

Analysis of activity-related brain network using functional connectivity and graph theory with EEG

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Analysis of activity-related brain network using functional connectivity and graph theory with EEG

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Abstract

The human brain is networked to solve many of the challenges of everyday life. Much of the research on brain networks uses a technique called functional connectivity (FC). Recently, graph theory, a mathematical technique, was used to evaluate complex network activity. However, there are still many unknowns about the activity of electrical networks in the brain. Therefore, we investigated brain network activity under a variety of conditions.

First, we determined functional connections from the EEG at each sleep stage, constructed networks, and compared clustering coefficients and characteristic path lengths to compare the characteristics of network activity at each sleep stage. We found that the characteristic path lengths of LowBeta (13-15 Hz) were significantly reduced in Stage 1 and later stages. However, there were no significant differences in the clustering coefficients. Our results were consistent with previous studies that show an approach to the small-world network during sleep. We also believe that our results suggest that the efficiency of network activity may have been influenced by sleep spindle waves. An example of an application of sleep EEG is the automatic identification of sleep stages in previous studies. In these previous studies, the accuracy of sleep stage 1 tended to be poor. Based on the results of this study, we believe that adding the characteristic path length of LowBeta as a factor may improve the accuracy of sleep stage 1. In conclusion, we believe that this study was able to capture the brain network activity according to sleep depth and showed the possibility of applying brain network analysis in EEG during sleep. We believe that the application of the network activity influenced by sleep depth obtained in this study may contribute to improving the accuracy of automatic discrimination of sleep stages in the future, and we believe that we have demonstrated the usefulness of using network analysis for analyzing brain activity during sleep.

In many cases of memory impairment, the underlying problem is not the loss of memory information per se, but rather a deficit in retrieval processes. Previous studies of memory retrieval, particularly those using EEG, have mainly focused on changes in power and connectivity in the gamma frequency range (>30 Hz). However, a more detailed investigation of brain network dynamics during memory retrieval has been somewhat lacking. To address this gap, the present study performed a quantitative comparison of retrieval and non-retrieval conditions using a network analysis of time-varying functional connectivity. Memory retrieval was assessed using a paired association learning task. Consistent with previous research, time-frequency analysis revealed a gamma-band response during memory retrieval, particularly in the high gamma frequency range. In addition, the study identified a significant increase in the characteristic path length within the high gamma band for the target condition compared to the distractor condition. The network is more efficient in the high gamma bandwidth (50-80 Hz) non-remiscent condition. We attributed this to the high workload, which led to distracted memory recall. In the non-recall condition, participants need to focus only on the next stimulus, which may improve network efficiency. On the other hand, the significant

characteristic path length observed in the time window in which GBA was observed suggests that the results of this study suggest that network activity may also have temporal characteristics depending on the task. Therefore, we believe that this study has demonstrated the possibility that incorporating this temporal network activity may lead to a more detailed elucidation of brain activity and applications to BCI, etc.

Third, we aimed to analyze dynamic connectivity changes during working memory tasks through functional connectivity analysis using EEG. In the theta band, dynamic functional connectivity analysis revealed a PLV peak after 300 ms between the posterior, frontal, and central regions. At the same time, clustering coefficients increased and characteristic path lengths shortened. Previous studies have reported on the relationship between working memory and theta-band EEG and the appearance of n300 and p400 after stimulus presentation during the n-back task. In addition, n300 and p400 were reported to emerge after stimulus presentation during the n-back task, and given these findings, it is suggested that the present results may represent the emergence of efficient network activity in response to stimuli. Furthermore, the increase in clustering coefficients and the decrease in characteristic path length at the 300 ms peak were associated with longer return times than before the peak as the task load increased. This result may be the result of memory recall and other processes lasting longer in the 1-back and 2-back tasks, which are more demanding than the 2-back task, and the network continues to build more efficiently. We believe that our results demonstrate that network activity appears as a temporal feature as well as a temporal feature of amplitude-based brain activity. It is maybe suggested that the duration for which this network efficiency is maintained may be a factor in determining task load, and the results of this study demonstrate the possibility of identifying task load in terms of the temporal characteristics of brain network activity and applying this to applications such as BCI.

In the present study, we used phase-based functional connectivity to analyze the network during sleep, memory recall, and memory storage and processing. As a result, we were able to identify efficient network activity that may be related to memory fixation during middle and deep sleep, as well as temporal characteristics of network activity during memory recall. We believe that these results indicate that brain networks may exhibit specific activity not only in specific situations but also in time and that it is important to focus on the temporal characteristics of brain networks. Therefore, we believe that this study will contribute to further elucidation of brain network activity in the future.

Keywords: EEG, functional connectivity, graph theory, default mode network, sleep, memory

1 Introduction

1.1 background

Early research on brain function sought to clarify the relationship between specific brain regions and their corresponding functions, primarily through the lens of functional localization. This theory posits that distinct regions of the brain are responsible for particular functions. Notable contributions to this framework include Broca's observation that damage to the inferior frontal gyrus (IFG) is associated with aphasia and Wernicke's identification of a link between damage to the superior temporal gyrus (STS) and language-related learning disabilities. These findings provided substantial evidence for the link between specific brain regions and language function [1]. However, as the complexity of cognitive tasks increases, brain activity does not remain confined to a single region; rather, several brain areas work together to perform more challenging tasks. For example, while the IFG has been associated with language processing, it also shows activation in relation to a variety of other cognitive functions. Similarly, the STS, which is involved in the perception of biological motion, is part of a broader cognitive network. Thus, neither the IFG nor the STS can be characterized as having a singular function; rather, they are involved in different cognitive processes and are part of multiple neural networks. This complexity has led to a growing body of research focused on understanding the interrelationships and interactions between brain regions within these extensive networks.

These large brain networks have been identified using functional brain imaging techniques such as EEG and fMRI. The dorsal attention network (DAN), working memory network (WMN), and default mode network (DMN) are prime examples of resting-state networks[2]. DAN is a network composed mainly of the Frontal Eye field (FEF) and Superior Parietal lobes (SPL), and this network is related to spatial attention. WMN is a network composed mainly of the Lateral Prefrontal Cortex (LPC) and Posterior Parietal Cortex (PPC), this network is related to working memory that simultaneously performs operations while holding information and executing functions such as planning, Suppression of the working brain, updating memory, distribution of attention.

Much research on brain networks has used a technique known as functional connectivity (FC), which examines the relationships between different brain regions. Unlike methods that focus on the physical connections between neurons, FC emphasizes the functional interactions between brain areas. Studies using FC have shown that phase synchronization within the alpha frequency band is associated with activity in the frontal-parietal network, as observed by fMRI. In addition, numerous studies have investigated brain networks using various forms of brain data, such as EEG. [1], [3], [4]. In recent years, graph theory has been applied to brain network analysis to quantitatively evaluate network structure[5], [6], [7], [8].

Network activity has also been observed during sleep, a critical resting state for the brain. Sleep spindles, which are characteristic of stage 2 sleep, have been proposed to facilitate the transfer of hippocampal-cortical information, potentially contributing to memory consolidation processes [9].

Previous research suggests that non-REM (NREM) sleep is particularly beneficial for declarative memory enhancement, while REM sleep is thought to support non-declarative learning [10]. For example, performing a declarative memory task at night has been shown to increase the density of sleep spindles during NREM sleep [11]. Sleep spindles have also been found to correlate with improved overnight memory retention in declarative word association tasks [12]. In contrast, Rasch et al (2009) reported a positive correlation between sleep spindle activity and improved performance on a procedural finger-tapping task when REM sleep was pharmacologically suppressed [13]. However, it remains unclear whether this correlation pertains to explicit or implicit aspects of the task. Additionally, sleep spindles have been linked to slow oscillations occurring during NREM sleep stages 3 and 4 [14]. Graph theoretical approaches have also been applied to analyze brain networks during sleep, revealing that clustering coefficients significantly increase from wakefulness to sleep, suggesting that graph theory may be a valuable tool for characterizing network activity during sleep [15], [16].

On the other hand, it is also thought that the brain builds a network to support problem-solving during task performance. In the Paired Associative Learning Task, a commonly used psychological task to assess memory function, research has shown that an increase in gamma-band power and functional connectivity (FC) - a feature referred to as gamma-band activity (GBA) - occurs early in the memory processing phase [17]. Memory retrieval involves both the intentional act of recalling and the focus on the target information [18]. Thus, memory retrieval is not a sudden occurrence at the moment of an event, but rather a deliberate process that requires effortful engagement to retrieve the information. In the previous research [17], the phase-locking value (PLV) was observed from stimulus onset to the peak of gamma-band activity (GBA) using time-frequency analysis. However, while the PLV was compared across conditions, it was not examined within the context of a broader network. Recently, complex network analysis based on graph theory has been employed to analyze networks of EEG-based FCs, offering a quantitative approach to evaluating brain activity [18]. The gamma band, typically defined as a high-frequency band above 30 Hz, is associated with processes such as attention and perception. The concepts of evoked GBA (eGBA) and induced GBA (iGBA) have been proposed within the study of gamma-band activity [19]. eGBA, observed in response to visual stimuli (such as those used in the previous research), typically occurs within about 100 ms of the stimulus and is associated with perceptual processing. In contrast, iGBA is a later response, appearing after 200 ms, and is thought to support higher-order cognitive functions, depending on the specific demands of the task.

WMN is the one of resting state networks. Working memory is the ability to store memory in a short time and process it at the same time. It is involved in many complex cognitive tasks, learning, reasoning, and decision-making, and directly influences our daily lives. The relationship between alpha power and working memory performance remains inconsistent, with some studies reporting a negative correlation with individual working memory ability [20], while others report no such correlation [21].

Theta wave power has been observed to increase with increasing workload [22]. Studies have also reported that frontal theta waves increase during memorization-related working memory tasks [23]. The changes in brain waves that result from stimulation are known as event-related synchrony (ERS) and event-related desynchrony (ERD). ERD is correlated with improved concentration, while alpha ERS is associated with facilitated attention [24]. Functional and causal connectivity have also been used in working memory research [25], [26], [27]. Jinyan et al. (2019) used near-infrared spectroscopy (NIRS) to assess connectivity during n-back tasks and found that long-range connections in the prefrontal cortex (PFC) were enhanced with increasing workload and that the left PFC was more connected to the right PFC than the right PFC. And strong information flow from the right PFC to the left PFC was reported [26]. Working memory was researched by many researchers. However, the time-varying of brain network activity during the working memory process is still unknown.

Although the existence of such brain networks has been clarified in many studies, there are still many parts that remain unclear. Currently, the development of applications and brain-computer interfaces that utilize brain network activity is progressing, and a deeper understanding of brain network activity is essential. Therefore, throughout this study, we aimed to further elucidate network activity during rest and task execution, which remain largely unknown.

In Chapter 2, with the aim of clarifying the details of changes in network activity during sleep and confirming the validity of network analysis using graph theory, EEG was measured during sleep, and brain network activity was calculated using graph theoretical methods. The brain network characteristics in each sleep stage were then compared.

In Chapter 3, complex network analysis was used to assess the time-varying functional connectivity (FC) network and to analyze network activity associated with memory retrieval. This approach was also used to quantitatively assess changes in the FC network prior to the completion of memory retrieval and to compare network activity during retrieval and non-retrieval periods. Based on the results of this comparison, networks specifically associated with memory retrieval were further investigated. This methodology also allowed for a focused investigation of gamma sub-bands, specifically the 30-50 Hz and 50-80 Hz frequency ranges, which have not been thoroughly investigated in previous studies. By controlling for the influence of miniature saccades, as suggested by previous research, we aimed to explore how these different gamma sub-bands functioned differently in relation to memory retrieval.[28].

In Chapter 4, we applied the time-varying network analysis used in Chapter 3 to capture dynamic connectivity changes during working memory tasks through a combination of functional and causal connectivity assessments. We believe that this provides new insights into the interactions between brain regions during working memory processes.

1.2 Basic notice

1.2.1 Functional Connectivity (FC)

Functional connectivity (FC) is a method for assessing the functional relationships between two brain regions. Rather than focusing on direct neural connections or interregional connectivity, this approach emphasizes how regions share common functional properties. The basic assumption of FC is that when regions work together during task performance, their activity becomes temporally synchronized, with these synchronized activities showing a high degree of correlation in terms of temporal fluctuations. Statistical methods such as t-tests and z-tests are commonly used to assess the significance of these network activities. FC has thus become a valuable tool for quantifying the activity of brain regions and understanding the dynamic interactions within neural networks.

1.2.2 Phase locking value (PLV)

The phase locking value (PLV) is a method used to quantify the degree of phase synchronization between two signals from different regions. The PLV is calculated using the following equation. (1) [29]:

$$PLV_t = \frac{1}{N} \left| \sum_{n=1}^N \exp(j\theta(t, n)) \right| \quad (1)$$

where N represents the total number of trials, and $\theta(t, n)$ is the phase difference, defined as $\varphi_1(t, n) - \varphi_2(t, n)$, between the phases $\varphi_1(t, n)$ and $\varphi_2(t, n)$ of the two signals at a specific time t . If the two signals are constant, the PLV is close to 1; if the phase difference between the two signals is not constant, the PLV is close to 0.

In this study, a Hilbert transform is performed on the acquired EEG data, and the time series phase data of each signal is extracted. The time series phase data is then used to calculate the PLV value by using equation (1) to calculate the phase difference between signals within a time window.

1.2.3 Clustering coefficient

The clustering coefficient is a metric that quantifies the degree of connectivity among neighboring nodes in a network, based on the number of triangles formed by edges connecting these nodes to a given node. It serves as an indicator of the functional segregation within a network. The local clustering coefficient for a specific node reflects the proportion of its neighbors that are directly connected to it, also referred to as its "neighbors."

For the network as a whole, the clustering coefficient is derived as the average of the local clustering coefficients across all nodes. This value ranges from 0 to 1, with higher values indicating a more tightly interconnected network. The clustering coefficient can be computed using the following formula[30]:

$$C^w = \frac{1}{n} \sum_{i \in N} \frac{2t_i^w}{k_i(k_i - 1)} \quad (2)$$

$$t_i^w = \frac{1}{2} \sum_{j, h \in N} (W_{ij} W_{ih} W_{jh})^{\frac{1}{3}} \quad (3)$$

$$k_i = \sum_{j \in N} a_{ij} \quad (4)$$

In this formula, N represents the total number of nodes in the network. In the present study, N corresponds to the number of electrodes, while t_i^W denotes the number of triangles surrounding node i . W_{ij} refers to the connection weight between nodes i and j , with the phase-locking value (PLV) being employed as the connection weight in this analysis. Additionally, k_i represents the degree of node i , and a_{ij} indicates the connection status between nodes i and j .

1.2.4 Characteristic path length

The characteristic path length is defined as the average of the shortest path lengths between all pairs of nodes in the network. It serves as an index of the network's functional integration. Smaller values of characteristic path length indicate a higher degree of integration, suggesting more efficient communication within the network. Functional integration refers to the ability of a network to transfer specific information between distant regions in the most efficient manner possible. The characteristic path length was computed using the following formula:

$$L^W = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}^W}{n-1} \quad (5)$$

$$d_{ij}^W = \sum_{a_{uv} \in g_{i \leftrightarrow j}^W} f(W_{uv}) \quad (6)$$

d_{ij}^W denotes the shortest weighted path length between nodes i and j ; $f(W_{uv})$ represents the mapping from the connection weight to the corresponding path length; $g_{i \leftrightarrow j}^W$ indicates the shortest path length between nodes i and j .

1.2.5 Small-worldness

A small-world network is characterized as a network that exhibits a high degree of clustering, similar to that of a random network while maintaining the same characteristic path length as a random network. The degree of small-worldness is quantified by the normalized clustering coefficient and the normalized characteristic path length. These two parameters can be calculated using the following equation:

$$\text{Normalized CC} = C/C_{\text{random}} \quad (7)$$

$$\text{Normalized CPL} = L/L_{\text{random}} \quad (8)$$

C_{random} represents the clustering coefficient calculated from a random network derived from the original network, while L_{random} refers to the characteristic path length calculated from the random network. The ratios C/C_{random} and L/L_{random} approach 1 in a random network. Conversely, when C/C_{random} is substantially greater than 1 and L/L_{random} remains close to 1, the network is classified as a small-world network. If both C/C_{random} and L/L_{random} exceed 1, the network is considered an ordered network.

2 Investigating changes in brain network activity based on EEG during non-REM sleep stages with sleep spindle (13-15Hz)

2.1 Background

In Chapter 2, we focus on network activity during sleep, which is one of the resting states. Previous studies[31] have revealed the effects of sleep on brain networks, such as the deterioration of brain network efficiency caused by sleep deprivation. However, little is known about network activity during sleep depending on the depth of sleep. Therefore, in this study, we aim to clarify the changes in network activity during sleep.

2.2 Method

2.2.1 Participants and apparatus

In this research, electroencephalography (EEG) was recorded from ten participants (age: 22-24 years) during sleep using Wave-guard connect (eemagine Medical Imaging Solutions GmbH, Germany) and PolymateV (Miyuki Giken Co., Ltd., Japan). In this study, nineteen active wet Sn (tin) electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2) were placed on the scalp according to the international 10-20 system. The reference electrode was positioned at CPz. Participants wore an EEG cap with electrodes placed on top, and the experimenter monitored electrode placement throughout the EEG measurements. If no issues were detected, data collection proceeded as planned. This study was conducted by the ethical principles of Kyushu university(ID: シス情認 2021-14) and the Declaration of Helsinki. Prior to the measurements, participants were provided with an explanation of the study, and informed consent was obtained. The sampling frequency was set to 500 Hz, and all electrodes were configured to ensure an impedance of less than 20 K Ω . Participants were instructed to sleep in a simple, shielded room, and EEG was recorded throughout the night during sleep.

2.2.2 Sleep scoring

EEG data collected during sleep were visually inspected, and sleep stages were classified according to standard criteria[32]. The characteristics of each sleep stage are outlined below:

Stage 1: Presence of low-amplitude alpha, theta, beta waves, and the appearance of vertex sharp waves.

Stage 2: Observation of K-complexes and sleep spindles (13-15 Hz).

Stage 3: Slow waves were present for 20-50% of a 30-second epoch.

Stage 4: Slow waves were present for more than 50% of a 30-second epoch.

To differentiate between non-REM (NREM) and REM sleep, REM sleep was excluded from the analysis based on the typical 90-minute sleep cycle. This exclusion was determined by the sudden disappearance of slow waves in stages 3-4 and the emergence of high-frequency activity, such as alpha waves. NREM sleep stages were reclassified as Stage 1 after 90 minutes had elapsed from the onset of Stage 1 within the cycle.

To distinguish sleep from wakefulness, participants were instructed to report any instances of waking prior to the start of the experiment. Considering the characteristics of the sleep EEG, Stage 1 was

classified as shallow sleep, Stage 2 as moderate sleep, and Stages 3 and 4 as deep sleep.

EEG data from three of the ten participants could not be reliably classified into sleep stages due to noise and other technical issues and were therefore excluded from subsequent analyses.

2.2.3 EEG pre-process

All EEG analyses were conducted using MATLAB (MathWorks Natick, USA) integrated with the Brainstorm [33] and Brain connectivity toolbox [34]. The EEG data were visually classified by the experimenter into sleep stages 1 through 4, and characteristic waves associated with each stage were extracted for 5-second intervals to create a total of 60 epochs. For each sleep stage, 60 epochs, each with a 5-second time window, were extracted from the EEG data, resulting in a total of 300 seconds (5 minutes) of EEG data for analysis. Epochs for each sleep stage were selected based on the features outlined in Section 2.2.2.

To investigate the effects of sleep spindle waves, epochs with and without sleep spindle activity were separately extracted from Stage 2 EEG data. A total of 60 epochs, each with a 0.5-second time window, were selected for both conditions (with and without sleep spindle waves), and data from 30 seconds of EEG were analyzed for each condition, resulting in a total of 60 seconds of data for analysis.

2.2.4 Brain network analysis

The EEG data were analyzed using graph theory, wherein the network is represented as a graph consisting of nodes connected by edges. In this study, functional connectivity was employed as the weight of the edges, with electrodes serving as the nodes. The phase locking value (PLV), a method of assessing functional connectivity, was utilized as the edge between nodes. For each sleep stage, the average PLV for each epoch was calculated across several frequency bands. These frequency bands were categorized as follows: delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), LowBeta (13–15 Hz), UpperBeta (15–30 Hz), Gamma1 (30–58 Hz), and Gamma2 (62–90 Hz).

