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RESEARCH

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Exploration of working memory retrieval stage for mild cognitive impairment: time-varying causality analysis of electroencephalogram based on dynamic brain networks

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Abstract

Background Mild Cognitive Impairment (MCI) is an intermediate stage between the expected cognitive decline of normal aging and Alzheimer's disease (AD). Its management is crucial for it helps intervene and slow the progression of cognitive decline to AD. However, the understanding of the MCI mechanism is not completely clear. As working memory (WM) damage is a common symptom of MCI, this study focused on the core stage of WM, i.e., the memory retrieval stage, to investigate information processing and the causality relationships among brain regions based on electroencephalogram (EEG) signals.

Method 21 MCI and 20 normal cognitive control (NC) participants were recruited. The delayed matching sample paradigm with two different loads was employed to evaluate their WM functions. A time-varying network based on the Adaptive transfer function (ADTF) was constructed on the EEG of the memory retrieval trials.to perform the dynamic brain network analysis.

Results Our results showed that: (a) Behavioral data analysis: there were significant differences in accuracy and accuracy / reaction time between MCI and NC in tasks with memory load capacity of low load-four and high load-six, especially in tasks with memory load capacity of four. (b) Dynamic brain network analysis: there were significant differences in the dynamic changes of brain network patterns between the two groups during the memory retrieval stage of the WM task. Specifically, in low load WM tasks, the dynamic brain network changes of NC were more regular to accommodate for efficient information processing, with important core nodes showing a transition from bottom to up, while MCI did not display a regular dynamic brain network pattern. Further, the brain functional areas associated with low load WM disorders were mainly located in the left prefrontal lobe (FC1) and right occipital lobe (PO8). Compared with low load WM task, during the high load WM task, the dynamic brain network changes of NC during the memory retrieval stage were regular, and the core nodes exhibited a consistent transition phenomenon from up to bottom to up, which were not observed in MCI.

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Conclusions Behavioral data in the low load WM task paradigm and abnormal electrophysiological signals in the left prefrontal (FC1) and right occipital lobes (PO8) could be used for MCI diagnosis. This is the first time based on large-scale dynamic network methods to investigate the dynamic network patterns of MCI memory retrieval stages under different load WM tasks, providing a new perspective on the neural mechanisms of WM deficits in MCI patients and providing some reference for the clinical intervention treatment of MCI-WM memory disorders.

Keywords Mild cognitive impairment, Electroencephalography, Working memory, Dynamic network

Introduction

Alzheimer's disease (AD), an aging-associated condition, is the leading cause of dementia and is quickly becoming one of the most expensive, lethal, and burdensome diseases of this century [1]. As the pathogenesis and mechanism of AD remain unclear, predicting, preventing or reversing the disease is still a worldwide challenge. Recently, attention has been paid to mild cognitive impairment (MCI), which is an intermediate state between normal aging and AD. It is viewed as a "window" in which it may be possible to intervene and delay progression to AD [2]. The diagnostic criteria for MCI include abnormal cognitive function in one or more domains, normal daily activity, and absence of dementia [3]. Among these different cognitive domains, memory decline is the most significant and common clinical manifestation, and it is also a core clinical standard for diagnosing MCI developing to AD [4], including episodic memory impairment [5] and working memory (WM) impairment [6].

WM is the fundamental function by which we break free from instinctive reaction to gain control over our own thoughts and is foundational to the organization of goal-directed behavior, resulting in many complex cognitive functions rely on WM [7, 8]. According to the current definition of WM, as a memory system, in which information can be stored for a short period of time and updated frequently, and can be quickly extracted [7, 9]. So it can be simply divided into three stages, including memory coding, memory delay, and memory extraction. In memory coding, the brain receives visual and auditory stimulus sequences from the external world. In memory delay, the brain consolidates WM information to deepen the memory while excluding irrelevant external information attention. In memory extraction, the brain quickly calls and extracts the relevant information to perform the following execution operations.

Based on the theory model of WM capacity, individuals have limited WM capacity referring to the fact that individuals can hold only a limited amount of mental content available for processing [10, 11]. Currently, measures of WM capacity are recognized as major determinants of cognitive development in childhood [12] and old age [13], as well as individual differences in intellectual abilities [14–16]. The impairment of WM capacity is mainly manifested through the difficulties with transient memory and delayed recall, a decline in association ability and impaired reading comprehension. These challenges hinder the ability of MCI patients to process, store and recall information effectively. As such, WM capacity, especially for visual components, has been used as a tool for distinguishing MCI patients [6, 17, 18] from healthy elderly individuals [19, 20].

Electroencephalogram (EEG) signal is an objective record of neuron electrical activities in the brain, reflecting neural activation and communications [21, 22]. Its objectivity and high temporal resolution provide an intrinsic advantage for studying cognitive neural mechanisms related to WM processing [23]. It is studied that cognitive process is related to EEG oscillations [24, 25]. At present, the neural oscillation frequency bands related to WM found in humans and non-primates are mainly concentrated in θ(4–8 Hz), α(8–13 Hz), β(13–30 Hz), and γ(> 30 Hz) [7]. Among them, the θ and α frequency bands are two widely studied frequency bands [26–33]. The θ neural oscillation was first discovered in the hippocampus entorhinal cortex system of animals. It originates from the interaction between glutamate and dopaminergic neurons and encodes spatial position information through phase precession. For WM, the θ oscillations play a critical role, persisting throughout the entire WM process [34, 35]. WM requires the coordinated effort of multiple brain regions with specific functions. For example, Babiloni et al. found abnormal cortical neural synchronization and altered functional connectivity between distant brain areas in individuals with MCI [36]. Wei et al. investigated the electroencephalographic changes during a color matching selective attention task in individuals with MCI and found that long-range functional integration in the brain is impaired, leading to decreased overall brain network functionality [37]. Compared to α oscillation, the θ oscillation is very suitable for large-scale neural integration, as it synchronizes in the cerebral cortex during the WM process θ oscillation can regulate information exchange between distant brain regions, thereby connecting different brain regions [38].

At present, the electrophysiological mechanism of MCI-WM disorders is still unclear. Previously, most studies were based on resting state EEG to explore the brain connectivity of MCI, and some preliminary results were obtained, but there was still controversy [39–44]. For example, in a previous brain network study based on resting state tasks, it was found that in the θ frequency band, the connectivity between the frontal and occipital lobes, as well as the connectivity between the central and occipital lobes, showed significant differences between MCI and NC. But in the α frequency band, there was no significant difference in the functional connectivity between the two groups [43]. However, in a review study, it was observed that the α synchronous specificity of the temporal parietal lobe (as well as the frontal parietal lobe) was reduced in MCI patients [44]. On the one hand, during resting state, many factors can alter data, such as specific instructions, pre-recording cognitive states, caffeine intake, or random spontaneous thoughts [45]. On the other hand, for the elderly population who are difficult to cooperate with and have memory impairment characteristics, memory related cognitive paradigms are more likely to obtain specific electrophysiology and reveal the electrophysiological mechanisms of memory impairment. Decades of brain mapping research have linked human WM to multiple neuroanatomical centers, including the frontal, parietal, temporal, and occipital regions [46–49]. By studying the abnormal cognitive processing patterns of patient groups at the level of global brain networks, including related network characteristics such as regular resource allocation during tasks (ordered networks) and network central nodes, it is possible to explore the brain mechanisms underlying WM impairments in MCI. It holds promise for providing diagnostic marker for the early detection of the MCI disease.

The memory retrieval stage reflects an individual's WM capacity and is considered as the core stage of WM. The memory extraction stage is a highly complex dynamic process that involves intertwined cognitive processes such as attention, information retrieval, recognition and activation, recognition and recall, as well as perception and interpretation. The time-varying brain network- dynamic brain network is a network model that can describe the temporal changes in connectivity patterns between brain regions, making it of great application value in neuroscience research, including network laterality in motor imagery processes, abnormal sensory gating in patients with schizophrenia, and abnormal brain community reconstruction in patients with Attention-deficit/hyperactivity disorder (ADHD) [50–54]. As such, exploring the dynamic brain network of memory retrieval stage is of great significance for better understanding of WM information processing. Furthermore, EEG research on MCI based on different WM load tasks (such as high and low loads) is of great value for understanding the cognitive mechanisms of MCI, evaluating disease severity, exploring intervention strategies, and promoting the development of related fields. Therefore, the purpose of this study is to (a) evaluate the WM memory ability of MCI based on high and low load WM tasks, and determine the relationship between MCI and WM load; (b) Based on large-scale dynamic brain network method, elucidate the dynamic network characteristics of MCI WM retrieval stage during high and low load WM task, reveal the relationship between WM disorders of MCI and EEG, investigate the effect of increasing WM load on brain connectivity in MCI, and provide diagnostic marker and recommended intervention strategies for early detection of diseases.

