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RESEARCH ARTICLE

Multimodal and hemispheric graph-theoretical brain network predictors of learning efficacy for frontal alpha asymmetry neurofeedback

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Abstract

EEG neurofeedback using frontal alpha asymmetry (FAA) has been widely used for emotion regulation, but its effectiveness is controversial. Studies indicated that individual differences in neurofeedback training can be traced to neuroanatomical and neurofunctional features. However, they only focused on regional brain structure or function and overlooked possible neural correlates of the brain network. Besides, no neuroimaging predictors for FAA neurofeedback protocol have been reported so far. We designed a single-blind pseudo-controlled FAA neurofeedback experiment and collected multimodal neuroimaging data from healthy participants before training. We assessed the learning performance for evoked EEG modulations during training (L1) and at rest (L2), and investigated performance-related predictors based on a combined analysis of multimodal brain networks and graph-theoretical features. The main findings of this study are described below. First, both real and sham groups could increase their FAA during training, but only the real group showed a significant increase in FAA at rest. Second, the predictors during training blocks and at rests were different: L1 was correlated with the graph-theoretical metrics (clustering coefficient and local efficiency) of the right hemispheric gray matter and functional networks, while L2 was correlated with the graph-theoretical metrics (local and global efficiency) of the whole-brain and left the hemispheric functional network. Therefore, the individual differences in FAA neurofeedback learning could be explained by individual variations in structural/functional architecture, and the correlated graph-theoretical metrics of learning performance indices showed different laterality of hemispheric networks. These results provided insight into the neural correlates of inter-individual differences in neurofeedback learning.

Keywords Frontal alpha asymmetry · Neurofeedback · EEG · MRI · Brain network

Introduction

Neurofeedback is a self-training technique that adjusts and enhances brain function by receiving feedback from visual representations of brain activity. Brain activity can be measured by Electroencephalographic (EEG), which records voltage fluctuations due to the flow of ionic current during synaptic excitations in the neurons of the brain (Baillet et al. 2001). EEG has a high temporal resolution, thus it is optimal for real-time feedback of brain processes (Enriquez-Geppert et al. 2017). EEG has both inter-subject and intra-subject variability because of multiple factors, including different brain structures among subjects, non-stationarity of brain activity, and some unknown factors (Wei et al. 2021). Neurofeedback training is an individualized intervention that takes into account the uniqueness of each individual's EEG (Sitaram et al. 2017). EEG neurofeedback has many advantages such as being safe, non-invasive, having lasting effects, and having few side effects, etc. Among the diversity of training protocols, frontal alpha asymmetry (FAA) neurofeedback is often used as an intervention tool to regulate emotions (Tolin et al. 2020; Melnikov 2021). Emotion regulation training with FAA neurofeedback has been explored in several studies (Allen et al. 2001; Baehr et al. 2001; Choi et al. 2011; Peeters et al. 2014a, b; Quaedflieg et al. 2016). However, the trainability and effectiveness of EEG

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neurofeedback have recently been questioned by some negative studies, because some participants neither learned to control their EEG signals nor showed a reduction in clinical symptoms (Tolin et al. 2020). It is suggested that these negative results may be related to individual differences in the short-term learning effect during neurofeedback training, i.e., the success in self-regulation of EEG activities. Several published studies demonstrated that only the individuals who successfully learned to self-regulate their brain activity were associated with improved cognitive performance (Hanslmayr et al. 2005a, b; Kouijzer et al. 2013). Previous studies indicated neuroanatomical and neurofunctional features correlated with individual differences in EEG neurofeedback training for a diversity of training protocols except for FAA neurofeedback (Weber et al. 2020). Therefore, it is necessary to find out the influencing factors of the learning performance during FAA neurofeedback so that the neurofeedback treatment protocol can be adapted to each individual.

Multimodal neuroimaging studies have indicated that individual differences in neurofeedback training can be traced to neuroanatomical and neurofunctional baseline features (Weber et al. 2020). Several studies have reported a correlation between rest EEG features before training and neurofeedback learning ability in healthy participants, including a significant positive correlation between the pre-training alpha amplitude and learning performance for alpha neurofeedback training (Wan et al. 2014) and distinguishing amplitude of low beta between learners from non-learners for beta/theta neurofeedback training (Nan et al. 2015). Further, some studies reported structural correlators of neurofeedback learning performance, such as gray matter volume of the right middle cingulate cortex and white matter volume of the cingulate tract for frontal-midline theta neurofeedback training (Enriquez-Geppert et al. 2013), and gray matter volumes in the supplementary motor area and left middle frontal gyrus for gamma neurofeedback training (Ninaus et al. 2015). A previous study by our group pointed out that the neurofeedback learning ability is related to both structural and functional brain imaging features (Li et al. 2021a, b). However, no neuroimaging predictors for FAA neurofeedback protocol have been reported so far. In addition, all the above-mentioned studies focused on regional measures of brain structure or function, and overlooked possible neural correlates of brain connectivity and network measures.

Neurofeedback is a form of training that enables subjects to learn self-regulation of brain networks implicated in a specific behavior (Mennella et al. 2017). One study collected functional magnetic resonance imaging (fMRI) data during FAA neurofeedback emotion regulation and revealed increased interaction/connectivity among multiple brain networks (Dehghani et al. 2020). Therefore, characteristics of brain networks might be more promising for explaining complex emotion-regulation performance than those measured based on local brain regions (Horien et al. 2020). Furthermore, the human brain is asymmetric in terms of structure and function (Tian et al. 2011). Considering, FAA is naturally a measure of the brain's asymmetry, the two hemispheric networks might be distinctively correlated with learning performance during FAA neurofeedback training. The graph theory approach is one of the most commonly used methods to quantify the brain's structural and functional networks, and it provides a means of quantifying individual differences in the topological structure of brain networks (Sporns 2018), which has been related to normal human cognitive functioning (Cohen and D'Esposito 2016), as well as emotion regulation ability (Uchida et al. 2015). Therefore, multimodal network construction and graph theory analysis might provide new and global insight into the structural and functional correlates of FAA neurofeedback learning performance.

In summary, FAA neurofeedback training exhibited a large individual difference in its effects on emotion regulation, but the predictors of learning performance have not been well understood yet. The combined analysis of multimodal brain networks and graph-theoretical features could be applied for a thorough investigation of predictors of the FAA neurofeedback training effect. Thus, in the present study, we conducted a single-blind pseudo-controlled FAA neurofeedback experiment to analyze individual differences in FAA neurofeedback training effects. We collected multimodal neuroimaging data [structural magnetic resonance imaging (sMRI) and diffusion tensor imaging (DTI), and resting-state functional MRI (fMRI)] from healthy participants before neurofeedback training. We aim to test the hypothesis that the individual differences in FAA neurofeedback learning ability can be explained using graph-theoretical features of multimodal brain networks.

