



OPEN Research on brain functional network property analysis and recognition methods targeting brain fatigue

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At present, researches on brain fatigue recognition are still in the stage of single task and simple brain region network features, while researches on high-order brain functional network features and brain region state mechanisms during fatigue in multi-task scenarios are still insufficient, making it difficult to meet the needs of fatigue recognition under complex conditions. Therefore, this study utilized functional near-infrared spectroscopy (fNIRS) technology to explore the correlation and differences in the low-order and high-order brain functional network attributes of three task induced mental fatigue, and to explore the brain regions that have a major impact on mental fatigue. Self-training algorithms were used to identify the three levels of brain fatigue. The results showed that during the fatigue development, the overall connection strength of the endothelial cell metabolic activity and neural activity frequency bands of the low-order brain functional network first decreased and then increased, while the myogenic activity and heart rate activity frequency bands showed the opposite pattern. Network topology analysis indicated that from no fatigue to mild fatigue, the clustering coefficient of endothelial cell metabolic activity and myogenic activity frequency bands significantly decreased, while the characteristic path length of myogenic activity significantly increased; when experiencing severe fatigue, the small-world attribute of the neural frequency band significantly weakened. However, each frequency band maintained its small-world attribute, reflecting the self-optimization and adaptability of the network during the fatigue process. During mild fatigue, neuronal activity bands' node degree, cluster coefficient, and efficiency rose in high-order brain networks, while low-order networks showed no significant changes. As fatigue progressed, the myogenic activity bands of high-order network properties dominated, but neural bands gained prominence in mild fatigue, approaching the level of myogenic bands in severe fatigue, indicating that brain fatigue orchestrated a shift from myogenic to neural dominance in frequency bands. In addition, during the process of fatigue, the four network attributes of the high-order network cluster composed of low-order nodes related to the prefrontal cortex region, left anterior motor region, motor assist region, and left frontal lobe eye movement region significantly increased, indicating that these brain regions had a significant impact on brain fatigue status. The accuracy of using both high-order and low-order features to identify fatigue levels reached 88.095%, indicating that the combined network features of both high-order and low-order fNIRS signals could effectively detect multi-level mental fatigue, providing innovative ideas for fatigue warning.

Keywords Brain functional network, Brain fatigue detection, fNIRS, Multitasking, Multiple fatigue levels

In contemporary society, numerous daily activities require a stable level of attention and cognitive performance. For example, extended drives on highways or hours of consecutive study or work often lead to mental fatigue. Mental fatigue, characterized by a sense of tiredness, manifests behaviorally as a decline in attention¹, cognitive abilities², and judgment capacity during unforeseen situations³. To effectively mitigate the adverse consequences of mental fatigue, it is crucial to gain a better understanding of its underlying neural mechanisms.

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Functional connectivity (FC) was initially proposed to calculate the temporal synchrony between different brain regions⁴, thereby assisting in the assessment of brain fatigue. Among them, the brain functional network connection method based on graph theory has now become one of the main methods for analyzing neuroimaging signals. However, this pairwise functional connectivity between brain regions only calculates the simple temporal synchrony between two brain regions, and the high-order relationships between brain regions may not be fully captured. Mental fatigue is a dynamically changing process, and traditional static functional connectivity cannot fully represent the relationship between network nodes over time. Additionally, most low-order feature fatigue recognition methods can only distinguish between two simple mental states of no fatigue and fatigue, which is not conducive to effective early warning of mental fatigue in specific applications. To address this issue, this study further proposes a high-order functional connectivity based on “correlation of correlations” on the basis of low-order brain functional networks. This method considers functional connectivity across multiple brain region nodes to characterize higher-level and more complex interaction patterns between brain regions. High-order interactions have been widely discussed in recent years in neuroscience-related research. Zhang et al.⁵ systematically evaluated two high-order functional network construction methods, associative high-order functional connectivity and terrain profile similarity-based high-order functional connectivity, using retest data. They found that these two indicators have good physiological reliability, providing guidance and suggestions for clinical research. Ryan et al.⁶ selected different nodes in the high-order brain functional network and applied them to determine task-specific intrinsic network relationships between schizophrenic patients and control subjects. Kralemann et al.⁷ restored the directional connectivity of the small oscillator network by reconstructing the high-order phase dynamics from the multivariate time series, realized the judgment of whether there was connectivity between high-order network nodes, and reproduced the high-order network structure. These studies all indicated that the high-order brain functional network had the potential to become a more objective and effective evaluation index for mental fatigue.

Therefore, this study aims to explore the changes in low-order brain functional network connectivity and the alterations in both low-order and high-order brain functional network properties across three levels of mental fatigue, induced by three distinct tasks. Furthermore, it endeavors to identify the brain regions that significantly contribute to mental fatigue and investigate the feasibility of utilizing low-order and high-order network information features derived from cerebral blood oxygenation data to distinguish among the three levels of mental fatigue in multitasking scenarios.

Materials and methods

Subject

This study recruited 36 undergraduate and graduate students (male: female = 27:9) from Soochow University. All participants were right-handed, in good health, and had regular schedules (the sleep time is from 11:00 p.m. to 6:30 a.m. the next day), with no history of mental illness or cerebrovascular disease. On the day of the experiment, participants were asked not to take naps, use medication, or consume caffeine or stimulating beverages. The studies involving human participants were reviewed and approved by the Ethics Committee of Soochow University (ECSU) approval No. SUDA20210909H01. The participants provided their written informed consent to participate in this study. All experiments were conducted in accordance with the Helsinki Declaration.

Experimental plan and data collection

Experimental plan design

Participants were required to ensure normal sleep the day before the experiment (a specified sleep time of 11:30 pm to 6:30 am, and to ensure no insomnia prior to the next day's experiment). They were randomly divided into three groups (12 individuals per group, including 9 males and 3 females) and performed different brain fatigue-inducing tasks for 40 min each, including normal mental work, fatigued driving, and psychomotor vigilance testing. Each participant repeated the tests three times during the morning (7:00–8:00), afternoon (14:00–17:00), and evening (20:00–23:00) before resting. The specific procedure is shown in Fig. 1a. In the morning, participants underwent the N-back behavioral test directly and then completed the MFI-20 Multidimensional Fatigue Inventory (totaling 8 min). In the afternoon and evening, the behavioral test and fatigue scale completion were conducted before and after each task. Throughout the experiment, near-infrared spectroscopy was used to simultaneously collect information on cortical hemoglobin.

Mental fatigue induction tasks

PVT test is a reaction time test with high attention load, as shown in (Fig. 1b). The subjects need to concentrate their attention on monitoring the display, and respond as fast as possible through the buttons on the keyboard when the stimulus (red square) is displayed in the middle of the display. Within the next 1 s, the corresponding reaction time will be displayed on the screen. The stimulus interval in the test is random and variable, ranging from 2 to 10 s. The PVT task simulates passive mental fatigue caused by prolonged simple attention tasks in this study.

Normal mental work involves mathematical calculation tasks and foreign language reading tasks that are appropriate for the participant's level, to simulate the mental fatigue state after real learning tasks.

The simulated driving task was designed with a semi-immersive driving simulation method, incorporating driving tasks on straight highways and complex mountain roads. This setup aims to mimic both the passive fatigue induced by low task load in a highly predictable and smooth driving state, as well as the active fatigue resulting from the depletion of brain resources due to high attentional demands.

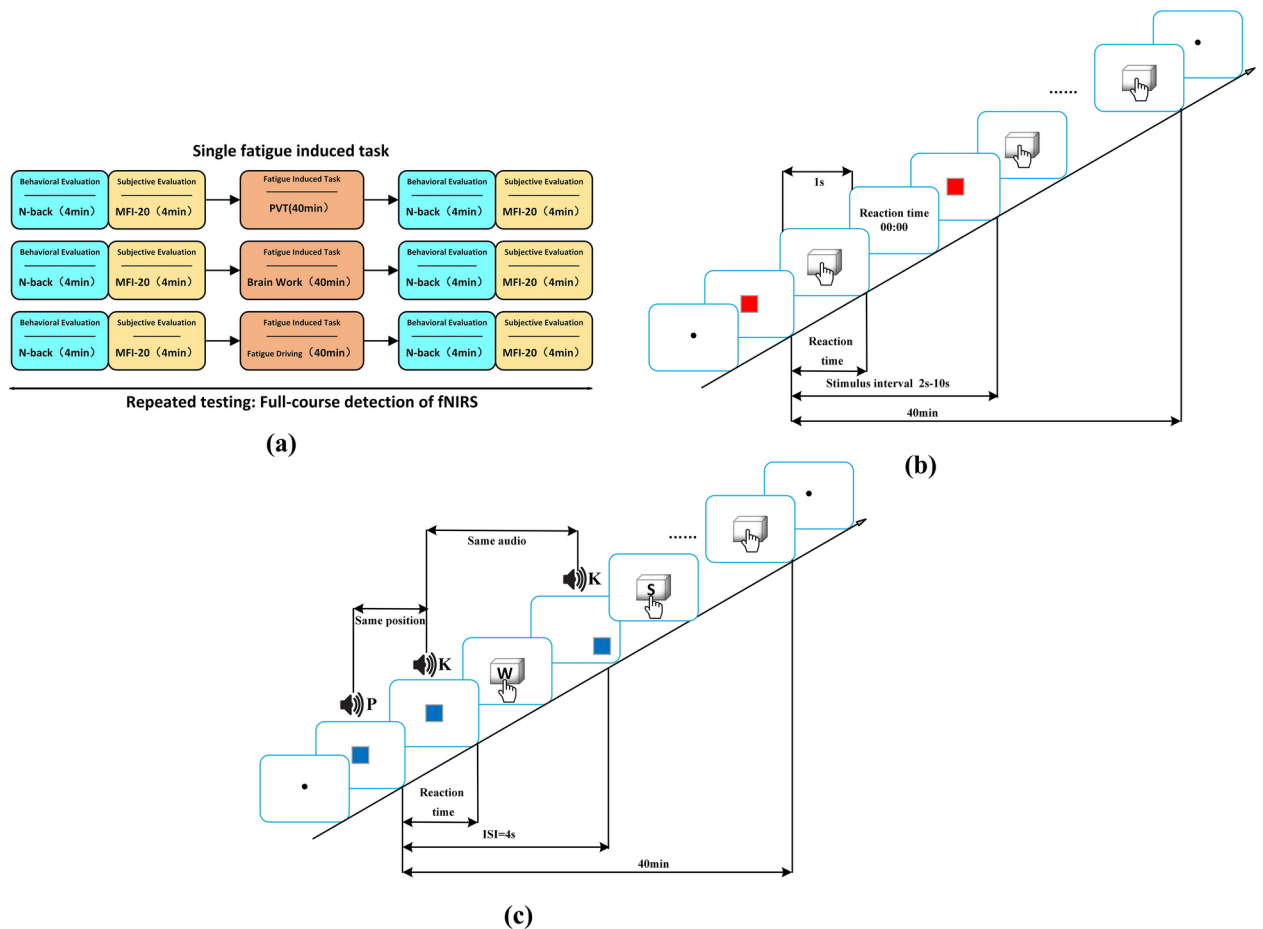


Fig. 1. (a) Three types of brain fatigue inducing tasks, with 1-back and MFI-20 performed before and after the tasks. (b) PVT testing process. (c) 1-back testing process.