Table 1 Descriptive statistics of the participants

	NC group	MCI group	t/x^2	*p*
No. of participants	20	21	-	-
Sex (Female/Male)	12/8	15/6	0.595	0.440
Age (years)	70.00 (3.39)	70.33 (2.85)	0.444	0.659
Education (years)	11.05 (3.63)	9.52 (3.50)	1.369	0.179
MOCA	26.70 (1.38)	19.91 (2.98)	9.284	< 0.001*
MMSE	28.05 (1.43)	26.76 (2.02)	2.343	0.024*

The number presented is the mean and standard deviation in the parentheses

NC: normal cognitive control; MCI: mild cognitive impairment; MOCA: Montreal Cognitive Assessment; MMSE: Mini Mental State Examination. *$p < 0.05$

Method

Participants

Twenty-one individuals with MCI and twenty normal cognitive control (NC) participated in this experiment. The detailed information of the participants was listed in Table 1. The purpose and content of this study have been informed to all participants, and all participants had signed informed consent forms in advance. The procedure of the study was in accordance with the Declaration of Helsinki, and has been approved by the Ethics Committee of West China Medical College, Sichuan University. (Approved Number: 2021(1447)).

The number presented is the mean and standard deviation in the parentheses.

NC: normal cognitive control; MCI: mild cognitive impairment; MOCA: Montreal Cognitive Assessment; MMSE: Mini Mental State Examination. *$p < 0.05$.

MCI Inclusion Criteria: Based on the "2018 Chinese Diagnosis and Treatment Guidelines for Dementia and Cognitive Impairment": Complaints of memory loss; Montreal Cognitive Assessment (MoCA) score < 26/30, Mini-Mental State Examination score (MMSE) > 24; Functional Activities Questionnaire score (FAQ) > 6/8, Activities of Daily Living (ADL) = 100; The range of age: 65–75; No history of anti-AD drugs; No history of neurological or psychiatric diseases;

MCI Exclusion criteria1: Other diseases that can lead to cognitive impairment, such as a history of stroke, neurological deficits, neurological disorders, and severe physical illnesses; Having hearing or visual impairments that prevent cooperation in completing the neurocognitive scale.

NC Inclusion Criteria: No complaints of memory loss; MoCA > 26/30, MMSE > 24; Age 65–75; No psychiatric or central nervous system diseases.

Experimental protocol

The EEG signals were acquired using the NeuroScan system, with 32 electrodes placed at 10–20 standard electrode positions internationally. The signal sampling frequency was 250 Hz, and to guarantee reliable data quality, throughout the experiment, the impedance for all electrodes was kept below 10 kΩ. Before the experiment, the participants would be informed about the procedures of the experiment, and practice the experimental task to be familiar with the entire process. They sat in a room with dim lighting and reduced sound facing the screen. All the participants have normal or corrected vision.

The experiment used the delayed matching sample paradigm. It simulates the practical application scenarios of WM by presenting specific stimuli and response requirements, and is one of the main paradigms in WM research. It typically includes target presentation stage, delay stage, and detection matching stage. The setting of WM load is mainly achieved by adjusting the number of memory items presented in the memory stage, which can help researchers comprehensively evaluate the WM ability of the participants. It is recognized that when memorizing objects with simple features, for healthy adults, the number of objects was around four that could be stably memorized. In order to explore the WM impairment of MCI, the memory load was set to four and six objects in this study, defined as low memory load and high memory load, respectively. The stimulus picture used in the experimental paradigm was a simple two-dimensional black figure. The detection matching stage, also known as the memory extraction stage, requires participants to make button reactions in response to whether the current detection image has appeared in the target presentation stage. The detection image of detection matching stage in each trial was pseudo random, with a 50% probability of being one of the previous four stimulus images of the current trial and 50% probability of not. Correspondingly, the reaction time of the participants is recorded. Due to the high level of attention required to complete the WM task, this experiment had only a run to ensure that we could obtain relatively accurate behavioral data and stable EEG data. The run consisted of two WM tasks with a 5-minute interval between them. Each task had 20 trials. The accuracy rate was calculated after the task. The specific experimental paradigm and flow were shown in Fig. 1.

Dynamic brain network analysis

Construction of the dynamic brain network

Currently, various time-varying directed connectivity analysis methods with different causal relationship definitions have been proposed based on time-varying multivariate autoregressive (TV-MVAR) models, such as adaptive directed transfer function (ADTF), adaptive partially directed coherence, and adaptive Granger causality (GC) [55]. Although there are numerous parametric methods, in time-varying directed EEG network construction, the most widely used method is ADTF because of its good performance in interpretations and accurately capturing of the time-variant causality between signals [56, 57]. As a non-parametric method, ADTF has inherent advantages in multi-channel signal causal analysis in different frequency bands, and can capture transient network information, so it has great application value in cognitive research, and helps us understand and explain the transient information flow and functional connectivity of the brain during the memory retrieval stage of WM tasks.

The memory retrieval data was used to construct the time-varying network with ADFT. Before the network construction, the raw EEG data was preprocessed with the following steps: average reference;1–30 Hz

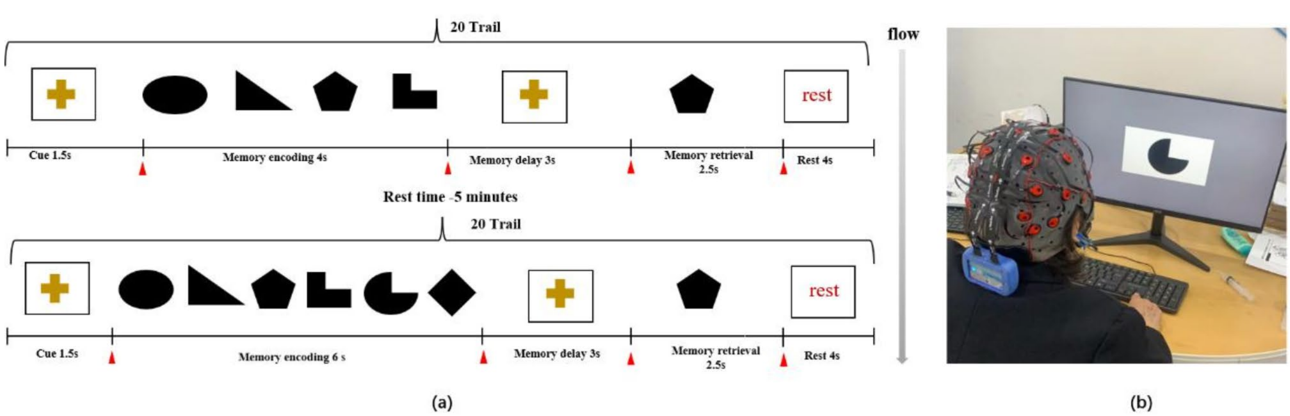


Fig. 1 Experimental setup. (**a**) Delayed sample matching Paradigm (memory load four and six) and the entire experimental process, (**b**) EEG data collection of the participant

bandpass filtering; The Fast Independent component analysis (ICA) was performed using a built-in function from EEGLAB v2022.0 with MATLAB R2018b (MathWorks Inc., USA). As a data decomposition technique, ICA decomposes EEG signals into multiple independent components, each representing a unique brain source or artifact source (such as eye movements, muscle activity, etc.). The ICA was utilized to remove artifacts with recognition artifact components greater than 80%, including blinking (>80%), vertical/horizontal eye movement (>80%), muscle (>80%), and electrocardiogram (>80%). On average, 8 of 32 components were discarded for each participant (different for each individual); Baseline correction and data segmentation. In the process of data segmentation, the length of EEG data used for memory retrieval stage is 2.5 s [0, 2.5] seconds, where 0 s represents the moment when the stimulus image is presented. For each participant, the dynamic time-varying network will be constructed based on trial-trial level. The construction process was as follows: Firstly, based on previous experimental records, we manually removed trial including incorrect artifacts, artifacts with incorrect reactions, and artifacts caused by technical issues. Next, all remaining artifacts free trial were further used to construct the time-varying network with the trial-by-trial. Then, the time-varying network corresponding to each trial of two task (low load task and high load WM task) of each participant were further averaged respectively. Finally, this averaging process will provide the final time-varying network corresponding to the two WM tasks of each participate.