Materials and methods

Participants

Sixty healthy participants (age: 22.28 ± 2.08, 28 males) were recruited by advertisements at Shenzhen University. The present study included only right-handed subjects and handedness was determined with the Edinburgh Handedness Inventory (Oldfield 1971). Participants were screened for eligibility using the following exclusion criteria: psychiatric history, neurological disease, drug or alcohol abuse in the past year, brain surgery, and any standard MRI counter-indications. All participants had a normal or corrected vision. The procedures of this experiment were approved by the Human Research Ethics Committee of Shenzhen University. All participants in this experiment signed an informed consent form.

Participants were assigned randomly to the real group (n = 30) or sham group (n = 30). A single-blind placebo-controlled design was applied, and the neurofeedback signals for the sham group were from previously tested participants of the real group. All participants had to complete one session of neurofeedback training and the real group had to complete another session of MRI scan.

Data acquisition

EEG was recorded using a BrainAmp amplifier and BrainVision Recorder software (BrainProducts, Germany) from 32 Ag/AgCl electrodes positioned in an elastic cap according to the international 10–20 system. The sampling rate was set at 1000 Hz. The electrodes at Fp1 and Fp2 recorded horizontal eye movements, and the electrode at IO above the right eye recorded vertical eye movements. Scalp-electrode impedance was kept below 5 kΩ to ensure high-quality EEG recordings. EEG signal was collected during ten neurofeedback training blocks (3 min each) and two rest blocks (3 min eyes-open and 3 min eyes-closed) before and after training. In order to explore the association between neurofeedback learning performance and characteristics of structural and functional networks, MRI images of all subjects in the real group were also collected (Supplementary Methods 1.1).

Neurofeedback training

Experimental design

All participants in the real and sham groups completed one neurofeedback training session. The complete session consisted of five sections: (1) the Positive and Negative Affect Schedule (PANAS) scale was used to measure self-reported emotions; (2) resting-state EEG data collection before neurofeedback training (pre-NF; eyes-open and eyes-closed, 3 min each); (3) ten neurofeedback training blocks; (4) resting-state EEG data collected after neurofeedback training (post-NF; eyes-open and eyes-closed, 3 min each); (5) an neurofeedback training effect questionnaire was used to measure participants' subjective feelings and strategies. Three questions were included in the questionnaire: (i) Please briefly describe the adjustment strategy of the feedback signal used in training. (ii) Please evaluate whether the strategy you use is effective (scale of 1–5). (iii) Please evaluate the degree of concentration during training (scale of 1–5).

The neurofeedback training session consisted of ten training blocks. In particular, the first training block was the baseline block, during which participants saw moving feedback signals and were instructed to relax without trying to control the feedback signals. The EEG signals recorded during the neurofeedback baseline block are used to calculate the initial individual threshold for the next block, and the threshold of the neurofeedback signal is adjusted after each block based on the previous block. Participants were provided with visual feedback consisting of a histogram reflecting the current FAA score. If the FAA score was below the threshold, the histogram was blue; when the FAA score exceeded the threshold (i.e., desired state), the histogram became yellow. All participants were instructed to maintain a positive mental/emotional state that kept the FAA score increased. If the asymmetry score was kept above the threshold for more than 10 s, they got reward points displayed on the screen. Participants of the real group received real-time feedback about their alpha activity. The sham group and the real group underwent identical procedures, except for the feedback provided to them. Specifically, the real group was presented with genuine real-time EEG activity and the sham group was given false EEG feedback using pre-recorded EEG data from participants who had undergone genuine neurofeedback training. After the completion of the neurofeedback training session, participants' regulation strategies and subjective feelings were recorded through questionnaires.

Learning indices

The neurofeedback training performance was assessed using two indices. The first learning index (L1) measured the learning effect on the FAA score during the neurofeedback training blocks (Enriquez-Geppert et al. 2013). Specifically, the mean of FAA scores for each training block was calculated and then a linear regression was performed on mean values. Then L1 was calculated as the regression slope. Another learning index (L2) measured the effect of the neurofeedback protocol on FAA at rest (Hanslmayr et al. 2005a, b; Alkoby et al. 2018). Specifically, L2 was calculated as the changes of FAA between the pre-NF resting-state and post-NF resting-state.

EEG data analysis

Offline analysis

Because interindividual differences in frequency bands are large for healthy adults (Klimesch 1999), the pre-NF resting-state EEG data were offline analyzed for estimation of individual alpha peak frequency (IAPF) to define alpha band for neurofeedback training as in previous studies (Quaedflieg et al. 2016; Gong et al. 2020). Besides, both pre-/post-NF resting-state EEG data were analyzed for the calculation of the FAA score. EEG data were processed using the Letswave toolbox (https://github.com/NOCIONS/letswave) and the self-written MATLAB scripts. The continuous resting-state EEG signals were sampled offline at 500 Hz and band-pass filtered between 0.5 Hz and 40 Hz using a 2nd-order Butterworth filter. After visual inspection, bad channels were interpolated with adjacent channels. Then eye artifacts were corrected by an infomax independent component analysis (ICA). The components related to eye blinking or movements were removed from the original data. Finally, all EEG signals were re-referenced to TP9 and TP10. Based on the power spectral density of the post-NF resting-state (eyes-closed) EEG signal recorded at the posterior electrode (Pz), the IAPF was defined as the frequency of absolute power gravity between 7.5 and 12.5 Hz (Corcoran et al. 2018). Then the alpha frequency band was defined individually for each participant as [IAPF − 2, IAPF + 2] Hz. The FAA score was calculated by subtracting the logarithm of left-alpha power from the logarithm of right-alpha power (log [F4] − log [F3]).

Online analysis

During neurofeedback training, the EEG signals were collected and analyzed in real time. Online analysis was completed by self-written MATLAB script, including epoching, filtering, online eye movement correction, re-referencing, spectral density estimation, and calculation of FAA scores. Specifically, the EEG raw signals were analyzed in a 6-s window, with a 0.4-s step. There has been a large variation in the choice of window width in previously published studies, most studies used a 2-s window (Quaedflieg et al. 2016; Enriquez-Geppert et al. 2017; Mennella et al. 2017), while one study used a 20-s window (Wang et al. 2019). Actually, a targeted neural feature is differently well captured with windows of different widths, low-frequency features as opposed to higher-frequency features necessitate the use of large windows (Darvishi et al. 2013). Thus, considering alpha-band features used in this study, we chose a relatively larger 6-s window width and a larger overlap between adjacent windows in order to provide smooth feedback to the participant. The EEG signals were first band-pass filtered between 0.5 and 40 Hz using a 2nd-order Butterworth filter and then re-referenced to TP9 and TP10 because these two channels have a higher signal-to-noise ratio than Cz according to previous FAA neurofeedback studies (Quaedflieg et al. 2016). Fast Fourier transform (FFT; 50% Hanning window) was applied for power spectral density estimation. Power density values were calculated by averaging spectral power within the individual alpha band (between IAPF − 2 and IAPF + 2) at right (F4) and left (F3) frontal channels and then the FAA score was calculated. The signal recorded at the IO electrode was used to detect and remove signals contaminated by ocular artifacts. Specifically, the individual threshold for the detection of eye movement was selected using pre-NF resting-state EEG data, and the online performance of ocular artifacts detection was checked after each NF run. The feedback was updated for every step (0.4-s) signal and it was inhibited if ocular noise was identified according to the IO channel.