The Brain Connectivity Toolbox was used to compute clustering coefficients and characteristic path lengths in order to compare network properties across the different sleep stages. Additionally, 100 random networks were generated based on the EEG-derived networks during sleep to assess the small-world properties of the network. The clustering coefficients and characteristic path lengths of these random networks were calculated and subsequently used to compute the small-world degree.

2.2.5 Statistical analysis

To examine the characteristics of network properties across sleep stages at each frequency, four network indicators (clustering coefficient, characteristic path length, ratio of clustering coefficient between the random network and the baseline network, and the ratio of characteristic path lengths between the network and the baseline network) were analyzed using one-way ANOVA. Following this, pairwise t-tests were conducted for each network indicator between different sleep stages. After applying a Bonferroni correction, the adjusted significance threshold was set at $p = 0.05/6 = 0.00833$.

To assess the effect of sleep spindles in Stage 2, EEG data with and without spindle activity were

extracted from Stage 2. Subsequently, t-tests were performed to compare the spindle and non-spindle EEG conditions.

2.3 Results

2.3.1 Subject parameters and behavior results

The mean age of the seven participants included in this study was 28.286 (SD: 0.951). The average sleep duration for these subjects was 6.962 h (SD: 1.185 h). Figure 1 shows the sleep stage time chart for one representative subject and Figure 2 presents the power spectrum averaged from electrodes F4, C4, and O2. The percentages of time spent in each sleep stage, as determined through visual inspection, were as follows:

Stage1: $38.07 \pm 10.91\%$, Stage2: $44.61 \pm 10.78\%$, Stage3: $9.16 \pm 3.41\%$, Stage4: $8.17 \pm 6.15\%$.

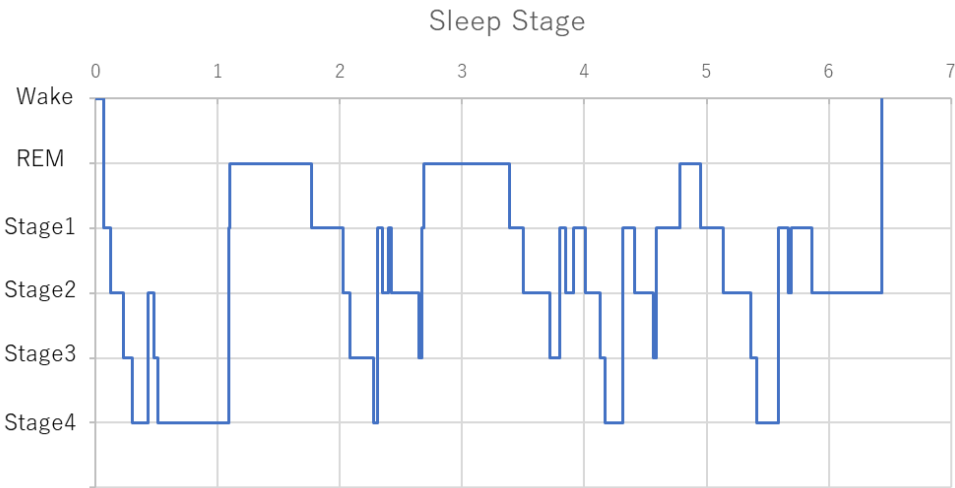


Fig 1. Timechart of sleep stage

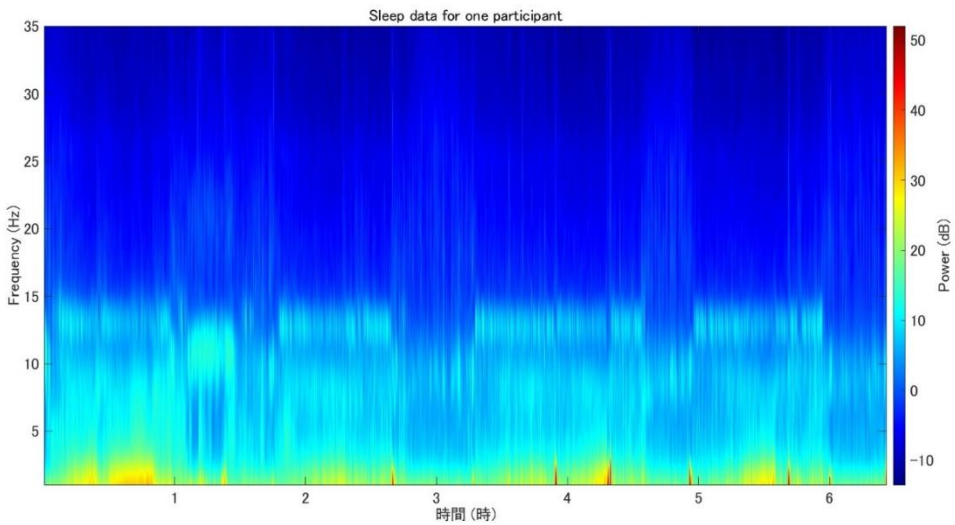


Fig 2. Averaged spectrum(F4,C4,O2)

2.3.2 The result of the Network Graph

In this study, we configured a network graph using PLV as the edge. The network graph of each stage in the Delta band is shown in Figure 3. In network graph, frontal electrodes (Fp1,Fp2,F3,F4,Fz) are positioned as red nodes, central electrodes (C3,C4,Cz) as green nodes, Posterior electrodes (P3,P4,Pz, O1,O2) as black nodes, and temporal electrodes (F7,F8,T7,T8,P7,P8) as blue nodes. The larger the PLV value between the electrode pairs, the thicker the edge between the electrode pairs. In addition, the network graph shows only the edges that are greater than the average value calculated from a total of 190 PLVs that appear in each state and each frequency band. The ANOVA ($P \leq 0.05/190=0.000263$) and t-test ($P \leq 0.05/6 = 0.00833$) results showed a significant difference in T8-F4. In T8-F4, there was a significant difference between stage1 and stage2, and stage2's PLV was significantly higher than stage1's PLV.

The network graph for each sleep stage in the Theta band is presented in Figure 4. Statistical analysis using ANOVA revealed no significant differences between the sleep stages in the Theta band.

The network graph of each stage in the Alpha band is shown in Figure 5. Statistical analysis using ANOVA revealed no significant differences between the sleep stages in the Alpha band.

The network graph of each stage in the LowBeta band is shown in Figure 6. The result of ANOVA ($P \leq 0.000263$) and t-test ($P \leq 0.00833$) revealed a significant difference between Stage 1 and the other sleep stages in 81 electrode pairs (T7-Fp1/Fp2/F7/F3/F4/F8, C3-Fp1/Fp2/F7/F3/Fz/F8, Cz-T7, C4-Fp2/F7/T7, T8-Fp2/F7/F8/T7/C3, P7-Fp1/Fp2/F7/F3/Fz/F4/F8/T7/C3/C4/T8, P3-Fp1/Fp2/F7/F3/Fz/F4/F8/C3, P4-Fp1/Fp2/F7/F8/T7/C4/T8/P7, P8-Fp1/Fp2/F7/F8/T7/C3/C4/T8/P7, O1-Fp1/Fp2/F7/F3/Fz/F8/T7/C3/T8/P7/P4/P8, O2-Fp1/Fp2/F7/F8/T7/C3/C4/T8/P7/P4/P8/O1). All electrode pairs have significant differences, there were significant differences between stage1 and other stages, and the stage1's PLV was significantly lower than the other stage's PLV.

The network graph of each stage in the UpperBeta band is shown in Figure 7. The result of ANOVA ($P \leq 0.000263$) and t-test ($P \leq 0.00833$) revealed a significant difference between Stage 1 and the other sleep stages in 12 electrode pairs (T8-F3/Fz, P7-F3, P3-Fp1/Fp2/F7, P4-Fp1/Fp2/F7/F4/F8, P8-F3/Fz, O1-F3/C3). Electrode pairs which have significant differences without P4-Fp1/Fp2/F7/F4/F8, there were significant differences between stage1 and other stages, and stage1's PLV was significantly lower than other stage's PLV.

The network graph of each stage in the Gamma1 band is shown in Figure 8. Statistical analysis using ANOVA revealed no significant differences between the sleep stages in the Gamma1 band.

The network graph of each stage in the Gamma2 band is shown in Figure 9. Statistical analysis using ANOVA revealed no significant differences between the sleep stages in the Gamma2 band.

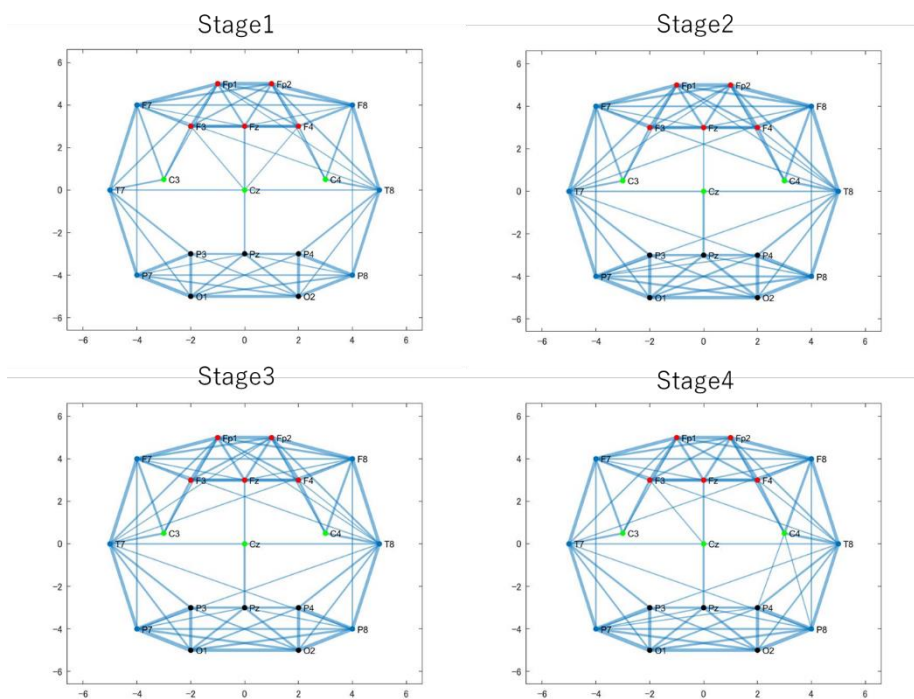


Fig 3. Network graph in Delta in each sleep stage

Thick edges: high PLV (strong connection) Thin edges: low PLV (weak connection)

(Red node: Frontal, Green: Central, Black: Posterior, Blue: Temporal)

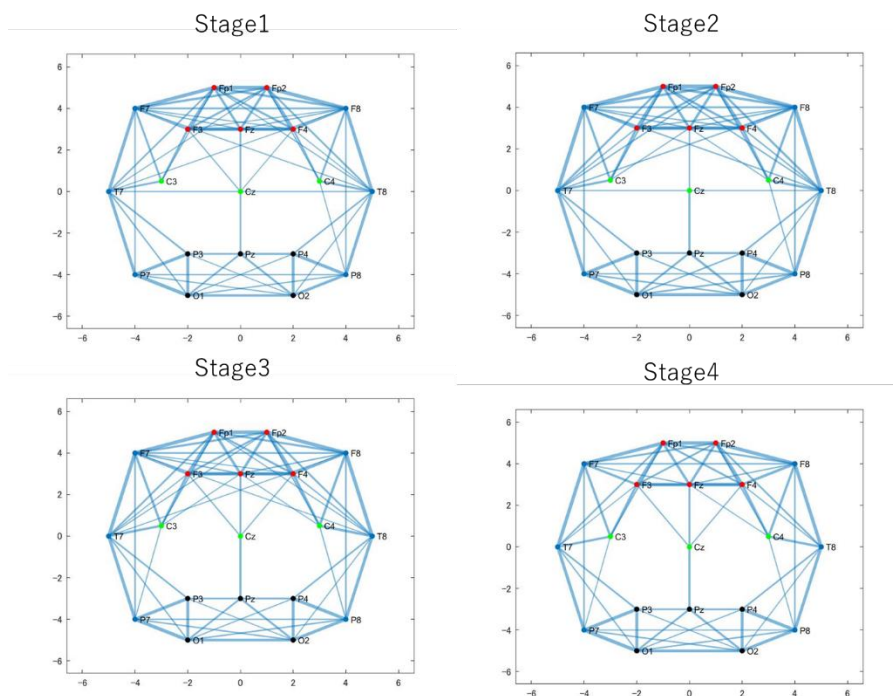


Fig 4. Network graph in Theta in each sleep stage

Thick edges: high PLV (strong connection) Thin edges: low PLV (weak connection)

(Red node: Frontal, Green: Central, Black: Posterior, Blue: Temporal)

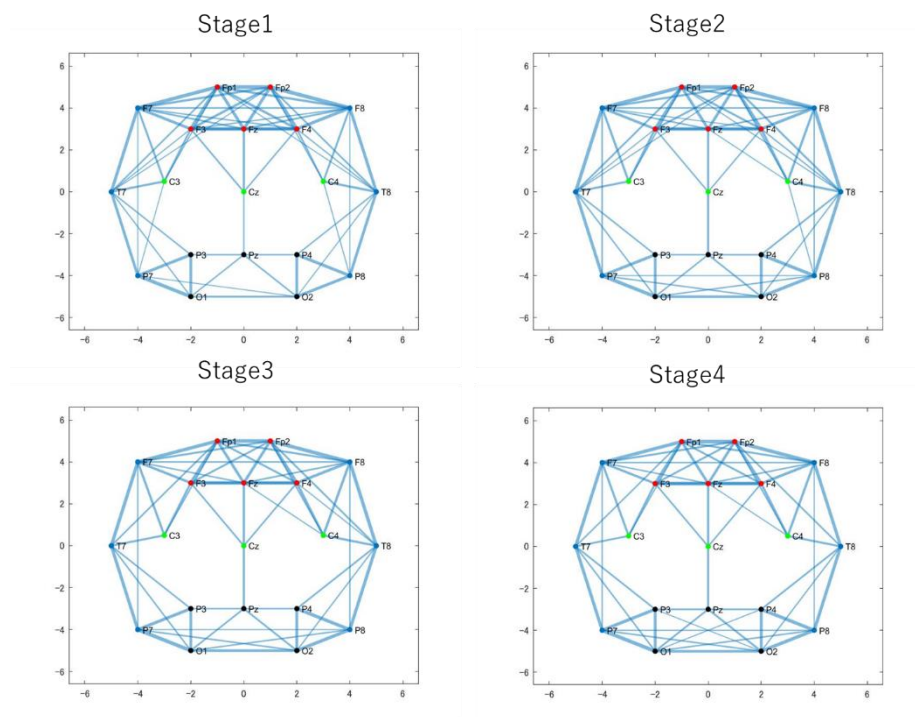


Fig 5. Network graph in Alpha in each sleep stage

Thick edges: high PLV (strong connection) Thin edges: low PLV (weak connection)

(Red node: Frontal, Green: Central, Black: Posterior, Blue: Temporal)

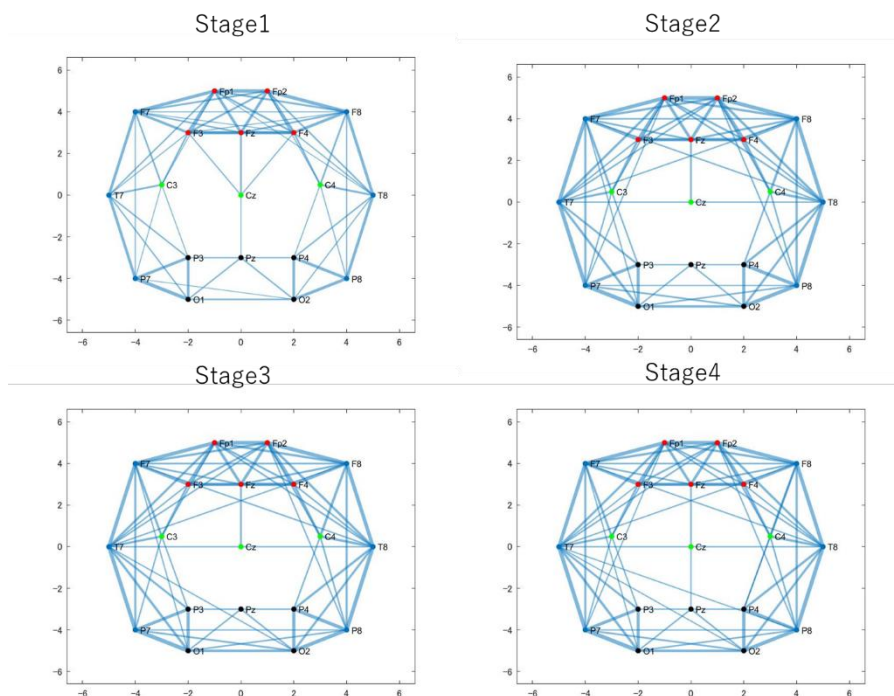


Fig 6. Network graph in LowBeta in each sleep stage

Thick edges: high PLV (strong connection) Thin edges: low PLV (weak connection)

(Red node: Frontal, Green: Central, Black: Posterior, Blue: Temporal)

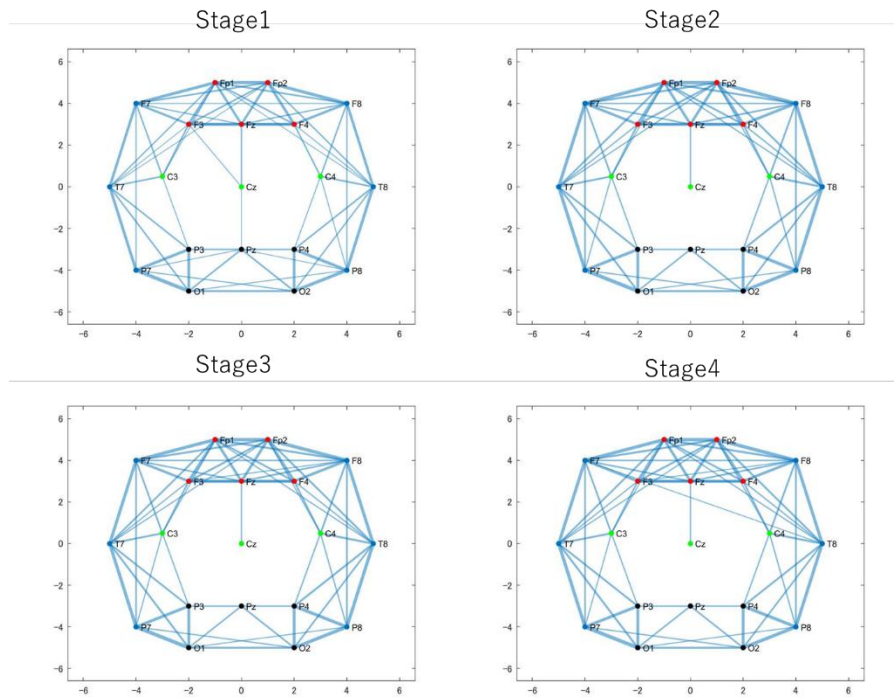


Fig 7. Network graph in UpperBeta in each sleep stage

Thick edges: high PLV (strong connection) Thin edges: low PLV (weak connection)

(Red node: Frontal, Green: Central, Black: Posterior, Blue: Temporal)