Mental fatigue assessment task

We used the MFI-20 Multidimensional Fatigue Inventory and the N-back task to evaluate the level of mental fatigue in participants:

The MFI-20 Multidimensional Fatigue Inventory was used for subjective evaluation of participants' mental fatigue level. The language of the MFI-20 scale is concise and easy to understand, allowing participants to complete it easily within five minutes. This subjective fatigue evaluation scale excludes somatic symptoms directly related to mental fatigue, such as "headache," effectively avoiding confusion between mental fatigue and similar symptoms of other physiological conditions. It assesses the degree of mental fatigue from multiple dimensions.

We used the accuracy of the N-back task to collaborate with the MFI-20 scale to more accurately determine the fatigue level of participants. The N-back task requires coordinated work across multiple brain regions. As shown in Fig. 1c, the 1-back task was used in the specific experiment, where participants were required to remember and compare the current stimulus with the previous one. During the test, a blue square is displayed on the screen every 4 s, and a random letter is spoken simultaneously. Participants need to compare whether the positions of the blue squares are the same for the two consecutive stimuli and whether the spoken audio is the same. If the positions are the same, they are required to press the W key, and if the audio is the same, they are required to press the S key. The reaction time and accuracy of each comparison task are recorded as a basis for assessing cognitive performance and alertness.

fNIRS data acquisition

This experiment employed a multi-channel near-infrared brain imaging device (Huichuang NirSmart) to record the blood oxygen activity of the cerebral cortex at a sampling frequency of 16 Hz. (Current research has indicated that a sampling frequency of approximately 10 Hz is appropriate⁸. Therefore, an actual frequency of 16 Hz is sufficient to meet the experimental needs.). Using Brodmann's anatomical region system for the cerebral cortex as a reference, a 4 × 4 cap layout was designed, incorporating 8 light emitters and 8 light receivers to form 24 effective test channels. These channels were further divided into several regions of interest (ROI), covering four brain functional areas: the prefrontal cortex (PFC), the frontal eye field (FEF), the supplementary motor area (SMA), and the premotor cortex (PMC). The corresponding acquisition channels for each brain functional area

ROI brain area number	ROI brain region name	ROI brain regions contain channels
1	PFCl	1, 4, 8
2	PFCm	2, 5, 6, 9
3	PFCr	3, 7, 10
4	FEFl	11, 12
5	FEFr	13, 14
6	PMCl	15, 18, 22
7	SMA	16, 19, 20, 23
8	PMCr	17, 21, 24

Table 1. Corresponding brain signal acquisition channels for ROI brain regions.

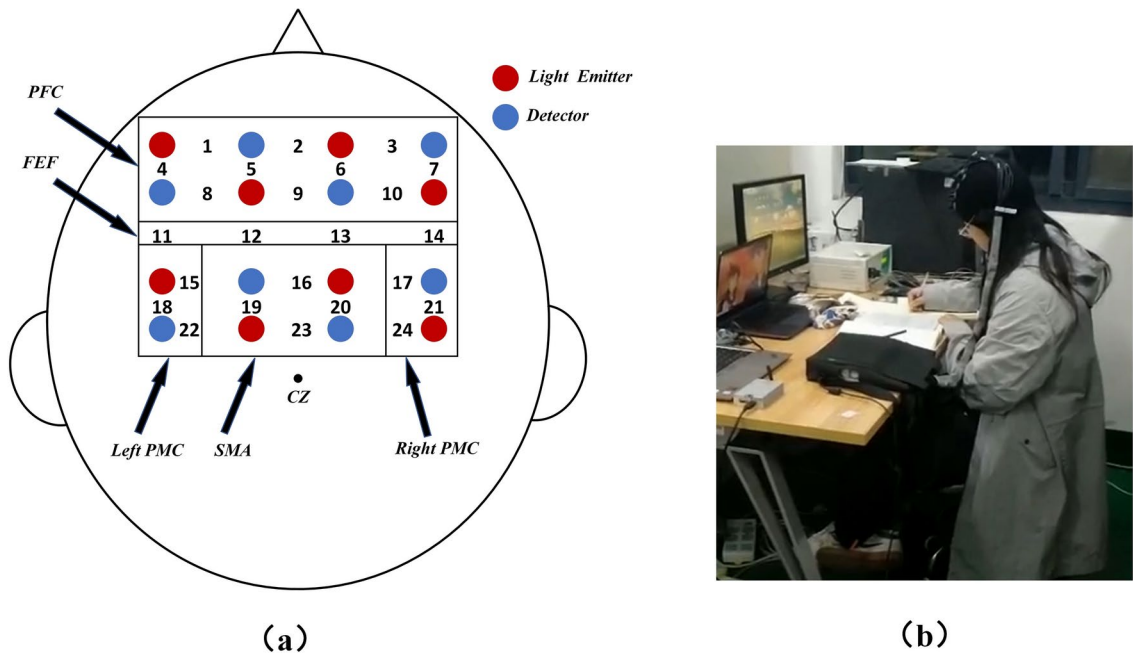


Fig. 2. (a) Channel distribution of experimental equipment, with red and blue corresponding to the emitter and receiver, respectively. (b) Experimental environment.

Frequency band number	Frequency range (Hz)	Physiological information
I	0.005–0.021	Endothelial cell activity
II	0.021–0.052	Neurogenic activity
III	0.052–0.145	Myogenic activity
IV	0.145–0.6	Respiratory function
V	0.6–2.0	Heart rate activity

Table 2. Corresponding table of physiological information and frequency bands in oxyhemoglobin.

are detailed in Table 1, with ‘l’, ‘m’, and ‘r’ representing the left, middle, and right regions, respectively. In the experiment, the 10–20 system⁹ was used as the positioning standard for locating brain functional regions, with the specific channel distribution of brain imaging shown in Fig. 2a, and the experimental environment shown in Fig. 2b.

Brain fatigue data processing and analysis

Bandpass filtering in multiple physiological frequency bands

Previous research has demonstrated that the hemoglobin information in the human brain carries numerous physiological details¹⁰, with the main five types of physiological information distributed across five non-overlapping frequency bands (Table 2). Studying the attributes and coupling relationships of brain functional networks across these physiological frequency bands can aid in understanding the mechanisms of information

synchronization within each band. Therefore, for the raw data, the Temporal Derivative Distribution Repair (TDDR) method was first employed to remove signal motion artifacts and baseline offsets¹¹. Then, as depicted in Fig. 3, a second-order Butterworth bandpass filter was applied to the signal for bandpass filtering into five frequency bands, simultaneously mitigating the detrimental effects of high-frequency noise on the signal.

Classification of brain fatigue levels

Based on the scores of the MFI-20 scale, an unsupervised K-means clustering analysis was conducted to classify the samples into two categories: non-fatigue and fatigue. According to the clustering analysis results, a score of 2.57 was used as the boundary, with scores below 2.57 classified as non-fatigue and scores greater than or equal to 2.57 classified as fatigue. Subsequently, based on the scores of the N-back behavioral task (reaction time/accuracy), the fatigue samples were further categorized into mild fatigue and severe fatigue. When samples with an MFI-20 scale score of 3 or above are classified as experiencing severe fatigue, the behavioral task scores corresponding to samples of mild fatigue and severe fatigue exhibit the most significant differences. Consequently, samples with scores of 3 or above are categorized as severely fatigued.

Low-order feature calculation of brain fatigue

To evaluate the changes in activity indicators of different brain cortical regions and eliminate individual differences in blood oxygen activation channels, a weighted average method based on entropy weights was adopted in the experiment to calculate the blood oxygen concentration of each ROI according to the different channels corresponding to each brain region in fNIRS. A total of 24 channels were grouped into 8 brain regions. The calculation formula is as follows:

$$y = \sum_j X_{ij} \omega_j \quad (i = 1, 2, 3, \dots, N, j = 1, 2, 3, \dots, M) \quad (1)$$

X represents an N -row M -column matrix consisting of original hemoglobin concentration values, and ω_j represents the weight of each channel calculated through the entropy of the blood oxygen concentration information in that channel¹².