MRI data analysis

Brain parcellation

The whole cerebral cortex was automatically divided into 116 regions of interest (ROIs) using the automatic anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al. 2002), which has been popularly used in previous studies of multimodal brain network analyses (Jiang et al. 2019; Yao et al. 2019). In order to check whether the network measures of the structural and functional networks of the hemispheres were related to the learning index, we also grouped the ROIs of the left and right hemispheres (58 ROIs for each hemisphere) according to the AAL atlas for constructing the hemispheric networks.

Construction of multimodal brain network

Predefined regions of interest (ROIs) were used for the construction of the whole-brain and hemispheric networks. The single-subject gray matter network (GMN) was constructed by calculating the inter-regional similarities of local brain morphology (Kong et al. 2015). The single-subject white matter network (WMN) was constructed by counting the number of fiber tracts connecting the two regions (Cui et al. 2013). The single-subject resting-state functional brain network (FBN) was constructed using the mean regional time series of resting-state fMRI data. For more details on the construction of multimodal brain networks, please refer to Supplementary Methods 1.2.

Global properties of network analysis

We used the Graph Theoretical Network Analysis (GRETNA) toolbox to calculate global graphic-based network metrics of both functional and structural brain networks (Wang et al. 2015). Because the physiological interpretation of negative correlations is ambiguous (Murphy and Fox 2017), functional connections with negative correlation values were not considered here. Binary undirectional structural or functional brain networks were built for each subject by thresholding the GMN/WMN/FBN matrices at predefined thresholds (from 10 to 40%, with 1%

intervals). This sparsity band was used to ensure that the network density was less than 50% and the average degree was greater than the natural logarithm of the number of nodes (Chen et al. 2019). The global metrics included small-world parameters (normalized clustering coefficient gamma, normalized characteristic path length Lambda), and network efficiency parameters (global efficient Eg and local efficiency Eloc). The metrics of small-worldness (gamma and lambda) quantify the balance between the segregation and integration of the information processing and communication in the brain (Humphries et al. 2006). The network efficiency is a biological relevant metric to describe brain networks from the perspective of information transfer (Achard and Bullmore 2007). For each network metric, we calculated the area under the curve (AUC) over the range of sparsity, which provides a summarized scalar for the topological characterization of brain networks independent of the single threshold selection. Besides, we also calculated these small-worldness and efficiency metrics for each hemispheric network (Fig. 1).

Statistical analysis

Statistical analysis was carried out using IBM SPSS 22. The Chi-square test was used for gender and independent two-sample t-tests were used for age and psychological ratings. Besides, a paired-sample t-test of the FAA score between pre-NF and post-NF resting-states was performed for each group, and two sample t-tests were performed to compare learning indices between the real group and sham group.

For the real group, we examined the correlations between learning indices (L1/L2) and graph-theoretical metrics of the multimodal MRI network by partial correlation analysis, controlling for age and sex as confounding variables ($P < 0.05$). Due to the exploratory nature of the analysis, uncorrected P values were retained.

Results

Sample characteristics and behavioral results

This study included 30 participants in the real group and 30 participants in the sham group. There were no significant differences in gender, age, pre-NF mood (PANAS score), and self-reported validity of neurofeedback between the two groups. There was a significant difference in self-reported attention between the two groups, with participants in the real group paying more attention during neurofeedback training than in the sham group (real group = 4.07 $\pm$ 0.63, sham group = 3.69 $\pm$ 0.66, $P = 0.03$). The descriptive statistics for each group was shown in Table 1.

Learning effects of neurofeedback training on FAA

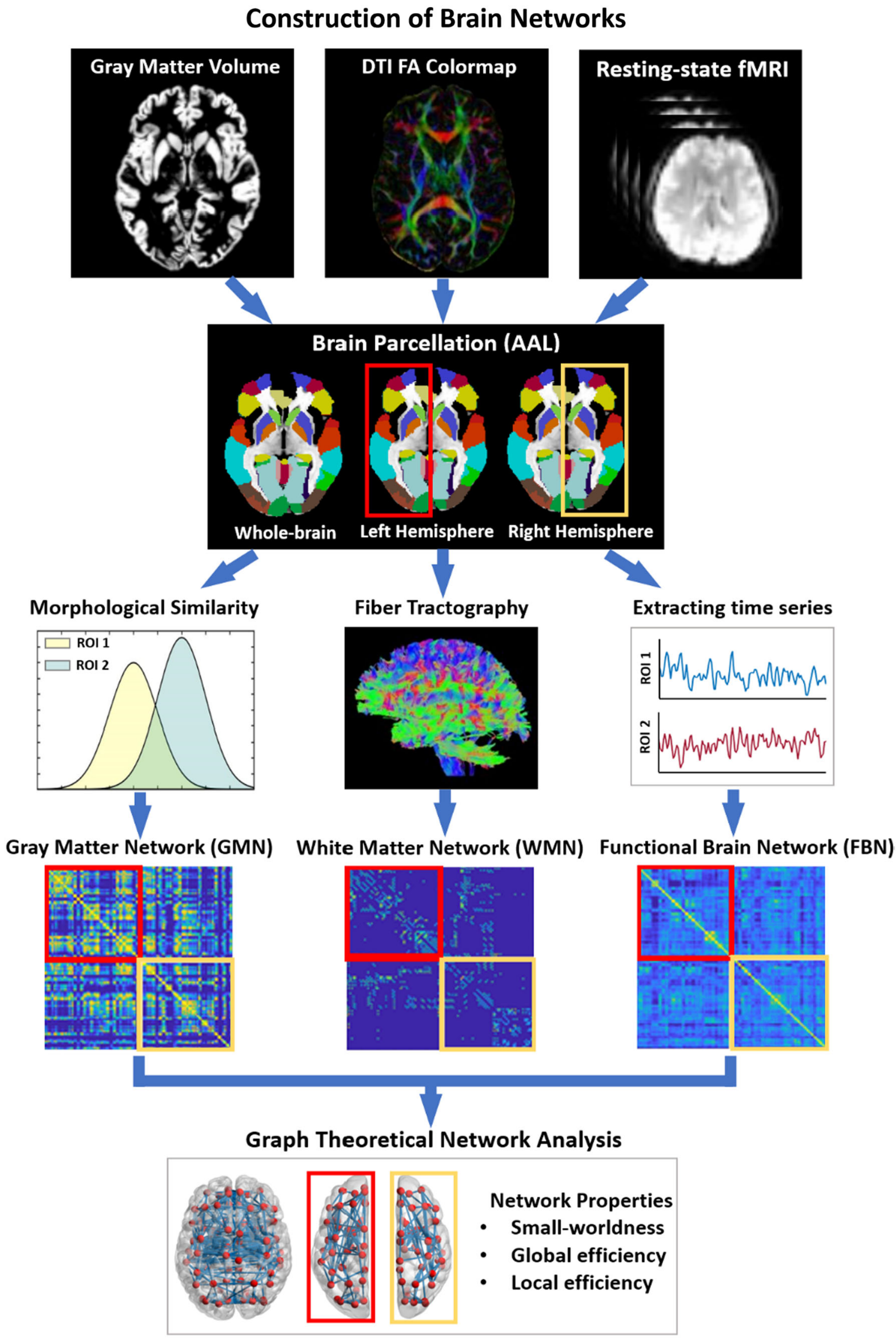
The learning performance of FAA neurofeedback training was assessed by investigating the effect of the neurofeedback protocol on changes of FAA during the neurofeedback blocks and at pre-NF/post-NF rests. Figure 2A provides a visual representation of the mean FAA score of 10 consecutive neurofeedback training blocks for each group. It can be seen that participants in the real group were able to significantly improve the FAA score during training (R = 0.84, $P = 0.002$), while participants in the sham group did not (R = 0.31, $P = 0.39$). According to Fig. 2B, the real group, but not the sham group, showed a significant increase in FAA at rest (post-NF compared with pre-NF; $P = 0.03$). The neurofeedback training performance was assessed using two neurofeedback learning indices (L1 and L2), and no significant group difference was observed for both L1 (FAA change during training blocks; Fig. 2C) and L2 (FAA change between pre-NF and post-NF resting-states; Fig. 2D).