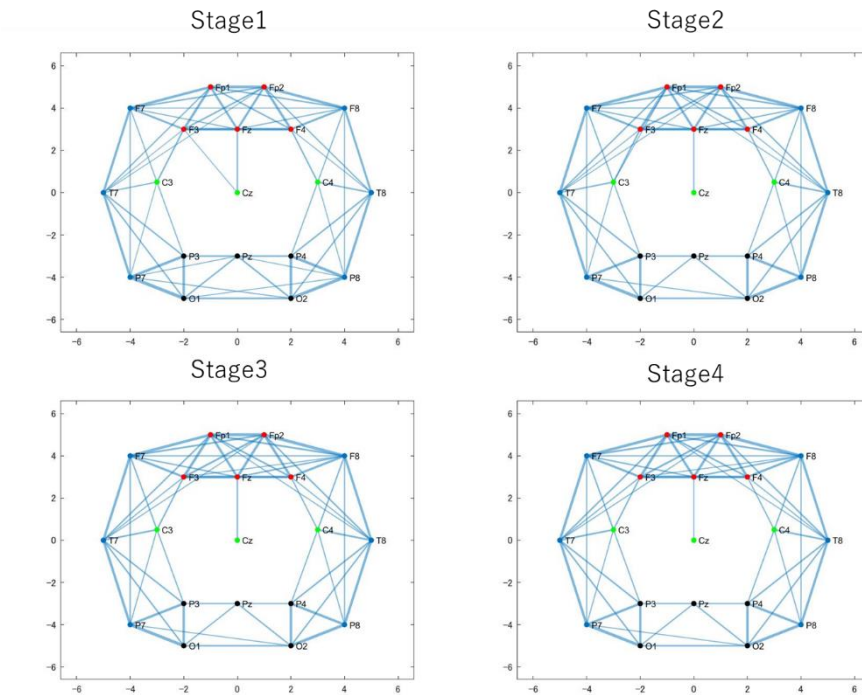


Fig 8. Network graph in Gamma1 in each sleep stage

Thick edges: high PLV (strong connection) Thin edges: low PLV (weak connection)

(Red node: Frontal, Green: Central, Black: Posterior, Blue: Temporal)

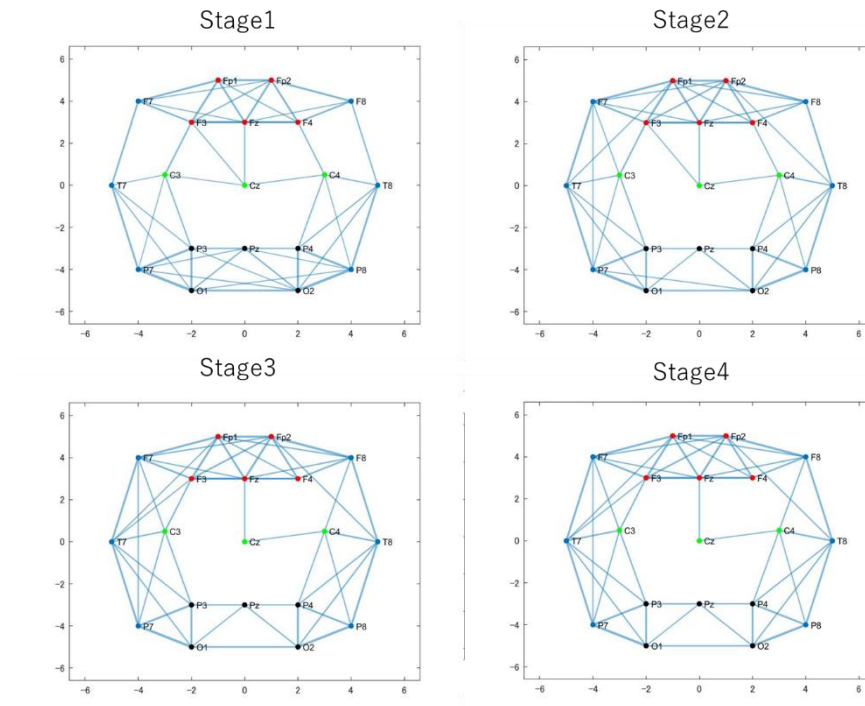


Fig 9. Network graph in Gamma2 in each sleep stage

Thick edges: high PLV (strong connection) Thin edges: low PLV (weak connection)
(Red node: Frontal, Green: Central, Black: Posterior, Blue: Temporal)

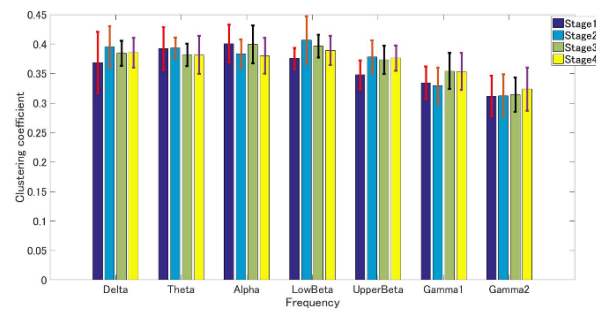


Fig 10. Clustering coefficient in each stage.

2.3.3 Results of clustering coefficient

The average value of the clustering coefficient for each frequency band is shown in Figure 10. Statistical analysis using ANOVA revealed no significant differences between each stage in each frequency band.

2.3.4 Results of characteristic path length

The average characteristic path length for each frequency is presented in Figure 11. Overall, the characteristic path length decreased during middle (Stage 2) and deep (Stages 3 and 4) sleep, with a particularly notable reduction in the LowBeta frequency.

ANOVA results indicated a significant difference between Stage 1 and the other stages in the LowBeta band ($P \leq 0.00833$). In the UpperBeta band, a significant difference was observed between Stage 1 and Stages 2 and 3 ($P \leq 0.00833$).

In Stage 1, the characteristic path lengths for both LowBeta and UpperBeta were at similar levels. However, as sleep deepened, there was a more pronounced decrease in characteristic path length in the LowBeta frequency.

2.3.5 Analysis of small-worldness

Small-worldness was calculated based on the ratio of the clustering coefficients and characteristic path lengths obtained from the baseline and random networks. Figure 12 shows the ratio of the clustering coefficient of the baseline network to that of the random network. Statistical analysis using ANOVA revealed no significant differences between the stages in any of the frequency bands.

Figure 13 shows the ratio of the characteristic path length of the baseline network to that of the random network. The results showed a decrease in this ratio from stage 2 to stage 4, reflecting deeper sleep compared to stage 1, with particularly noticeable changes in the low beta band. ANOVA analysis revealed a significant difference ($P \leq 0.00833$) between the values for stage 1 and those for stages 2 to 4 in the low beta band.

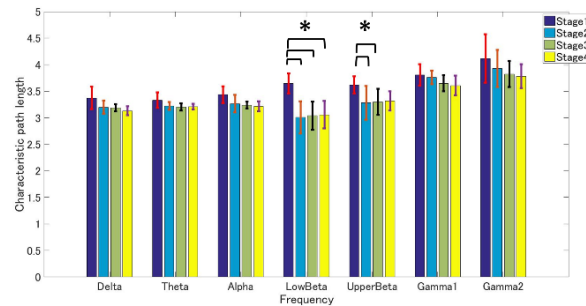


Fig 11. Characteristic path length in each stage.

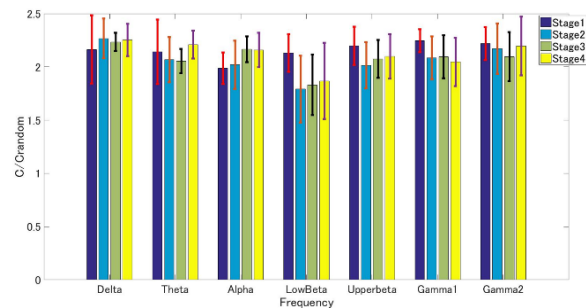


Fig 12. The ratio of the clustering coefficient of the base network to the clustering coefficient of the random network.

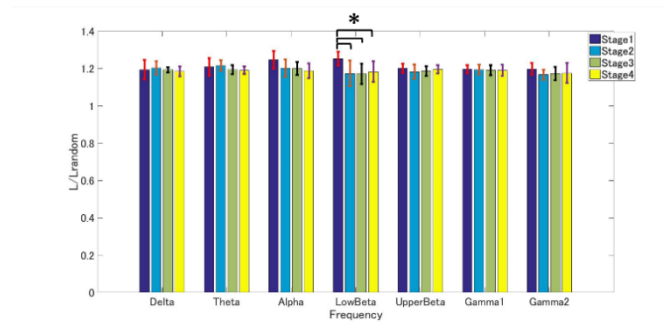


Fig 13. The ratio of the characteristic path length of the base network to the characteristic path length of the random network.

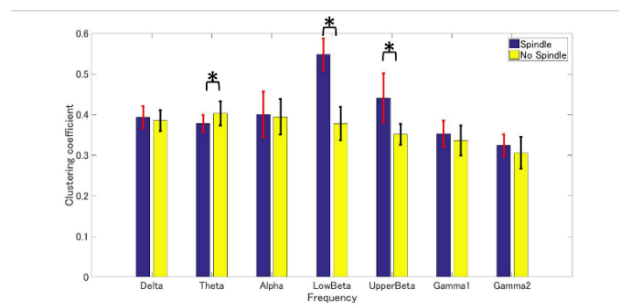


Fig 14. Clustering coefficient of spindle and no spindle.

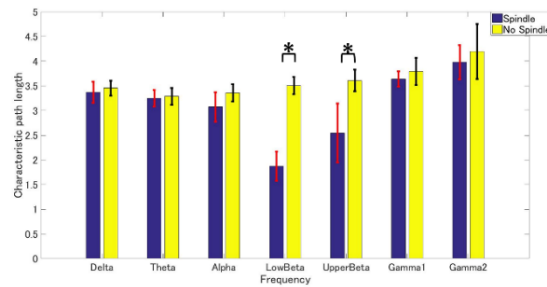


Fig 15. Characteristic path length for spindle and no spindle.

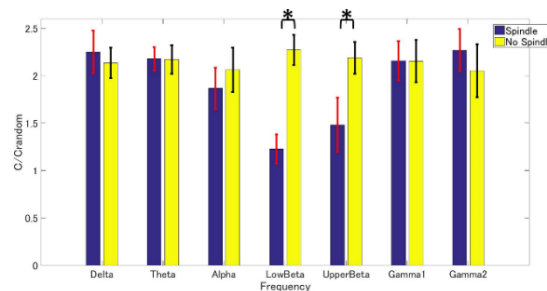


Fig 16. The ratio of the clustering coefficient of the base network to the clustering coefficient of the random network between spindle and no spindle.

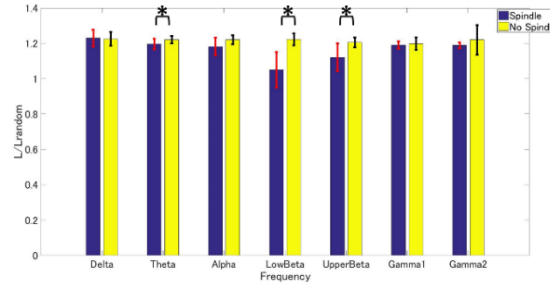


Fig 17. The ratio of the characteristic path length of the base network to the clustering coefficient of the random network between the spindle and no spindle state.

2.3.6 Analysis of the spindle effect

Figure 14 presents the mean clustering coefficient for the spindle and no-spindle states. ANOVA results revealed significant differences in the theta, LowBeta, and UpperBeta bands ($P \leq 0.05$). In the theta band, the clustering coefficient was higher in the no-spindle state compared to the spindle state, whereas in the LowBeta and UpperBeta bands, the clustering coefficient was lower in the no-spindle state than in the spindle state.

Figure 15 shows the mean characteristic path length for the spindle and no-spindle states. Statistical analysis via ANOVA indicated significant differences in the LowBeta and UpperBeta bands ($P \leq 0.05$). The characteristic path length was greater in the no-spindle state compared to the spindle state in both the LowBeta and UpperBeta bands.

Figure 16 shows the ratio of the clustering coefficient of the baseline network to that of the random network for the spindle and no-spindle states. The ANOVA results showed a significant difference in the LowBeta and UpperBeta bands ($P \leq 0.05$). The C/C_{random} was significantly higher in the no-spindle state compared to the spindle state in both the LowBeta and UpperBeta bands.

Figure 17 shows the ratio of the characteristic path length of the baseline network to that of the random network for the spindle and no-spindle states. Statistical analysis via ANOVA revealed significant differences in the theta, LowBeta, and UpperBeta bands ($P \leq 0.05$). The L/L_{random} was notably higher in the no-spindle state compared to the spindle state in the theta, LowBeta, and UpperBeta bands.

2.4 Discussion

In this study, we investigated brain network activity during different stages of sleep. The results showed a reduction in characteristic path lengths as sleep deepened, particularly in the low-beta (13-15 Hz) frequency band, with the shortest path lengths observed during stage 2. In particular, stage 2 was characterized by the appearance of sleep spindles, typically around 14 Hz. Previous research has suggested that sleep spindles are associated with memory consolidation during sleep. Thus, the results of this study may reflect functional integration within networks related to brain activities influenced

by sleep spindles. In contrast, previous studies have examined clustering coefficients and characteristic path lengths during wakefulness, light sleep, and deep sleep [35]. and reported a decrease in clustering coefficients and an increase in characteristic path lengths as sleep deepened. These results show an opposite trend to that observed in our study, which may be due to the fact that previous studies did not focus on specific frequency bands in their analysis.

Several previous studies have examined the characteristic path length in healthy individuals versus those with Alzheimer's disease (AD). Some studies have reported a reduction in path length in AD patients compared to healthy controls[17,18], while others have found an increase in characteristic path length in AD patients[19–21]. Despite these conflicting findings, it has been consistently reported that changes in path length are associated with impaired memory and cognitive function in AD patients, suggesting that these changes may reflect enhanced integration of brain networks accompanied by suppressed cognitive abilities. Furthermore, F. Vecchio et al.(2016) [41] reported a correlation between small-worldness and short-term memory performance, with a positive association between small-worldness in the gamma band (30-45 Hz) and performance on both forward and backward digit span tasks. This finding is consistent with previous research suggesting that gamma-band oscillations (>30 Hz) are involved in several cognitive processes, including memory[42]. In other research, Z. Dai et al. (2017) [43] investigated cortical brain networks using EEG during working memory tasks (2-back task) and control tasks (0-back task), using graph theory analysis to better understand these dynamics. The results showed that the normalized characteristic path length in the theta band (4-7 Hz) was significantly lower during the working memory task than during the control task. In addition, the clustering coefficient in the alpha band (8-12 Hz) was significantly lower during the working memory task than during the control task. These findings suggest an improvement in the efficiency of the brain network, which allows information to propagate more effectively through the network. Consequently, these results suggest that brain network metrics could serve as potential biomarkers for predicting task performance in working memory tasks. Building on findings from previous research, network metrics such as small-worldness and characteristic path length have proven useful for analyzing brain network dynamics during memory processes. Thus, the observed reduction in characteristic path length in the low-beta band during sleep may reflect increased brain network activity associated with memory consolidation, which is consistent with the properties of sleep spindle waves and supports previous hypotheses. Ferri et al. (2007) [44] conducted a comparison of small-worldness and found that the brain exhibits a small-world network-like structure during sleep. In their previous research, they defined the characteristics of a random network by assessing the values of C/C_{random} and L/L_{random} , where both values close to 1 would indicate a random network. Conversely, if C/C_{random} was greater than 1 and L/L_{random} remained close to 1, the network was identified as a small-world network. If both values were higher than 1, the network was considered to be an ordered network. They reported that the network derived from slow-wave EEG during sleep conforms to a

small-world network structure.

In this study, in the delta band, C/C_{random} was higher in Stage 2 through Stage 4 compared to Stage 1; however, no significant differences were observed. Moreover, L/L_{random} values were similar across all stages. Thus, in the delta band, as sleep deepens, the brain network structure increasingly resembles that of a small-world network. These findings align with those of prior research, which demonstrated that small-world networks are established during slow-wave sleep.

In the LowBeta band, C/C_{random} in Stage 2 to 4 decreased compared to stage 1; however, no significant differences were observed. Conversely, a reduction in L/L_{random} was observed across Stages 2 to 4, with significant differences between Stage 1 and Stages 2 to 4. M. Koenis et al. (2013) [45] reported that sleep deprivation influenced C/C_{random} and L/L_{random} during both eye-closed and eye-open resting conditions, making alpha-band networks more random and gamma-band networks more ordered. This suggests that sleep may impact C/C_{random} and L/L_{random} within the brain network. In this study, significant differences in L/L_{random} were observed between Stage 1 and Stages 2 to 4. This result suggests that functional brain networks are more integrated during medium and deep sleep in LowBeta. The network also changes to a more small-world network in medium and deep sleep compared to light sleep. These results indicate that this may be the result of increased integration of brain networks during deeper sleep. There is also a significant difference between the stage 2 spindle and no spindle states in LowBeta and UpperBeta on each graph-theoretic measure. This significant difference indicates that network efficiency may have increased during the appearance of sleep spindle waves, suggesting that the network efficiency that progressed during middle and deep sleep may have increased in response to the appearance of sleep spindle. Considering the role of sleep spindles from previous studies and these results, it is possible that the network efficiency seen when the spindles appeared is related to the role of the sleep spindle, such as memory enhancement, and that the stage 3 and stage 4 results may be due to similar activity.

Based on the above, we believe that the statistically significant differences in indices such as characteristic path length and clustering coefficient between sleep stages seen in this study represent various network activities related to memory associated with sleep. Examples of using biological information during sleep include automatic discrimination of sleep stages. In the case of EEG, there are previous studies that use convolutional neural networks (CNNs) to input EEG data and discriminate sleep stages. These studies have reported that they can discriminate sleep stages with a discrimination rate of over 80% [46], [47], [48]. In recent years, graph neural networks (GNNs), which treat graph structures as input, have become a machine learning method. Previous studies have applied GNNs to EEG, such as emotion estimation. It is expected that the changes in network structure according to sleep stages revealed in this study can be applied to the automatic discrimination of sleep stages based on network activity using GNNs.

However, this study did not include tasks related to cognitive function and memory before or after

sleep. Therefore, it is not possible to say with certainty whether the results of this study show that the network is altered by memory and cognitive function during sleep. In addition, this study attempted to extract non-REM sleep EEG from sleep EEG by considering 90 minutes as one sleep cycle. However, EOG and EMG were not measured. Therefore, the inability to discriminate between NREM and REM sleep using EOG and EMG and the unreliability of non-REM sleep extraction are limitations of this study.

2.5 Conclusion

In this study, a detailed brain network analysis during each sleep stage was conducted using sleep EEG to confirm the validity of graph theory-based network activity analysis during sleep. The results showed that in the low-beta band, which corresponds to the frequency range of sleep spindles associated with memory enhancement, there was a significant reduction in characteristic path length during middle and deep sleep compared to light sleep. The observed differences in functional connectivity and network metrics that are likely related to brain functions during sleep, such as sleep spindle activity, could be used in future research to improve the accuracy of automatic sleep stage classification and to further our understanding of brain activity during sleep. We hypothesize that these results reflect an integrated brain network during middle and deep sleep, facilitated by sleep spindles. Thus, these findings suggest the usefulness of graph theoretical analysis as a valuable tool for investigating detailed network activity during sleep as captured by EEG.

Acknowledgment

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Conflicts of interest

The authors have no conflicts of interest directly relevant to the content of this article.

3 Analysis of time-varying brain network activity using functional connectivity and graph theory during memory retrieval within gamma band(50-80 Hz)

3.1 Background

In Chapter 2, we clarified the functional integration of networks during sleep in the low beta band, which is thought to be the effect of sleep spindles, which are related to memory consolidation during sleep. Therefore, we thought it was necessary to clarify network activity during memory task performance in order to clarify the relationship between memory consolidation and network functional integration. Therefore, in this study, we aim to clarify the relationship between memory processing and changes in network activity using the pair-associative learning task, which is one of the psychological tasks used to evaluate memory function.

3.2 Method

3.2.1 Participants

In this study, the EEG of 14 subjects (age: 22-27 years, 14 males) was measured using the Polymate Pro (Miyuki Giken Corporation, Japan). In this study, nineteen active wet Sn (tin) electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2) were attached to the scalp in accordance with the International 10-20 method (Fig. 18). The reference electrode was placed at CPz and the signals were re-referenced using the average of both earlobes. Participants were instructed to wear an EEG cap, on which the electrodes were placed. The experimenter monitored the correct placement of the electrodes throughout the EEG recording. Prior to data acquisition, electrode impedance was measured to ensure minimal noise in the waveform, and measurements were only initiated if impedance values were below 10 K Ω . This study was conducted in accordance with the ethical guidelines of Kyushu University and the Declaration of Helsinki. Participants were fully informed about the experiment and informed consent was obtained. EEG signals were sampled at a frequency of 1 kHz.