A detailed introduction to ADTF can be described as follows:

For the time series of each trial, the TV-MVAAR model coefficient is calculated by the following formula:

$$X\left(t\right)=\sum{}_{i=1}^{P}A\left(i,t\right)X\left(t-i\right)+E\left(t\right) \tag{1}$$

Where $X(t)$ is the multi-channel EEG data of the whole trial time series, P is the optimal order of the TV-MVAAR model, $A(i, t)$ is the coefficient of the TV-MVAAR model estimated by the Kalman filter algorithm, and $E(t)$ is the white noise of the signal $X(t)$.

Here, the model order P is automatically evaluated by Akaike information criterion (AIC) in the range of 1–30, which is defined as follows:

$$AIC\left(P\right)=In[\det\left(S\right)+2M^{2}P/N] \tag{2}$$

Where M is the number of time-varying network nodes, P is the order of TV-MVAAR model, N is the number of signal sampling points, and S is the covariance matrix. In our study, the optimal model orders were in the range of 2–20. The observation equation and state equation are obtained by the forgetting factor of recursive least squares (RLS).

After the coefficients of TV-MVAAR model are obtained based on formula (1), $H(f, t)$ can be further obtained through the transformation of $A(i, t)$ frequency domain. The element $H_{ij}(f, t)$ in $H(f, t)$ represents the flow of information from node j to node i at time point t and frequency point f. Its relevant definitions are as follows:

$$A\left(f,t\right)X\left(f,t\right)=E(f,t) \tag{3}$$

$$X\left(f,t\right)=A^{-1}\left(f,t\right)E\left(f,t\right)=H\left(f,t\right)E(f,t) \tag{4}$$

Here: $H\left(f,t\right)=A^{-1}\left(f,t\right),A\left(f,t\right)=\sum{}_{k=0}^{p}A_{k}\left(t\right)\ e^{-j2\pi\ f\Delta\ tk}$

A_{k} is the coefficient matrix of the model,$X(f, t)$ and $E(f, t)$ are the conversion forms of signal $X(t)$ and its corresponding white noise $E(t)$ in the frequency domain.Standardized ADTF, i.e. $\gamma^2 (f, t)$, in which the elements $\gamma_{ij}{}^{2} (f, t)$ describes the direct information flow from j to i, and is often defined in the range of (0, 1). Its specific definition is as follows:

$$r_{ij}^{2}\left(f,t\right)=\frac{\left|H_{ij}\left(f,t\right)\right|^{2}}{\sum{}_{m=1}^{n}\left|H_{im}\left(f,t\right)\right|^{2}} \tag{5}$$

Finally, ADTF is defined as ADTF normalized within the frequency band of $[f_1, f_2]$, as follows. For more information on the ADTF method, please refer to Wilke's research [7].

$$\Theta_{ij}^{2}\left(t\right)=\frac{\sum{}_{k=f_{1}}^{f_{2}}r_{ij}^{2}(k,t)}{f_{2}-f_{1}} \tag{6}$$

Considering that the frequency range of the WM memory retrieval stage is mainly θ Hz, where f_1 is 4 Hz and f_2 is 7 Hz.

Network parameter analysis

Based on the objective decision-making indicators occurring in the 220–350 ms time window [58], to some extent, memory retrieval can also be seen as a decision-making behavior, which can be understood as a complex cognitive process that includes a variety of decision-making links. Therefore, we divided memory retrieval stage into three period according to decision-making theory: the pre-retrieval period, the retrieval period, and the post-retrieval period. As ADTF captures the dynamic networks for each time point, and the time points nearby showed the high similar brain networks, in this study, the time-varying network with time interval of 60ms, which resulted in nine dynamic brain networks for the memory retrieval stage.

After obtaining the nine brain networks of the memory retrieval stage of each participant under two tasks, we hope to identify specific differences between the two groups. Firstly, in order to investigate the differences of brain network changes during dynamic memory retrieval stage, we statistically analyzed the brain connectivity values of the two groups and obtained the dynamic differential network patterns of the memory retrieval processes of the two groups in two tasks. Then, in order to further determine the heterogeneity sources of the significantly different brain network patterns between the two groups, such as abnormal brain regions, we identified the abnormal core nodes based on the significantly different brain networks at the group level. Finally, in order to obtain more important specific EEG indicators and key EEG nodes to serve the clinical diagnosis and intervention of MCI, we conducted further analysis on these core nodes including correlation analysis between the outdegree of core nodes and behavioral data, as well as statistical significance analysis of outdegree of core nodes in two groups.

The out-degree is one of the attributes of the EEG network and is commonly used to measure the characteristics of brain information sources and dissemination. A node with a significant out-degree is often regarded as a command center that sends information to other nodes. Based on the constructed time-varying network, the out-degree information of each node at each sampling time point can be obtained by the following formula:

$$k_i\left(t\right) = \sum\ _{j?N} a_{ij}\left(t\right), i \neq\ j \tag{7}$$

Where N is the number of all nodes in the network; $aij(t)$ is the connectivity from node i to node j at time point t.

Based on the time-varying network of significant differences between two groups, we obtained some nodes with significant differences. Next, we calculated the output degree information of each node with significant differences at each sampling time point. Finally, we identified these nodes with output degrees greater than (mean + standard deviation) as core nodes.

The specific data processing flowchart was shown in the Fig. 2.

Statistical analysis

Data analysis was performed using SPSS 21.0 statistical software. Independent sample t-tests and Mann-Whitney