The correlation between learning effect and graph-theoretical metrics of structural networks

The global graph-theoretical metrics of the whole-brain and hemispheric structural networks (GMN and WMN) were calculated for the real group, and the correlation analyses between graph-theoretical metrics and neurofeedback learning indices (L1/L2) were performed. Significant results were only observed between global graph-theoretical metrics of GMN and neurofeedback performance during training blocks (as assessed by learning index L1). As shown in Fig. 3A, D, significant negative correlations between graph-theoretical metrics and L1 were mainly observed in the right hemisphere (normalized clustering coefficient, R = − 0.51, $P = 0.005$; local efficiency: R = − 0.44, $P = 0.02$). No significant correlation was observed between characteristic path length and global efficiency and L1 (Fig. 3B, C). For neurofeedback learning index L2, which assessed the changes of FAA between pre-NF and post-NF resting-states, no significant correlation was observed for all global graph-theoretical metrics.

The correlation between learning effect and graph-theoretical metrics of functional networks

The neurofeedback learning index L1 according to FAA change during training blocks showed a significant positive correlation with local efficiency of the right hemispheric



Construction of Brain Networks
Gray Matter Volume
DTI FA Colormap
Resting-state fMRI
Brain Parcellation (AAL)
Whole-brain
Left Hemisphere
Right Hemisphere
Morphological Similarity
ROI 1
ROI 2
Fiber Tractography
Extracting time series
ROI 1
ROI 2
Gray Matter Network (GMN)
White Matter Network (WMN)
Functional Brain Network (FBN)
Graph Theoretical Network Analysis
Network Properties
• Small-worldness
• Global efficiency
• Local efficiency

◀ **Fig. 1** The flowchart depicts the main analytic process of constructing the multimodal brain networks

FBN (R = 0.46, P = 0.01, Fig. 4B), but no significant correlation with global efficiency (Fig. 4A).

For the learning index L2, which assessed the FAA change between pre-NF and post-NF rests, significant correlations were mainly observed for the whole-brain and left hemispheric FBN. Such as negative correlation with small-worldness (Fig. 5A; whole-brain normalized clustering coefficient, R = − 0.38, P = 0.04), negative correlation with global efficiency (Fig. 5C; whole brain, R = − 0.37, P = 0.047; left hemisphere, R = − 0.42, P = 0.02), and negative correlation with local efficiency (Fig. 5D; whole brain, R = − 0.54, P = 0.002; left hemisphere, R = − 0.47, P = 0.01), but no significant correlations was observed for the characteristic path length (Fig. 5B).

Table 1 The demographic and behavioral results

	Real group (n = 30)	Sham group (n = 30)	t/X^2, P
Age	22.13 ± 2.05	22.43 ± 2.14	t= − 0.55, P = 0.58
Gender	14 M/16F	14 M/16F	X^2= 0, P = 1
PANAS.pos	31.73 ± 5.72	30.70 ± 5.27	t= 0.73, P = 0.47
PANAS.neg	17.33 ± 4.94	19.20 ± 5.52	t= -1.38, P = 0.17
Self-reported validity score	3.68 ± 0.55	3.40 ± 0.84	t= 1.51, P = 0.14
Self-reported attention score	4.07 ± 0.63	3.69 ± 0.66	t= 2.24, P = 0.03*

Both mean and SD are shown. *P < 0.05

M, male; F, female; PANAS.pos, positive score of the Positive and Negative Affect Schedule; PANAS.neg, negative score of the Positive and Negative Affect Schedule