In the experiment, a network based on Pearson correlation was calculated. Firstly, the sliding window method was used to intercept the brain blood oxygen time window data. According to research¹³, for fNIRS signals, a window length greater than 30 s can ensure the stability of correlation features. Considering both the validity of analyzing data at lower frequency bands and the fineness of features, a window length of 1 min with a step size of 10 s was selected for this study. Within each time window, the Pearson correlation coefficients between the cerebral blood oxygen signals of paired ROI brain regions were calculated, and these coefficients were used to

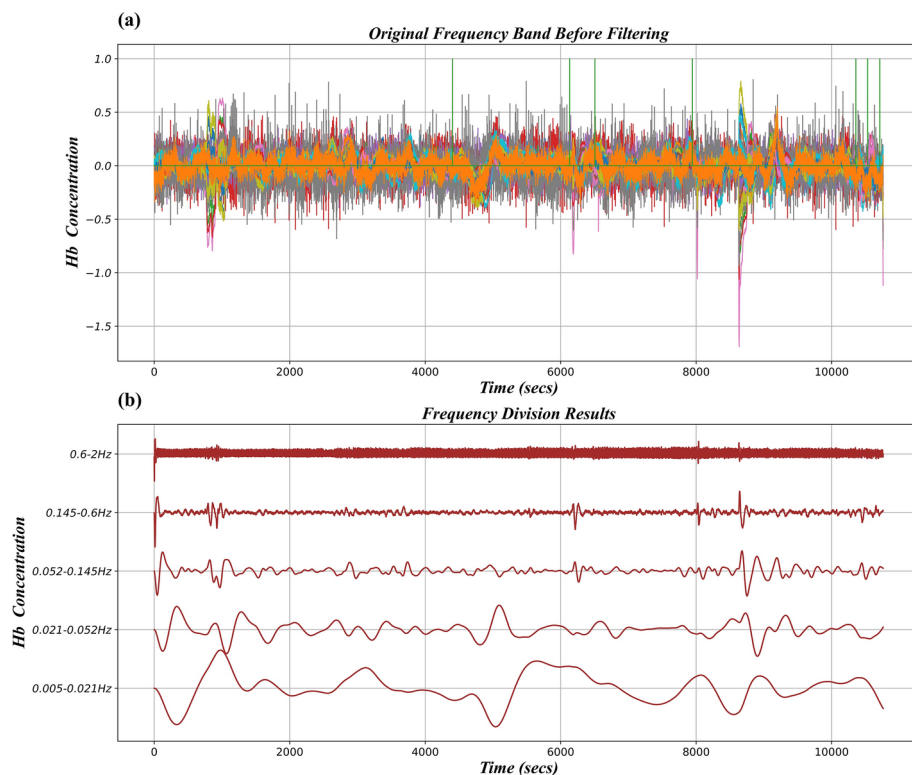


Fig. 3. (a) Original undivided blood oxygen concentration information of channel 1. (b) Divided blood oxygen concentration information.

construct an 8×8 adjacency matrix representing the low-order functional connectivity network. The low-order functional connectivity between regions was defined as follows:

$$LOFC_{ij} = \frac{\sum_{t=1}^T (x_i(t) - \bar{x}_i)(x_j(t) - \bar{x}_j)}{\sqrt{\sum_{t=1}^T (x_i(t) - \bar{x}_i)^2 \sum_{t=1}^T (x_j(t) - \bar{x}_j)^2}} \quad (2)$$

In the given formula, $x_i(t)$ and $x_j(t)$ represent the signals of region i and region j at time point t , respectively, while $\bar{x}_i$ and $\bar{x}_j$ denote the average value of the signals in the region.

The clustering coefficient is a metric used to measure the degree of aggregation among nodes in a network. A higher value indicates stronger connections among nodes or within the network, indicating a more clustered network topology. In a weighted network, the clustering coefficient of node (also known as the local clustering coefficient) can be expressed as:

$$C_u = \frac{1}{\deg(u)(\deg(u) - 1)} \sum_{v,w} (\widehat{w_{uv}} \widehat{w_{uw}} \widehat{w_{vw}})^{1/3} \quad (3)$$

Among them, $\deg(u)$ is the degree of node u , and u, v, w are three tuples associated with the edges of the node u . The tuple can form three edges in the network that can form a triangle. The weight $\widehat{w_{uv}}$ is normalized by the edge with the largest weight in the network, $\widehat{w_{uv}} = w_{uv} / \max(w)$.

The clustering coefficient is defined as the mean value of all local clustering coefficients:

$$C = \frac{1}{n} \sum_{v \in G} C_v \quad (4)$$

Characteristic path length refers to the average of the shortest path lengths between any pair of regions in a network. It serves as a measure of the overall routing efficiency of a brain functional network. A low characteristic path length indicates a high efficiency of parallel information transmission in the network. In a weighted network, the path length d_{ij} between two nodes, i and j , is the sum of the lengths of the edges along the connecting path. These edge lengths are calculated as the reciprocal of the edge weights. The characteristic path length is the mean of the shortest d_{ij} values across the entire network, and its mathematical definition is as follows:

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

Small-worldness is a summary metric for small-world attributes, which is estimated as the ratio of clustering coefficient to characteristic path length. These two metrics have been normalized by dividing their values by those of equivalent random networks. The specific calculation formula is as follows:

$$\sigma = \frac{C_{\text{real}}}{C_{\text{random}}} / \frac{L_{\text{real}}}{L_{\text{random}}} \quad (6)$$

The small-world property is obtained by normalizing the clustering coefficient ($\gamma = C_{\text{real}}/C_{\text{random}}$) and the characteristic path length ($\lambda = L_{\text{real}}/L_{\text{random}}$). Among them, C_{real} and L_{real} represent the clustering coefficient and characteristic path length of the analyzed network, respectively. C_{random} and L_{random} represent the averages of the clustering coefficient and characteristic path length of 100 random networks matched with the analyzed network, respectively.

Based on the weighted graph within each low-order network window, the clustering coefficient, characteristic path length, and small-world properties of the network were extracted as features of low-order functional connectivity.

Calculation of high-order features of brain fatigue

In the experiment, the calculation method of dynamic high-order functional connectivity networks was employed, with the calculation steps shown in (Fig. 4). The specific steps are as follows: (1) Use a sliding window to divide the entire fNIRS signal into multiple overlapping segments with a window length of 1 min and a step size of 10 s. (2) For each participant, within each frequency band, each channel of the fNIRS device is treated as a node, and pairwise correlation coefficients are computed to construct a set of 24×24 low-order functional connectivity matrices. These matrices form a dynamic functional connectivity time series. (3) The dynamic functional connectivity time series of all participants are concatenated along the time dimension. Subsequently, based on the K-means clustering algorithm, the correlation coefficients within each frequency band are grouped into 10–30 clusters according to their magnitudes. By calculating the mean silhouette score for each clustering outcome, it is observed that the mean silhouette score reaches its maximum (the highest mean silhouette score = 0.113) when clustering into 24 clusters. Consequently, the correlation coefficients are ultimately clustered into 24 clusters. (4) Each cluster is transformed into a new node through the entropy weight method, and Fisher's Z transformation is applied to the data of each node to meet the normality requirement for computing Pearson correlation. The high-order functional connectivity network is then constructed by calculating the correlation between the average dynamic functional connectivity time series of each pair of nodes. (5) Extract the average

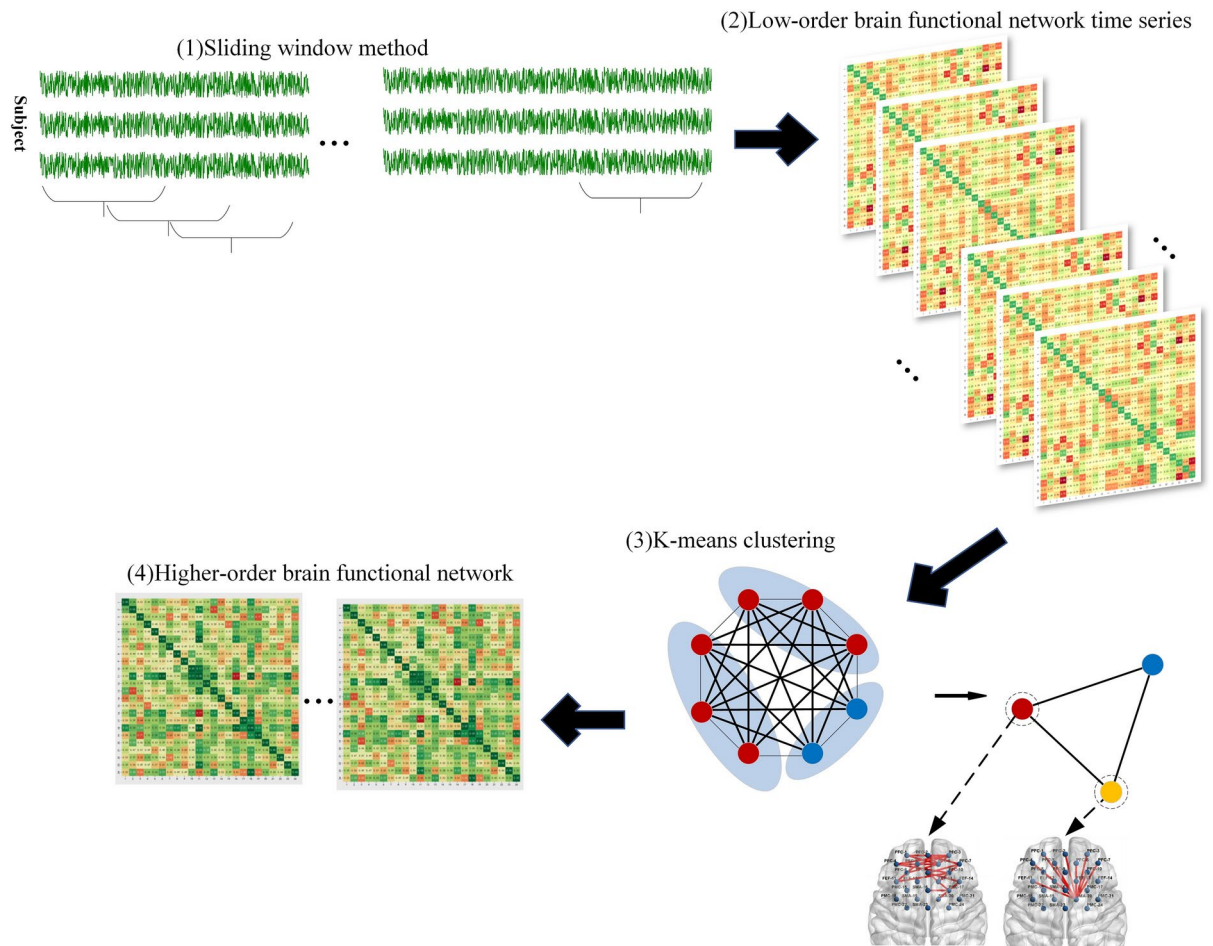


Fig. 4. Schematic diagram of the computational construction method for high-order brain functional networks. Based on the construction of Pearson correlation coefficient time series and the similarity of size intervals, 276 correlation coefficients were clustered into 24 clusters as nodes for constructing high-order networks.

node degree, clustering coefficient, global efficiency, and characteristic path length based on the weighted graph within each high-order network window as features for high-order functional connectivity.