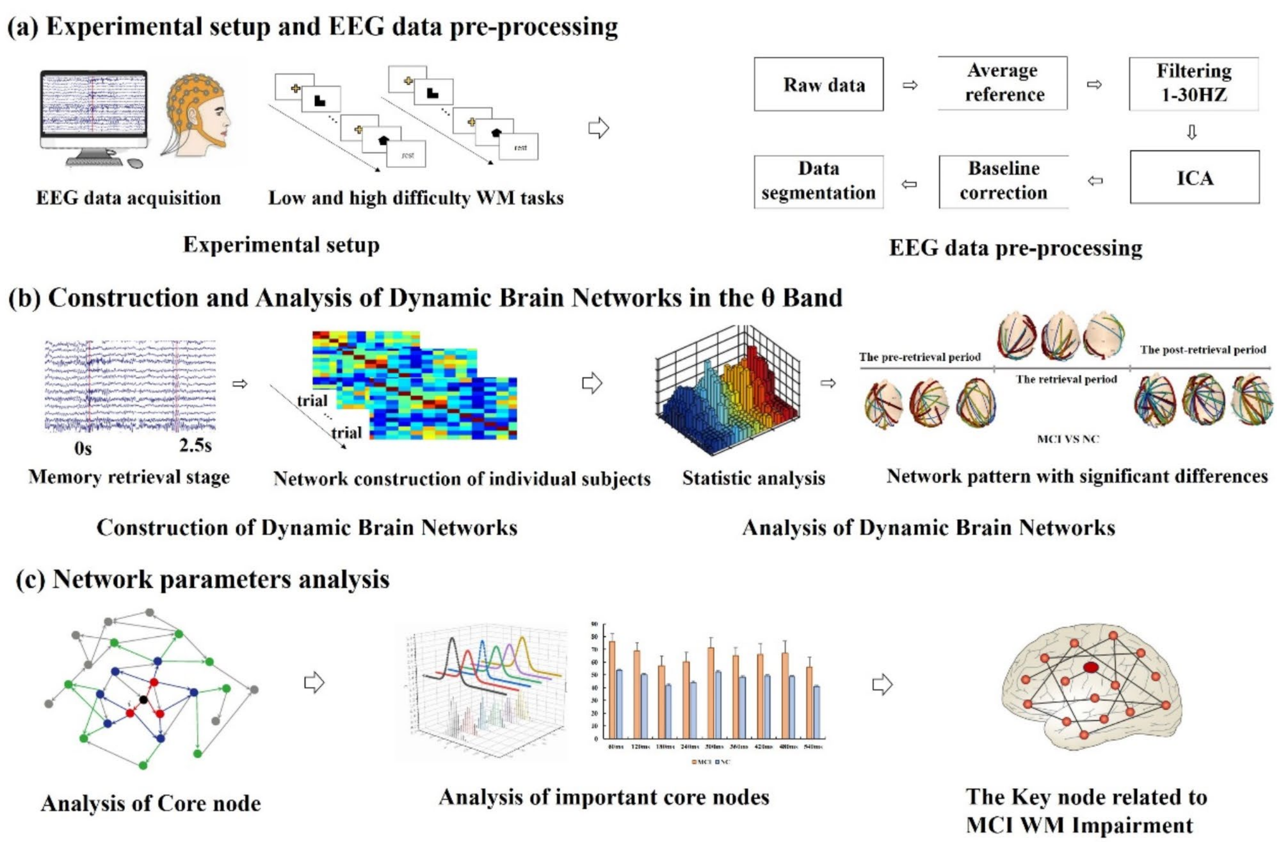


Fig. 2 Specific data processing flowchart. (**a**) Experimental setup and EEG data preprocessing (**b**) Construction and Analysis of Dynamic Brain Networks in the θ Band (**c**) Analysis of network parameters

U tests were used to compare the neurocognitive Scale, behavioral data (reaction time and accuracy), and ADTF mean (corrected by using false discovery rate (FDR)) in the θ frequency band between two groups. A p-value less than 0.05 was considered statistically significant.

Results

Behavior analysis

During two WM tasks, in low load WM tasks, there were significant differences in accuracy ($p<0.001$) and the ratio of accuracy to reaction time ($p<0.001$), i.e., accuracy/reaction time, between the NC group and MCI group, but no significant difference in reaction time ($p=0.745$); In high load WM tasks, there were significant differences in accuracy ($p=0.037$) and accuracy/response time ($p=0.008$) between the NC group and MCI group, but there was no significant difference in reaction time ($p=0.175$). For the behavioral data within NC and MCI two groups, in the NC group, the results showed that there were significant differences in accuracy ($p<0.001$) and accuracy/ reaction time ($p<0.001$) between the high and low load WM tasks, but there was no significant difference in reaction time ($p=0.464$). In the MCI group, there was no significant difference in accuracy ($p=0.612$), reaction time ($p=0.101$), and accuracy/ reaction time ($p=0.122$) between high and low load WM tasks. As shown in Fig. 3.

Time-varying network of the memory retrieval stage

We statistically analyzed the time-varying dynamic brain network in two groups during different load WM tasks. There were significant differences in the brain network patterns of the two groups in the three period of WM memory retrieval stage ($p<0.05$), as shown in Fig. 4. In low load WM tasks, brain network of NC with significant connectivity mainly appeared in the pre and memory retrieval period, and the brain network pattern did not change significantly over time. The dynamic causal network of the brain showed brain connectivity from the occipital lobe area to the anterior side of the brain; In MCI, the brain networks with significance connectivity emerged throughout the memory retrieval stage, with little change in brain network patterns over time. The significant brain network connectivity mainly appeared during the post-retrieval period. The dynamic causal network showed a flow from the anterior brain region to other regions. In high load WM tasks, in NC, the trend of network change over time throughout the entire memory retrieval stage was not significant. MCI had a significant network change over time throughout the entire memory retrieval stage, especially during the retrieval period.

I-nodes analysis

The core node of the brain network plays an important role in the integration of brain function. The analysis of core nodes helps to understand the relationship between MCI WM damage and various brain regions. Our results showed that there were significant differences in the transfer of the core node of the significant difference network over time between the two groups as shown in the Fig. 5. Specifically, in the low load WM retrieval stage, the core nodes of NC were mainly distributed in the occipital lobe and parietal lobe, that was, the pre brain region was less involved in tasks. The important core nodes (I-nodes) in NC were mainly distributed in the parietal lobe (CP1、P3). The core node had a trend of moving from occipital lobe to parietal lobe. However, the core nodes of MCI in the whole memory retrieval stage were relatively scattered, and the I-nodes in MCI were F3, FC1, CP5, PO8. In the entire dynamic process, there was no obvious rule of the core node. In high load WM tasks, the core nodes of NC were mainly distributed in the prefrontal and parietal lobes, that was, the occipital lobe was almost less involved. The I-nodes was located in F4, CP2, and PZ. In the process of memory retrieval stage, the core node appeared to shift from parietal lobe

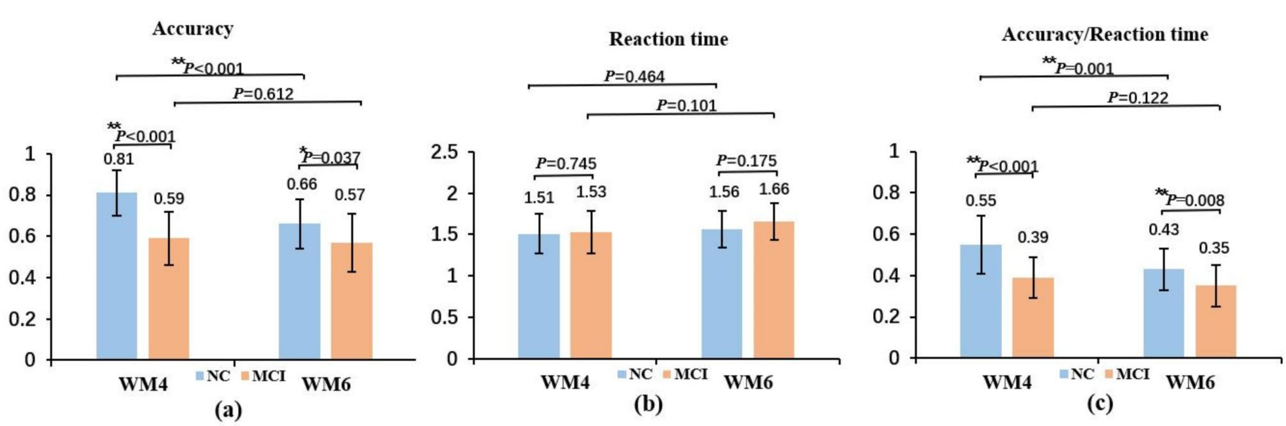


Fig. 3 Statistical analysis of behavioral data of two groups under WM task (left: load four, right: load six). (**a**) Statistical analysis of accuracy of two groups, (**b**) Statistical analysis of reaction time of two groups, (**c**) Statistical analysis of accuracy/reaction time of two groups. *$p<0.05$, **$p<0.001$