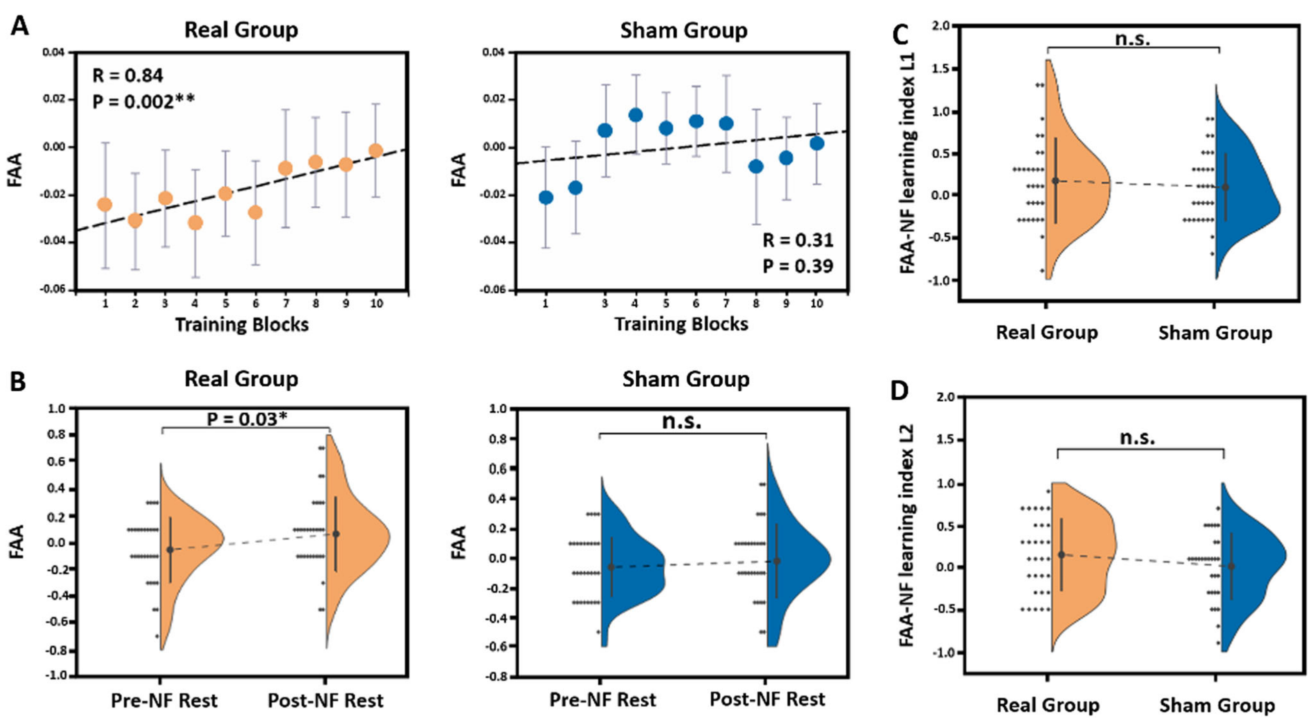
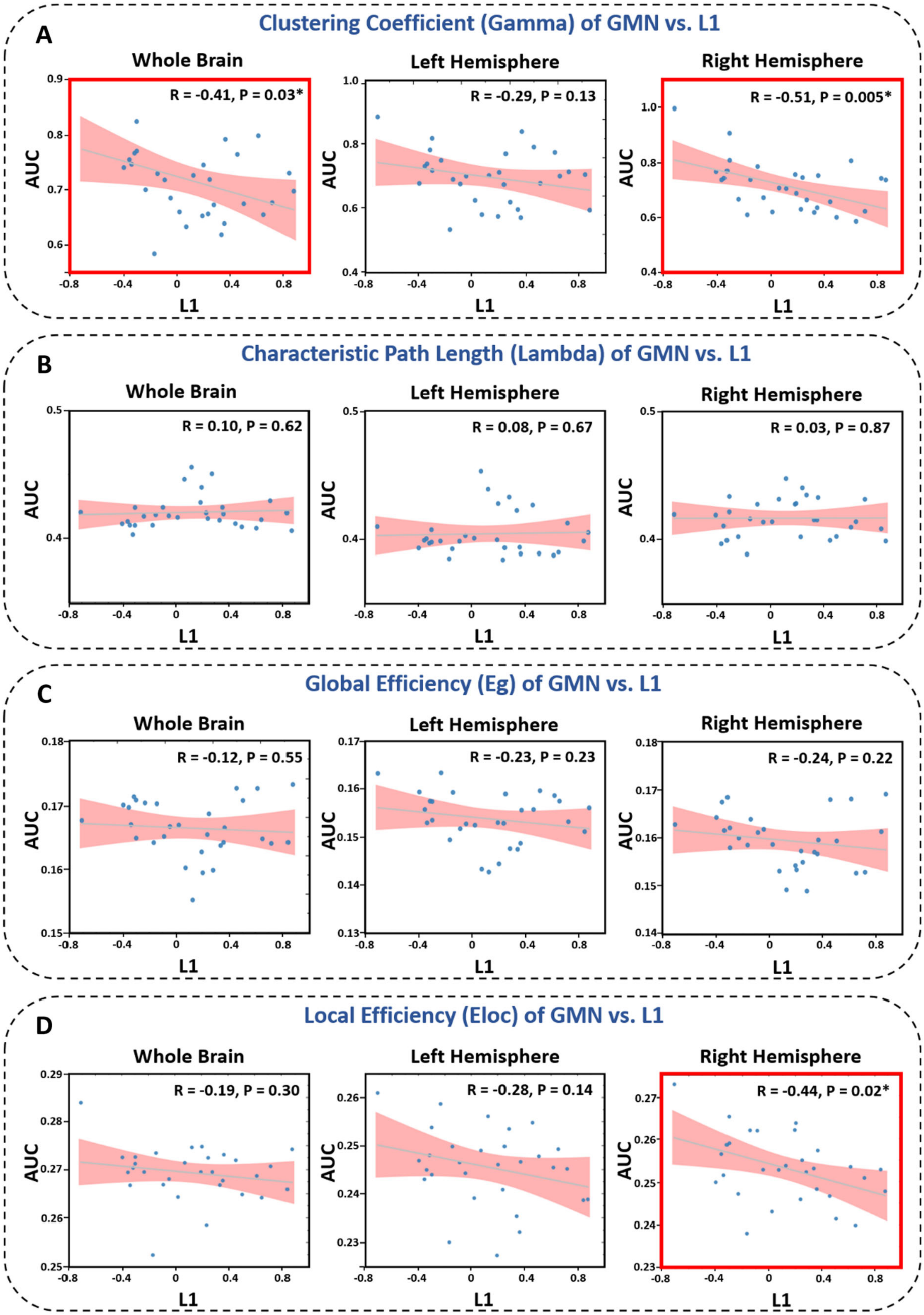


Fig. 2 Neurofeedback modulation of FAA. **A** The real group, but not the sham group, showed a significant increase in FAA during training blocks. **B** The real group, but not the sham group, showed a significant increase in FAA at rest. **C** No significant group difference was observed for learning index L1 (FAA change during training blocks). **D** No significant group difference was observed for learning index L2 (FAA change between pre-NF and post-NF resting-states). *FAA* frontal alpha asymmetry, *NF* neurofeedback


A
Clustering Coefficient (Gamma) of GMN vs. L1
Whole Brain
R = -0.41, P = 0.03*
Left Hemisphere
R = -0.29, P = 0.13
Right Hemisphere
R = -0.51, P = 0.005*
B
Characteristic Path Length (Lambda) of GMN vs. L1
Whole Brain
R = 0.10, P = 0.62
Left Hemisphere
R = 0.08, P = 0.67
Right Hemisphere
R = 0.03, P = 0.87
C
Global Efficiency (Eg) of GMN vs. L1
Whole Brain
R = -0.12, P = 0.55
Left Hemisphere
R = -0.23, P = 0.23
Right Hemisphere
R = -0.24, P = 0.22
D
Local Efficiency (Eloc) of GMN vs. L1
Whole Brain
R = -0.19, P = 0.30
Left Hemisphere
R = -0.28, P = 0.14
Right Hemisphere
R = -0.44, P = 0.02*
AUC
L1