Node degree refers to the number of edges directly connected to a node, which is used to measure the importance and connectivity of the node in the network. The higher the node degree, the more important the node is in the network and the stronger its ability to control other nodes. Its mathematical definition is as follows:

$$k_i = \sum_{j=1}^N A_{ij} \quad (6)$$

where K_i represents the degree of node i , A_{ij} represents whether there is an edge connected between node i and node j (if connected, it is 1; if not connected, it is 0), and n represents the total number of nodes.

The average node degree is the average of all node degrees in the network, which is used to measure the strength of connections between nodes in the network. It reflects the overall connectivity of the network, and the higher the node degree, the better the connectivity of the network. Its mathematical definition is as follows:

$$K = \frac{1}{n} \sum_{i=1}^n k_i \quad (7)$$

Global efficiency is an important metric for evaluating the efficiency of information flow throughout the network. It measures the average length of the shortest path from one node to another, reflecting the overall efficiency of information propagation in the network. A high global efficiency indicates fast information flow and tighter connections between nodes. The specific calculation formula is as follows:

$$E = \frac{1}{n(n-1)} \sum_{i \neq j} \frac{1}{d_{ij}} \quad (8)$$

where E represents global efficiency, n represents the number of nodes, and d_{ij} represents the path length between node i and node j .

Analysis of brain network differences between fatigue levels

For low-order brain functional networks, within each physiological frequency band, we investigated the changes in brain connectivity reflected by correlation coefficients among participant samples under conditions of no fatigue, mild fatigue, and severe fatigue. Independent sample t-tests were applied to calculate the statistical significance of these differences. Furthermore, this statistical testing method was utilized to assess the statistical differences in clustering coefficient, characteristic path length, and small-world properties, which are three topological network metrics, between the three fatigue states. The objective was to comprehensively explore the physiological patterns reflected by pairwise brain region node connections during the development of brain fatigue. After completing the tests, Bonferroni correction was applied to the results to adjust for potential Type I errors.

For high-order brain functional networks, within each physiological frequency band, independent sample t-tests were employed to calculate statistical differences in average node degree, clustering coefficient, global efficiency, and characteristic path length across no fatigue, mild fatigue, and severe fatigue states. This explored high-order changes in network coefficients within bands during brain fatigue development, seeking physiological patterns reflected by cross-regional node connections. Upon finding statistically significant bands, clusters within them with statistical differences in node degree, local clustering coefficient, local efficiency, and shortest path across fatigue levels were analyzed. Low-order nodes with more connections in these clusters were identified to uncover brain regions and channels with primary influence on brain fatigue. Furthermore, for each fatigue state, independent sample t-tests assessed statistical differences in each network property across five physiological frequency bands, aiming to identify shifts in dominant bands impacting brain fatigue. Bonferroni correction was applied post-testing to avoid potential Type I errors.

Fatigue recognition

Dataset partitioning and data annotation

Regarding the data samples, the 36 participants in the experiment were randomly stratified and partitioned into a cross-validation set and a test set in a 7:3 ratio, with 26 individuals in the cross-validation set and 10 in the test set. Specifically, within the PVT and mental workload tests, 9 participants were assigned to the cross-validation set and 3 to the test set, respectively. For the simulated driving experiment, 8 participants were assigned to the cross-validation set, and 4 to the test set. The test set remained consistent throughout the model training process.

In terms of data annotation, based on the previously mentioned mental fatigue level calculation method, signal samples from the 2nd–3rd minute and 38th–39th minute of the full 40-min sessions were labeled as samples with definitive fatigue levels. The 1st minute and the last 1-min samples were designated as unlabeled samples. The discrimination of mental fatigue levels was achieved using a semi-supervised algorithm, which not only enhanced the model's generalization ability but also reduced the cost of data annotation.

Model recognition framework

The model architecture is illustrated in (Fig. 5). For the raw feature space, the Kolmogorov–Smirnov (KS) non-parametric test (two-sided test with approximate calculation) was first applied to remove samples with no significant differences ($p > 0.05$), resulting in intermediate features. Subsequently, the Boruta algorithm¹⁴ (based on a random forest core model with a threshold of 0.6) was employed to further derive the final features. Then, a genetic algorithm¹⁵ (with an initial population of 60 and a mutation range of 0.001–0.1) was used to select parameters for the SVM classifier (employing fivefold cross-validation). The final SVM classifier (with a linear kernel and a C-value of 33) was determined based on a comparison of classification accuracies. Finally, a self-training algorithm¹⁶ (using an SVM model with a threshold of 0.6) was adopted to achieve a three-level classification of mental fatigue.

Results

Analysis of fatigue level and task performance

The results of variance analysis on MFI-20 scale scores indicated that fatigue level ($F = 303.607$; $p < 0.001$; $\eta^2 = 0.749$) had a significant main effect on MFI-20 scores, while no significant main effects were observed for task ($p = 0.708$) or the interaction between fatigue level and task ($p = 0.824$). Furthermore, the variance analysis on N-back task scores revealed a significant main effect of fatigue level on N-back scores ($F = 14.329$; $p < 0.001$; $\eta^2 = 0.134$), with neither task ($p = 0.279$) nor the interaction between fatigue level and task ($p = 0.251$) exhibiting significant effects. Additionally, as shown in Fig. 6a, post-hoc analysis demonstrated that in MFI-20 task performance, there were significant increases in MFI-20 scores between no fatigue and mild fatigue ($t = -14.973$, $p < 0.001$), between mild fatigue and severe fatigue ($t = -16.059$, $p < 0.001$), and between no fatigue and severe fatigue ($t = -21.431$, $p < 0.001$). In N-back task performance, as depicted in Fig. 6b, significant increases in N-back scores were observed between no fatigue and severe fatigue ($t = -5.221$, $p < 0.001$) and between mild fatigue and severe fatigue ($t = -3.554$, $p < 0.001$).

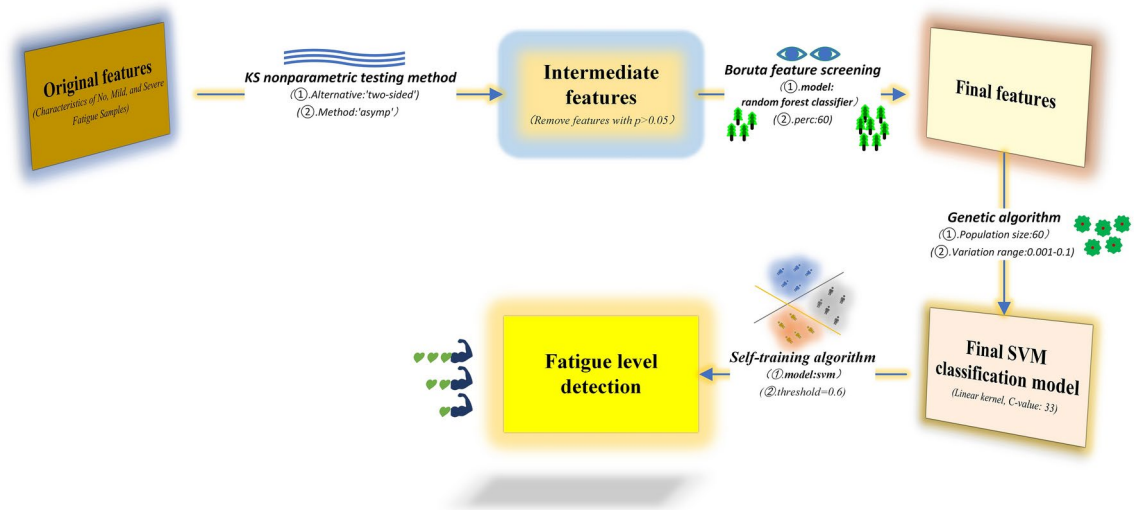


Fig. 5. Fatigue detection model framework. Using KS and Boruta algorithms to screen features, selecting the optimal SVM model using genetic algorithm, and finally implementing brain fatigue detection through self-training algorithm.

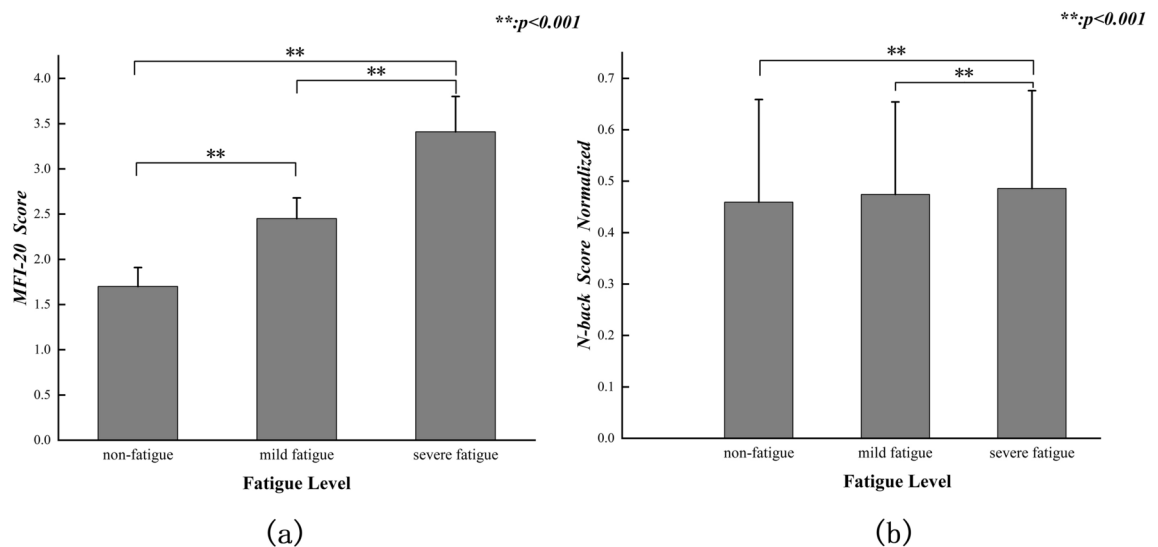


Fig. 6. (a) Differences in MFI-20 scores corresponding to different fatigue levels. (b) Normalized differences in N-back scores corresponding to different fatigue levels.