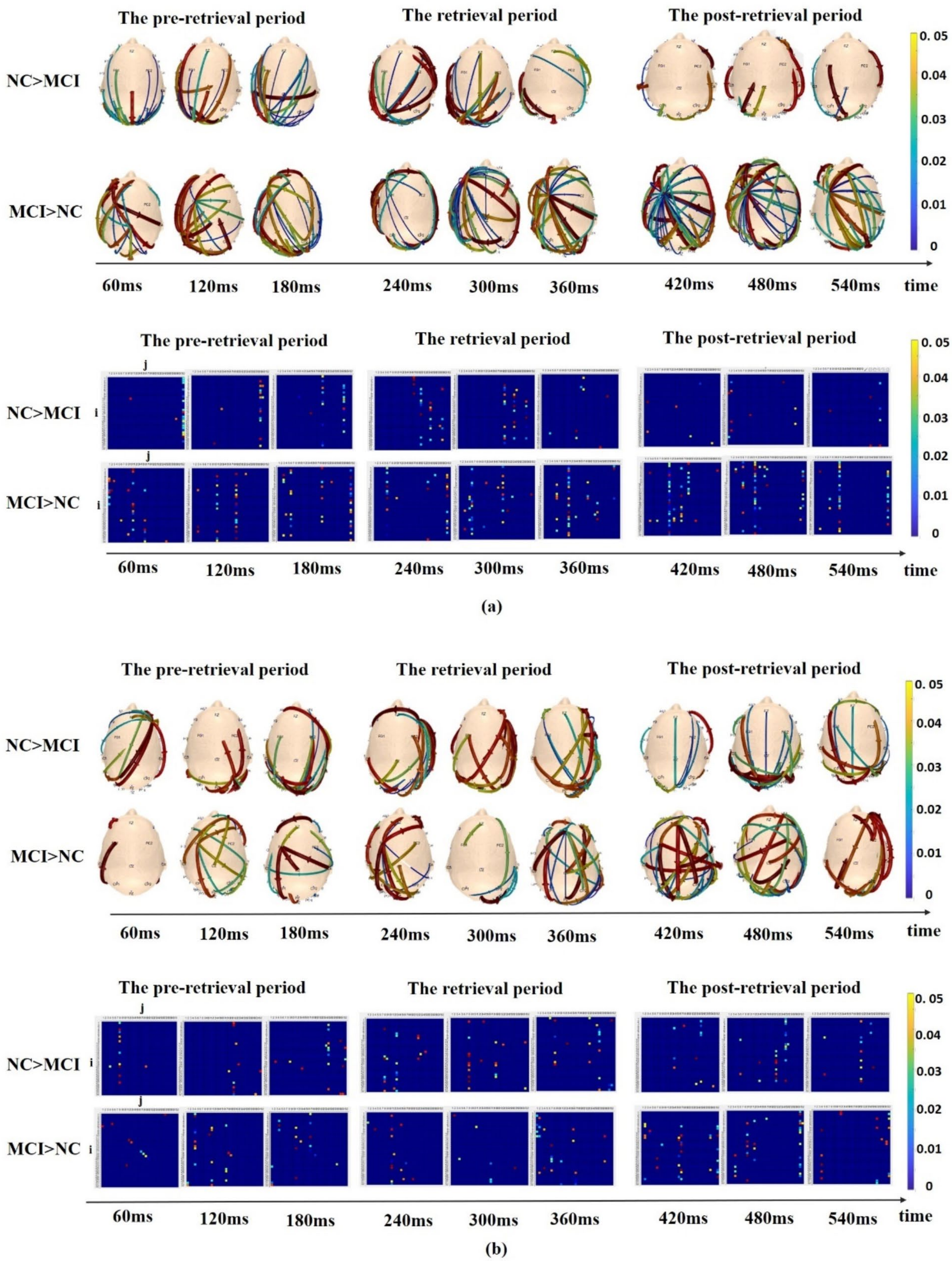


Fig. 4 Significantly stronger brain functional connectivity in WM task. (memory retrieval stage) (**a**) the low-load WM task, (**b**) the high-load WM task. Information flow Image *j*>>*i*.NC>MCI: More significant brain connectivity in NC. MCI>NC: More significant brain connectivity in MCI. ($p<0.05$, FDR correction)

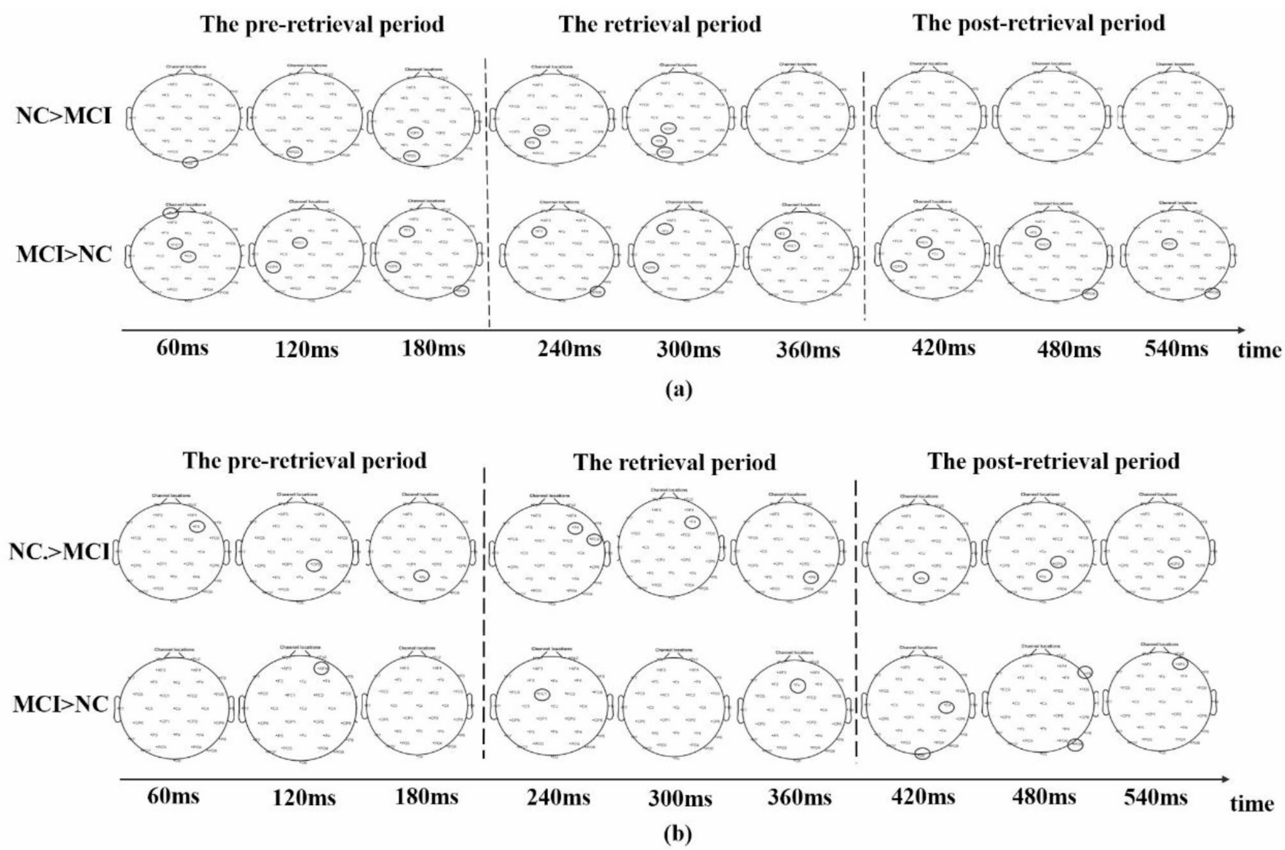


Fig. 5 The dynamic change process of significant core nodes over time between two groups under WM task (memory retrieval stage). (**a**) the low load-WM task, (**b**) the high-load WM task. NC > MCI: More significant core nodes in NC. MCI > NC: More significant core nodes in MCI