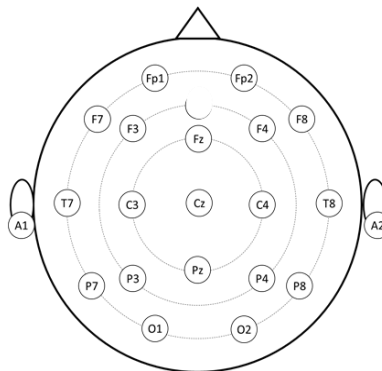


Fig 18. Electrode position

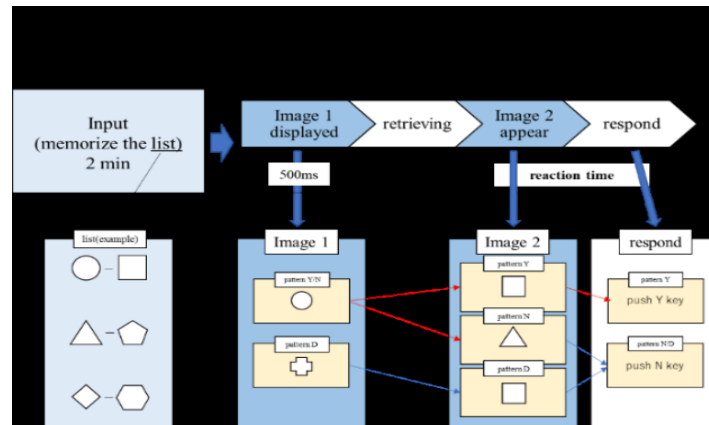


Fig 19. Experiment flow of the paired-associative learning task.

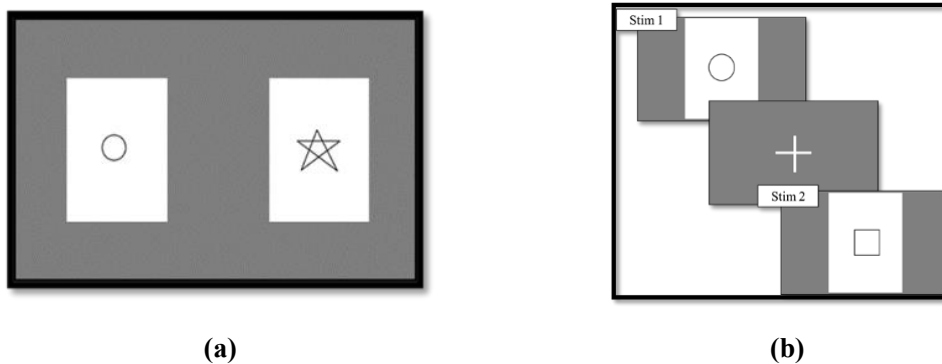


Fig 20. Example of each experimental stage. (a) Example of encoding pair during memory input phase. Participants memorized four-figure pairs in 120 s. (b) Example of the flow of the PAL task. Participants saw stimulus 1, then they remembered the other figure of the pair before stimulus 2 appeared. After stimulus 2 appeared, the participants recalled whether stimulus 1 and stimulus 2 were paired or not

3.2.2 Experiment design

The present study employed a paired-associative learning (PAL) task to examine the dynamics of memory retrieval during free recall. PAL is a well-established paradigm in memory research, wherein items, such as words or numbers, are learned in pairs, and the retrieval of one item prompts the recall of its paired counterpart [49].

First, a resting EEG was recorded for three minutes with the participants' eyes open in a standard room environment. During this resting period, participants fixated on a cross displayed on a 26.8 cm × 47.6 cm screen. After the rest period, participants performed the PAL task. The experimental procedure for the PAL task is shown in Figure 19. The task consisted of three phases: an encoding period, a memory check, and a test. During the encoding phase, participants were required to memorize four pairs of figures. The pairs were presented horizontally on the display, and participants were asked to remember these pairs. Each encoding period lasted 120 seconds, as each pair was shown for 10 seconds and displayed three times, as depicted in Figure 20(a).

A memory check was then conducted to assess whether the participants had successfully memorized the pairs. The procedure for the memory check is shown in Figure 20(b). In this phase, four shapes from one of the pairs were sequentially presented, and participants were instructed to press the "Y" key on the keyboard when they could recall the pair. Two distinct tasks were performed during the experiment, with each task using entirely different shape pairs. The final phase of the task, the test phase, consisted of 90 trials. Each trial began with a 500 ms interval, followed by the presentation of Stimulus 1 for 100 ms, which was then followed by a 1900 ms search period. Subsequently, Stimulus 2 was displayed. Stimulus 1 appeared in two patterns: remembered shapes (Target) and unfamiliar shapes (Distractor).

The target presented as stimulus 1 was the figure to the left of the pair shown during the encoding phase. If the figure presented as stimulus 1 matched one of the figures remembered from the encoding phase, participants were asked to recall the corresponding figure from the pair during the retrieval phase. If stimulus 2 matched the correct pair for stimulus 1, participants responded by pressing the "Y" key (Y pattern). If stimulus 2 did not form the correct pair, participants responded by pressing the "N" key (N pattern). In cases where the figure presented as Stimulus 1 was unfamiliar, participants were not required to engage in recall during the retrieval phase (D pattern). Furthermore, when stimulus 2 was presented in these situations, participants responded by pressing the "N" key, as it could not be considered a valid pair for any figure.

Following the presentation of Stimulus 2, the interval for the next trial commenced upon receiving input from the keyboard. The D, N, and Y patterns each appeared 30 times across the 90 trials. However, since the N and Y patterns were functionally identical during the retrieval phase, the analysis focused on comparing the D (Distractor) pattern with the T (Target) pattern. The N and Y patterns were included in the experiment to ensure that participants were performing the task correctly.

3.2.3 EEG analysis

All EEG analyses were conducted using MATLAB (MathWorks Natick, USA) integrated with the Brainstorm [33] and Brain connectivity toolbox [34]. EG data were first processed using band-pass filters in the frequency ranges of 20–60 Hz and 40–90 Hz, along with a 60 Hz notch filter to eliminate power supply noise. Following filtering, Independent Component Analysis (ICA) was applied to remove components associated with artifacts, such as eye movements, using the Infomax algorithm in Brainstorm. The Infomax algorithm is the one of ICA methods that maximize joint entropy $H(u) = H(x) + \log|W|$, via a gradient-based approach. After performing ICA, we discarded the components that exhibited significant power in the frontal regions, which were identified as eye saccade artifacts. Epochs were then extracted from -500 ms to 1000 ms, with 0 ms corresponding to the presentation of Stimulus 1 for each condition.

To detect Gamma-Band Responses (GBRs), which are indicators of memory retrieval, we conducted time-frequency analysis on these epochs in both the low-gamma (30–50 Hz) and high-gamma (50–80 Hz) bands, following methods established in previous research [50]. A Morlet wavelet transform was

Table 1. Accuracy of the task for each participant

Participants No.	Test 1	Test 2
1	97 %	100 %
2	98 %	83 %
3	97 %	97 %
4	99 %	99 %
5	94 %	98 %
6	94 %	96 %
7	52 %	63 %
8	96 %	99 %
9	97 %	97 %
10	98 %	94 %
11	98 %	99 %
12	99 %	97 %
13	99 %	97 %
14	99 %	99 %

applied to each epoch of the Target and Distractor conditions for each participant. The baseline was defined as the average from -400 ms to -100 ms prior to the first stimulus presentation. The data were then averaged across the 23 trials for each condition (Target and Distractor).

3.2.4 Complex network analysis

PLVs) were calculated in both the low gamma band (30–50 Hz) and high gamma band across multiple time windows: 0–100 ms, 100–200 ms, 200–300 ms, 300–400 ms, and 400–500 ms, with intervals of 100 ms, following the presentation of Stimulus 1. To assess EEG activity not only as functional connectivity (FC) between electrodes but also as a network, we performed a complex network analysis, treating electrodes as nodes and the inverse of the PLV as edges. Specifically, we computed clustering coefficients as a measure of functional segregation and characteristic path lengths as a measure of functional integration. These values were standardized using random networks to investigate small-worldness. In previous research [6], [50], thresholding connection weights have been employed when constructing network graphs, with some studies binarizing the connection weights[51], [52]. However, the results of network analyses were shown to be sensitive to the thresholding method applied. Conversely, studies that used weighted connections when constructing the network graph did not employ thresholding. In the present study, consistent with previous research, no thresholding was applied during network construction, as each edge was weighted based on PLVs to minimize the influence of thresholding on the analysis.

3.3 Result

3.3.1 Behavioral analysis results

The percentage of correct responses for each participant on the task is presented in Table 1. Most

participants achieved scores close to 100% on both tests. However, Participant No. 2 scored below 90% on Test 1, and Participant No. 7 scored below 90% on both Test 1 and Test 2. Participant No. 7 was excluded from the subsequent analysis due to a low accuracy rate of approximately 50% and 60% for Test 1 and Test 2, respectively. Although Participant No. 2's performance on Test 2 was relatively high (83%), the trials in which the participant failed were inconsistent. Additionally, in the post-experimental questionnaire, Participant No. 2 reported not completing Test 2, and thus, this test result was excluded from further analysis. Consequently, 23 trials from 12 participants were included in the EEG analysis.

3.3.2 Time-frequency analysis result

3.3.2.1 High-gamma band (50–80 Hz)

After performing a time-frequency analysis of the high gamma band, the difference between the Target and Distractor conditions (Target - Distractor) is shown in Figure 21. The results show that the Target condition showed higher activity from approximately 200 ms to 400 ms after the first stimulus presentation. The power spectrum of the two conditions at 70 Hz at approximately 300 ms is shown in Figure 22, where greater power was observed throughout the brain in the Target condition.

3.3.2.2 Low-gamma band (30–50 Hz)

The results of the comparison between the Target and Distractor conditions (Target - Distractor) derived from the time-frequency analysis of the low gamma band are presented in Figure 23. The power spectrum at 30 Hz around 100 ms is depicted in Figure 24. Notably, higher activity was observed across a broader range in the Distractor condition compared to the Target condition. In both conditions, elevated activity was observed predominantly in the central regions of the brain.

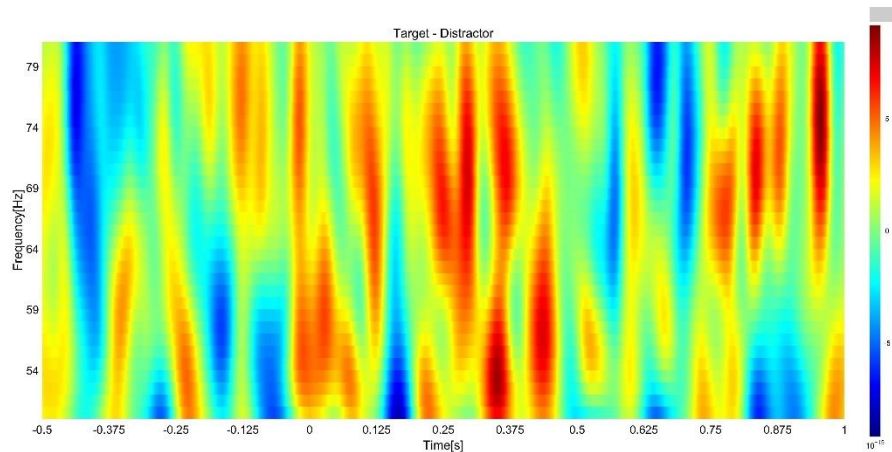
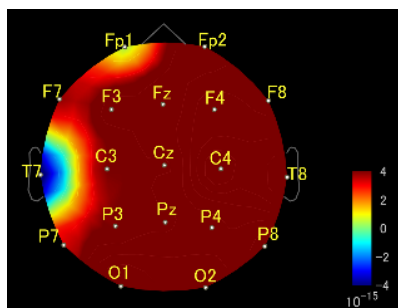
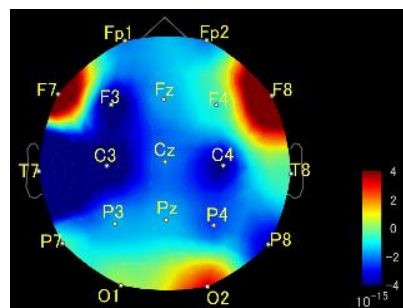


Fig 21. The time-frequency analysis results for the high-gamma band (50–80 Hz).

(a) Target condition. (b) Distractor condition (vertical axis: Hz, horizontal axis: ms).



(a)



(b)

Fig 22. The power of the high-gamma band (70 Hz) at 300 ms.

(a) Target condition. (b) Distractor condition.

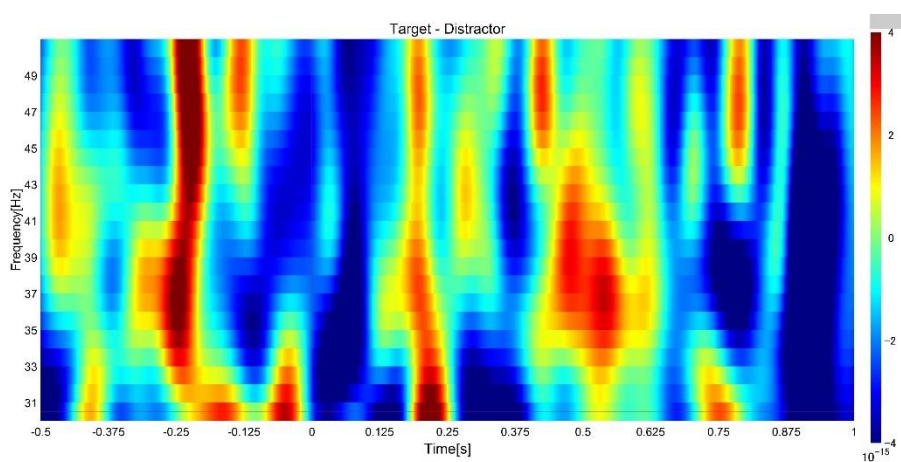
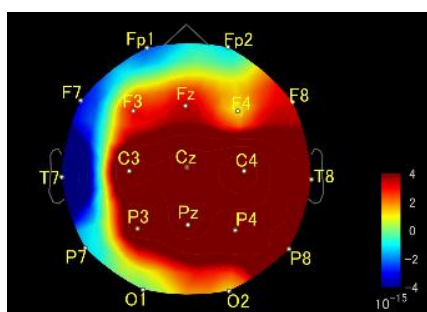
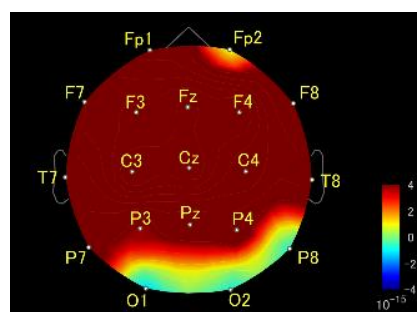


Fig 23. The time-frequency analysis results for the low-gamma band (30–50 Hz).

(a) Target condition. (b) Distractor condition (vertical axis: Hz, horizontal axis: ms).



(a)



(b)

Fig 24. The power of the low-gamma band (30 Hz) at 100 ms.

(a) Target condition. (b) Distractor condition.

3.3.3 The complex network analysis result

3.3.3.1 High-gamma band (50–80 Hz)

The average clustering coefficients for the high gamma band across each time segment (0-100 ms, 100-200 ms, 200-300 ms, 300-400 ms, and 400-500 ms) within each brain region are presented in Table 2. The results of the averaged clustering coefficients across regions are shown in Figure 25. Asterisks(*) in the figure indicate significant differences between the Target and Distractor conditions, as determined by a t-test. In the frontal regions, the clustering coefficients were significantly higher in the Distractor condition across all time windows. In other regions, significant differences were observed between the two conditions in multiple time windows. Notably, in the left temporal region, significant differences were found only in the 400-500 ms time window.

Table 3 presents the average characteristic path lengths for the high gamma band in each time segment within each region. Figure 26 displays the results of the characteristic path lengths across the specified time segments (0-100 ms, 100-200 ms, 200-300 ms, 300-400 ms, and 400-500 ms) for each region. Characteristic path lengths were generally shorter in most time windows across the global, frontal, right, and left hemispheres. However, no significant differences were observed in the posterior regions. The results of the averaged small-worldness in the high gamma band for each time window across regions are provided in Table 4. No significant differences in small-worldness were found between the Target and Distractor conditions at any of the time segments.

Table 2. Clustering coefficient in the high-gamma band (*: P<0.05)

	ALL		Frontal		Posterior		Right		Left	
	Target	Distractor	Target	Distractor	Target	Distractor	Target	Distractor	Target	Distractor
0–100 ms	0.515	0.544	0.755	0.775	0.483	0.528	0.524	0.545	0.640*	0.698*
100–200 ms	0.509*	0.558*	0.744*	0.790*	0.482	0.545	0.520*	0.556*	0.643*	0.698*
200–300 ms	0.508	0.548	0.748*	0.777*	0.480	0.534	0.519	0.549	0.640*	0.696*
300–400 ms	0.510*	0.546*	0.754	0.770	0.479	0.528	0.521	0.553	0.639*	0.702*
400–500 ms	0.509*	0.559*	0.742*	0.774*	0.483*	0.549*	0.518*	0.558*	0.637*	0.706*

Table 3. Characteristic path length in the high-gamma band (*: P<0.05)

	ALL		Frontal		Posterior		Right		Left	
	Target	Distractor	Target	Distractor	Target	Distractor	Target	Distractor	Target	Distractor
0–100 ms	2.32*	2.07*	2.17*	1.88*	1.83	1.75	2.39	2.13	2.37*	1.95*
100–200 ms	1.99*	1.70*	1.81*	1.53*	1.49	1.42	2.03*	1.78*	2.04*	1.60*
200–300 ms	1.99*	1.63*	1.74*	1.41*	1.39	1.34	1.96*	1.74*	1.96*	1.51*
300–400 ms	2.26*	1.97*	2.09*	1.78*	1.78	1.67	2.31*	2.07*	2.32*	1.89*
400–500 ms	2.42*	2.16*	2.23	2.03	1.94	1.90	2.46*	2.27*	2.48*	2.04*

Table 4. Small-worldness in the high-gamma band (*: P<0.05)

	ALL		Frontal		Posterior		Right		Left	
	Target	Distractor	Target	Distractor	Target	Distractor	Target	Distractor	Target	Distractor
0–100 ms	0.944	0.955	0.997	0.992	0.998	0.999	0.971	0.978	0.980	0.987
100–200 ms	0.947	0.965	0.995	0.996	0.997	0.999	0.974	0.976	0.979	0.990
200–300 ms	0.943	0.956	0.998	0.996	0.998	0.999	0.967	0.981	0.976	0.990
300–400 ms	0.949	0.960	0.995	0.996	0.998	0.999	0.974	0.976	0.983	0.983
400–500 ms	0.944	0.967	0.996	0.997	0.998	0.998	0.965	0.981	0.976	0.988

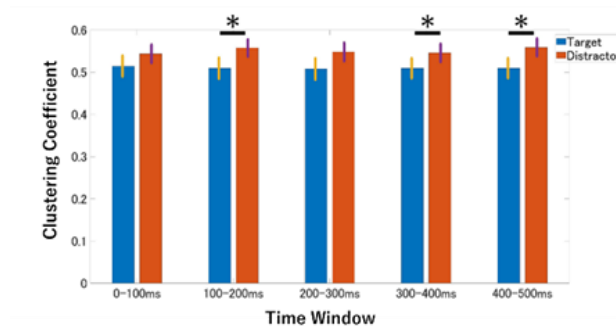


Fig 25. The clustering coefficient of all areas in each 100-ms window for the high-gamma band (50–80 Hz)

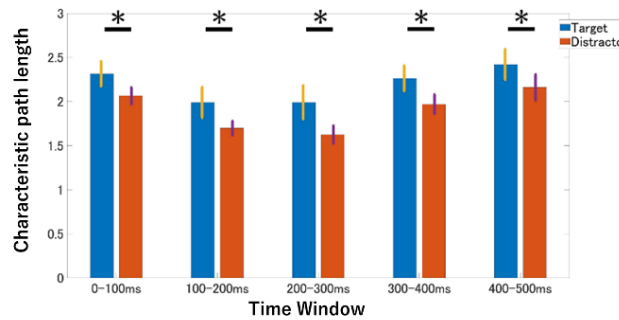


Fig 26. The characteristic path length of all areas in each 100-ms window for the high-gamma band (50–80 Hz)

3.3.3.2 Low-gamma band (30–50 Hz)

Table 5 shows the clustering coefficients for the low gamma band. Figure 27 shows the averaged clustering coefficients over the whole region for each time window (0-100 ms, 100-200 ms, 200-300 ms, 300-400 ms, and 400-500 ms). Significant differences were observed only in the 0-100 ms time window in both the global and right hemisphere regions, where the distractor condition showed higher values.