◀ **Fig. 3** Scatter plots with linear regression fit and a 95% confidence interval for the correlations between global properties of GMN and individual learning performance during training blocks (L1). *GMN* gray matter network, *AUC* the area under curve. L1, neurofeedback learning index according to FAA change during training blocks

Discussion

The present study applied graph-theoretical analyses on both functional MRI and structural MRI data to identify the multimodal brain network predictors related to the learning ability of participants during FAA neurofeedback training. Our study revealed three main findings: (i) The predictors of learning performance were different for evoked EEG modulations during training blocks and at rest, so it is necessary to evaluate the efficacy of EEG neurofeedback training in different ways and investigated its related predictors separately. (ii) At the overall topological level, the learning performance in evoked EEG modulations was correlated with topographic metrics of both functional and structural brain networks, so individual differences in neurofeedback learning performance could be explained with (stable) trait-like variation in structural/functional architecture. (iii) Despite common small-world organization for both the hemispheres and imaging modalities, correlated global topological metrics of different learning performance indices showed different laterality of hemispheric brain networks.

Efficacy of FAA neurofeedback training in evoked EEG modulations

FAA is thought to reflect the balance between the left and right prefrontal lobe activity (Davidson et al. 1990; Cook et al. 1998). Accordingly, greater left-sided activity (reduced alpha at left) has been related to the approach system and positive emotions (Sutton and Davidson 1997; Jackson et al. 2003). On the other hand, greater right-sided activity (reduced alpha at right) has been associated with the withdrawal system and negative emotions (Tomarken et al.

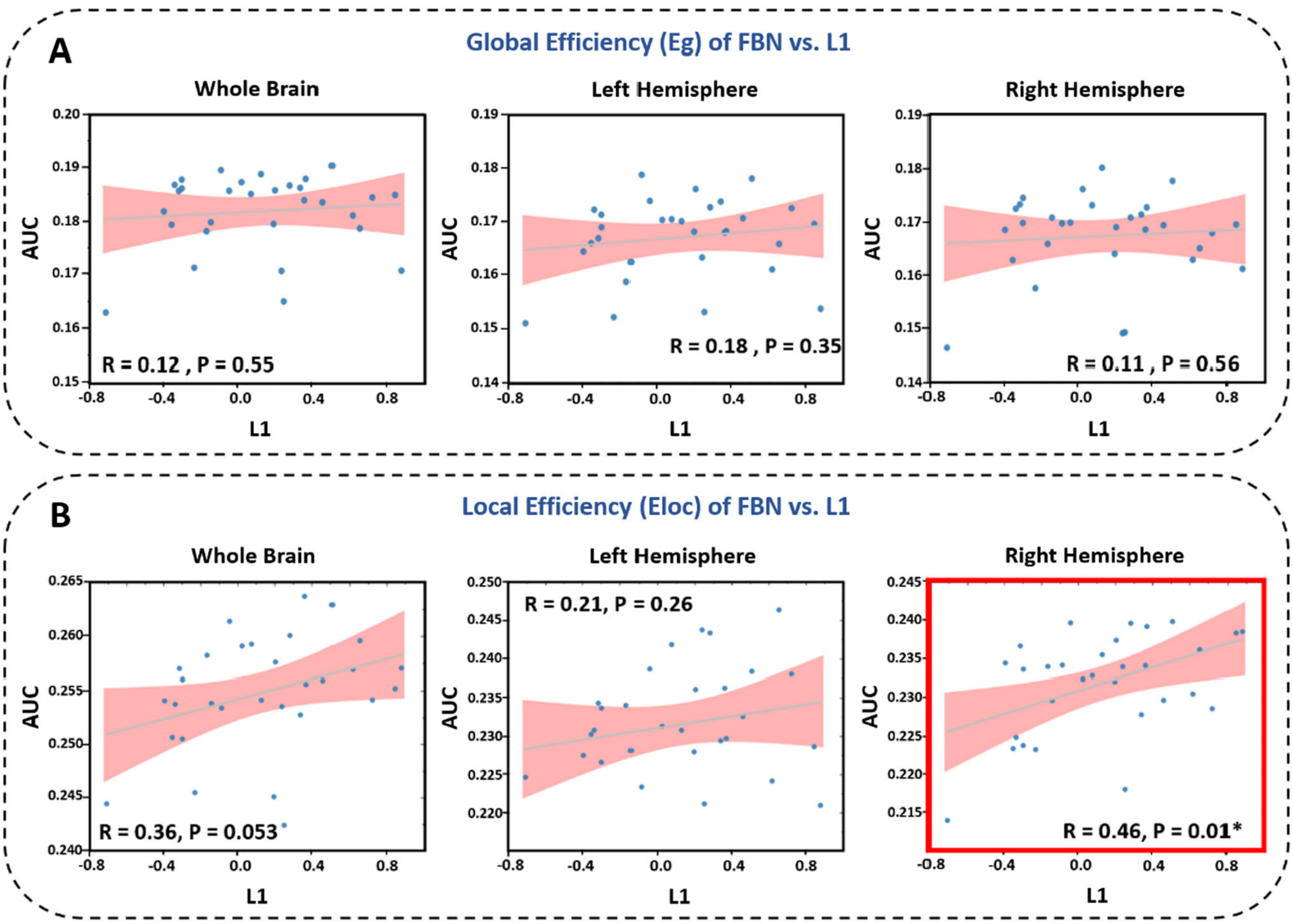
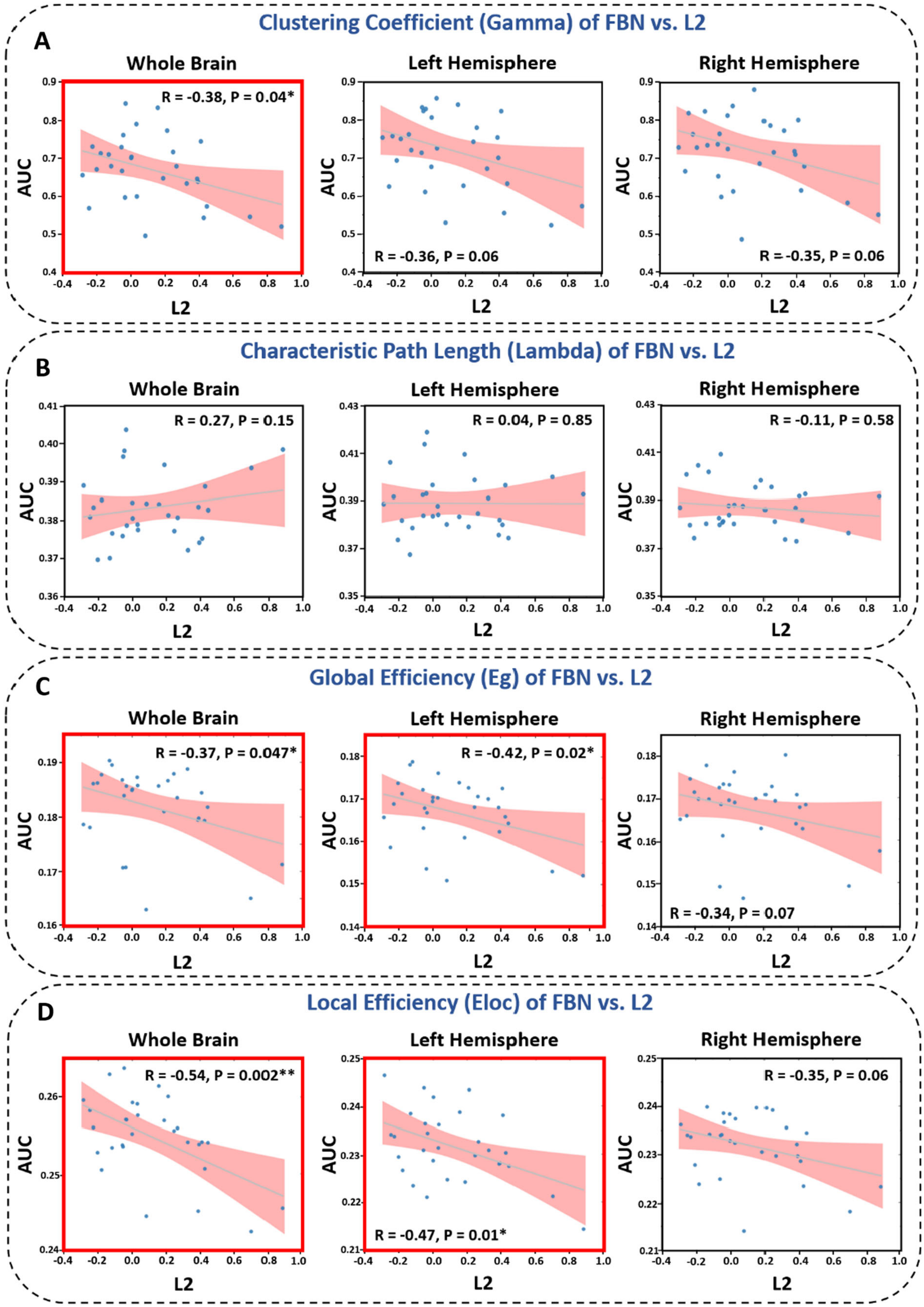


