Network Analysis of Magnetoencephalogram Signals in Schizophrenia Patients When Viewing Emotional Facial Stimuli

Dengxuan Bai, Wenpo Yao, Wei Yan, and Jun Wang

***Abstract*— Schizophrenia is a serious mental disorder. Network analysis of magnetoencephalogram signals may help to identify potential biomarkers of schizophrenia. The goal of this investigation was to identify potential biomarkers in the magnetoencephalogram signals of patients with schizophrenia, global brain connectivity measures was used for emotion recognition in discriminating the patients from controls. First, we employed a mutual information method to explore the topological characteristics of the brain network in patients with schizophrenia among different frequency bands in response to four different stimulus conditions. Second, multidimensional cross-recurrence quantification analysis was performed to investigate the differences in dynamic coupling among different frequencies of brain magnetic waves in patients with schizophrenia in response to four different stimulus conditions, as the major novel contribution of our study. We found that the differences in topological features of the brain network appear in different frequency bands under different stimulus conditions. The differences are evident in the alpha 1 (8-10 Hz) and beta (13-30 Hz) frequency bands in response to negative stimuli, in the alpha 1 (8-10 Hz) frequency band in response to positive stimuli, and in the theta (4-8 Hz) and alpha 1 (8-10 Hz) frequency bands in response to neutral and gray-cross stimuli. In addition, differences in dynamic coupling among pairs of frequency bands were the most prominent in response to positive stimuli. The characteristics identified by our methods may be potential markers of schizophrenia present in magnetoencephalogram data, which can facilitate the clinical identification of schizophrenia patients. Our method provides a comprehensive perspective of brain networks in patients with schizophrenia and has practical applications for the clinical diagnosis of this disease.**

***Index Terms*— Schizophrenia, magnetoencephalogram, functional network, topological characteristics, dynamic coupling analysis.**

I. Introduction

SCHIZOPHRENIA is a common and serious mental disorder with symptoms including hallucinations, delusions, disordered thoughts, and cognitive impairment [1], [2]. Although schizophrenia has been studied for many years, its pathophysiological pathogenesis is still unclear [3]. In addition, the diversity and complexity of its symptoms have led schizophrenia treatments to focus on symptom reduction [4]. However, identifying potential biomarkers of schizophrenia is of particular interest [1], [5], [6]. Magnetoencephalogram (MEG) signals not only have high temporal resolution but also high spatial resolution, which can be used to accurately locate the source of neural activity. Many studies have employed MEG for diagnosing schizophrenia [6], [7], [8], [9], hence, using MEG to study schizophrenia is a hot topic in this field recently.

To obtain a comprehensive understanding of the dynamics of the human brain, images of emotional faces are often used to elicit changes in brain activity, as the brain responds differently to different facial emotion stimuli [10], [11], [12]. Similar facial emotion stimuli are used in schizophrenia research. Notably, Hempel et al. [13] found that the heart rate of patients with schizophrenia increased when viewing positive stimuli (i.e., pictures of faces exhibiting positive emotions). In addition, Duval et al. [14] verified that viewing negative stimuli (i.e., pictures of faces exhibiting sadness) enhanced the neurophysiological responses of schizophrenia patients. Moreover, Chu et al. [15] proved that electroencephalogram (EEG) signals of patients with schizophrenia exhibited different levels of entropy when viewing different facial emotion

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stimuli. Martin et al. [16], [17] also found that changes the late positive potential (LPP) of patients with schizophrenia differed when viewing different stimuli. The above examples show that the physiological characteristics induced by different stimuli are different; thus, exploring the MEG signals of patients with schizophrenia when viewing different facial emotion stimuli may help to reveal potential biomarkers of schizophrenia.