Changes in low-order network structure

Variations in low-order brain functional connectivity networks

As depicted in Fig. 7, the average brain network connectivity across three levels of fatigue under five frequency bands is presented. From left to right, they correspond to no fatigue, mild fatigue, and severe fatigue, respectively. For the physiological frequency band I (0.005–0.021 Hz), as the state progressed from no fatigue to mild fatigue, the overall brain network connectivity decreased. Notably, the connectivity between FEF1 and PMCr significantly decreased ($t=2.306$, $p=0.023$), and the connectivity between FEFr and SMA also significantly decreased ($t=2.247$, $p=0.026$). Conversely, when mild fatigue evolved into severe fatigue, the overall brain network connectivity increased. Specifically, the connectivity between FEFr and PMCr, PMCr, and SMA significantly rose (FEFr-PMCr: $t=-2.056$, $p=0.043$; FEFr-PMCr: $t=-2.552$, $p=0.012$; FEFr-SMA: $t=-2.319$, $p=0.023$).

Regarding the physiological frequency band II (0.021–0.052 Hz), as multiple individuals progressed from a state of no fatigue to mild fatigue, a significant decrease was observed in the overall connectivity of their brain networks collectively. Notably, the connections between PFCm and SMA, as well as PFCm and PMCr, exhibited marked declines (PFCm-SMA: $t=2.069$, $p=0.041$; PFCm-PMCr: $t=2.054$, $p=0.042$). Similarly, the connections between FEF1 and SMA, as well as FEF1 and PMCr, also showed significant reductions (FEF1-SMA: $t=2.672$, $p=0.009$; FEF1-PMCr: $t=2.712$, $p=0.008$). Additionally, the connection between FEFr and SMA

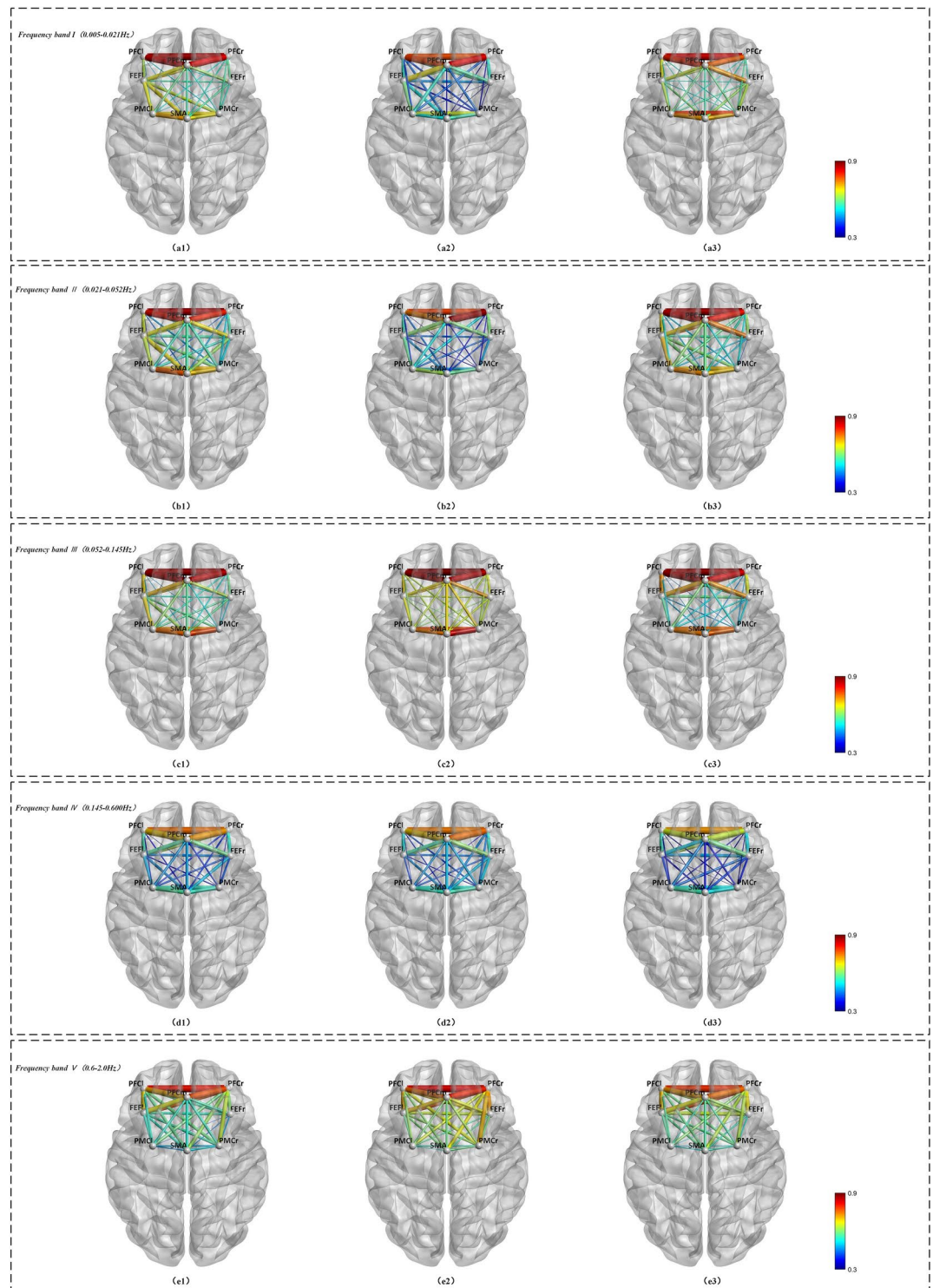


Fig. 7. Three level low-level brain network connectivity diagram under five frequency bands. From left to right, they are respectively fatigue free, mild fatigue, and toxic fatigue; From top to bottom, they are frequency band I (a: 0.005–0.021 Hz), frequency band II (b: 0.021–0.052 Hz), frequency band III (c: 0.052–0.145 Hz), frequency band IV (d: 0.145–0.600 Hz), and frequency band V (e: 0.6–2.0 Hz).

was notably weakened ($t=2.123$, $p=0.035$). Conversely, when mild fatigue progressed to severe fatigue, the overall connectivity of the brain network increased. Specifically, the connections between PFCm and FEFr, as well as PFCm and SMA, exhibited significant enhancements (PFCm-FEFr: $t=-2.172$, $p=0.033$; PFCm-SMA: $t=-2.110$, $p=0.038$). Furthermore, the connection between FEFr and PMCr also showed a notable increase ($t=-2.444$, $p=0.017$).

For the physiological frequency band III (0.052–0.145 Hz), during the transition from non-fatigue to mild fatigue, the overall brain network connectivity increased. Specifically, significant increases in connectivity were observed between PFCl and SMA, as well as between PFCl and PMCr (PFCl-SMA: $t = -2.336$, $p = 0.021$; PFCl-PMCr: $t = -2.461$, $p = 0.015$). Additionally, PMCr's connectivity with PFCm and PFCr also significantly increased (PMCr-PFCm: $t = -2.418$, $p = 0.017$; PMCr-PFCr: $t = -2.337$, $p = 0.021$). However, as fatigue progressed from mild to severe, the overall brain network connectivity decreased. Notably, significant decreases in connectivity were found between SMA and PFCl, PFCm, PFCr (SMA-PFCl: $t = 2.728$, $p = 0.008$; SMA-PFCm: $t = 2.752$, $p = 0.007$; SMA-PFCr: $t = 2.449$, $p = 0.016$), as well as between PMCr and PFCl, PFCm, PFCr (PMCr-PFCl: $t = 2.840$, $p = 0.006$; PMCr-PFCm: $t = 2.312$, $p = 0.023$; PMCr-PFCr: $t = 2.508$, $p = 0.014$).

In the physiological frequency band IV (0.145–0.6 Hz), as an individual progressed from a state of no fatigue to mild fatigue and then to severe fatigue, there was no significant change in the overall connectivity of the brain network, and no significant differences were observed in the connections between brain region nodes ($p > 0.05$).

For the physiological frequency band V (0.6–2.0 Hz), when the fatigue-free state developed into mild fatigue, the overall brain network connectivity increased. Among them, the connectivity between FEFr and PFCl, PFCr, PMCl, PMCr, and SMA increased significantly (FEFr-PFCl: $t = -2.233$, $p = 0.027$; FEFr-PFCr: $t = -2.273$, $p = 0.025$; FEFr-PMCl: $t = -2.295$, $p = 0.024$; FEFr-PMCr: $t = -2.257$, $p = 0.026$; FEFr-SMA: $t = -2.027$, $p = 0.045$). The connection strength among PFCl, PFCm, and PFCr remained relatively stable. When mild fatigue progressed into severe fatigue, the overall brain network connectivity decreased slightly. There was no significant difference in the connection between brain region nodes ($p > 0.05$).

In addition, PFCl, PFCm, and PFCr, as well as SMA, PMCl, and PMCr, all maintained relatively stable high-intensity connections among the three stages of mental fatigue in the five frequency bands.