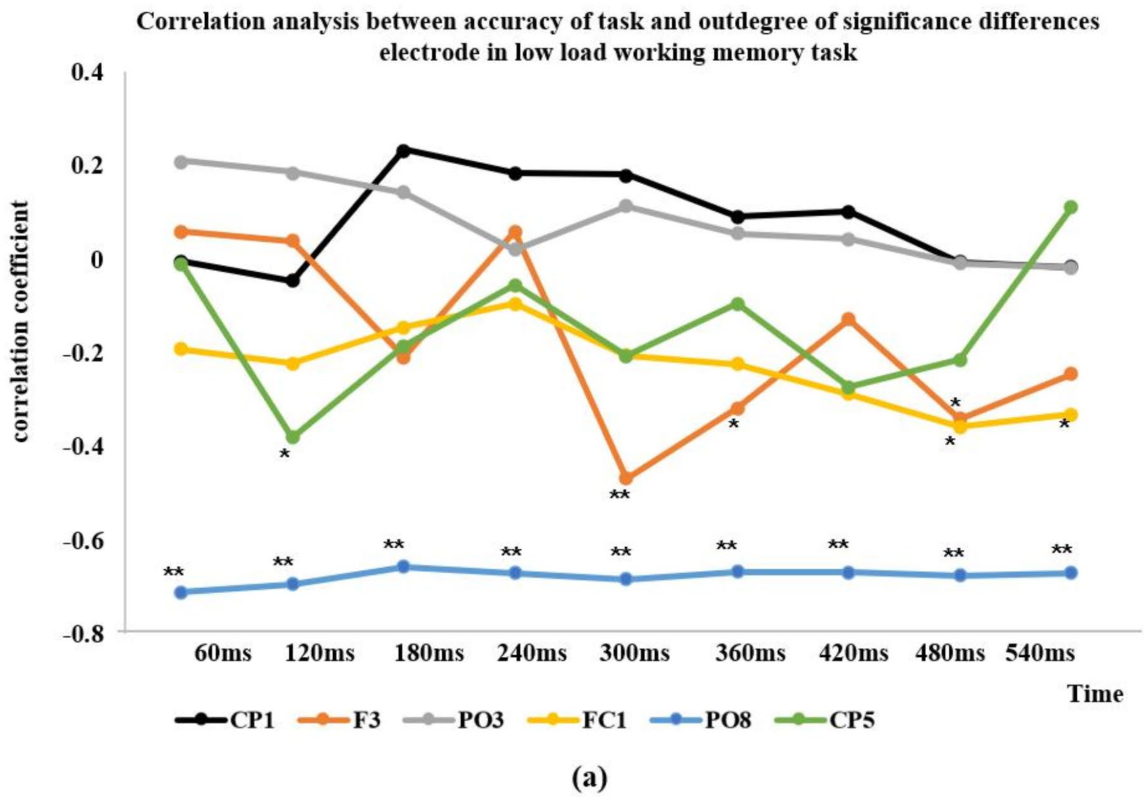
to frontal lobe, that was, the core node moves forward. The core node of MCI was mainly distributed in the prefrontal and occipital regions, with less involvement of the parietal lobe, and the I-node was AF4. There was no obvious rule in the whole process of the memory retrieval stage.

Correlation between the I-node and memory accuracy

In order to determine the more important I-nodes in two groups during different load WM tasks, we analyzed the relationship between the I-nodes outdegree and memory accuracy. Our results indicated that the correlation coefficient between memory accuracy and I-nodes in low load WM tasks was significantly higher compared to that in high load WM tasks. As shown in Fig. 6. Specifically, in low load WM tasks, there was a strong correlation between the occipital lobe (PO8) and the memory accuracy throughout the entire retrieval stage. The frontal lobe had a moderate to weak correlation with the WM memory accuracy in the retrieval period and the post-retrieval period (F3、FC1), while the parietal lobe had a weak correlation with the WM memory accuracy in the pre- retrieval period (CP5). In high-load WM tasks, the frontal lobe (F4) showed a moderate correlation with WM memory accuracy in pre-retrieval and retrieval period, while other core nodes had no significant correlation with memory accuracy.

k-nodes analysis

In order to further explore the heterogeneity of brain regions - key cores nodes (K-nodes) in two groups under different load WM tasks and provide some strategies for later intervention, we analyzed the outdegree of all I-nodes. The results showed that there was a more significant difference in the outdegree degree values of I-nodes between the two groups in low load WM tasks, providing corresponding EEG evidence for the more significant behavioral differences in the low load WM task, as shown in Fig. 7. Specifically, in low load WM tasks, there were significant differences in the outdegree values of FC1 and PO8 between the two groups during the entire memory retrieval stage, suggesting that there may be abnormalities in the left frontal and right occipital brain regions of MCI. Meanwhile, K-nodes FCI and PO8 electrodes can serve as sensitive channels to distinguish between the two groups. However, there were almost no significant nodes in high-load WM task.



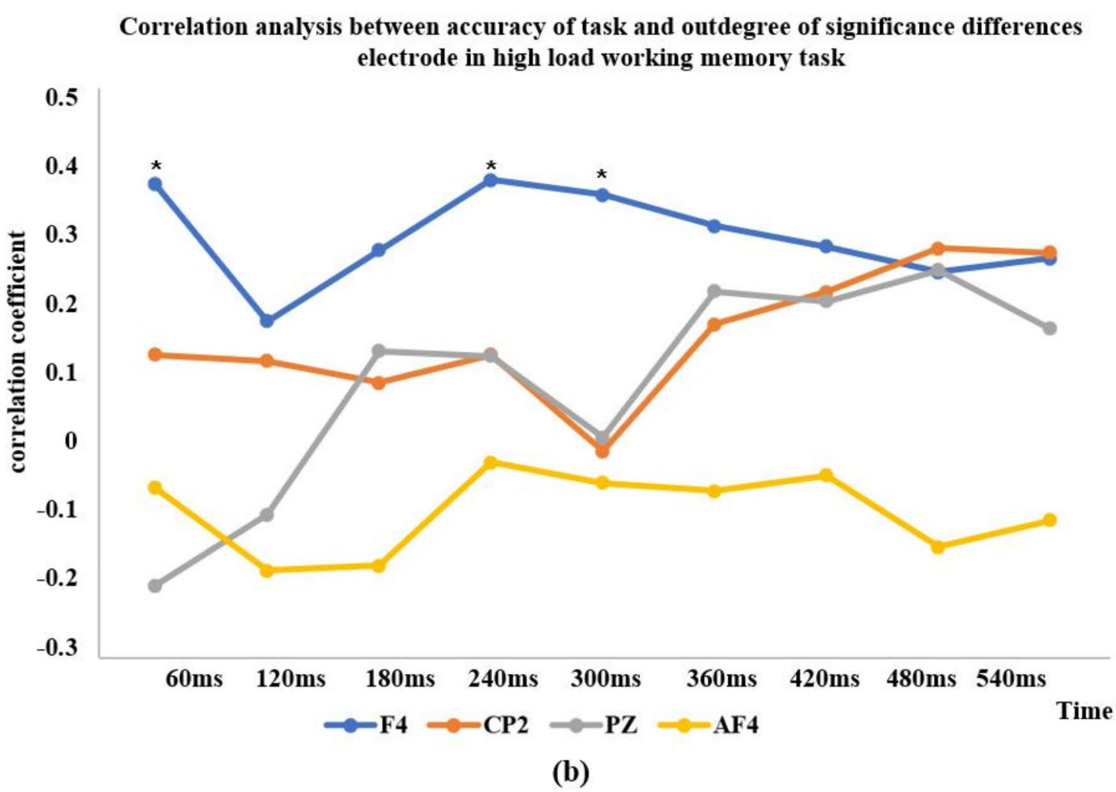


Fig. 6 Correlation analysis between memory accuracy and outdegree of electrode with significance difference during WM task. (**a**) the low load-WM task, (**b**) the high-load WM task. *$p < 0.05$, **$p < 0.01$