The results for the characteristic path lengths in the low gamma band are shown in Table 6. Figure 28 shows the averaged characteristic path lengths for each time segment (0-100 ms, 100-200 ms, 200-300 ms, 300-400 ms, and 400-500 ms) across all regions. The characteristic path lengths for the distractor condition were significantly shorter in the 0-100 ms time window across all regions (ALL) and in the right hemisphere.

Table 7 summarises the results for small-worldness in the low gamma band. No significant differences were found in any of the time windows or regions.

Table 5. Clustering coefficient in the low-gamma band (*: P<0.05)

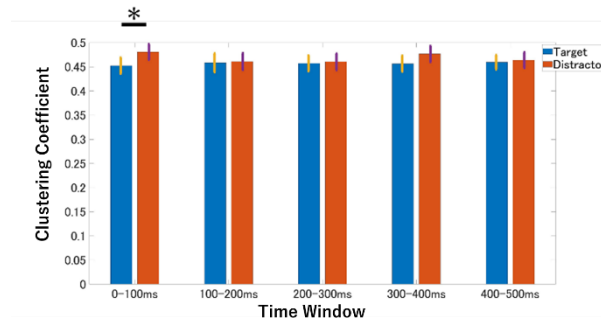
	ALL		Frontal		Posterior		Right		Left	
	Target	Distractor	Target	Distractor	Target	Distractor	Target	Distractor	Target	Distractor
0–100 ms	0.453*	0.481*	0.655	0.656	0.740	0.756	0.471*	0.489*	0.471	0.496
100–200 ms	0.458	0.461	0.655	0.660	0.742	0.729	0.474	0.474	0.480	0.478
200–300 ms	0.457	0.461	0.654	0.671	0.742	0.749	0.470	0.463	0.475	0.486
300–400 ms	0.457	0.477	0.648	0.668	0.735	0.749	0.468	0.496	0.483	0.490
400–500 ms	0.460	0.464	0.664	0.647	0.738	0.737	0.476	0.471	0.483	0.488

Table 6. Characteristic path length in the low-gamma band (*: P<0.05)

	ALL		Frontal		Posterior		Right		Left	
	Target	Distractor	Target	Distractor	Target	Distractor	Target	Distractor	Target	Distractor
0–100 ms	2.45*	2.30*	1.73	1.66	1.39	1.37	2.42*	2.29*	2.44	2.33
100–200 ms	2.43	2.40	1.71	1.68	1.39	1.41	2.41	2.38	2.38	2.38
200–300 ms	2.43	2.39	1.69	1.63	1.39	1.38	2.40	2.43	2.42	2.34
300–400 ms	2.42	2.34	1.72	1.68	1.40	1.38	2.42	2.27	2.37	2.34
400–500 ms	2.41	2.38	1.67	1.67	1.40	1.41	2.38	2.38	2.37	2.38

Table 7. Small-worldness in the low-gamma band (*: P<0.05)

	ALL		Frontal		Posterior		Right		Left	
	Target	Distractor	Target	Distractor	Target	Distractor	Target	Distractor	Target	Distractor
0–100 ms	0.938	0.945	0.995	0.993	0.998	0.997	0.961	0.976	0.968	0.966
100–200 ms	0.940	0.942	0.999	0.996	0.998	0.998	0.963	0.966	0.967	0.965
200–300 ms	0.938	0.934	0.996	0.998	0.998	0.998	0.966	0.962	0.967	0.962
300–400 ms	0.940	0.940	1.000	0.996	0.998	0.998	0.963	0.973	0.971	0.970
400–500 ms	0.939	0.939	0.999	0.995	0.998	0.998	0.963	0.962	0.970	0.963

**Fig 27. The clustering coefficient of all areas in each 100-ms window for the low-gamma band (30–50 Hz)**

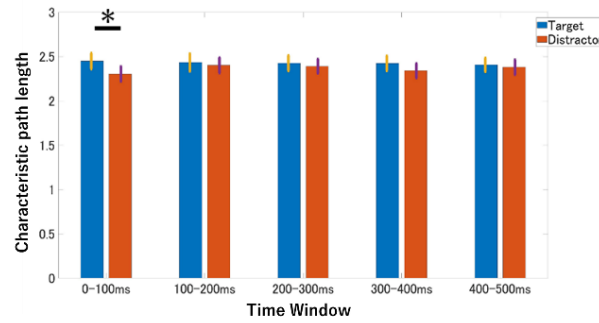


Fig 28. The characteristic path length of all areas in each 100-ms window for the low-gamma band (30–50 Hz)

3.4 Discussion

In the present study, a time-frequency analysis was conducted using the average EEG data from all electrodes, consistent with previous research. The results confirmed the presence of a gamma-band response (GBR) in the high gamma band, which is associated with the end of memory retrieval. Similar GBRs were observed in the target condition, which aligns with findings from earlier studies[17], showing similar frequency bands. However, a difference was found in the latency of the GBRs in this study, which was shorter compared to previous research. This discrepancy in latency can likely be attributed to differences in participants' performance between the current study and earlier studies. Based on these findings, we conclude that GBR, indicative of memory retrieval, can be effectively measured using scalp EEG after removing the influence of micro-saccades through Independent Component Analysis (ICA). Considering the results in the high gamma band, the low gamma band focused on the time segment before 300 ms. Differences in power between the target and distractor conditions were observed immediately after stimulus presentation and approximately 100 ms later. This may be because the distractor condition showed higher activity over a larger area than the target condition, as shown by the power spectrum results for the two conditions at 100 ms after stimulus presentation. However, previous studies have shown inconsistent results regarding the effects of object perception on GBA [53]. In this study, the distractor was considered a 'meaningless' object in that it did not require an active search. However, it was not entirely devoid of meaning, as a response to Stimulus 2 was still required in the distractor condition. Additionally, in this condition, the object pair was not memorized in advance and needed to be learned during the task, which likely led to increased attention compared to the already memorized figure pair. Regarding the inhibitory response observed between approximately 200 ms and 500 ms, it was detected at frequencies below approximately 35 Hz. From this perspective, the increase in pre-stimulus β -band activity is thought to enhance memory retrieval performance [54]. While the gamma band is typically defined as frequencies above 30 Hz, some studies include frequencies below 35 Hz within the β -band [55], leading to varying

interpretations of the low-gamma band across studies. This suggests that within the 30-50 Hz frequency range considered low gamma in the present study, the 30-35 Hz range may be associated with task preparation.

In the high-gamma band, we observed that the clustering coefficient in the target condition was lower compared to the distractor condition, while the characteristic path length in the target condition was longer than in the distractor condition. These findings suggest that the brain network in the distractor condition is more efficient than in the target condition across nearly all time windows, except for the occipital region. In contrast, a previous study compared PLVs in the gamma band between the target and interference conditions during a separate task, where participants were simply presented with test-like stimuli. The results indicated an increase in PLV in the target condition. However, to perform memory recall, the intention to retrieve the memory and attention to the specific memory to be retrieved are required [56]. We believe that the results derived from the comparison with previous studies may not be directly related to memory recall alone. To address this, we compared recall and non-recall conditions across successive tasks. The findings indicated that, as previously mentioned, network activity in the high gamma band was nearly identical in both conditions. In most instances, network efficiency was higher in the distractor condition, though the statistical differences were minimal. This may reflect the participants' tendency to wait for the presentation of stimulus 2, irrespective of the distractor condition. While performance improved during recall, it is possible that the observed effects were not as pronounced as anticipated due to the simplicity of the shapes used in the task, which likely required minimal cognitive effort for recall. However, it is difficult to draw definitive conclusions based on this experiment alone.

The results of the low-gamma network analysis showed significantly higher clustering coefficients and shorter characteristic path lengths in the 0-100 ms window in the distractor condition. This is consistent with the time-frequency analysis, which showed higher power in the distractor condition at 100 ms, with a broader distribution compared to the target condition, possibly indicating increased attention to the task. Although we hypothesized that there might be a specific function related to memory retrieval, our results did not support this notion. There are two possible explanations for this finding. First, the low gamma band may not be directly involved in memory retrieval. Alternatively, as mentioned above, the task may have been too simple to evoke the necessary neural activity and thus failed to produce a discernible difference. Future experiments with more challenging task conditions are needed to clarify this issue.

We also examined the clustering coefficients and characteristic path lengths between the two conditions in different brain regions. In the high gamma band, significant differences in clustering coefficients between the two conditions were observed in every region. However, no significant differences in characteristic path lengths were found within the frontal and posterior regions. These results suggest that characteristic path lengths may be influenced by more widespread network activity

across the brain. In the low gamma band, significant differences in both clustering coefficients and characteristic path lengths were only observed in the right hemisphere. Given that the right hemisphere is involved in memory and visual processing, these results may reflect the influence of activation in brain areas related to memory retrieval and visual processing, which likely contributed to the observed differences in clustering coefficients and characteristic path lengths.

We believe that the present study has captured changes in brain network activity during induced memory retrieval. The results showed that the efficiency of the network decreased during the presentation of the target image at around 300-500 ms when the GBR should have been observed. As mentioned above, this result was contrary to the hypothesis of this study, but we believe that we were able to capture the temporal characteristics of the inefficiency of the network. Temporal features of the EEG during motor recall have been used as input in the field of brain-computer interfaces[57]. There is also previous research showing that phase-based functional connectivity and alpha-band spectral density can be used to improve the discrimination rate between motor recall and real movement[58]. Based on the above, we believe that the temporal features of network activity, as well as the power spectrum of the EEG, could be used in BCI for more accurate or more complex state identification.

A limitation of this study is that the experiments used in this study did not adequately capture the reaction time and accuracy of the retrieval itself. Therefore, it was not possible to determine the exact relationship between retrieval performance and brain activity. The results of this study also raise the question of whether the memory load was too low. Based on these findings, future experiments should be conducted using tasks with a higher memory load, where the timing of retrieval can be visualised. Although the present study only compared retrieval with and without recall, it is possible that the most demanding memory tasks for participants are those that they cannot recall despite their best efforts. Therefore, it may be necessary to compare the patterns of inability to recall despite effort that occur when more memory demanding tasks are performed. As a new task, we are considering using tasks with a higher memory load, such as pair-associative learning tasks where more pairs of numbers have to be remembered, or n-back tasks, to better analyze the time variation of the brain network during memory retrieval.

3.5 Conclusions

In this study, two hypotheses were proposed:

- (1) FC actively operates as a network during memory retrieval, and this network activity can be quantitatively assessed using complex network analysis,
- (2) Differences may exist in the low-gamma band, which is associated with attention, in relation to memory retrieval.

To address these hypotheses, we conducted an investigation based on the study by Gruber et al[17]. Time-frequency analysis of the high-gamma band yielded results consistent with previous research.

Additionally, a network analysis was performed to compare network efficiency during memory retrieval and non-retrieval conditions. Contrary to expectations, network efficiency was found to be higher during the non-memory retrieval condition. For the low-gamma band, neither time-frequency nor network analysis revealed significant activity related to memory retrieval. Several factors may explain these findings. One possible reason is the difference in the comparison conditions between our study and that of Gruber et al. In their study, retrieval was compared with other tasks, whereas our study compared retrieval and non-retrieval within a series of tasks. This difference may account for the higher gamma band activity observed in the distractor condition, which likely reflects participants' focused attention on awaiting stimulus 2. There are two possible explanations for the lack of significant findings in the low-gamma band. First, it is possible that the low-gamma band is not associated with memory retrieval. Alternatively, the lack of difference may be attributed to methodological issues, such as network thresholding and memory load. Regarding the threshold issue, we did not apply a threshold to the network edges, following the approach of previous research [59]. This was due to the lack of a clear guideline for an appropriate threshold. The absence of thresholding may have impeded the detection of meaningful differences in network activity. Regarding memory load, previous studies on working memory have shown that GBA increases under conditions of higher memory load [60]. Therefore, future research could explore whether the observed results are influenced by the complexity of the task materials. While the results of this study were unexpected, we believe that our analysis provides a novel approach to network analysis that captures temporal changes in network activity. Future work will address the thresholding issue, refine the distractor conditions, and investigate retrieval versus non-retrieval tasks using more complex stimuli.

Institutional Review Board Statement

The study was conducted by the Declaration of Helsinki and approved by the ethical principles of Kyushu University (シス情 2021-14).

Informed Consent Statement:

Informed consent was obtained from all participants involved in the study.

Acknowledgments:

This study was supported by JSPS KAKENHI Grant Number B 21H03853.

Conflicts of Interest:

The authors declare no conflicts of interest directly relevant to the content of this article.

4 Analysis of the time-varying of EEG-based network activity during n-back task in theta band (4-8 Hz)

4.1 Background

In Chapter 3, we performed an analysis to clarify memory processing and changes in network activity. As a result, it was revealed that when a target image was presented, which involves memory search and recall, an inefficient network was observed in which parts of the brain moved separately. This is thought to be because the pair associative learning task used was a complex task, and the brain was paying attention to processing information and the next stimulus.

Therefore, in this study, we used a simpler memory task, the 2-back task, and performed network analysis by focusing only on memory processing. At the same time, we took advantage of the high time resolution of EEG to conduct research focusing on more detailed changes in network structure over time.

4.2 Method

4.2.1 Participants

In this study, EEG was recorded in 14 participants (age: 22–27 years, Male: 14) using Polymate Pro (Miyuki Giken Co., Ltd., Japan). In this study, nineteen active wet Sn (tin) electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, and O2) were placed on the scalp according to the international 10-20 system (Figure 2). The reference electrode was placed at CPz and the signals were re-referenced using the average of both earlobes. Participants were instructed to wear an EEG cap, on which the electrodes were placed. The experimenter monitored the correct placement of the electrodes throughout the EEG recording. Before data acquisition, electrode impedance was measured to ensure minimal noise in the waveform, and measurements were only initiated if impedance values were below 10 K Ω . This study was conducted in accordance with the ethical guidelines of Kyushu University and the Declaration of Helsinki. Participants were fully informed about the experiment and informed consent was obtained. EEG signals were sampled at a frequency of 1 kHz.

4.2.2 Experiment design

In this study, we used the n-back task to clarify the dynamics of memory retrieval in free replay. During the experiment, the participant performed three variants of the task: 0back, 1back, and 2back. Alphabetic letters served as visual stimuli. A fixation point was placed between each stimulus to eliminate any potential confusion regarding the stimuli. In the 0back condition, the target stimulus was communicated to the participant before the start of the experiment. In the 1back task, if the current stimulus corresponded to the previous stimulus, it was referred to as the target stimulus. Similarly, in the 2back task, if the current stimulus matched the two preceding stimuli, it was reported as the target stimulus. In both cases, the participant was instructed to press the "J" key when the target stimulus was displayed and to press the "L" key when a non-target stimulus was displayed.

Figure 2 shows the experiment flow. First, we recorded an eye-opening resting EEG in 3 min in the

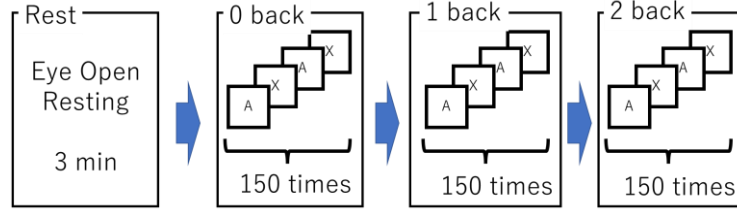


Fig 29. Experiment flow.

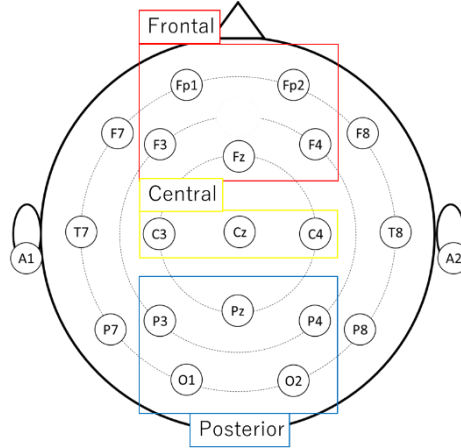


Fig 30. Electrode position and region of interest.

normal room. Participants gazed at the fixed cross on the screen which the display size is 26.8 cm $\times$ 47.6 cm. Participants then completed the n-back task. In this study, Participants were asked to perform the Tasks in the order 0, 1, and 2back. Participants got visual stimuli 150 times in each trial. The ratio of target and non-target stimuli is 1:2 (50:100). Between tasks, participants take a resting at least 1 min. Stimulus presentation was conducted so that it took at least 1 s from one presentation of the alphabet to the next.

4.2.3 EEG preprocess

The EEG data were analyzed using MATLAB (MathWorks Natick, USA) embedded with the Brain connectivity toolbox [34]. The raw data underwent bandpass filtering (1-30 Hz, linear phase FIR filter, Kaiser window). Subsequently, an independent component analysis (ICA, Infomax) was performed to eliminate signal components considered to be artifacts resulting from blinks and body movements. Finally, trial data containing residual artifacts were visually inspected and excluded from the analysis to obtain the data for analysis.

4.2.4 Time-Network analysis

For time-varying network analysis, we calculated time-varying PLV in each epoch. We calculated average time-varying PLV between frontal-posterior, central-posterior and frontal-central areas (Figure 29) to compare network activity across brain regions. In order to evaluate the EEG activity as a network rather than just the PLV between electrodes, a complex network analysis was performed using the electrodes as nodes and the inverse of the PLV as edges. First, phase information was

extracted from each channel of EEG data by Hilbert transform in the theta (4-8 Hz) and alpha (8-12 Hz) bands. Then, PLVs are calculated in a 100 ms time window at each epoch and this time window is shifted by 10 ms to calculate time-varying PLVs. Thus, 100 PLVs are calculated per epoch. For each task, the average of 150 time series of the PLVs obtained is calculated and compared. Then, as a dynamic network analysis, the clustering coefficient and characteristic path length were calculated for each time window of the time-series PLV. To compare PLV, clustering coefficient and characteristic path length between tasks, each value is averaged for 6 subjects and compared between tasks.

In this study, betweenness centrality is calculated every 100 ms after stimulus presentation to focus on changes in which region becomes the main hub of information transmission. The higher the value, the more important it is as a key network pathway chosen for information transmission.

This betweenness centrality is calculated using the following formula.[30], [61]

$$b_i \equiv \frac{\sum_{i_s=1; i_s \neq i}^N \sum_{i_t=1; i_t \neq i}^{i_s-1} \frac{g_i(i_s i_t)}{N_{i_s i_t}}}{(N-1)(N-2)/2}$$

where $g_i(i_s i_t)$ is the number of shortest paths from the starting point v_{i_s} to the ending point v_{i_t} that pass through v_i and $N_{i_s i_t}$ is the total number of shortest paths from the starting point v_{i_s} to the ending point v_{i_t} .

The present study compares the change in betweenness centrality at each electrode during 0, 1 and 2 backtracking tasks.

4.3 Results

4.3.1 Functional connectivity analysis result

Figure 30 shows the result of time-varying PLV between frontal and posterior, central and posterior, and frontal and central area in theta band. However, there are no significant differences between tasks at each time.

Figure 31 shows the result of time-varying PLV between frontal and posterior, central and posterior, and frontal and central area in the alpha band. However, there are no significant differences between tasks at each time.

4.3.2 Time network analysis result

Figure 32 shows the results for time-varying clustering coefficients in the theta band. The clustering coefficients increased approximately 300 ms after stimulus onset. No significant differences were found in the clustering coefficients between tasks at the degree time points.

Figure 33 shows the results for the time-varying characteristic path length in the theta band. The characteristic path length decreased by approximately 300 ms after stimulus onset. No significant differences were found in the characteristic path length between tasks at the degree time points.

Figure 34 shows the results for the time-varying clustering coefficients in the alpha band and Figure 35 shows the results for the time-varying characteristic path length in the alpha band. In the α -band, no significant differences in the two indicators between states could be identified.