Fig. 4 Scatter plots with linear regression fit and a 95% confidence interval for the correlations between global properties of FBN and individual neurofeedback learning performance L1 during training blocks. *FBN* functional brain network, *AUC* the area under curve. L1, neurofeedback learning index according to FAA change during training blocks



Clustering Coefficient (Gamma) of FBN vs. L2
A
Whole Brain
Left Hemisphere
Right Hemisphere
R = -0.38, P = 0.04*
R = -0.36, P = 0.06
R = -0.35, P = 0.06
Characteristic Path Length (Lambda) of FBN vs. L2
B
R = 0.27, P = 0.15
R = 0.04, P = 0.85
R = -0.11, P = 0.58
Global Efficiency (Eg) of FBN vs. L2
C
R = -0.37, P = 0.047*
R = -0.42, P = 0.02*
R = -0.34, P = 0.07
Local Efficiency (Eloc) of FBN vs. L2
D
R = -0.54, P = 0.002**
R = -0.47, P = 0.01*
R = -0.35, P = 0.06
AUC
L2

◀ **Fig. 5** Scatter plots with linear regression fit and a 95% confidence interval for the correlations between global properties of FBN and individual neurofeedback learning performance L2 during resting-states. *FBN* functional brain network, *AUC* the area under curve. L2, neurofeedback learning index according to FAA change between pre-NF and post-NF resting-states

1992; Davidson 1998). EEG neurofeedback has been proposed as a tool to modulate FAA, and the successful self-regulation of EEG activity is necessary to achieve the essential purpose of neurofeedback (Weber et al. 2020). The assessment criteria of neurofeedback learning are heterogeneous as reported in recent reviews (Alkoby et al. 2018; Weber et al. 2020). Since the current study only included one training session, the learning ability was assessed by the changes within a short period. According to existing studies, the efficacy of neurofeedback training in evoked EEG modulations was typically evaluated by comparing the targets of brain activity (neurofeedback signal) recorded within/between training sessions or before and after the whole training (Rogala et al. 2016). Previous studies focused on the comparison of these parameters of neurofeedback efficacy between the experimental and control groups, and the observed significant difference could indicate successful training in the EEG domain.

Here in this study, participants from both real and sham groups could increase their FAA during training blocks by maintaining a positive emotional state. Because false feedback signals of the sham group were not conducive to real-time adjustment of regulatory strategies, the increasing trend of FAA during training blocks was more obvious for the participants in the real group. Besides, only the real group showed a significant increase in FAA at rest. Even though measured training efficacy during training blocks was not significantly different between the real group and sham group, we can also qualify them as a success when the comparison between the pre-training and post-training measurements provided a different outcome in the real and sham group. Because it is possible that real neurofeedback training is more effective in changing tonic rather than phasic FAA as tonic alpha changes occur at a slower rate (Hanslmayr et al. 2005a, b; Quaedflieg et al. 2016). After the examination of neurofeedback effects on EEG for the whole group, the large inter-individual difference in neurofeedback learning should be noticed, which is consistent with previous studies (Quaedflieg et al. 2016; Mennella et al. 2017). However, so far the reason for the FAA neurofeedback learning difference has been rarely investigated.

Predictors of the efficacy of FAA neurofeedback during training blocks

The assessment of learning ability varies among previous studies (Weber et al. 2020), within-session changes have been proposed to be more useful to identify changes resulting from neurofeedback training (Dempster and Vernon 2009). As one of the most studied assessments of learning ability, we defined the learning index L1 to capture immediate responsiveness. In order to investigate if the individual differences in neurofeedback learning performance can be explained by trait-like variation in brain architecture, global topographic measures that reflect long-term functional/structural network organization were analyzed. Resting-state FBN may reflect stable functional brain organization sculpted by long-term experiences and the nature of these intrinsic networks was associated with inter-individual differences in cognitive functions (Cohen and D'Esposito 2016; Vriend et al. 2020). GMN is a robust and valuable tool for investigating topological organization and it can provide information complementary to resting-state brain network analysis (Alexander-Bloch et al. 2013). Compared with FBN, structural networks (such as GMN and WMN) could reflect more stable patterns of the anatomical organization affected by heredity, and experience-related plasticity (Kong et al. 2015). Besides, it is widely acknowledged that the left and right hemispheres of human brains display both anatomical and functional asymmetries (Tian et al. 2011), and FAA is a measure of the hemispheric differences in alpha oscillations, therefore possible predictors of hemispheric metrics were also investigated.