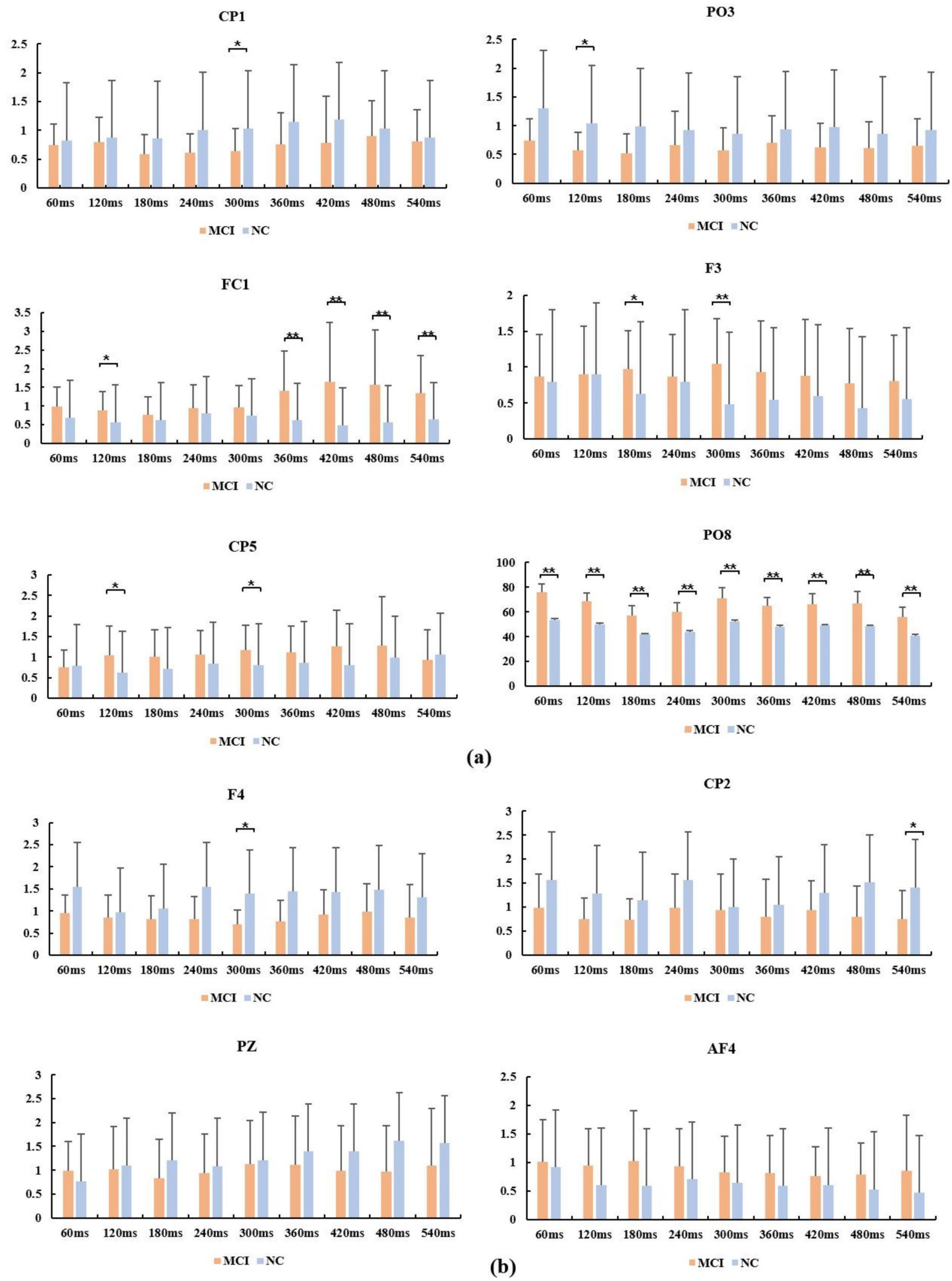


Fig. 7 Statistical significance analysis of the core node outdegree of the two groups of people in WM task (memory retrieval stage) over time. (**a**) the low load-WM task, (**b**) the high-load WM task. $*p<0.05$, $**p<0.01$

Discussion

This study employed a large-scale EEG dynamic effect network method to explore the WM impairment of MCI under different loads. To our knowledge, this was also the first exploration of the dynamic brain network patterns and EEG characteristics of WM disorders in MCI. Our research findings indicated that: (a) Behavioral data analysis: In WM tasks with different memory loads, there were significant differences in accuracy and accuracy/reaction time between MCI and NC. Compared to load six, load four task was more conducive to distinguishing MCI from NC. (b) Dynamic brain network analysis based on EEG: There were significant differences in the dynamic network patterns of memory retrieval stages between the two groups in different load tasks, with the differences mainly occurring in low load tasks, and the brain functional areas related to low load WM injury were mainly located in the left prefrontal lobe and right occipital lobe. In the low load WM task, NC exhibited more regular dynamic causal network pattern changes, and the core nodes were mainly distributed in the occipital lobe and parietal lobe, and there was a bottom-up core node transfer phenomenon in per and memory retrieval period. While the dynamic causal brain network of MCI showed no obvious regularity, with core nodes mainly distributed in the frontal lobe, and the difference between the two groups of k-nodes mainly located in FC1 and PO8. In contrast to low load memory, in the high load memory retrieval stage, NC also showed regular changes in dynamic causal network patterns, the core nodes were mainly distributed in the prefrontal and parietal lobes, and there was an up-bottom-up transfer phenomenon of the core nodes in the pre middle post memory retrieval period. While the dynamic causal brain network of MCI showed no obvious regularity, the core nodes of MCI were mainly distributed in the prefrontal and occipital regions.

Current research on WM has primarily focuses on the difference in memory load among individuals with normal cognition, with less attention given to the impact of memory capacity load on those with MCI. The existing research has proved that when remembering objects with simple characteristics, the WM capacity of healthy adults is stable at about 4, which is a widely accepted view [59, 60]. This means that when the capacity is 4, normal subjects can process simple objects and react correctly. However, our results revealed a significant difference between MCI patients and normal individuals when the memory capacity was set at four. That is, the WM of the MCI appeared to be compromised. With the increase in memory load, individuals with normal cognition struggle to manage multiple goals effectively, leading to a decrease in their accuracy rate. Conversely, the accuracy rate of MCI did not show significantly changes. But there were still notable differences between the two groups. It can be inferred that MCI patients did receive a certain degree of impairment in WM ability, which was distinct from NC when WM capacity load was 4 items, suggesting that the paradigm of WM task load 4 items is effective in differentiating between the two groups, and hold greater clinical diagnostic value.

Critically, the rate of these WM "failures" is strongly predictive of WM capacity as a whole. A key question, then, is why WM task failures occur. During the memory retrieval stage with different memory loads, there were significant differences in the dynamic brain network patterns between the two groups of participants. The dynamic network with significant differences was driven by dynamic core nodes, reflecting abnormal changes in the activation patterns of dynamic brain regions. These results also provide electrophysiological evidence that WM of MCI population is severely damaged compared with NC group. Our research indicated that in the process of memory retrieval, in NC, the core nodes of the low load memory retrieval stage were mainly distributed in the occipital and parietal regions, and there was a bottom-up transfer trend of network core nodes moving from the occipital to parietal lobes. With the increase of memory load capacity, the core nodes of the network were mainly distributed in the anterior brain area, and there was a bottom-up transfer phenomenon of the network core nodes migrating from the parietal lobe to the prefrontal lobe. In a word, the dynamic changes in the brain network of NC exhibited a regular memory load effect, while MCI showed no significant rule in both WM tasks. From the perspective of WM mechanism, WM is an attention control system with limited resources. Individuals can flexibly allocate and transfer attention resources according to their goals. Previous studies have demonstrated that under conditions of low WM load during memory-matching visual search tasks, there is a strong coupling between prefrontal cortex and posterior visual area [61]. The coupling suggests that visual fixation will dominate in the early stage of memory retrieval, at this period, the core part of brain area will fall in the occipital region. Attention is generally considered as the core executive function to promote WM retention, and it will be involved in the three stages of coding, retention and retrieval of WM [62]. Attentional control can actively maintain relevant information and inhibit the ability of irrelevant information [63], thus enhancing WM performance. With the retrieval of memory, the core node of NC began to migrate from the occipital region to the parietal lobe. For a long time, the posterior parietal cortex has been considered as the key brain region involved in controlling the amount of information stored in visual WM. It is proposed that the storage of visual WM includes not only the quantity dimension of memory information, but also the accuracy dimension of storage [64, 65]. Therefore, the transfer from occipital lobe to parietal lobe in the low load WM retrieval stage reflected a bottom-up cognitive processing process in the normal low load WM retrieval stage. When the WM capacity was six, with the increasing difficulty of the task, at the stage of the memory retrieval process, different from the low load task, the NC's core node had already existed the migration phenomenon - the core node change process moved forward from the parietal lobe to the frontal lobe, and there was almost no occipital lobe activation. This is the same as the result of a previous studies [66]. The researchers used multivariate analysis to explicitly study the change of primary visual cortex activity with the amount of information stored in visual WM, found that the accuracy of decoding the stored content of visual WM from the activity of primary visual cortex decreased with the decrease of memory accuracy, which was also in line with the phenomenon of flexible resource allocation with more goals for individuals. That is, when the task difficulty increases, reduce the allocation of occipital visual resources. In different load tasks, compared to low load tasks, the dynamic brain network changes of NC in high load tasks appear less regular. This means that the controllability of the brain network decreases with increasing difficulty, which is consistent with the results of a previous fMRI study based on n-back tasks [67]. This may be due to the increasing complexity of the task, which limits the brain's ability to re allocate resources and dynamically adjust them, leading to a decrease in network controllability. Nonetheless, compared to MCI, NC still exhibited a relatively regular and stable brain network pattern in WM tasks with different loads, which had a positive impact on the performance of WM tasks. It can improve the efficiency and accuracy of WM tasks by optimizing the connections and communication between neurons, promoting coordination and cooperation between different brain regions, and adapting to changes in task requirements. However, there are significant differences in the dynamic network connectivity patterns of MCI, whether under high or low WM loads, such as irregular changes in the dynamic network and disordered dynamic core nodes. This is also similar to a previous study based on fMRI, where the network connection mode of MCI in WM tasks is more dispersed compared to NC [68]. Disordered dynamic networks may lead to a decrease in resource allocation and configuration efficiency [69]. When the core nodes of the network are relatively dispersed, it means that the power and control of the network are relatively dispersed, the network's anti-interference ability is poor, and the efficiency of processing information is low, these factors might collectively contribute to suboptimal behavioral outcomes.