Figures 35-42 show the results of Betweenness centrality in the θ band every 100 ms after stimulus presentation, with ANOVA and t-test statistical analysis showing a significant difference between the 0-back and 2-back tasks of F3 in the 2-300 ms time window, with a higher Betweenness centrality obtained during the 0-back task. In the 3-400 ms time window, significant differences were also observed between the 0-back and 1- and 2-back tasks of Fz, with the highest Betweenness centrality also obtained during the 0-back task.

Figures 43-49 show the results for betweenness centrality in the alpha band every 100 ms after stimulus presentation; statistical analyses by ANOVA and t-test revealed no significant differences for any electrode in any time window.

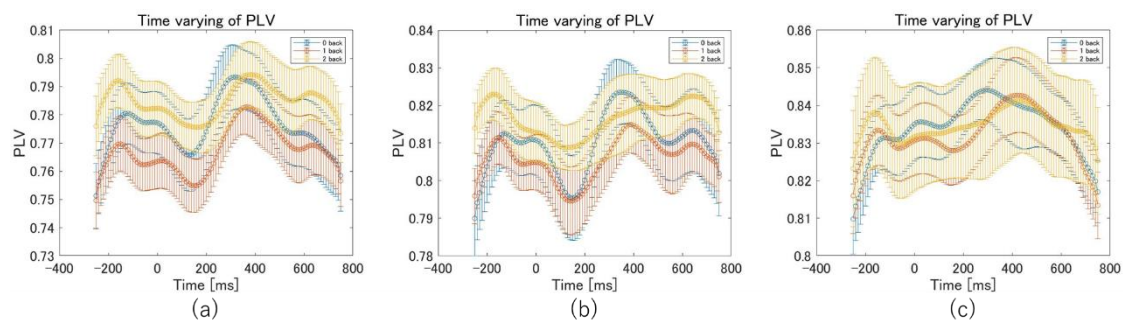


Fig 31. Time-varying phase locking value in theta band.

(a)between the frontal and posterior area (b)between the central and posterior area

(c)between the frontal and central area

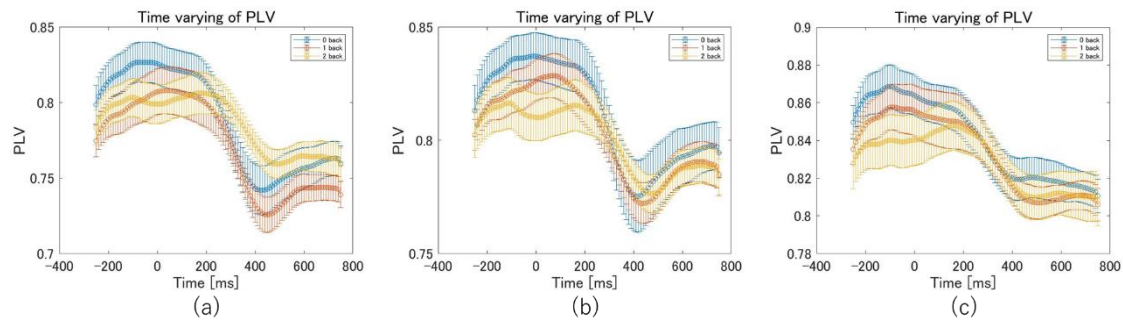


Fig 32. Time-varying phase locking value in alpha band.

(a)between the frontal and posterior area (b)between the central and posterior area

(c)between the frontal and central area

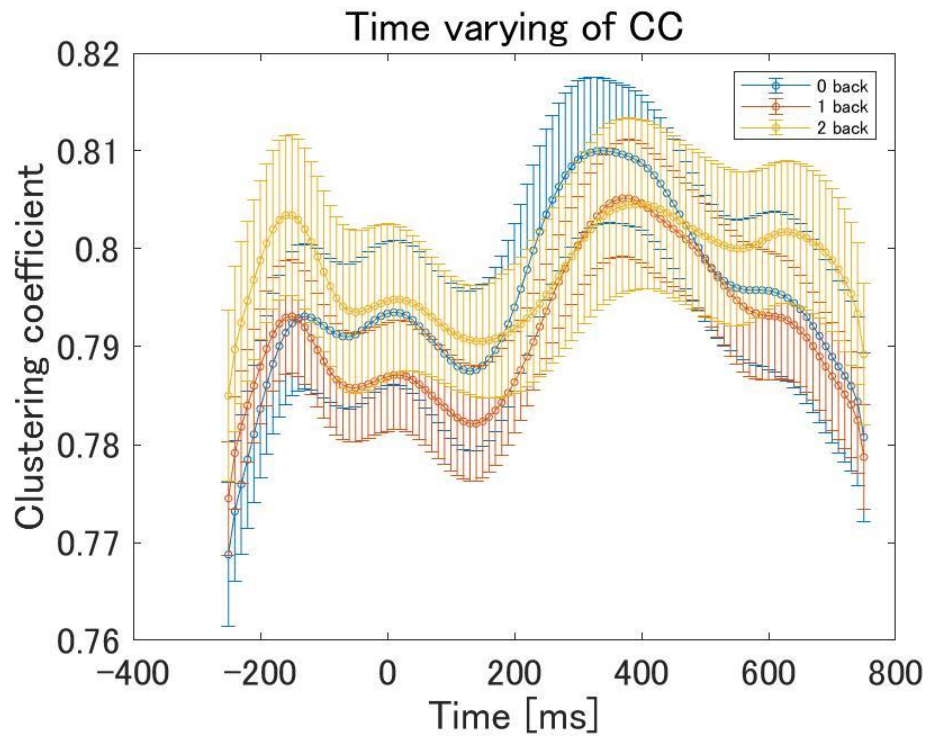


Fig 33. Time-varying Clustering coefficients in the theta band.

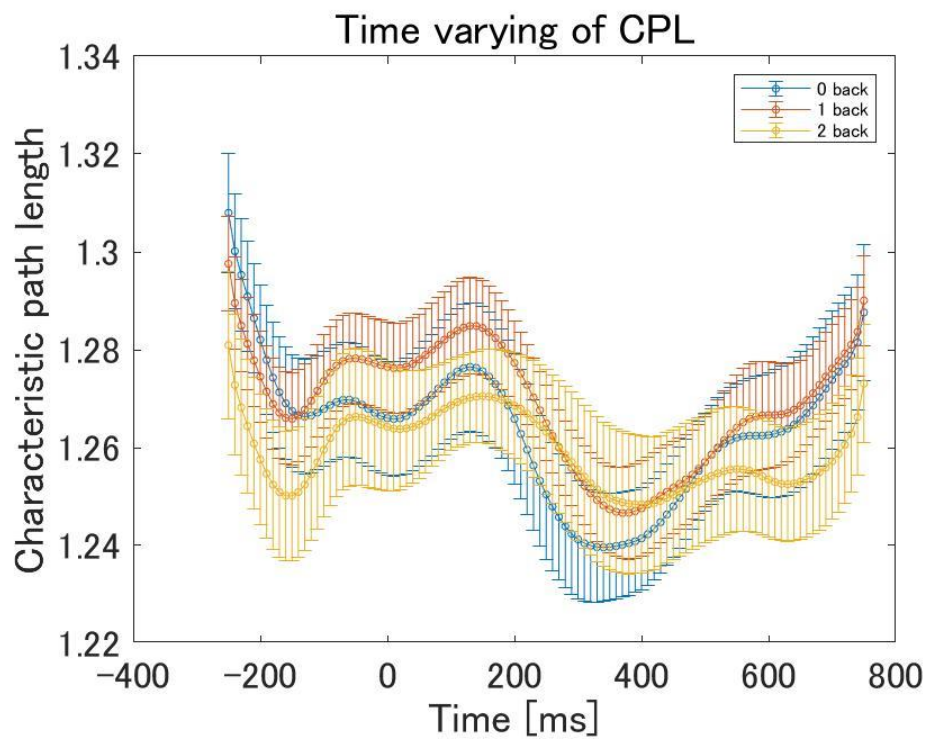


Fig 34. Time-varying characteristic path length in the theta band.

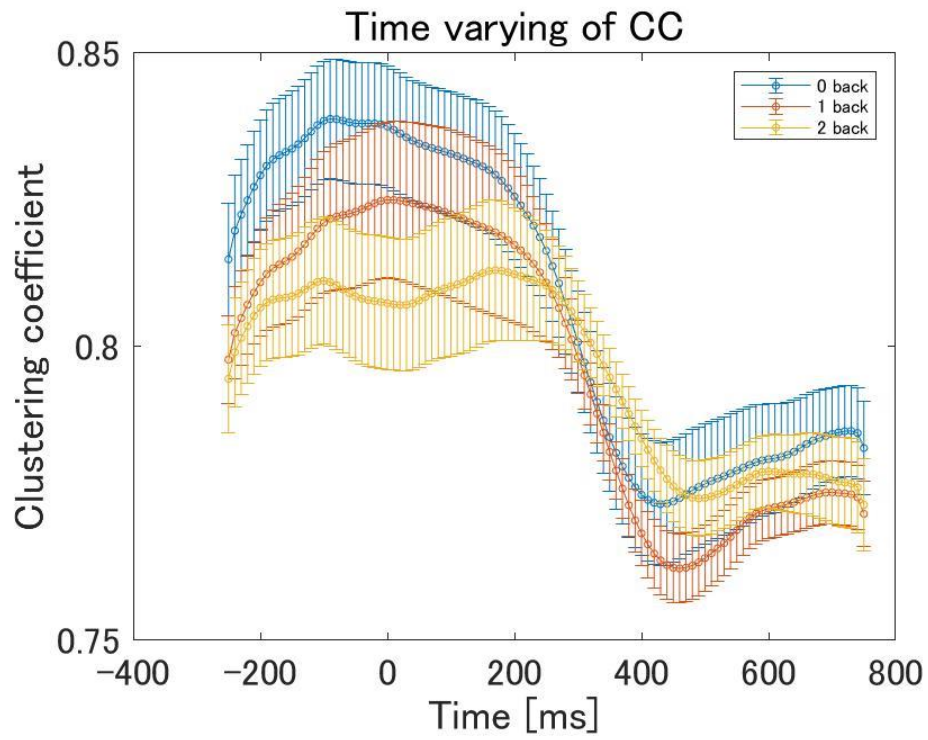


Fig 35. Time-varying Clustering coefficients in the alpha band.

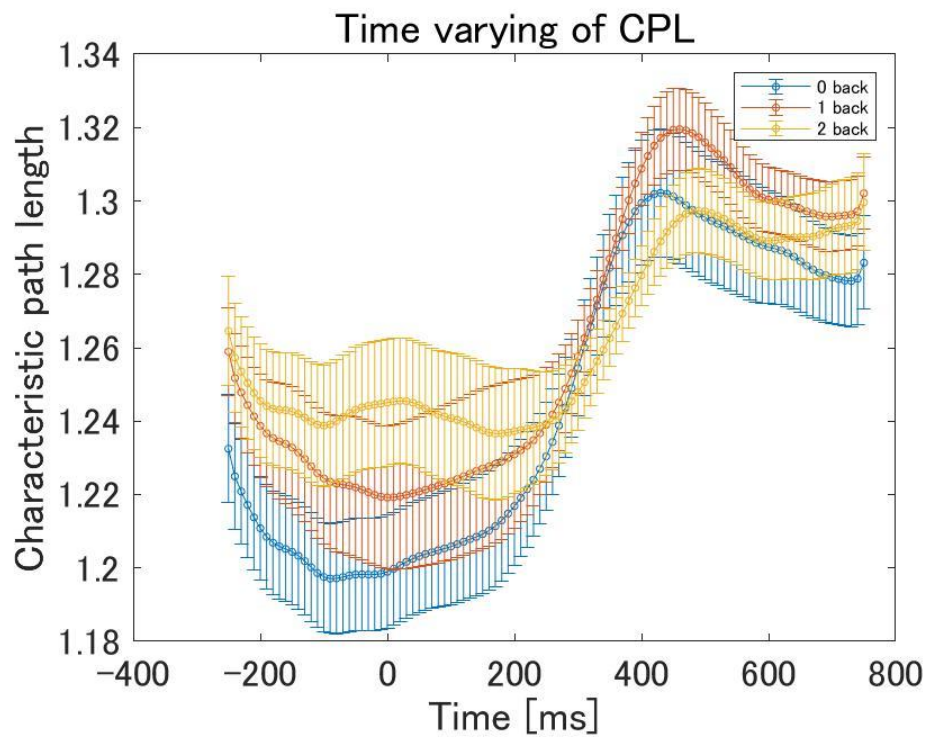


Fig 36. Time-varying characteristic path length in the alpha band.

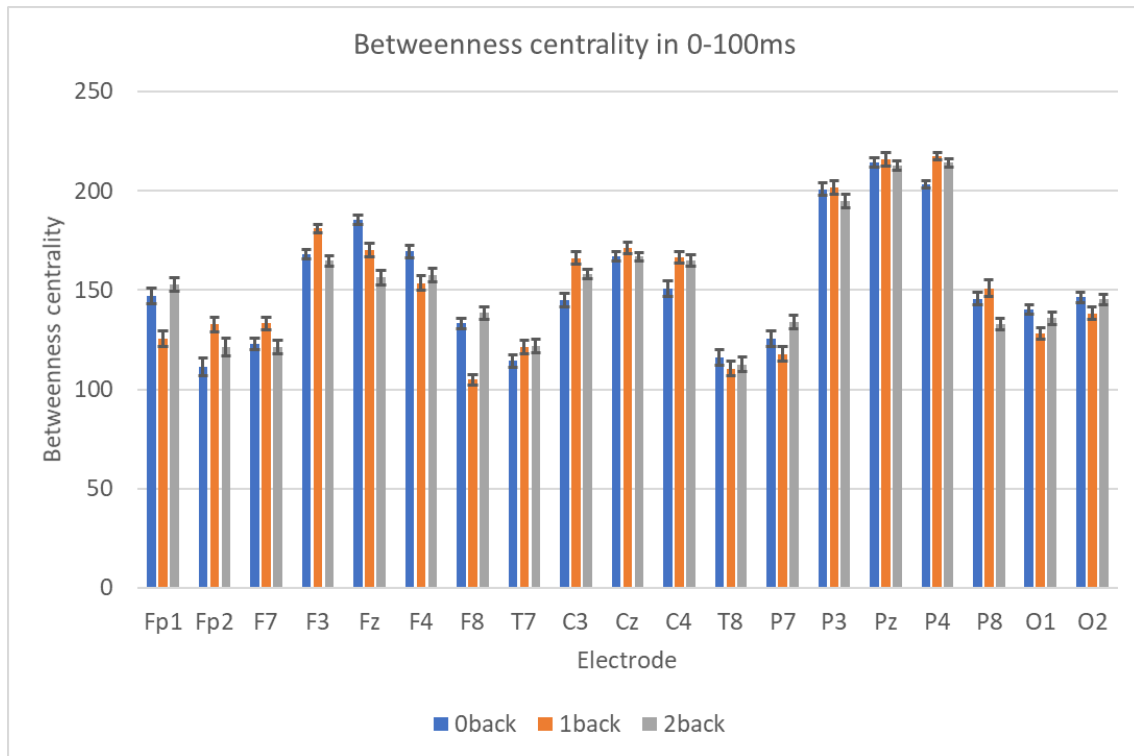


Fig 37. Betweenness centrality in 0-100ms time window in the Theta band.

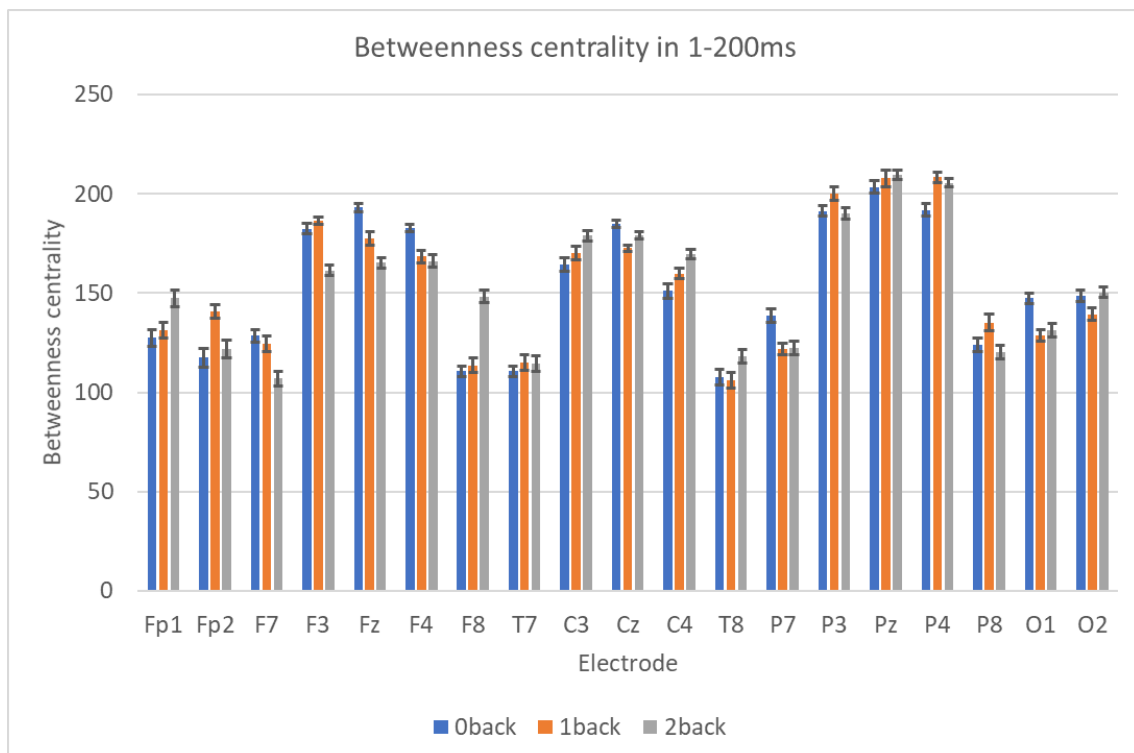


Fig 38. Betweenness centrality in 1-200ms time window in the Theta band.

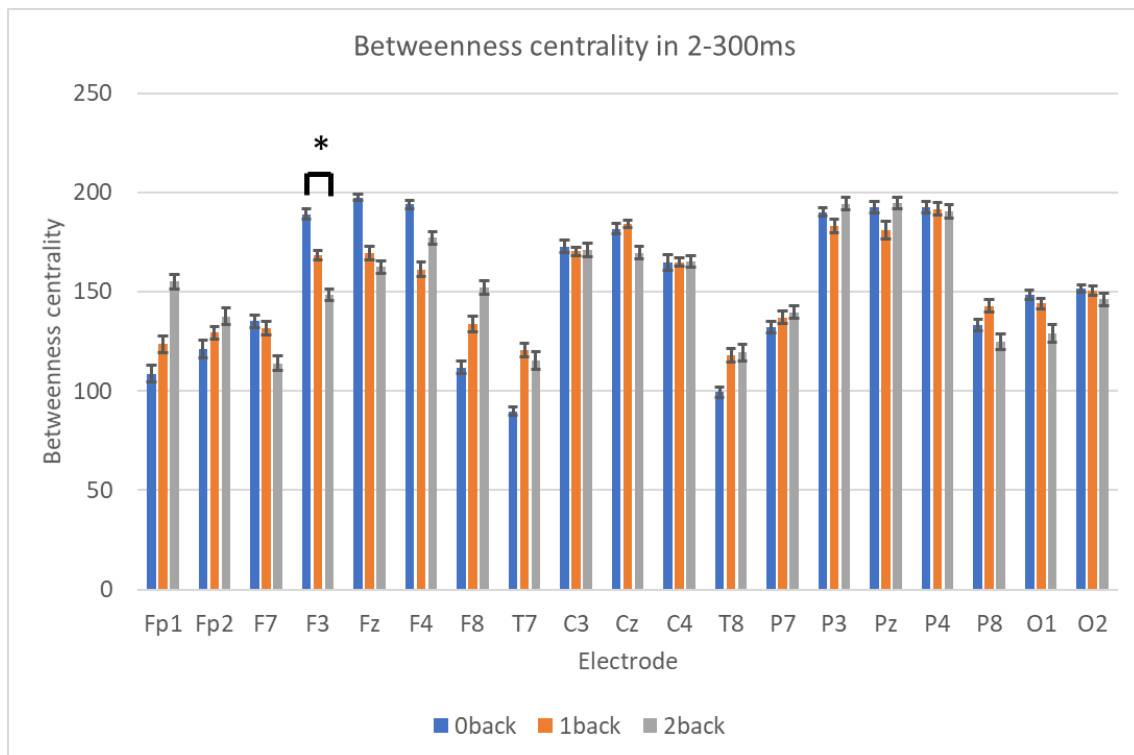


Fig 39. Betweenness centrality in 2-300ms time window in the Theta band.