The proposal of the small-world network [18] provides a new perspective for studying complex systems [19]. When analyzing time series by complex network, the dynamic information in time series can be mined by analyzing the topological characteristics of the network [20], [21], [22], [23], [24]. The brain consists of a complex networks with characteristics similar to those of networks in physical systems. Studying brain networks enhances overall understanding of nervous system activity [25], [26], [27], [28], [29], [30]. Since Rubinov and Sporns [23], methods of analyzing complex networks have been widely employed in investigations of various brain signals [29], [31], [32], [33], [34]. There are many examples of the use of such methods in schizophrenia research. Through the network analysis of brain signals, Hadley et al. [35] found that the topological characteristics of the brain network in patients with schizophrenia were related to the treatment that they received. Importantly, Jiang et al. [36] utilized a causal network to analyze the causality of changes in brain structures in patients with schizophrenia. Moreover, Lee et al. [37] successfully predicted the clinical symptoms of schizophrenia by using brain network features. Furthermore, Strauss et al. [38] utilized network analysis and found that alogia and avolition were the main negative symptoms of schizophrenia and demonstrated that these symptoms were also related to the patient's sex. Strauss et al. [39] further used complex network analysis to explore the underlying structural characteristics of patients with negative schizophrenia symptoms. Li et al. [40] successfully identified patients with schizophrenia using a classifier trained on brain network topology parameters. Through network analysis, Karyakina and Shmukler [41] proved that the cognitive processing speed of patients with schizophrenia was markedly slowed. Kong et al. [42] verified that neurological soft signs (NSS) were closely related to changes in brain network topology in patients with schizophrenia. Ye et al. [43] employed network analysis and found that as the course of the disease progressed, the relationships among different symptoms in patients with schizophrenia weakened, and the probability of positive symptoms increased. Masychev et al. [44] extracted information on the efficient connectivity of brain networks in schizophrenia and used it to successfully differentiate between schizophrenia patients and controls. In conclusion, the above applications of complex network-based analysis of brain signals from schizophrenia patients illustrate the feasibility of applying this method to analyze the MEG data of patients with schizophrenia. The complex network analysis of MEG time-series data has provided valuable insights for schizophrenia research.

Interestingly, Lin et al. [45] demonstrated that the interaction among brain rhythms differed according to sleep stage, providing a new model for network research on sleep-related brain signals. Inspired by their findings, we hypothesized that schizophrenia patients might demonstrate differences in the coupling of brain rhythms among frequency bands under different conditions. However, most of the network analyses of brain signals in schizophrenia have used statistical correlations of time-series data to describe the information exchange (i.e., the functional connectivity) within the brain of schizophrenia patients [46], [47], [48], [49], [50]; they did not explore the coupling among brain rhythms. We believe that simple network analysis is insufficient for examining the biomarker in MEG signals of patients with schizophrenia. It is also necessary to understand the relationships among MEG signals of different frequency bands to obtain a more comprehensive network analysis of MEG data in patients with schizophrenia. Therefore, we believe that it is necessary to explore the interactions among different brain rhythms in patients with schizophrenia.

The complexity, synchronization, and functional network of brain signals exhibit different emotional characteristics under different stimulus conditions [51], [52], [53]. Therefore, we proposed the following hypotheses for the network analysis of MEG data elicited by facial emotion images in patients with schizophrenia. First, we predicted that there are differences in the network characteristics of MEG signals of different frequency bands in schizophrenia patients when viewing different facial emotion stimuli. Second, we predicted that different facial emotion stimuli would elicit differences in the coupling strength of MEG signals among frequency bands in schizophrenia patients. To verify these hypotheses, we analyzed the network topology of MEG signals among six frequency bands in schizophrenia patients under four stimulus conditions. In addition, we examined the dynamic coupling among MEG signals of different frequency bands in schizophrenia patients under different stimulus conditions; these data are the major novel contribution of this study. Thus, this study provides a new perspective on the network analysis of MEG signals in patients with schizophrenia.

The remainder of this paper is organized as follows: Section II introduces the acquisition and preprocessing of experimental data, the experiment design and related algorithms employed in the experiment. Section III presents the experimental results. Section IV introduces some discussions about this research. Section V draws conclusions of this investigation.

II. Methods

A. Participants

A total of 17 schizophrenia patients (age: 24.67 ± 2.640) and 15 healthy controls (age: 23.06 ± 5.494) participated in the study. All patients were clinically diagnosed with schizophrenia by psychiatrists and were recruited from outpatient clinics in the Nanjing Brain Hospital. Healthy controls were recruited by the hospital's psychiatrists via an advertisement posted on the hospital's home page. The inclusion criteria for all participants were as follows: a) not diagnosed with other mental disorders, b) no severe brain trauma, c) normal cognitive function, d) normal or corrected-to-normal vision, e) not currently pregnant, and f) no abuse of drugs or alcohol in the

two weeks prior to MEG recordings. All participants signed an informed consent form after the relevant details of this investigation were explained. This study was approved by the Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University (2017-KY015).