Variations in low-order brain functional attribute networks

The statistical analysis of network topological properties among the three levels of brain fatigue is shown in Fig. 8a, b. Each horizontal line and its associated symbol represent the p-value of the t-test (*: $p < 0.05$; **: $p < 0.01$). When fatigue-free developed into mild fatigue, the clustering coefficients of frequency bands I

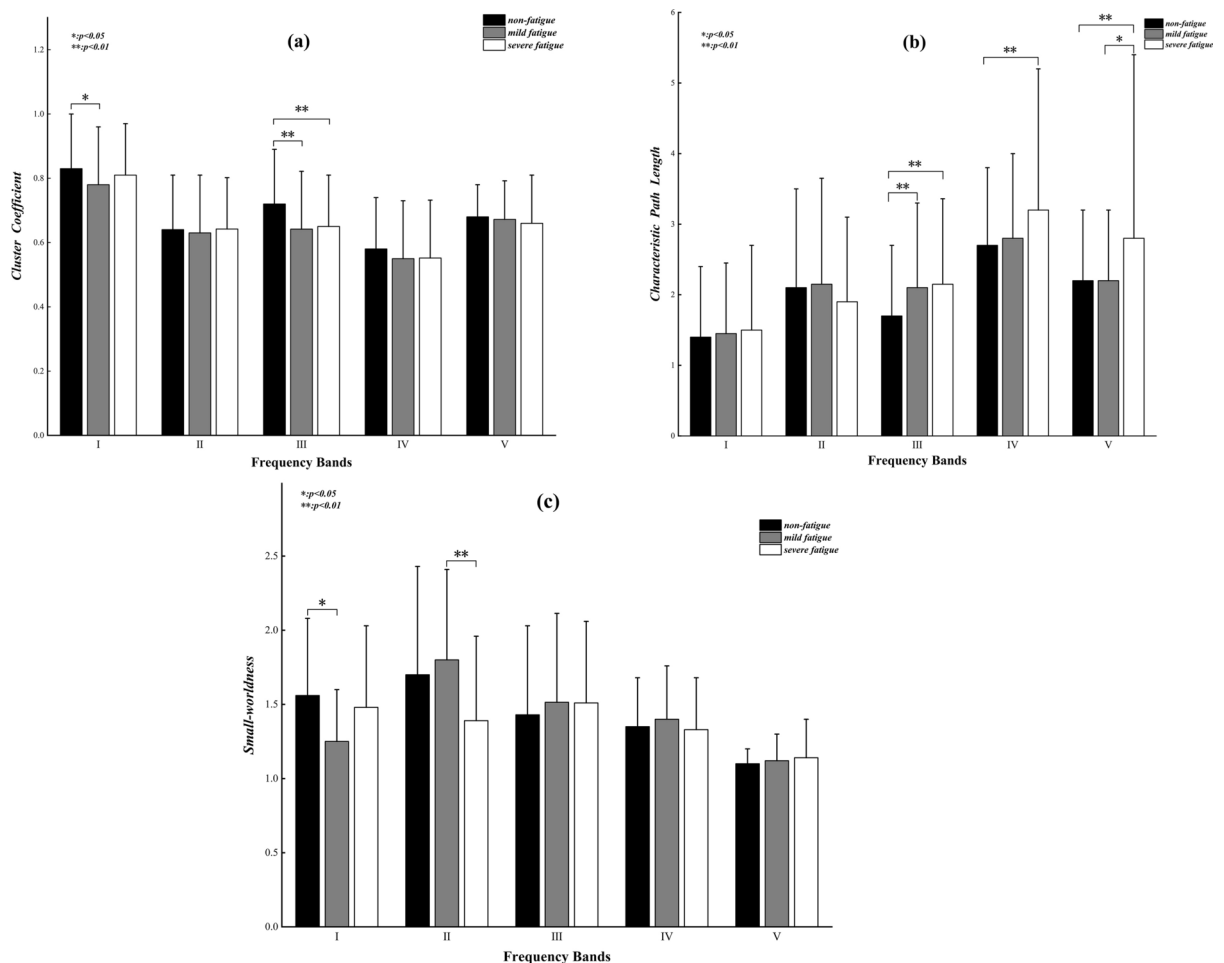


Fig. 8. Network statistical differences between non-fatigue, mild fatigue, and severe fatigue in various physiological frequency bands (*: $p < 0.05$, **: $p < 0.01$). (a) Clustering coefficient. (b): Characteristic path length. (c) Small-world property.

and III decreased significantly ($t=2.018$, $p=0.045$; $t=3.963$, $p<0.001$). When fatigue-free developed into severe fatigue, the clustering coefficient of frequency band III decreased significantly ($t=1.972$, $p<0.001$). When fatigue-free developed into mild fatigue, the characteristic path length of frequency band III increased significantly ($t=-3.382$, $p<0.001$). When fatigue-free developed into severe fatigue, the characteristic path length of frequency bands IV and V increased significantly ($t=-2.786$, $p=0.005$; $t=-3.016$, $p=0.002$).

The small-world properties corresponding to fatigue states in each frequency band are shown in Fig. 8c. Under the five physiological frequency bands, the small-world properties of the three fatigue states were all greater than 1, indicating that the connection networks under the three fatigue states in each frequency band possess small-world properties. During mild fatigue, the small-world property of frequency band I decreased ($t=2.137$, $p=0.035$). During severe fatigue, the small-world property of frequency band II decreased significantly ($t=2.388$, $p=0.019$).

Changes in high-order network structure

The statistical analysis of the overall high-order network topology properties between three levels of brain fatigue is shown in Fig. 9, where each horizontal line and associated symbol represents the p-value of the t-test (*: $p<0.03$; **: $p<0.01$). All four high-order network topological properties showed significant differences in the mild fatigue stage of frequency band II, specifically with increased average node degree, clustering coefficient, and global efficiency (average node degree: $t=-6.764$, $p=0.014$; clustering coefficient: $t=-7.478$, $p=0.010$; global efficiency: $t=-6.458$, $p=0.016$), and decreased characteristic path length ($t=5.431$, $p=0.027$).

At the same time, there were also significant differences among the three types of mental fatigue states in different frequency bands, which were reflected in the following aspects:

When there was no fatigue, there were significant differences between frequency bands III and I, as well as between frequency bands III and II, in all four network attributes: average node degree (frequency bands I and III: $t=-10.251$, $p=0.004$; frequency bands II and III: $t=-9.669$, $p=0.005$), clustering coefficient (frequency bands I and III: $t=-8.224$, $p=0.009$; frequency bands II and III: $t=-8.597$, $p=0.008$), global efficiency (frequency

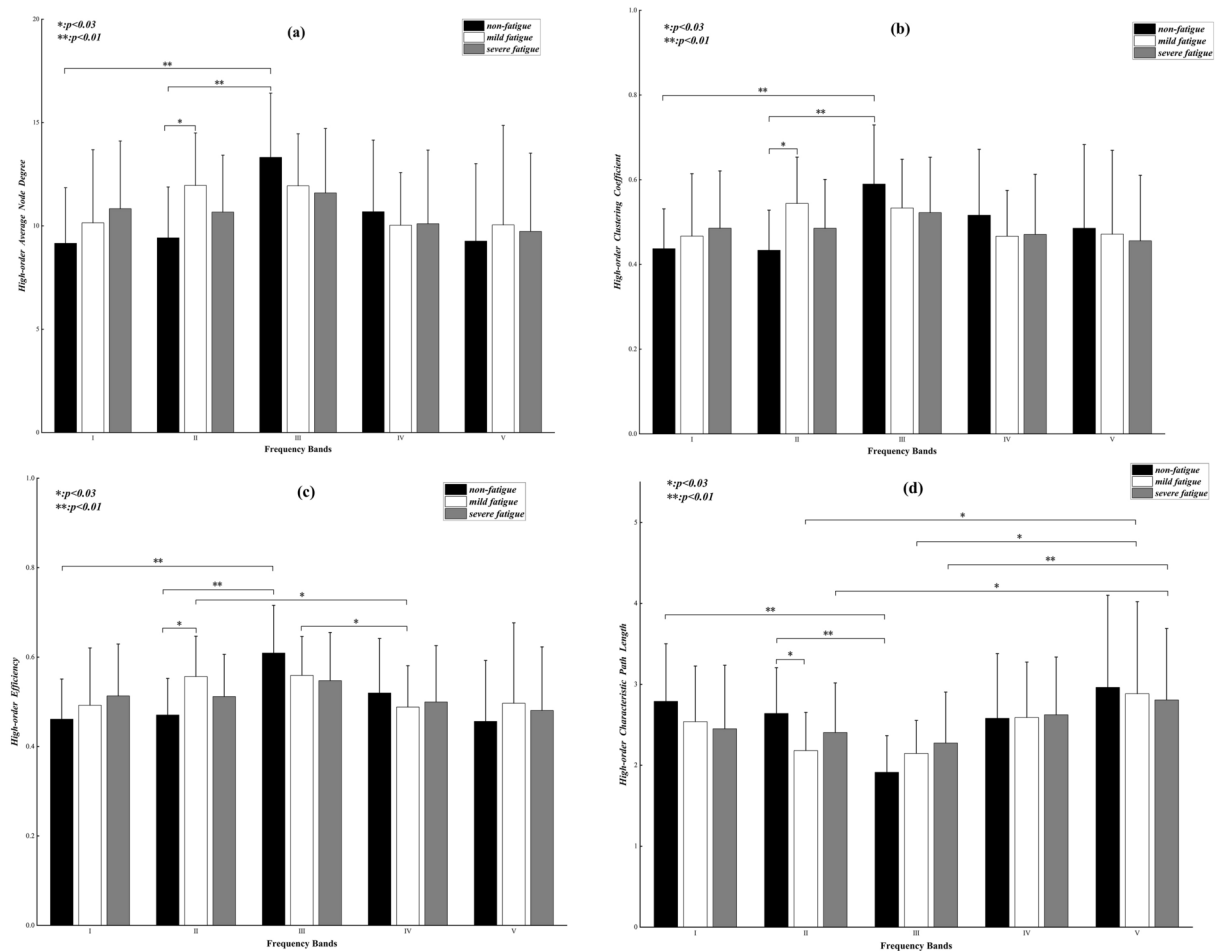


Fig. 9. High-order network statistical differences between non-fatigue, mild fatigue, and severe fatigue in various physiological frequency bands (*: $p<0.05$, **: $p<0.01$). (a) High-order average node degree. (b) High-order clustering coefficient. (c) High-order efficiency. (d) High-order characteristic path length.

bands I and III: $t = -11.228$, $p = 0.003$; frequency bands II and III: $t = -10.605$, $p = 0.003$), and characteristic path length (frequency bands I and III: $t = 10.806$, $p = 0.003$; frequency bands II and III: $t = 10.071$, $p = 0.004$).