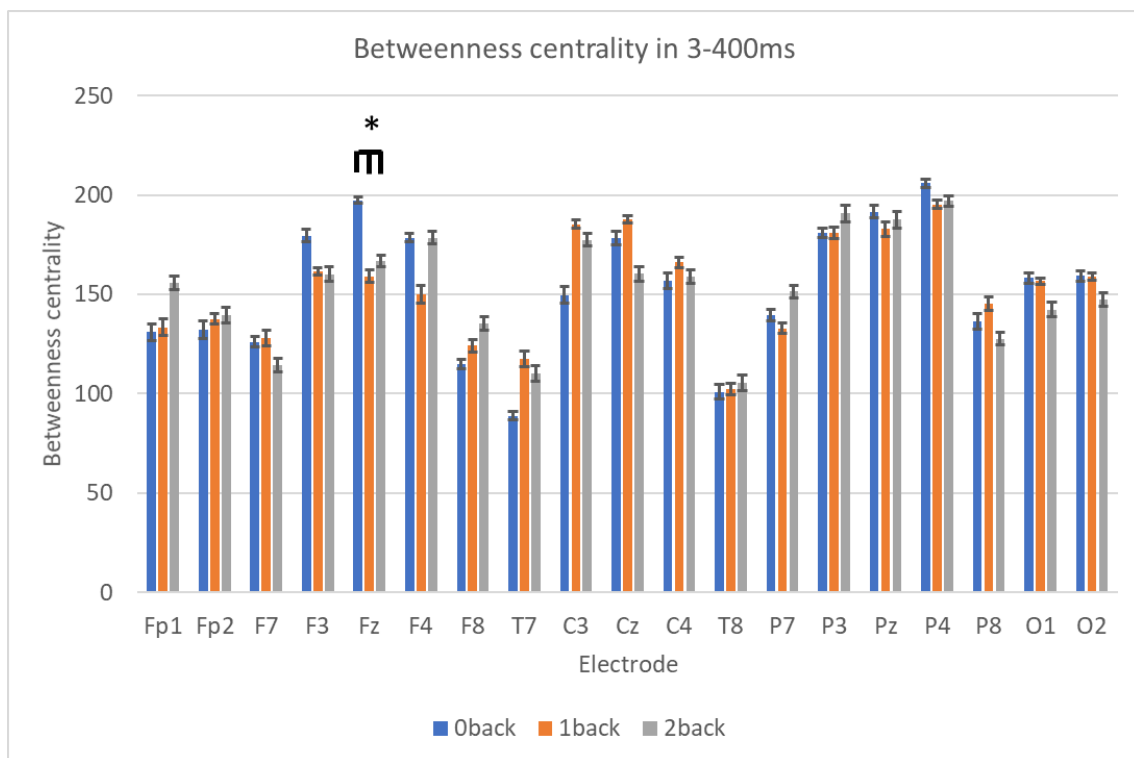


Fig 40. Betweenness centrality in 3-400ms time window in the Theta band.

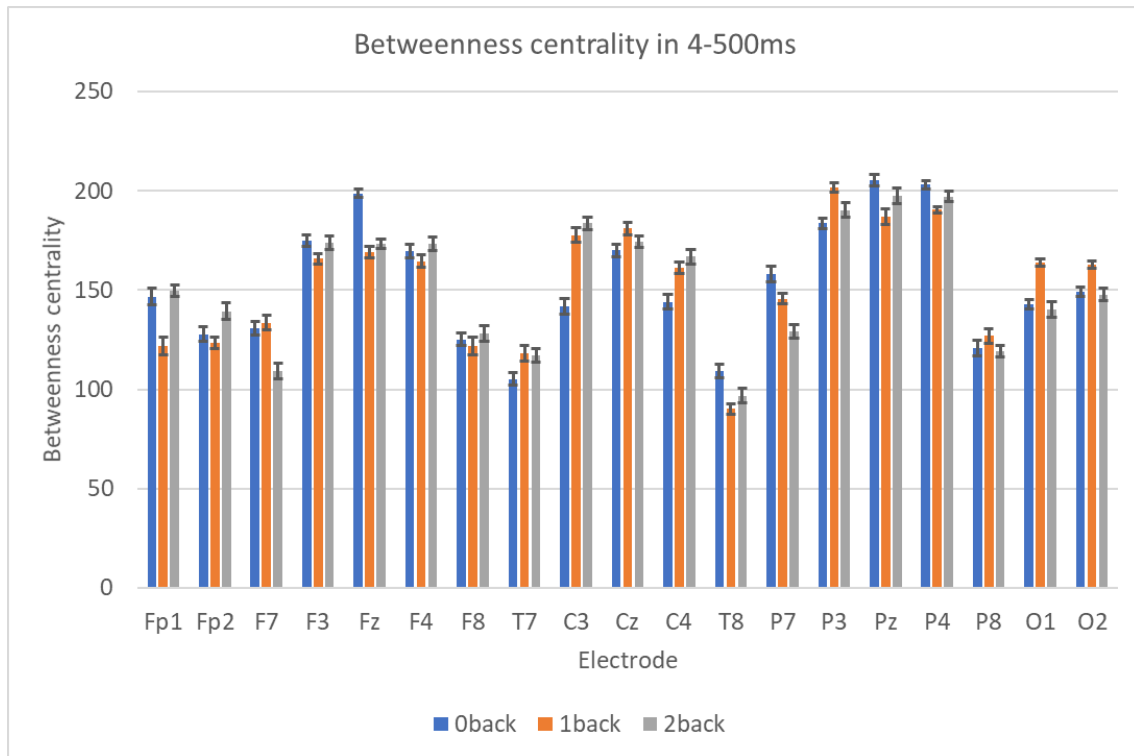


Fig 41. Betweenness centrality in 4-500ms time window in the Theta band.

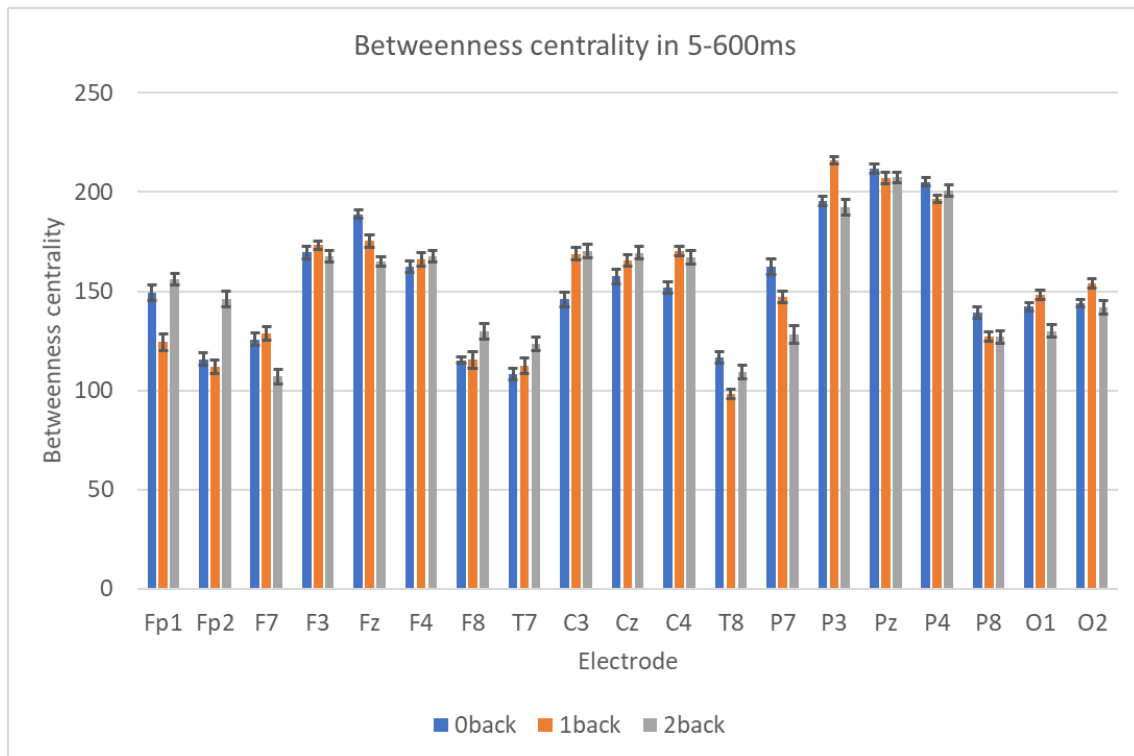


Fig 42. Betweenness centrality in 5-600ms time window in the Theta band.

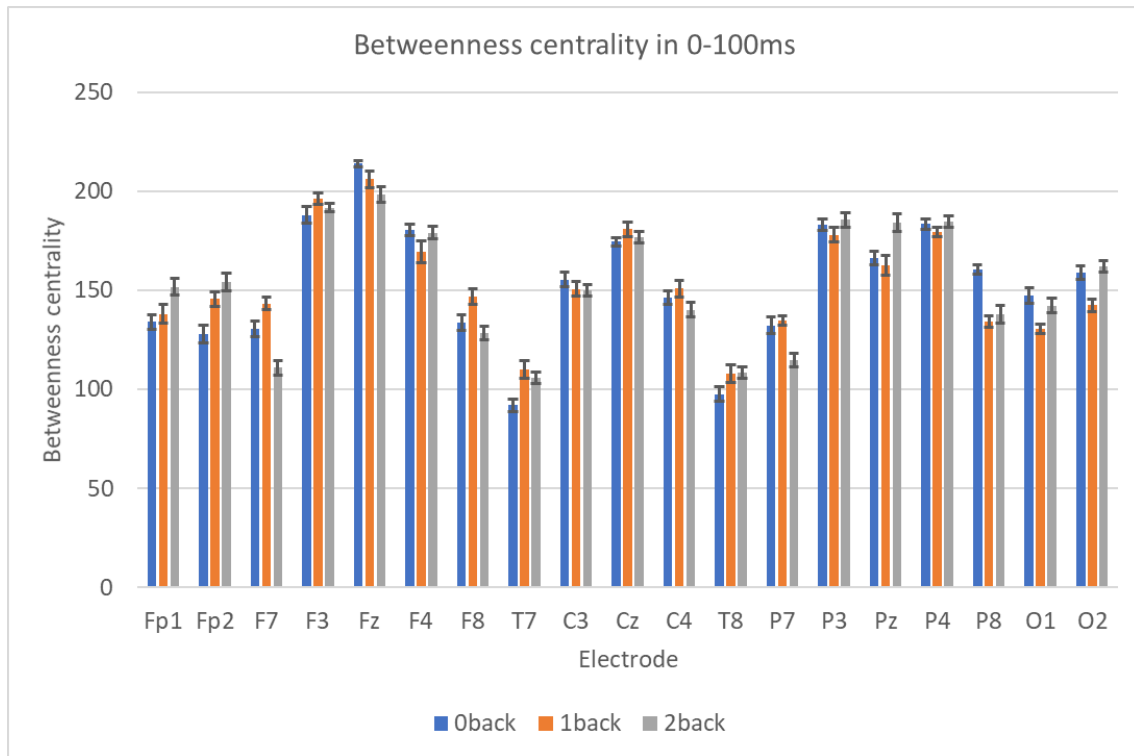


Fig 43. Betweenness centrality in 0-100ms time window in the Alpha band.

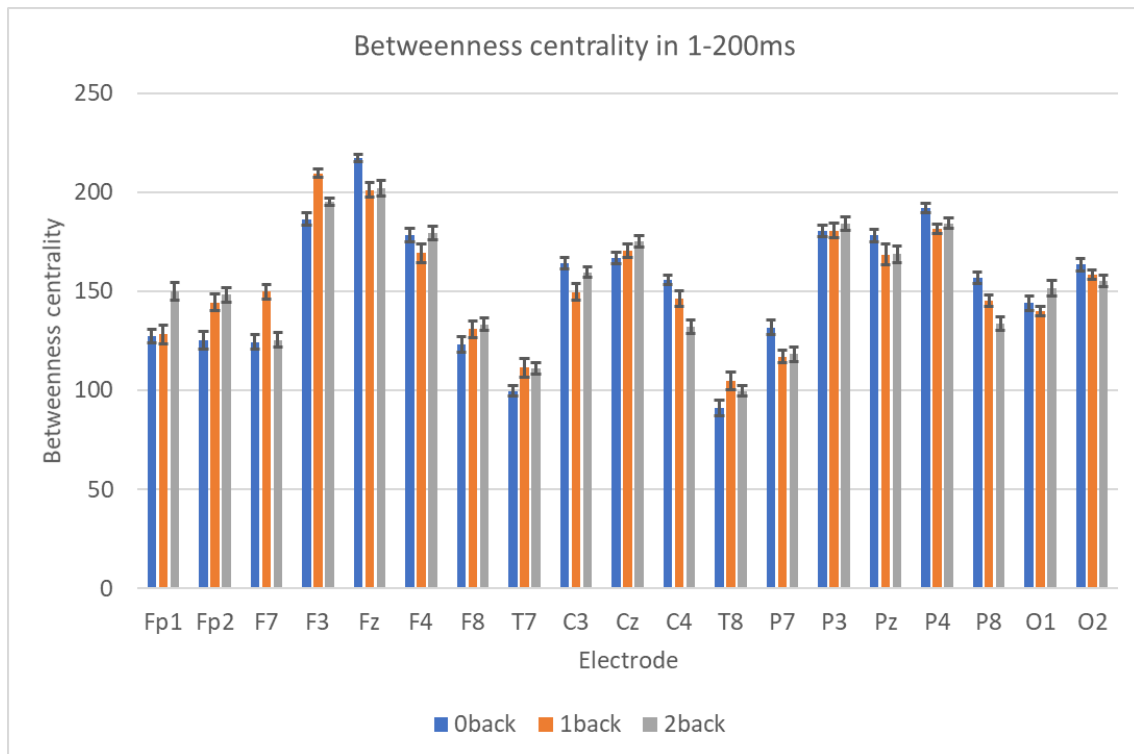


Fig 44. Betweenness centrality in 1-200ms time window in the Alpha band.

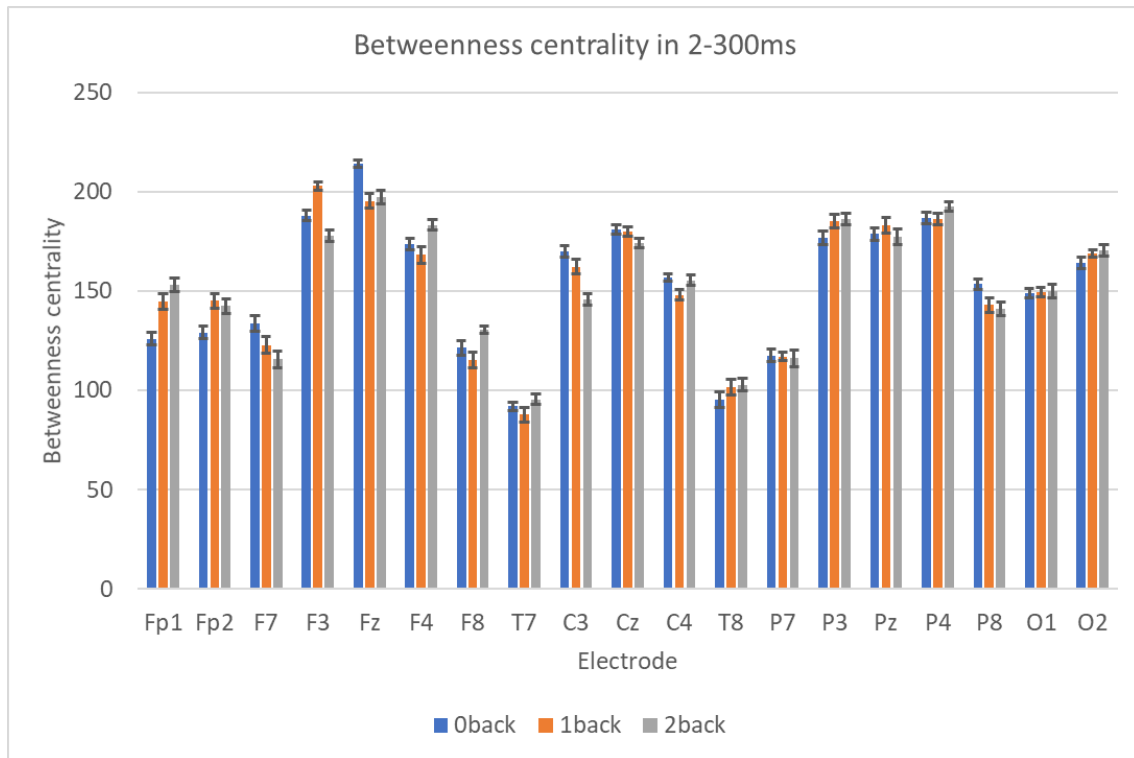


Fig 45. Betweenness centrality in 2-300ms time window in the Alpha band.

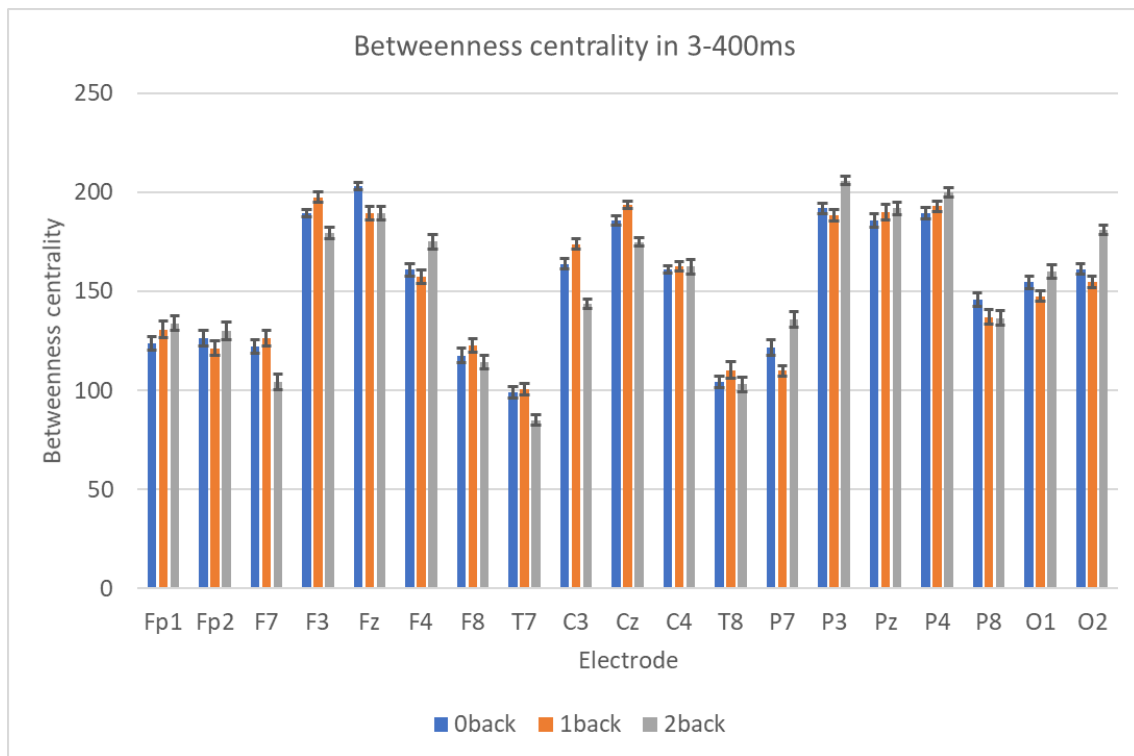


Fig 46. Betweenness centrality in 3-400ms time window in the Alpha band.