B. Experimental Design

We utilized pictures from the Chinese Affective Facial Picture System (CAFPS) [54] as stimuli and categorized them into negative stimuli, positive stimuli, neutral stimuli and gray-cross stimuli. Negative stimuli included sad faces, positive stimuli included happy faces, and neutral stimuli included neutral faces. For each of these three types of stimuli, 24 corresponding images of facial expressions were selected (12 males and 12 females), and each picture was randomly repeated 3 times, for a total of 72 stimuli. The gray-cross stimuli were comprised of 72 pictures of a gray cross. During stimulus presentation, the four categories of stimuli appeared randomly, with each stimulus presented for 600 ms and an stimulus interval of 650 ms to 800 ms, for a total of 288 stimuli. Four additional stimuli (the numbers 1, 3, 5, and 7) were included to evaluate participant attention; when these four stimuli appeared, the participants were instructed to press the corresponding keys.

C. Collection of MEG Signals

MEG signals were collected and recorded by a senior engineer using the Canadian CTF/VSM 275 channel full-head MEG system. Before MEG signal collection, all subjects were asked to remove all metal-like objects on their person that could impair electromagnetic signals. Each participant entered the collection room with electromagnetic shielding, sat quietly on the test chair, placed their head in the array of helmet-shaped sensors and stared at the display in front of them. At the time of MEG collection, three coils were placed (one on the tip of the participant's nose and one in front of each ear) to detect the relative position of the brain to the sensor array. After ensuring that the participants were in a relaxed state, the stimuli were projected onto the monitor in front of the participants, and MEG signals were collected and recorded simultaneously, with a sampling frequency of 1,200 Hz. During the whole MEG signal recording, the electrocardiogram (ECG) and electrooculogram (EOG) signals of the participants were simultaneously recorded to facilitate manual inspection of MEG signals in the later stage. During the scanning process, participants were monitored and instructed via cameras and intercoms located in the electromagnetic shielded room. Participants were instructed not to move, as blinks and muscle movements could impact the reliability of the data during the MEG signal recording. If any participant movements were found to affect the reliability of the data, the signal was dropped and recorded again.

D. Preprocessing of MEG Data

First, the MEG data were manually checked (removed artifacts) through the MATLAB toolbox EEGLAB 12.0, and the data sets with excessive interference were removed. Then, the MEG data were preprocessed. All MEG data preprocessing was performed offline using the SPM8 toolbox in the MATLAB environment. First, SPM8 was used to intercept data segments from 200 ms before each stimulus to 600 ms after each stimulus. Then, the intercepted MEG data were separated according to different stimuli, and the 50 Hz power line components were removed by using the relevant band stop filter for notching. Finally, the MEG signal was decomposed into signals of different frequency bands by using relevant bandpass filters of different frequency bands [52], [53]. More specifically, the different frequency bands were delta (1-4 Hz), theta (4-8 Hz), alpha 1 (8-10 Hz), alpha 2 (10-13 Hz), beta (13-30 Hz), and gamma (30-60 Hz) [32], [55].

E. Establishment of a Functional Network and Analysis of its Topological Parameters

A functional network was established at the sensor level, in which each sensor served as a node of the network. Since the MEG acquisition system had 275 channels, the established functional network had 275 nodes. We used mutual information, a characteristic of information theory, to measure the network connectivity. Mutual information provides a good measure of the coupling of time-series data and is defined as follows. Assuming that the two random processes are X and Y, the probability distributions of the variables are $p(x)$ and $p(y)$, respectively. In addition, their joint probability is $p(x, y)$, and their mutual information can be calculated by formula (1).

$$I(X;Y) = \sum p(x,y) \log \frac{p(x,y)}{p(x)p(y)} \tag{1}$$

The calculation formula of the connection matrix $A_{(i,j)}$ of the functional network is shown in formula (2).

$$A_{(i,j)} = \begin{cases} a_{ij} = I(S_i; S_j) & (i \neq j) \\ a_{ij} = 0 & (i = j) \end{cases} \tag{2}$$

where S_i and S_j represent two single subseries in a multi-dimensional time series (in this work, the i-th channel and the j-th channel of MEG signals), and a_{ij} represents the connection strength between the i-th node and the j-th node. Usually, to ensure the network connections are not redundant, thresholding is performed on the connection matrix $A_{(i,j)}$. The selection of threshold parameters referred to the suggestions of Wijk et al. [56], Stam et al. [57] and Heuvel et al. [58]. A threshold parameter that is too large will result in a disconnected network, and too small will result in a redundant network connection. To eliminate false connections and ensure the connectivity of the network, in this work, we integrated the above suggestions for network threshold parameter selection and retained connections with more than 75% of the strongest connection strength; all other connection strengths were set to 0. Then, we analyzed network topology parameters after threshold processing.