When there was mild fatigue, there were significant differences between the global efficiency of frequency band IV and those of frequency band II and III (frequency band II, IV: $t = 5.325$, $p = 0.026$; frequency band III, IV: $t = 5.919$, $p = 0.019$). There were significant differences between the characteristic path length of frequency band V and those of frequency band II and III (frequency band II, V: $t = -6.199$, $p = 0.017$; frequency band III, V: $t = -7.101$, $p = 0.011$).

When severe fatigue occurred, there were significant differences between the characteristic path length bands V and band II, as well as between bands V and III (band II, V: $t = -5.036$, $p = 0.027$; band III, V: $t = -8.659$, $p = 0.004$).

Additionally, as illustrated in Fig. 10, a statistical analysis of four network metrics was performed on 24 cluster nodes within frequency band II, comparing the no-fatigue and mild-fatigue stages. The findings revealed that across six clusters, there was a significant increase in node degree, local clustering coefficient, and local efficiency, accompanied by a notable decrease in the shortest path length ($p < 0.05$). By pinpointing the low-order nodes with higher connectivity within these clusters, it became evident that the six nodes were concentrated in the prefrontal cortex, left premotor area, supplementary motor area, and left frontal eye field.

Fatigue classification results based on low-order and high-order networks

The study found that the classification accuracy of fatigue levels based on low-order network parameters alone was 78.57%, the classification accuracy of fatigue based on high-order network features alone was 83.33%, and the comprehensive fatigue classification accuracy based on both low-order and high-order network features was 88.095%.

Discussion

Analysis of the significance of changes in low-order network structure

From no fatigue to mild fatigue, the performance of the subjects declined to varying degrees, but the overall decline was not significant. The functional connectivity strengths of the brain networks within the endothelial cell activity band and the neurogenic activity band decreased significantly. In particular, the connectivity between the endothelial cells and the neurogenic activity band in the frontal eye field and the neurogenic activity band in the prefrontal cortex to other brain regions declined significantly. Moreover, the clustering coefficient and small-world property of the endothelial cell activity band declined significantly, indicating reduced brain operating

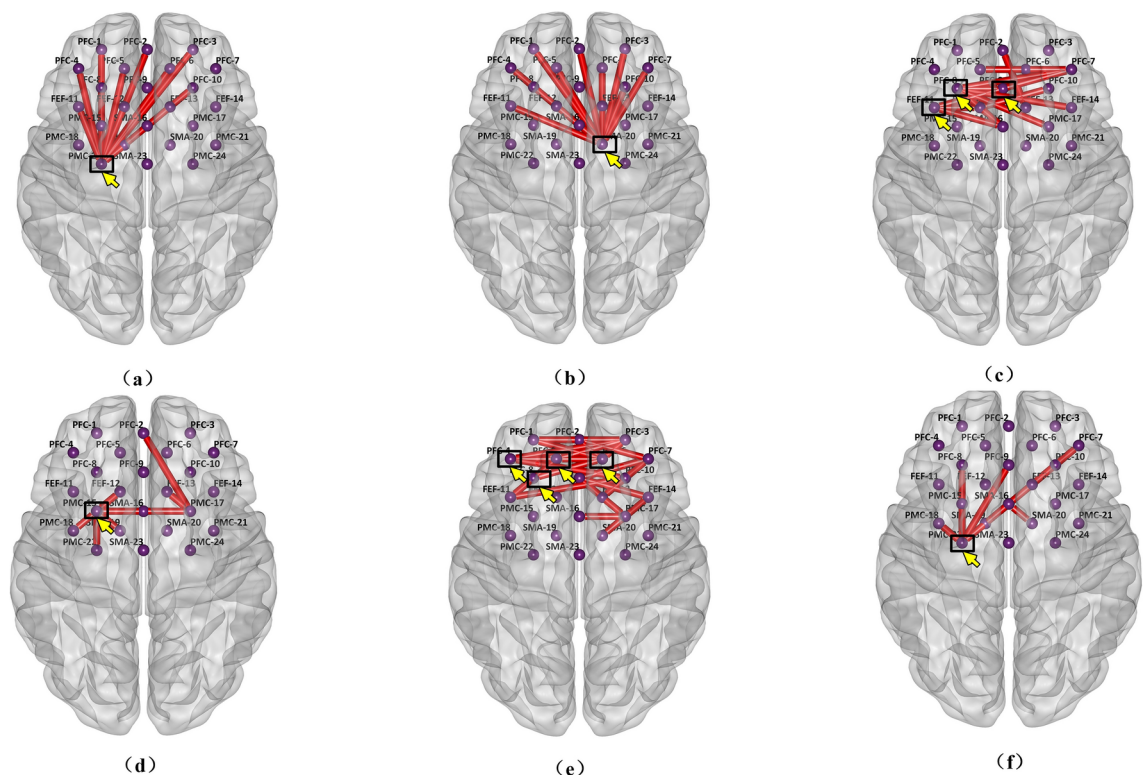


Fig. 10. Clusters with significant differences in Band II. Subgraph a represents node 22 (PMCI) as a prominent node, (b) represents node 20 (SMA) as a prominent node, (c) represents nodes 8 (PFCI), 9 (PFCm), and 11 (FEFI) as prominent nodes, (d) represents node 15 (PMCI) as a prominent node, e represents nodes 4 (PFCI), 5 (PFCm), 6 (PFCr), and 8 (PFCI) as prominent nodes, and f represents node 22 (PMCI) as a prominent node.

efficiency. Research has shown that under fatigue, the brain slows down its activity and its capabilities decrease¹⁷. Neurons and neurotransmitters in the brain are inhibited, leading to reduced signal transmission efficiency¹⁸. This slows down the metabolic rate of endothelial cells and weakens neurogenic activity. It results in a significant decline in the connectivity between the frontal eye field, prefrontal cortex, and other brain regions. In addition, Zhang et al.¹⁹ found in their research that during the development of mental fatigue, the characteristic path length of the brain neural network would increase significantly, the clustering coefficient would decrease, and the overall connectivity of network nodes would decline. Our results were consistent with these findings, demonstrating that during mild fatigue, the overall properties of the brain functional network declined, and the connectivity between the frontal lobe and other brain regions decreased significantly.

The oscillations in frequency bands III and V, which respectively represent the myogenic activity of cerebral vascular smooth muscle and the heart rate activity of the subjects, showed a marked increase in the functional connectivity strength of the brain network, in contrast to the previous two frequency bands. Specifically, there was a significant increase in the connectivity between the left prefrontal lobe and the right premotor area in the myogenic activity band, and between the right frontal eye field and other brain regions in the heart rate activity band. Furthermore, the clustering coefficient of the myogenic activity band decreased significantly, while the characteristic path length increased significantly, indicating a more decentralized brain network structure. Numerous studies have uncovered significant alterations in eye movements and heart rate variability during brain fatigue. These changes are manifested as sinus arrhythmia²⁰ and a marked increase in blink frequency²¹, accompanied by additional activation in the frontal eye field region²². Researchers²³ have discovered that myogenic activity increases in subjects during mild fatigue stages. Combining our findings, we suggest that the brain, in a state of mild fatigue, redirects limited resources to enhance connections within brain regions related to vascular smooth muscle activity and heart rate regulation, thereby optimizing blood supply and cardiovascular function. This ensures the supply of nutrients to critical frontal lobe and eye movement regions, maintaining basic task demands, which may also explain the decrease in network coefficients.

During severe fatigue, subjects' performance decreased significantly compared to the initial stages. Notably, there was a marked increase in network connectivity between endothelial cells and neural activity bands. This manifested as enhanced connectivity between the right frontal eye field in the endothelial cell activity band, the left frontal eye field and prefrontal lobe in the neural activity band, and other brain regions. However, the small-world properties in the neural activity band decreased significantly, indicating a substantial decline in the efficiency of global information integration within the brain's functional network. Research shows that when under severe fatigue, in order to cope with the depletion of local resources in brain regions, the brain will increase the functional connectivity strength between brain regions²⁴, and the task performance under fatigue is related to the small-world properties of brain networks²⁵. Consequently, the decrease in subjects' performance in the later stages of the task may be attributed to the reduction in small-world properties within the neural activity band. In summary, the increase in brain region connectivity during severe fatigue represents an emergency measure taken by the brain to compensate for resource deficiencies, as it attempts to maintain task execution through enhanced inter-regional collaboration. Nevertheless, this compensatory enhancement fails to effectively halt the decline in cognitive abilities and instead exacerbates the consumption of brain resources. This suggests that fatigue profoundly impacts neuronal communication efficiency and network synchrony, resulting in limited information processing capabilities and ultimately manifesting as a marked decline in task performance.

Contrary to mild fatigue, the overall network connectivity in the myogenic activity and heart rate activity bands decreased. Specifically, there was a significant reduction in the connectivity between the supplementary motor area and premotor area in the myogenic activity band with other brain regions. Additionally, the clustering coefficient in the myogenic activity band decreased significantly, while the characteristic path length in the heart rate activity band increased significantly, indicating lower network node connectivity and coordination efficiency in the brain network. This aligned with the findings of Sun et al.²⁶, who observed a significant decrease in functional connectivity within the brain neural network during severe fatigue in driving tasks. Previous studies²² had shown that subjects would have heart rate variability when they were extremely fatigued. Under normal circumstances, the brain achieved rapid information transmission and integration through a highly optimized network structure²⁷. However, during severe fatigue, this optimization was disrupted, and the brain had to reallocate resources in response to sustained energy consumption and resource constraints. It prioritized essential life-sustaining functions such as heartbeat and blood flow, while relatively reducing resource allocation to non-urgent tasks (e.g., fine motor control), resulting in decreased network properties and diminished task performance among subjects.