The next question is which core nodes of the brain network mediate the differences in WM abilities between two groups. Delving into this issue would help us gain a deeper understanding of the mechanisms of WM and reveal the sources of inter-individual variability in WM performance. Such insights are helpful for the advancement of diagnostic protocols and the development of targeted therapeutic interventions, for example, researchers can later put more energy to study these areas where active hubs lie in such as placing Transcranial alternating current stimulation (tACS). The behavioral data of the two groups in the low load WM task were more significantly different compared with high load WM task, and the cause of WM impairment in the MCI may be the abnormal representation of the left prefrontal lobe (FC1) and the right occipital lobe (PO8) in the functional brain regions. In the process of WM, the frontoparietal network plays an important role in higher cognitive processes such as executive control, and its components also include bilateral dorsolateral prefrontal cortex and bilateral posterior parietal cortex. The frontal cortex is mainly responsible for coding prospective action information [70] as well as the control process of attention [71], which runs through almost the whole WM task process. Therefore, functional impairment and degeneration of the frontal lobe may be an important cause of WM impairment in MCI. As a recent ERP study based on short-term memory tasks analyzed distinguishable brain wave patterns in the normal control group, amnestic MCI (aMCI), and AD brains, the results showed that the left frontal signal associated with WM may be a potential effective ERP biomarker, indicating cognitive decline and predicting cognitive status 5 years later [72]. At the same time, the research based Magnetic Resonance Imaging (MRI) showed that in the visuospatial WM task, aMCI patients showed the characteristics of reduced activity in the frontal lobe and visual cortex during the coding and recognition periods [73]. Attention related to the occipital lobe is an important component of executive control mechanisms, and damage to attention allocation during memory retrieval may be a significant factor in WM damage in the MCI group. The evidence from imaging showed that in the WM task, the brain regions from posterior cingulate gyrus to medial precuneus in MCI group were inactivated, and at the same time, the activation of medial parietooccipital lobe and right parietal cortex also decreased in the retrieval stage, and the subsequent follow-up investigation further found that the above changes could predict the decline of living cognitive level of these people to a certain extent after two year [74]. Similar to these results, in our study, we found that MCI exhibited abnormal activation in the left prefrontal and right occipital lobes throughout the entire memory retrieval process, resulting in defects in the target attention, information update, target stimulus detection, conflict processing, and other processes of in WM task, ultimately leading to a decrease in WM ability. In the literature on MCI, an interpretation of abnormal brain activity that has been advanced is the concept of development of compensatory networks [75–79]. Existing research in the exploration of mechanisms underlying MCI-WM has yielded a variety of divergent conclusions, such as abnormalities in brain functional areas, including the hippocampus, medial temporal lobe, anterior cuneiform lobe, prefrontal lobe, and parietal lobe, and abnormal brain connectivity, including frontoparietal network and default network, mainly due to differences in research methods across studies (in the predominant utilization of Functional Magnetic Resonance Imaging (fMRI) techniques), WM paradigm, inclusion criteria, and sample size, resulting in a lack of comparability of results. Furthermore, WM tasks involve the involvement of different brain regions in the memory, retention, and extraction stages. For example, in the stage of memory encoding, the activation areas of the dorsolateral prefrontal lobe mainly tend to the posterior and lateral regions [80], while in the delayed memory stage, the activation areas of the dorsolateral prefrontal lobe mainly tend to the anterior and central regions [81, 82]. In our previous MCI brain network research based on EEG, we found that the differential brain network nodes activated during the memory encoding stage were mainly located in the frontal lobe FZ and parietal lobe PZ, which is different from the core nodes in the memory extraction stage in current research [83]. Given the scarcity of research on WM deficits in MCI through EEG, it remains uncertain which stage's core node exerts a more significant influence. Therefore, we aspire for subsequent studies to ascertain the importance of our identified targets, particularly through the lens of electrical stimulation intervention. Such research could furnish more reliable evidence to bolster clinical interventions for MCI.

At present, behavioral performance data derived from WM paradigms have not yet become the primary basis for clinical diagnosis. Instead, they serve as supplementary tools, or as indicators for further investigation in cases where individuals exhibit pronounced deviations through the current WM paradigms. While the WM paradigm holds certain value and promise in clinical application, ongoing research and refinement are essential to enhance its utility and diagnostic accuracy in clinical practice. Meanwhile, the correlation between EEG electrodes is high, and there may be some systematic errors in using brain network data for analysis. In the follow-up work, fMRI and other measurement methods can also be added to verify the rationality of the current results. Further, at present, the dynamic network of subjects is based on the superposition of trials at a single time point. However, the memory retrieval stage of WM tasks involves complex cognitive processes such as attention, recognition, and decision-making. Tracking and analyzing the characteristic features of each subject at different time windows based on trial-by-trial can further obtain important and critical information. In future research, it may be necessary to introduce time window analysis to capture the dynamic characteristics of behavioral changes, while considering many other aspects such as the trade-off between time resolution and noise, limitations in window length selection, computational complexity, etc., in order to more accurately and reliably reveal the dynamic activity of the brain. By increasing the number of experiments and tracking analysis at different trial-by-trial levels, we can gain a deeper understanding of behavioral patterns. Furthermore, in research, we can emphasize the diversity within and between disciplines through interdisciplinary collaboration, diverse sample selection, and other methods to improve the universality and applicability of the results. Finally, our current results are based on the horizontal comparison of the WM processing mechanism of MCI and NC. For the subjects, a longer-term follow-up and follow-up are needed to verify the previous results.

Conclusion

MCI patients had significant WM impairment. Meanwhile, the WM disorder of MCI is associated with abnormal dynamic brain network patterns during the memory retrieval stage. Behavioral data in the low load WM task paradigm and abnormal electrophysiological signals in the left prefrontal (FC1) and right occipital lobes (PO8) may be more conducive to distinguish MCI. These findings are of great significance for improving our understanding of cognitive processes, revealing cognitive mechanisms, predicting cognitive performance, and applying them to cognitive interventions.

Abbreviations

MCI	Mild cognitive impairment
WM	working memory
EEG	electrophysiological
NC	normal cognitive control
AD	Alzheimer's disease
SD	standard deviation
MOCA	Montreal Cognitive Assessment
MMSE	Mini Mental State Examination
FAQ	Functional Activities Questionnaire score
ADL	Activities of Daily Living
TV-MVAR	time-varying multivariate autoregressive
ADTF	adaptive directed transfer function
GC	Granger causality
AIC	Akaike information criterion
RLS	recursive least squares
FDR	false discovery rate
I-nodes	important core nodes
K-nodes	key cores node
tACS	Transcranial alternating current stimulation
MRI	Magnetic Resonance Imaging

fMRI Functional Magnetic Resonance Imaging

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Author contributions
YJ conducted data collection, processing and analysis, image preparation, and completed the initial draft. ZW G conducted data processing and analysis, as well as article revisions. XB Z participated in the revision of the article. NJ participated in the supervision of the entire project process and the revision of the article. JY H participated in the management of the entire project and the revision of the article. All authors reviewed the manuscript. and approved the final manuscript.

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Data availability
Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of West China Medical College of Sichuan University (Approved Number: 2021(1447)). All participants provided written informed consent prior to their participation.

Consent for publication
All authors have approved the publication.

Competing interests
The authors declare no competing interests.

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