We used the average node degree, average clustering coefficient, average shortest path length and average global efficiency to analyze the topological structure of the functional brain network.

The node degree is the sum of the connection strengths of all links connected to the node. It characterizes the importance of that node in the network. It can be calculated by formula (3), where N represents the number of nodes in the network.

$$k_i = \sum_{j \in N} a_{ij} \tag{3}$$

The clustering coefficient is a parameter used to measure the clustering of network nodes. For a single node, the clustering coefficient is defined as the ratio of the number of connected nodes to the possible maximum number of edges [18], [59], which can be calculated by formula (4), where N represents the number of nodes in the network.

$$C_i = \frac{\sum_{j,m \in N} a_{ij} a_{im} a_{mj}}{k_i (k_i - 1)} \tag{4}$$

The clustering coefficient of the entire network is the average of the clustering coefficients of all nodes. It can be calculated by the formula (5).

$$C = \frac{1}{N} \sum_{i \in N} C_i \tag{5}$$

In a complex network, the distance between two nodes is defined as the number of edges in the shortest path connecting these two nodes. The average shortest path length L of a network is the average of the distances between all nodes [59], which is calculated by formula (6), where N represents the number of nodes in the network.

$$L = \frac{1}{N(N-1)} \sum_{i \neq j} d_{ij} \tag{6}$$

where d_{ij} represents the distance between node i and node j.

The global efficiency of the network is defined as the average of the efficiency of all network nodes. It measures the efficiency of information exchange in a complex network [60] and is calculated by formula (7), where N represents the number of nodes in the network.

$$E = \frac{1}{N} \sum_{i \in N} E_i = \frac{1}{N} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}^{-1}}{N-1} \tag{7}$$

F. Multidimensional Cross-Recurrence Quantification Analysis

Our MEG device had 275 channels; therefore, MEG datasets from a subject consisted of 275 time series. Therefore, the MEG data can be mathematically viewed as a multidimensional signal, and the general method of describing the correlations of one-dimensional time-series data is not appropriate for analysis. We employed a multidimensional cross-recurrence quantification analysis [61] to measure the nonlinear dynamic coupling among different frequency bands. The multidimensional cross-recurrence quantification analysis is defined as follows.

A d-dimensional time series P is given, as is shown in formula (8).

$$P = \begin{pmatrix} P_1 \\ P_2 \\ \vdots \\ P_n \end{pmatrix} = \begin{pmatrix} p_{1,1} & p_{1,2} & \cdots & p_{1,d} \\ p_{2,1} & p_{2,2} & \cdots & p_{2,d} \\ \vdots & \vdots & \ddots & \vdots \\ p_{n,1} & p_{n,2} & \cdots & p_{n,d} \end{pmatrix} \tag{8}$$

where $p_{i,j}$ is the value of the j-th dimension of the time-series data at time i, d is the number of dimensions of the multidimensional time series. Thus, we can obtain the phase space vector V of the time-series data P, as shown in formula (9).

$$V = \begin{pmatrix} V_1 \\ V_2 \\ \vdots \\ V_n \end{pmatrix} = \begin{pmatrix} P_1 & P_{1+\tau} & \cdots & P_{1+(D-1)\tau} \\ P_2 & P_{2+\tau} & \cdots & P_{2+(D-1)\tau} \\ \vdots & \vdots & \ddots & \vdots \\ P_{n-(D-1)\tau} & P_{n-(D-2)\tau} & \cdots & P_n \end{pmatrix} \tag{9}$$

where D is the embedding dimension, and τ is the embedding delay. The estimation of embedding dimension D and embedding delay τ followed the multidimensional false-nearest neighbors (MdFNN) method [62].

