synchrony [37]. Thus, increased efficiency in high-frequency bands can be interpreted as increased connections within the subnetwork. We have shown that DEX induces the conversion of the brain network to present random behaviors from 1/f analysis on a global scale. Random networks render the system less effective as adding more noise impairs network performance. Therefore, it could be thought that the increase in efficiency in high frequency bands rather impairs the overall performance. Interestingly, the reorganization of the network can occur after perturbing the system [38]. An increase or decrease in the number of functional connections inhibits the system's performance [39].

The spectral powers are altered in the presence of a sedative effect. For lower frequency bands, DEX increases the power of the delta band across the brain and augments the theta band, which is prominent in the occipital area [40]. We have also shown an increase in delta and theta powers during DEX sedation. The modulation of the delta band is related to DEX concentration [41]. Previous studies suggest that the modulation of DEX at low frequency is linked to a sedative effect [40,42]. Interestingly, the increase in global efficiency could be related to enhanced spectral power in a low-frequency network [43]. Taken together, it could be interpreted that DEX augmented network efficiency in delta and theta frequency bands may be attributed to its effect on alterations in brain topography. Interestingly, DEX effect on topography and decreases in functional distances was prominent in these frequency bands.

Unlike other sedatives, DEX acts via the alpha-2 adrenergic receptor and augments sleep-inducing pathways. A recent study applying a deep learning algorithm suggested that EEG during DEX sedation resembles that of non-rapid eye movement (NREM) sleep [44]. It has been reported that the subjects under DEX sedation are easily arousable by external stimuli, similar to sleep. Interestingly, thalamocortical connectivity decreases during the transition to light sleep, while corticocortical connectivity increases [45]. Similar to sleep, easy arousal during DEX sedation may be explained by more preserved subcortical and cortical connections [32]. Interestingly, a recent study suggested that cortical connectivity in the delta-theta band changes with the levels of unconsciousness [46]. In this study, we have shown that DEX decreases functional distances between many brain pairs and increases network efficiency in lower frequency bands. In this regard, increased efficiency in these frequency bands on a global scale may expand our understanding of the unique a sleep-like state promoting DEX actions but not strong enough to generate an anesthetic state.

A previous study [13] analyzed the alteration of graph topology from neuroimaging data. It focused on how DEX affects the topology of the brain network as a whole and not at specific frequency levels. Numerous studies underscore the importance of brain synchronization at specific frequency levels [47–49]. Unlike previous studies, we investigated the network properties changes at frequency levels. To the best of our knowledge, this is the first study to investigate the mechanisms of DEX, focusing on the alterations of the graph-related parameters at frequency levels from EEG data. With this approach, we found different effects of DEX on network properties depending on frequency levels, which was different from the results of the other sedatives with the same analytic approach. Unlike previous studies, we also investigated how network properties changes with analyzing 1/f dynamics. In addition to alterations at specific frequency bands, DEX induces the changes of brain network patterns as a whole, favoring transition towards a random network behavior. Taken together, we have shown that DEX alters brain networks locally and globally, leading to its sedative effect.

However, we note some limitations in this study. First, although we monitored BIS to evaluate the sedation levels, there may be a possibility that sedation depth levels differed between the subjects. In this study, we focused on moderate sedative states equivalent to the Observer's Assessment of Alertness/Sedation (OAA/S) score 3 ~ 4 rather than deep sedation. However, there may be the possibility of different results under deep sedation. Second, we acquired EEG data from healthy adult volunteers. However, DEX induced network alterations may be different for other population such as mentally disables patients with different anesthetic features [50] and children. Further studies should be required to elucidate these issues in detail.

In conclusion, we have shown that DEX converts the brain network topology to a less efficient system on a global scale. However, the disturbances only affected the alpha frequency band differently. This frequency dependence of the DEX effect on brain topology may explain the differences in features between DEX and other anesthetics and warrants additional study.

CRediT authorship contribution statement

Pil-Jong Kim: Writing – original draft, Writing – review & editing, Investigation, Formal analysis, Software. **Hyun-Tae Kim:** Writing – original draft, Writing – review & editing, Investigation, Formal analysis. **Bernard Choi:** Conceptualization, Funding acquisition, Formal analysis, Writing – review & editing. **Teo Jeon Shin:** Conceptualization, Funding acquisition, Supervision, Formal analysis, Project administration, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

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