In this study, we constructed structural and functional networks based on whole-brain and separate hemispheres and observed small-worldness (Figures S1 and S2 in the supplementary materials). According to our results, the individual differences in learning ability during training blocks can be explained by the topographic metrics of both functional and structural networks of the right hemisphere, including clustering coefficient and local efficiency. During FAA neurofeedback training, the participants were trying to maintain a positive emotional state by recalling happy memories, and the right hemisphere was thought to dominate related emotional functions (Gainotti 2019). This explains why the observed predictors for learning ability during training blocks were mainly on the right hemisphere. Specifically, the neurofeedback learning index L1 showed a significant positive correlation with local efficiency of the right hemispheric FBN, which means participants with a less integrated brain network during resting-state showed better learning performance. The ability of the brain for integration and segregation is vital for cognitive processes (Cohen and D'Esposito 2016), and a previous study proposed that individuals with a more integrated brain during resting-state are less able to further increase network efficiency when transitioning from rest to task state, leading to slower response during cognitive tasks (Vriend et al. 2020).

Contrary to the functional network, we observed significant negative correlations between graph-theoretical metrics (clustering coefficient and local efficiency) of the morphological structural network of right hemispheric and neurofeedback learning index L1. The disparity in the results related to functional and structural brain networks may be attributed to the distinct neural mechanisms underlying morphological and functional brain network alternations (Reid et al. 2016). A more integrated morphological network has been associated with a higher score of cognitive intelligence (Li et al. 2021a, b). A study reported that individuals who have a higher score of intelligence could perform better in learning self-control of gamma during neurofeedback training (Khodakarami and Firoozabadi 2020). Because no intelligence assessment was included in the current study, future studies are needed to further verify the potential relationship between topographic metrics of the morphological network, learning performance during FAA neurofeedback training, and cognitive intelligence.

Predictors of the efficacy of FAA neurofeedback at resting-states

Different evaluation criteria in neurofeedback learning may lead to different results of learning performance, but they are not conflicted because they evaluated different aspects of neurofeedback learning. Two types of learning indices were widely used in published studies: one type of indices focuses on the learning performance during training blocks (such as L1 in the current study) (Enriquez-Geppert et al. 2013; Wan et al. 2014; Nan et al. 2015; Ninaus et al. 2015; Reichert et al. 2015; Kober et al. 2017, 2018), while another type of indices usually focuses on the learning performance across training sessions (Enriquez-Geppert et al. 2013; Wan et al. 2014; Nan et al. 2015). Because here the participants only performed one training session, the learning performance across sessions cannot be evaluated. One previous study of FAA neurofeedback training has assessed neurofeedback learning by the changes of training parameters between pre-NF and post-NF resting-states (Quaedflieg et al. 2016). Their results indicated that significant cross-sessions change in FAA was only found during the rest and not during the training blocks (Quaedflieg et al. 2016). The results here in the current study showed a significant change of FAA during resting-state only for the real group, not the sham group. Therefore, it is necessary to investigate whether there are any parameters related to learning ability during resting-states.

For the learning index L2, which assesses the FAA change between pre-NF and post-NF resting-states, significant negative correlations were mainly observed for the whole-brain and left hemispheric FBN. Specifically, participants with better learning performance during resting-states were associated with less clustering coefficient, global efficiency, and local efficiency. These graphic metrics can all be seen as complementary measures of how efficiently the information is transferred throughout the brain (Bullmore and Sporns 2009). The local efficiency can be thought of as the global efficiency of the sub-network consisting only of a node's neighbors, and the average local efficiency at the whole-network level reflects the network's ability to effectively compensate for the localized failure of a single node. Similarly, the clustering coefficient at the whole-brain level can be thought of as the average efficiency of information transfer throughout the brain. The previous study has reported that higher levels of trait emotional awareness are associated with more efficient global information integration, greater local processing efficiency, and clustering of resting-state functional brain network (Smith et al. 2018). Hence, the modulation effect of resting-state FAA might be more efficient for individuals with low emotional awareness, reflecting the effectiveness of FAA feedback training as an emotion regulation training approach. However, compared with the predictors obtained for the learning performance during neurofeedback training (L1), the predictors of learning performance at resting-states (L2) showed different laterality. So far, there were two main models concerning the relationship between emotions and brain laterality. The first model posits a general dominance of the right hemisphere for all emotions, regardless of affective valence (Gainotti 2012); the second model assumes an opposite dominance of the left hemisphere for positive emotions and of the right hemisphere for negative emotions (Killgore and Yurgelun-Todd 2007). Due to the lack of evaluation of emotional state changes, we can only assume that the learning effect during resting-states might be derived from a more positive emotional state after training, which is more related to the left hemisphere.

Limitations and future directions

The findings of this study still need further validation. One important limitation of our study is the single-session neurofeedback training design and the learning ability was assessed by the changes within a short period. Most prior research in this area has focused on learning performance across multiple training sessions for both self-regulation of

EEG activities and the long-term effects of enhanced behavioral performance (Weber et al. 2020). Second, MRI data have not been collected for the sham group, however, the sham group also showed some level of learning effect, and comparing the predictors of learning effect between groups would help to control for the non-specific effects possibly driving learning. Third, considering reported gender-related differences in topographic metrics of both whole-brain and hemispheric networks (Tian et al. 2011), future studies with larger sample sizes could report data analysis results separately for male and female participants. Fourth, the neuroimaging predictors correlated with the learning ability are different among different neurofeedback paradigms, depending upon some psychological and physiological mechanisms. Therefore, the specificity of these brain network predictors of FAA neurofeedback should be considered in future studies. Last but not least, it is unclear how these predictors can be transferred to patient groups, such as patients with major depression. Despite that one recently published meta-analysis questioned FAA as a biomarker of depression disorders (Kolodziej et al. 2021), existing evidence provides a strong rationale for the use of FAA neurofeedback training for the reduction of depressive symptoms in clinical settings (Peeters et al. 2014a, b; Quaedflieg et al. 2016; Zotev et al. 2020). Thus, we need to recruit patients in future experiments to investigate whether the identified network metrics correlated with neurofeedback learning performance can be generalized to patient groups.

Conclusion

As the first study to date, we investigated the correlation between the learning performance of FAA neurofeedback training and the global topographic metrics of multimodal large-scale brain networks. Our results suggested that individual differences in FAA neurofeedback learning performance could be explained by trait-like variation in large-scale brain network architecture, which improves our knowledge about the mechanisms of inter-individual differences in neurofeedback learning. These findings have the potential to be used for designing individualized neurofeedback protocols as well as the promotion of neurofeedback training techniques in clinical applications. To achieve this purpose, future research should consider using a long-term training evaluation design with multiple training sessions and include patients with mood disorders to validate and extend the results of this study.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

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