In the same way, the phase space W of another d-dimensional time series Q can be obtained. Then, the multidimensional cross-recurrence plot is defined as equation (10).

$$MdCR_{i,j}^{P,Q} = H\left(r - \left\| V_i - W_j \right\|\right) \tag{10}$$

where $H(x)$ is the Heaviside function, r is a threshold parameter, and $\|\bullet\|$ is the Euclidean distance between V_i and W_j. According to Wallot's suggestion [61], when the embedding dimension required by multidimensional time-series data was far less than the actual dimension of the time-series data, embedding was not required. Therefore, the multidimensional cross-recurrence plot was simplified as equation (11).

$$MdCR_{i,j}^{P,Q} = H\left(r - \left\| P_i - Q_j \right\|\right) \tag{11}$$

When analyzing the dynamic coupling of different MEG frequency bands in patients with schizophrenia, according to a MdFNN method, we calculated the embedding dimension $D = 2$ for the MEG signals. The actual dimension of our MEG signals was high. Therefore, in this work, we used the simplified model of multidimensional cross-recurrence plot. Then, we used the feature quantity recurrence rate (RR) of the cross-recurrence plot to measure the coupling strength between the two multidimensional time series. The RR quantifies the ratio of recurrence points to the total number of points in the recurrence plot plane and can be calculated by formula (12). In addition, according to the suggestion of Webber and Zbilut [63] to keep the RR at 1%-5%, we set the threshold parameter r to 0.62.

$$RR = \frac{1}{n^2} \sum_{i,j=1}^{N} MdCR_{i,j}^{P,Q} \tag{12}$$

G. Statistical Analysis

First, a two-factor ANOVA with group (patients with schizophrenia and controls) and stimulus condition (positive,

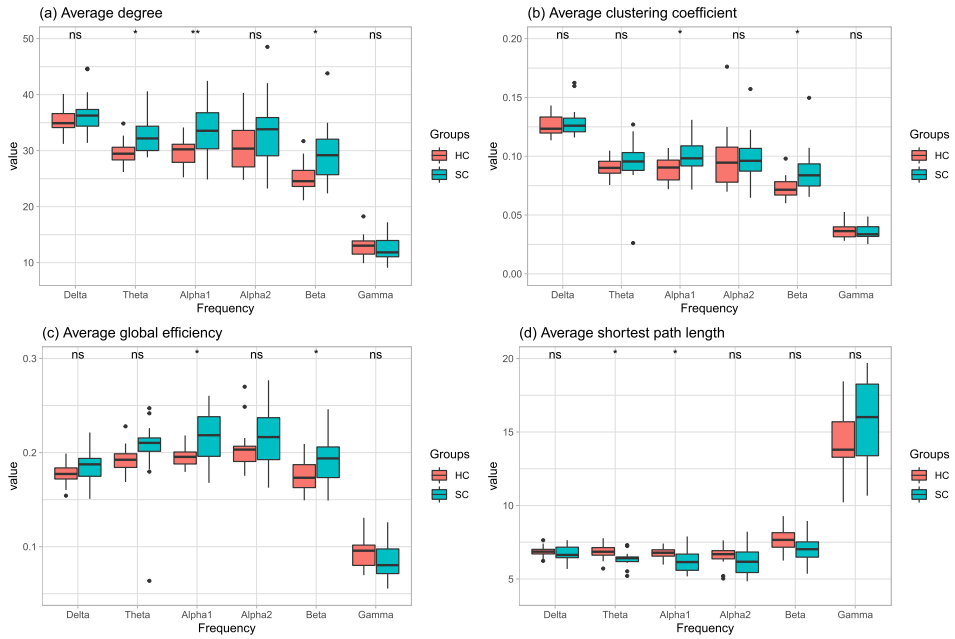

Fig. 1. The brain network topology parameters of schizophrenia patients and controls in the negative stimulus condition. In the figure, HC indicates the MEG signals of healthy controls, and SC represents the MEG signals of patients with schizophrenia. In the figure, ns indicates $p \geq 0.05$, * denotes $p < 0.05$, ** means $p < 0.01$, *** represents $p < 0.001$.

negative, neutral and gray cross) was performed. Subsequently, post hoc independent sample t-tests were used to explore the significant difference between patients and the controls under a single stimulus condition.

III. Experimental Results

A. Analysis of Topological Characteristics of the Functional Network

We analyzed the topological characteristics of the corresponding network of MEG signals among schizophrenia patients and controls under different stimulus conditions. The results of the two-factor ANOVA for the topological parameters of the brain network are shown in Table I. It is clear from Table I that the topological parameters differed according to group and that there was no interaction between the two factors (Group and Stimulus condition). We also found significant differences between the patient and control groups mainly in the theta, alpha 1 and beta bands. The results of the post hoc independent sample t-test within specific stimulus conditions were as follows.