It is noteworthy that although there were no significant changes in the respiratory frequency band throughout the development of brain fatigue, the overall connectivity remained low, suggesting that respiration has a relatively minimal impact on the brain network. As a fundamental process for life maintenance, the stability of respiratory status reflects the relative stability of physiological baseline conditions²⁸. Furthermore, the connections within the prefrontal cortex and between regions of the motor cortex exhibited a high degree of tightness across various frequency bands throughout the fatigue cycle. Research indicates that the prefrontal cortex serves as the central hub for advanced cognitive control and motor execution²⁹, while the motor cortex is primarily responsible for controlling and coordinating basic autonomous movements and the execution of complex motor skills³⁰. Consequently, this stable connectivity pattern may reflect the enhanced synergy between the prefrontal cortex and motor areas as the brain responds to fatigue challenges, ensuring a certain level of information processing efficiency and motor coordination even in states of fatigue. This robust internal network connectivity represents adaptive changes undertaken by the brain to counter the decline in resource mobilization and integration functions caused by fatigue, contributing to sustained performance in individuals facing prolonged tasks or physical activities.

Analysis of the significance of changes in high-order network structure

Changes in high-order network frequency band II: During a period of mild fatigue, the node degree, clustering coefficient, and global efficiency of frequency band II for neuronal activity increased, while the characteristic path length decreased, indicating a higher brain operational efficiency. However, no differences were observed in the global network parameters of the low-order functional connectivity networks corresponding to those frequency bands across different fatigue levels. Based on the construction methods of low-order and high-order brain functional networks, this suggests that during mild brain fatigue, the connections between pairs of brain regions are relatively weak, while the high-order connections across multiple brain regions are relatively tighter. According to the theory of global neuronal workspace³¹, the brain needs to support higher task demands by improving resource integration among multiple brain regions (after mild fatigue, the original task demands relatively increase). The shorter characteristic path length and higher clustering coefficient, global efficiency, and node degree mean more efficient information transmission among cortical node groups. Previous studies have shown that under mental fatigue, the brain can maintain sufficient task performance by recruiting mental activities between multiple brain regions²³. The changes in high-order networks during mild brain fatigue are likely to reflect this compensatory effect.

Changes in main activity frequency bands: Comparing the network topological properties among different frequency bands, we observed significant differences during the non-fatigue stage. Specifically, the muscle-related activity frequency band exhibited the highest values for node degree, clustering coefficient, and global efficiency, while having the lowest characteristic path length. This indicates that the muscle-related activity of cerebrovascular smooth muscle plays a dominant role among the five frequency bands during this stage. However, as fatigue progressed to the mild stage, some of these significant differences between the muscle-related activity band and the endothelial cell and neural activity bands dissipated. We observed decreases in node degree, clustering coefficient, and global efficiency within the muscle-related band, and increases in these parameters within the endothelial cell and neural activity bands. The characteristic path length showed opposite trends across all bands, with more pronounced changes in the neural activity band. This suggests a gradual increase in node synchronization during the mild fatigue stage. As fatigue worsened to the severe stage, a significant difference emerged in the characteristic path length of the heart rate band compared to the neural and muscle-related activity bands. Specifically, the values for the muscle-related and neural activity bands were similar and significantly lower than those for the heart rate band. Our findings indicate that while there is a tendency for muscle-related activity to decrease during brain fatigue, it continues to dominate the active frequency band. Furthermore, as fatigue deepens, there is a shift in the dominant frequency band towards neural activity.

The distribution of brain regions that affect mental fatigue: The study found that the high-order network nodes composed of related nodes in the prefrontal cortex, left premotor area, supplementary motor area, and left frontal eye field exhibited significant differences in all four network coefficients during mild fatigue. Anatomically, the prefrontal cortex is located at the apex of sensory and motor hierarchies³². It guides and regulates the functional connectivity patterns among brain regions by integrating sensory stimuli and motor plans through attentional guidance, resulting in a top-down flow of brain functional network information throughout the frontal-parietal-sensory regions³³. Transient functional impairment of the prefrontal cortex directly leads to brain fatigue³⁴. Additionally, during brain fatigue, subjects often experience increased blink frequency²², manifesting as activation in the frontal oculomotor area. The motor and motor auxiliary areas are brain regions associated with motor function or compensatory mechanisms after brain fatigue³⁵. Research has shown that when fatigue occurs, the level of desynchronization in the evoked magnetic fields of the motor and motor auxiliary areas increases, and there is a positive correlation with the level of prefrontal activity to support task performance during fatigue³⁶. Similar to our findings, significant differences in high-order network properties were observed among the nodes related to the prefrontal cortex, left premotor area, supplementary motor area, and left frontal eye field during the development of brain fatigue. This may suggest that these four brain regions play a pivotal role in modulating brain function throughout the fatigue process, reflecting the influence of brain resource states on inter-regional information transmission efficiency. Consequently, this may further affect the ability of regions to collaborate in problem-solving and the accuracy of behavioral performance, potentially contributing to the deepening of brain fatigue objectively.

In summary, compared to low-level brain functional networks, high-level brain functional networks establish functional connections among three or more brain regions. They can represent the deep interaction relationships between brain areas during brain fatigue, accurately pinpointing the brain regions associated with fatigue. This allows for a better understanding of the impact of brain fatigue on the overall brain state. Additionally, in the field of fatigue detection and management, by monitoring changes in low-order and high-order multi-frequency bands and network connections in the brain during fatigue, we can develop more precise fatigue detection systems. These systems can assist high-risk professionals such as athletes, drivers, and night shift workers in preventing safety incidents caused by fatigue, thereby ensuring both work efficiency and personnel safety.

Fatigue state identification results

The study employed both high-order and low-order brain neural network features, as well as a combined approach using both, to classify three fatigue levels: non-fatigue, mild fatigue, and severe fatigue. The classification results showed that the method using combined high-order and low-order network features achieved the highest accuracy, improving by 9.525% compared to using only low-order features and by 4.765% compared to using only high-order features. Low-order brain functional networks characterize the connectivity between static pairs of brain regions³⁷, whereas high-order brain functional networks represent relationships involving more than three brain regions³⁸. Therefore, using low-order features alone loses detailed topological information about multi-region associations, while using high-order features alone completely discards the basic classification information provided by pairwise brain region connectivity. This could be one of the reasons for a decrease in

model classification performance. Additionally, research has shown that integrating low-order and high-order features allows for the full utilization of the interaction between the two types of brain network topologies³⁹, enabling classifiers to learn more diverse information, enhancing their generalization capability, and thereby significantly improving the classification performance of the model⁴⁰. Our classification results were similar to this. Overall, the combined use of high-order and low-order brain network features is of significant importance in research areas such as fatigue level classification.

However, the study also has limitations. Firstly, using the MFI-20 scale and N-back behavioral task scores as the basis for defining fatigue levels may introduce biases in individuals' perception of fatigue. While combining N-back behavioral task scores can mitigate subjective factors, the experimental process needs to consider the acceptability of the behavioral task difficulty for participants, limiting the effectiveness of N = 1 in reducing subjectivity. Furthermore, circadian rhythms may subtly influence the study results. Specifically, during the morning hours when participants are at their peak alertness, they may exhibit higher efficiency and accuracy in tasks that induce brain fatigue. Conversely, from afternoon to evening, as the circadian rhythm leads to a gradual decline in alertness, participants' reaction speed and attention focus during tasks may slightly decrease. Additionally, there were relatively fewer severe fatigue samples in the study. With more severe fatigue samples, the patterns might be more evident, and the recognition results could potentially improve. Despite these limitations, the potential and application prospects of low-order and high-order brain neural network features in fatigue level classification remain significant.

Conclusion

This paper studied the changing patterns of low-order and high-order brain functional network structures under brain fatigue induced by different tasks, and classified and recognized brain fatigue into three levels: no fatigue, mild fatigue, and severe fatigue, based on the separate and combined features of low-order and high-order functional networks.

The low-order brain functional network connectivity revealed that during the development of brain fatigue, the frequency bands related to endothelial cell metabolic activity and neural activity first decreased and then increased, while the frequency bands related to myogenic activity and heart rate activity showed an opposite trend, first increasing and then decreasing. Analysis of network topological properties indicated that the clustering coefficient for the frequency bands of endothelial cell metabolic activity and myogenic activity significantly decreased from the no-fatigue to mild-fatigue state, and the characteristic path length for myogenic activity also significantly increased. In contrast, the small-world properties of the frequency bands related to neural activity significantly decreased from mild to severe fatigue. However, all frequency bands maintained small-world properties across the three fatigue states, suggesting that the network underwent self-optimization and adaptive adjustments during the fatigue process.

In the high-order brain functional network, during mild fatigue, the node degree, clustering coefficient, and global efficiency of the frequency bands related to neuronal activity increased, while the characteristic path length shortened, whereas there were no significant changes in the low-order network. As fatigue intensified, the frequency bands related to myogenic activity consistently dominated the network properties, but the frequency bands related to neural activity gradually became more significant during mild fatigue and approached the level of myogenic activity bands during severe fatigue, indicating that brain fatigue primarily affected the transition from myogenic to neural activity. Additionally, the high-order network properties of key brain regions such as the frontal lobe and motor areas exhibited significant differences during mild fatigue, highlighting their importance in fatigue regulation.

Using the self-training algorithm based on distinctive features to classify the three levels of fatigue, the classification method that combines both low-order and high-order features proved to be the most accurate, improving by 9.525% compared to using low-order features alone and by 4.765% compared to using high-order features alone. These results demonstrated the significance of the combined low-order and high-order features in fatigue level classification.

Data availability

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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Author contributions

Y wrote the main manuscript text and some images, P prepared Figs. 4–6 and paper citations, M provided programming technical support, L and H reviewed and edited the manuscript, and provided financial support.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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