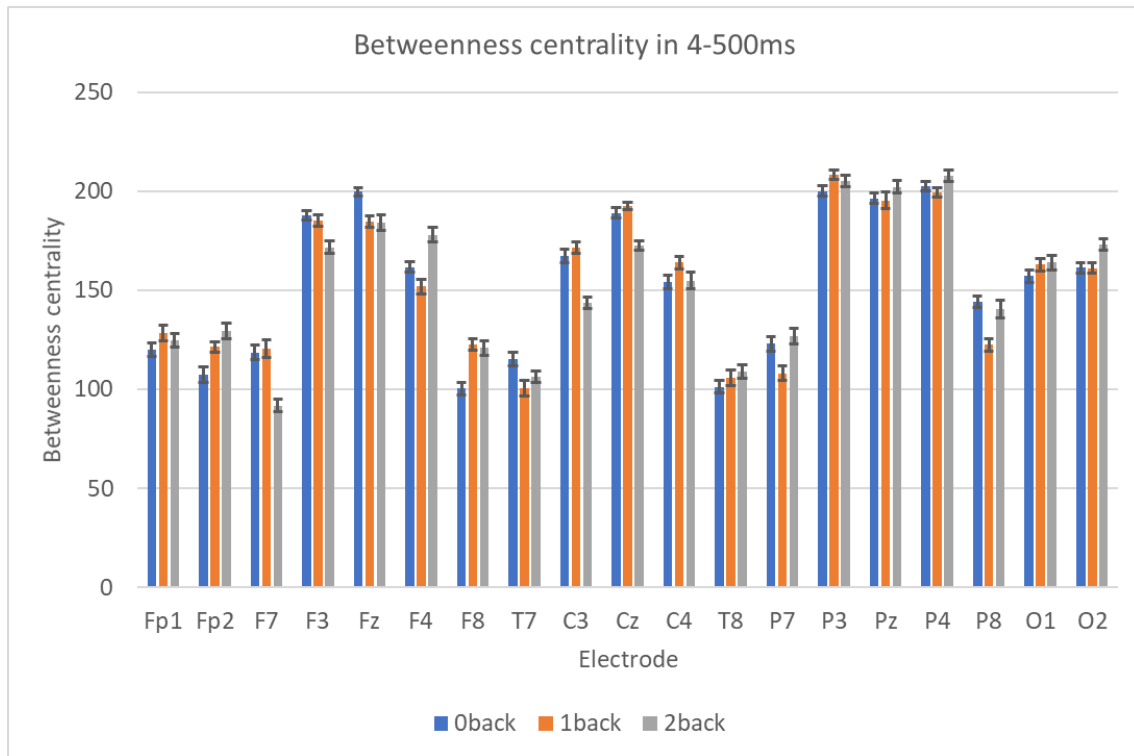


Fig 47. Betweenness centrality in 4-500ms time window in the Alpha band.

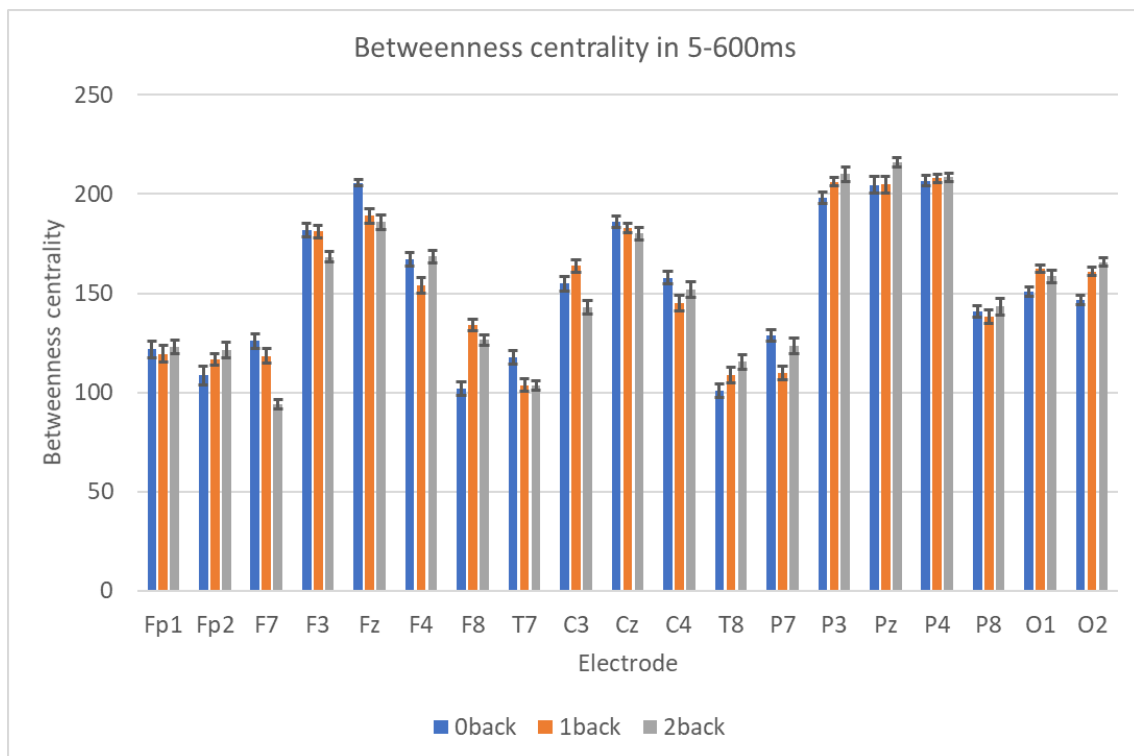


Fig 48. Betweenness centrality in 5-600ms time window in the Alpha band.

4.4 Discussion

The present study analyzed temporal changes in functional connectivity and brain network activity during the n-back task.

In the theta band, dynamic functional connectivity analysis revealed a PLV peak at 300 ms between the posterior, frontal, and central regions. At the same time, clustering coefficients increased and characteristic path lengths decreased. Previous studies have reported that theta-band EEG is associated with working memory [21], [22], [62]. Previous studies have also reported the appearance of P300 and N400 components in n-back tasks [63], [64]. The N400 component is known to respond to meaningful (potentially meaningful) stimuli such as visual words, signs, pictures, faces, and words. The P300 is a response to visual stimuli. Based on these reports, we believe that our results suggest that increased PLV and optimization of the brain network (increased clustering coefficient and decreased characteristic path length) are associated with responses to visual stimuli. The duration of decreasing clustering coefficients and increasing characteristic path length after 300ms was longer depending on workload. We believe that this result may be influenced by memory processing: at low workloads, such as 0-back tasks, no time was required to process the task. On the other hand, high workloads, such as 1- and 2-back tasks, required more time to process the task and recall the post-stimulus that the participant remembered and compared to the current stimulus. Therefore, the optimization of the brain network that is maintained longer in response to task load would be expected to be maintained for longer periods of time to solve 1 and 2-back tasks, which require the retrieval of stored memories and comparison with the current stimulus.

In the alpha band, dynamics of functional connectivity analysis showed a decrease of PLV around 400ms in each task. Comparing the PLV of 0 back task and 1,2 back tasks before 300ms, the average PLV in 0 back task was higher than in 1 and 2 back task. During the retention phase of working memory, alpha event-related synchronization (ERS) has been identified in the occipital region [65]. Also, it has been reported that alpha oscillations and functional connectivity in the alpha band are related to areas associated with working memory [66]. From these reports, our results that PLV was higher 300 ms earlier in the 0 back task than in the 1,2 back task were influenced by the occipital alpha ERS during memory retention. In the 0 back task, participants only retained target letters that were not updated during the task. In contrast, in the 1 back task, participants had to retain the target to be updated later in each trial, and in the 2 back task, participants had to remember up to two previous letters. Therefore, the difference in PLVs before 300 ms between the 1- and 2-back task and the 0-back task was that more ERSs appeared in the occipital area during the 1- and 2-back task, which required memory updating on each trial than during the 0-back task, which did not require memory updating, and The results suggest that this may be due to synchronized higher activity in the occipital area than in the frontal and parietal lobes, resulting in lower PLVs between the frontal/parietal and occipital areas. The results of the temporal network analysis showed that clustering coefficients were higher in the alpha

band around 200 ms during the 1- and 2-back tasks than during the 0-back task. The clustering coefficient is the degree of functional separation in the network. We considered that this result might be influenced by the fact that the ERS was higher during the 1- and 2-back tasks than during the 0-back task. Brain activity in the occipital regions was synchronized because of the higher ERS in the occipital regions for the maintenance of complex memories. The synchronization of the occipital regions during the 1-back task was higher than during the 0-back task so the brain networks were more segregated during the 1- and 2-back tasks than during the 0-back task. Considering the results from the two frequency bands, a decrease in the interregional PLVs in the alpha band and in the theta band was found at about 300 ms after stimulus presentation. Both of these changes occur 300 ms after stimulus presentation, and we believe that the results of this study indicate that the brain network changes dynamically in response to performance changes such as ERPs associated with the WM task and that the brain may solve the task through functional integration of the network.

With regard to Betweenness Centrality, a decrease in Betweenness Centrality was also observed around 300 ms after stimulus presentation in the 1- and 2-back tasks, which have a higher task load than the 0-back task in F3 and Fz, which are frontal regions. A previous study [67] reported that betweenness centrality showed a significant positive correlation with cognitive function in older people, particularly in the frontal theta band network, where subjects with high cognitive function scores had significantly higher betweenness centrality. However, the present results confirmed that it decreased during Tasks 1 and 2, which require higher cognitive function. However, although no significant differences were found between tasks, there was an increasing trend in prefrontal areas such as Fp1 and 2, temporal areas such as F8 and T7, and parietal areas such as C3, and in the 500-600 ms time window after stimulus presentation, there appeared to be a transition in areas with high mediation centrality towards occipital areas such as P3, P4 and Pz. In the 500-600 ms time window, some time after stimulus presentation, there appears to be a transition from areas with high mediation centrality to occipital areas such as P3, P4 and Pz. Furthermore, a previous study [68] reported on the alternation between high and low frequencies and showed that opposite changes were observed during the transition from resting to performing a cognitive task. As the results of this study only included network evaluation during the task, it is suggested that in the future, by capturing changes between rest and task performance using temporal network analysis, it may be possible to gain a deeper understanding of the corresponding switching of brain networks.

We also believe that the present results again demonstrate the possibility of temporal features in brain network activity. In particular, the present study analyzed fine temporal changes in functional connectivity clustering coefficients and characteristic path lengths, both of which are thought to represent network activity in response to stimulus presentation. ERPs have been applied to brain-machine interfaces, such as the P300 speller, and have been used in rehabilitation and other applications. We believe that the temporal characteristics of the network obtained in this study can be

linked to more complex applications using temporal network activity through application to GNNs, etc., as introduced in Chapter 2.

As a limitation of this research, we only compared dynamics of functional connectivity (PLV) and brain network activity (clustering coefficient and characteristic path length). We discussed our result using ERS. However, we didn't analyze ERS at this time. Therefore, it is difficult to conclude our result was affected by ERS. Also, in this study, we have only 6 participants' data. Therefore, it is difficult to apply statistical analysis to this result.

In this study, the edges of the weighted network with PLVs as weights were not removed by the thresholding process when determining the clustering coefficients and characteristic path lengths. However, previous research [39][40] has discussed threshold processing of edges during graph construction, and the results of network analysis change depending on the method of threshold processing. On the other hand, some studies that used weighted connections during network graph construction did not perform threshold processing. Therefore, setting thresholds and reducing edges may make it easier to observe network characteristics.

Future plans include further data correction of the ERS in these two frequency bands and comparing ERS results with functional connectivity and brain network activity dynamics. If we can confirm the usefulness of dynamic network analysis by making these comparisons, we will be able to clarify the temporal characteristics of brain network activity, and this research will be useful in elucidating brain functions that are still largely unknown.

Conclusions

In this study, we analyzed temporal changes in functional connectivity and brain network activity during the n-back task to reveal the mechanism of temporal brain network activity.

We observed the result time-varying of functional connectivity increased clustering coefficients and decreased characteristic path length. Theta band results show a network efficiency increase at the same timing as P300, which was observed in previous power-based EEG results. Alpha band results also show a PLV decrease at 400 ms, which is close to the timing of the ERS in previous studies. We considered these results may be related to visual stimuli because characteristic time-varying of functional connectivity and functional integration of theta band brain network appeared 300ms after the presentation of visual stimuli. Therefore, we consider these results may suggest the relationship between time-varying brain network activity in theta and alpha band related to retention of memory and processing of working memory.

We believe that our results suggest that, as in previous EEG studies, temporal analysis of network indices together with network indices may lead to a more detailed functional elucidation of brain network activity, such as changes in the duration of the efficient network in response to task load.

Institutional Review Board Statement:

The study was conducted by the Declaration of Helsinki, and approved by the ethical principles of Kyushu University (シス情 2021-14)

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Conflicts of Interest:

The authors have no conflicts of interest directly relevant to the content of this article.

5 General Discussion

In our research, we have revealed brain network activity from EEG data. Also, we focus on time-varying of brain network activity.

In Chapter 2, we focused on brain network activity during sleep and analyzed brain network activity during each sleep stage of non-REM sleep. This network analysis was quantitatively evaluated using graph theory. In network analysis using graph theory, the Clustering coefficient, which represents the functional separation of the network, and Characteristic path length or Small-worldness, which represents functional integration, are often used [5], [6], [69], [70]. In the present study, network analysis of each sleep stage was also performed using these indices. The results showed a significant difference in Characteristic path length between Stage 1 and other stages in LowBeta (13-15 Hz). This difference may be because the Characteristic path length was shorter in Stage 2-4, where sleep was deeper than in Stage 1, where sleep was shallow ($P \leq 0.00833$). Stage 2, which has the shortest Characteristic path length, is characterized by the Sleep spindle. The Sleep spindle is involved in the enhancement of memory during sleep, and the same network analysis was performed for the epochs in which the Sleep spindle was observed and the epochs in which it was not observed. Clustering Coefficients were also significantly higher in the case of Spindle. These results suggest that the Sleep spindle affects the efficiency of network activity in the brain. These results suggest that memory enhancement and other activities are performed in the brain when sleep is deepened, and that network activity is observed for this purpose, which may lead to a better integration of the brain network. The functional connectivity, clustering coefficients, and characteristic path lengths that emerged as significant differences may be applied to more accurate automatic discrimination of sleep stages through future applications as input elements for GNN and other machine learning. We believe that the results of this study will clarify the changes in brain network activity related to memory enhancement during sleep, and will help to elucidate the function of brain network activity during sleep.

In Chapter 3, we analyzed network activity in the brain during a paired associative learning task, one of the memory tasks. The paired association task is associated with memory retrieval [49], and the purpose of this study was to clarify the dynamics of memory retrieval. The motivation for this study

stemmed from the idea that brain network analysis of memory processing could be dynamically informed by insights into brain network activity related to sleep stages and memory, as discussed in Chapter 2. This approach aims to further elucidate the underlying mechanisms of memory processing in the brain. The study was guided by two primary hypotheses: (1) that functional connectivity (FC) actively functions as a network during memory retrieval, and that this network activity can be quantitatively assessed through complex network analysis, and (2) that there may be differences in the low-gamma band, which is associated with attention, during memory retrieval. To address these hypotheses, we conducted an investigation building upon the previous research by Gruber et al.[17]. In the Pair associative learning task, the participants were first asked to remember the four-figure pairs, then presented with an image and asked if the next image that appeared was a pair. Network analysis was conducted every 100 ms, with 0 ms being when the first image was shown before the comparison was made. Simultaneously, a time-frequency analysis was also performed to analyze the relationship between power-based temporal brain activity and network analysis. The results of the time-frequency analysis showed that in high-gamma (50-80 Hz), the Target (when one of the stored image pairs was shown) was higher than the Distractor (when irrelevant images were shown) in the 60-70 Hz range around 300 ms. This is in line with the results of previous studies. The observed result is similar to the Gamma Band Response (GBR) documented in previous studies. However, in the time-varying network analysis, contrary to our initial expectations, network efficiency appeared to be higher in the non-retrieval condition. Specifically, in the high-gamma band, the clustering coefficient was lower in the target condition compared to the distractor condition, and the characteristic path length was longer in the target condition than in the distractor condition. Similarly, in the low-gamma band, network efficiency was higher in the distractor condition, as evidenced by significantly greater clustering coefficients and shorter characteristic path lengths in the 0–100 ms window. This may reflect the fact that participants in the distractor condition had no task-specific memory associations and simply awaited the presentation of stimulus 2. Although power increased during retrieval, the results may not have been as pronounced as anticipated, potentially due to the simplicity of the figures used in the task, which did not demand a substantial cognitive effort for retrieval. Although the present results differ from the hypothesized results, we were able to clarify the dynamics of brain network activity in memory retrieval, and we believe that we may have proposed a method for dynamic network analysis. In Chapter 4, we conducted a dynamic brain network analysis during the n-back task, which is a working memory task. This is because, based on the results of the dynamic brain network analysis of memory retrieval in Chapter 4, we wanted to confirm the usefulness of the method used in the previous study and to clarify the function of temporal brain network activity in working memory by conducting dynamic network analysis on working memory, whose brain activity has been studied in many studies so far. We also wanted to elucidate the function of the temporal brain network activity of working memory. As a result, in the theta band, dynamic functional connectivity analysis revealed a PLV peak

after 300ms between the Posterior, Frontal, and Central regions. The clustering coefficient increased and the characteristic path length shortened at the same time. Previous studies have reported that theta band EEG is associated with working memory [21], [22], [62]. Previous studies have also reported the appearance of P300 and N400 components in n-back tasks [63], [64]. Previous studies have also reported the appearance of P300 and N400 components in n-back tasks [63], [64]. The N400 component is known to respond to meaningful (potentially meaningful) stimuli such as visual words, signs, pictures, faces, and words. The P300 is a response to visual stimuli. From these reports, we consider that our result suggested increasing of PLV and Optimization of the brain network (increasing of clustering coefficient and decreasing of characteristic path length) were related to the reaction of visual stimuli. The duration of decreasing clustering coefficients and increasing characteristic path length after 300ms was longer depending on workload. We consider this result may be affected by memory processing. Low workload such as 0 back task did not need time to process task. On the other hand, High workloads such as 1, and 2 back tasks need time to process the task and to remember past stimuli which participants memorize and compare current stimuli. Therefore, optimization of brain networks that are maintained longer in response to task load is expected to be maintained for longer periods to solve 1,2back tasks that require retrieval of retained memories and comparison with current stimuli. In the present study, characteristic changes in network indices (clustering coefficient and characteristic path length) were observed at the same time as P300, which is related to the n-back task, and these changes were longer in proportion to workload. We believe that these results capture the characteristic temporal changes in the theta band of working memory used in the n-back task.

In this doctoral thesis, by using Phase Locking Value which is phase-based functional connectivity, to analyze networks, the following findings were made.

- 1) Clustering coefficients and characteristic path lengths are influenced by brain network activity, possibly due to memory enhancement during non-REM sleep, suggesting that brain network structure may be more efficient during middle and deep sleep and that there are differences in graph structure between light sleep and middle and deep sleep.
- 2) Temporal features of brain activity seen in time-frequency analysis, such as event-related potentials in EEG, may also appear as brain network activity.
- 3) It may be possible to capture changes in dynamic network activity, such as changes in the time required to maintain network efficiency in response to task load, by performing network analysis in a finer time window.

In 1), we were able to show the differences in network activity between shallow and deep sleep that have been reported in previous studies [71], while also clarifying the stage at which network activity changes, and we believe that we have demonstrated the possibility of treating network activity during sleep as a meaningful parameter.

In 2) and 3), we focused on temporal changes in memory-related network activity, analyzed temporal

network activity, and were able to capture the temporal characteristics of network activity, which may indicate that the temporal component of network activity may also be important for future elucidation of brain function.

Through these studies, we believe we have demonstrated the utility of network analysis using graph theory. In particular, based on the finding that task-dependent brain networks change over time and become more efficient by analyzing temporal changes in brain networks, we believe that focusing on temporal changes in brain network analysis can lead to a more detailed clarification of functions. We also believe that the graph-theoretic analysis used in this study can be applied to the development of more accurate discriminators by incorporating network indicators as a new element in machine learning fields such as GNN, which has been researched in recent years. We believe that the results of this paper have contributed to brain network research by capturing brain network activity related to sleep and memory, and by proposing the importance of dynamic network analysis.

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