The brain network topology parameters of schizophrenia patients and controls in the negative stimulus condition are shown in Fig. 1. In the theta, alpha 1, and beta frequency bands, the average node degree of the brain network of schizophrenia patients was significantly higher than that of the controls, while in the theta and alpha 1 frequency bands, the average shortest path length of the brain network of schizophrenia patients was significantly shorter than that of the controls. In addition, the average clustering coefficient and average global efficiency of the brain network in the alpha 1 and beta bands in schizophrenia patients were significantly higher than those in the controls.

TABLE I
The Results of the Two-Factor ANOVA for the Topological Parameters of the Brain Network

Parameters	Frequency Band	Group	Stimulus	Group & Stimulus
Average node degree	Delta	p=0.090	p=0.525	p=0.562
	Theta	p<0.001*	p=0.999	p=0.994
	Alpha 1	p<0.001*	p=0.987	p=0.989
	Alpha 2	p=0.280	p=1.000	p=0.998
	Beta	p<0.001*	p=1.000	p=0.994
	Gamma	p=0.161	p=0.992	p=0.984
Average clustering coefficient	Delta	p=0.056	p=0.439	p=0.453
	Theta	p=0.007*	p=0.925	p=0.962
	Alpha 1	p<0.001*	p=0.975	p=0.971
	Alpha 2	p=0.822	p=1.000	p=0.993
	Beta	p<0.001*	p=0.999	p=0.995
	Gamma	p=0.344	p=0.982	p=0.953
Average global efficiency	Delta	p=0.003*	p=0.692	p=0.806
	Theta	p=0.001*	p=0.931	p=0.931
	Alpha 1	p<0.001*	p=0.996	p=0.994
	Alpha 2	p=0.070	p=0.999	p=0.999
	Beta	p=0.001*	p=0.999	p=0.991
	Gamma	p=0.059	p=0.987	p=0.982
Average shortest path length	Delta	p=0.020*	p=0.293	p=0.444
	Theta	p=0.493	p=0.652	p=0.672
	Alpha 1	p<0.001*	p=0.974	p=0.986
	Alpha 2	p=0.174	p=1.000	p=0.999
	Beta	p=0.003*	p=0.998	p=0.992
	Gamma	p=0.056	p=0.955	p=0.959

* denotes that there is a significant difference.

The results of the brain network topology parameters of schizophrenia patients and controls in the positive stimulus condition are shown in Fig. 2. The average node degree of the brain network in the theta, alpha 1 and beta bands of schizophrenia patients was significantly higher than that of the controls. In addition, the average clustering coefficient and average global efficiency of the brain network in

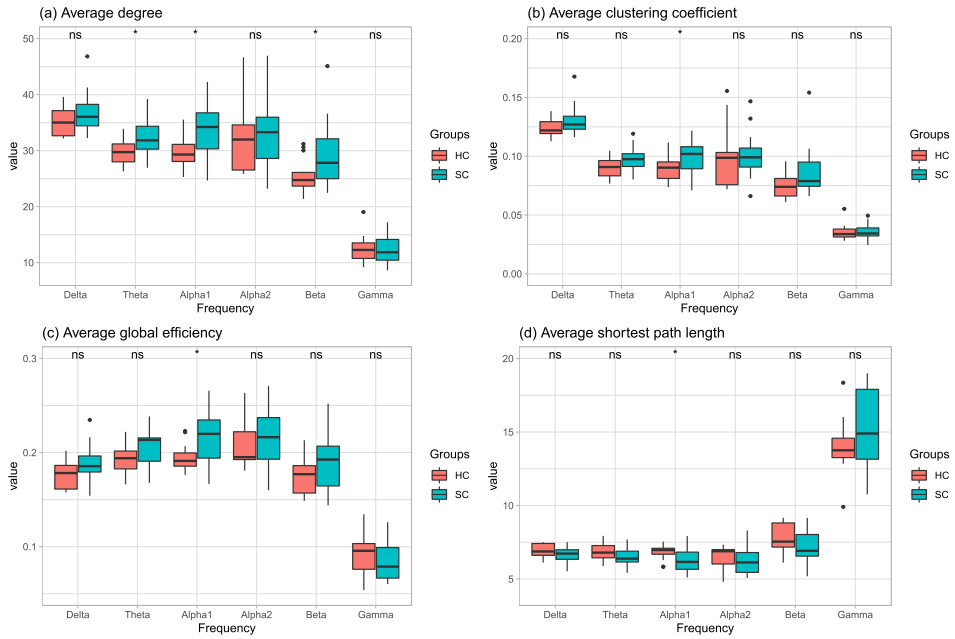

Fig. 2. The brain network topology parameters of schizophrenia patients and controls in the positive stimulus condition. In the figure, HC indicates the MEG signals of healthy controls, and SC represents the MEG signals of patients with schizophrenia. In the figure, ns indicates $p \geq 0.05$, * denotes $p < 0.05$, ** means $p < 0.01$, *** represents $p < 0.001$.

the alpha 1 frequency band in schizophrenia patients were significantly higher than those in controls, but the average shortest path length of the brain network in schizophrenia patients was significantly lower than that in controls at this frequency band.

The results of the topological parameters of the brain networks of patients with schizophrenia and the controls in the neutral stimulus condition are shown in Fig. 3. First, in the neutral stimulus condition, the average node degree of the brain network in the theta, alpha 1, and beta bands was significantly higher in patients with schizophrenia than that in controls. Second, in the alpha 1 and beta bands, the average clustering coefficients of brain networks in schizophrenia patients were significantly higher than those in controls. Third, the average global efficiency of the brain network in the theta and alpha 1 bands was significantly higher in schizophrenia patients than that in the controls, but the average shortest path length of the brain network in schizophrenia patients was significantly shorter than that in controls in these two frequency bands.

Fig. 4 shows the results of the topological parameters of the brain network in schizophrenia patients and controls in the gray-cross stimulus condition. First, in the gray-cross stimulus condition, the average node degree of the brain network in the theta, alpha 1, and beta bands was significantly higher in schizophrenia patients than that in the control group. In addition, the average clustering coefficient and average global efficiency in the theta and alpha 1 bands of the brain network in schizophrenia patients were significantly higher than those of participants in the control group. Third, the average shortest path length in the alpha 1 band of the brain network in schizophrenia patients was significantly shorter than that of participants in the control group.

For the four different stimulus conditions, significant differences in topological brain network characteristics between schizophrenia patients and controls mainly occurred in the theta, alpha 1 and beta bands. In these three frequency bands, a significant difference in the average node degree was observed under the four different stimulus conditions. Therefore, the stimulus condition had little effect on the importance of the corresponding functional network nodes of MEG data in patients with schizophrenia. For the average clustering coefficient, the significant difference between schizophrenia patients and controls varied according to stimulus condition. The difference in the average clustering coefficient between the two groups of participants mainly appeared in the alpha 1 and beta bands under negative and neutral stimulus conditions. When gray-cross stimuli were presented, there was a significant difference in the theta and alpha 1 frequency bands, while under the positive stimulus condition, there was a significant difference in only the alpha 1 band. For the average global efficiency, there was a significant difference between the two groups in the alpha 1 and beta bands under the negative stimulus condition. In the neutral and gray-cross stimulus conditions, the significant difference between the two groups of participants mainly appeared in the theta and alpha 1 bands, but there was a significant difference in only the alpha 1 band under the positive stimulus condition. For the average shortest path length, there were significant group differences in the theta and alpha 1 bands under the negative and neutral stimulus conditions, while there were significant differences in only the alpha 1 frequency band under the positive and gray-cross stimulus conditions. The above analysis of the brain network topology characteristics of schizophrenia patients and controls under different stimulus conditions demonstrated that negative stimuli mainly affect the network topology characteristics in

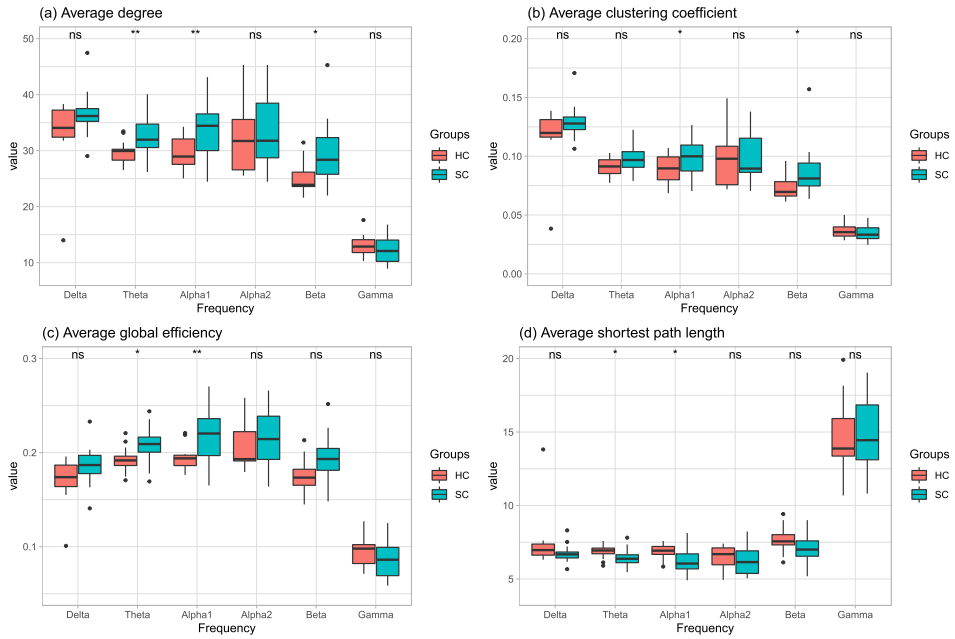

Fig. 3. The topological parameters of the brain networks of patients with schizophrenia and the controls in the neutral stimulus condition. In the figure, HC indicates the MEG signals of healthy controls, and SC represents the MEG signals of patients with schizophrenia. In the figure, ns indicates $p \geq 0.05$, * denotes $p < 0.05$, ** means $p < 0.01$, *** represents $p < 0.001$.

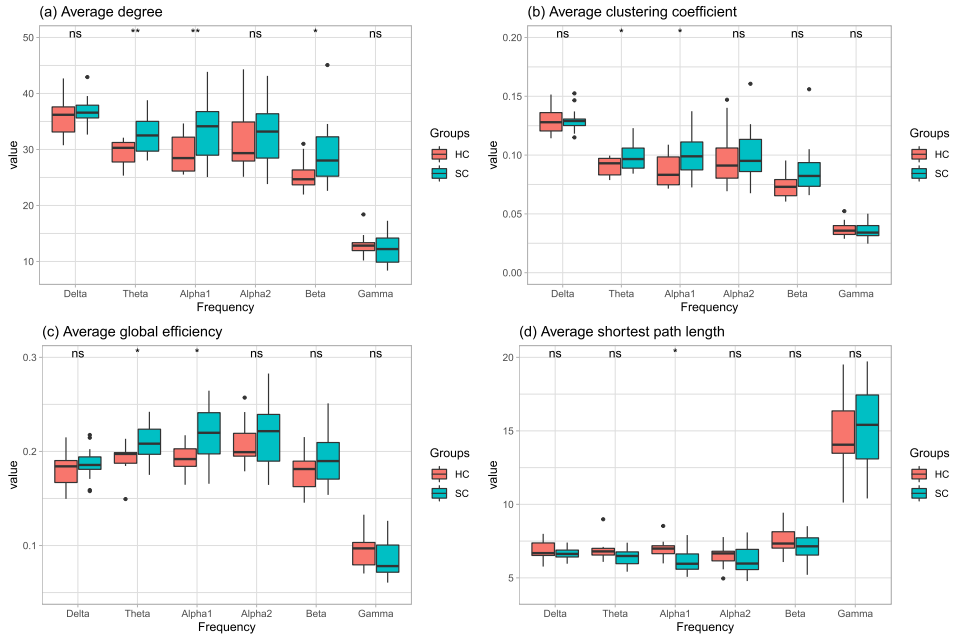

Fig. 4. The topological parameters of the brain network in schizophrenia patients and controls in the gray-cross stimulus condition. In the figure, HC indicates the MEG signals of healthy controls, and SC represents the MEG signals of patients with schizophrenia. In the figure, ns indicates $p \geq 0.05$, * denotes $p < 0.05$, ** means $p < 0.01$, *** represents $p < 0.001$.

the alpha 1 and beta bands of schizophrenia patients, and positive stimuli mainly affect the brain network topology in the alpha 1 band of patients with schizophrenia. The influence of neutral stimuli and gray-cross stimuli on the topological characteristics of the brain network mainly appeared in the theta and alpha 1 bands in schizophrenia patients.

B. Analysis of the Dynamic Coupling Strength Among MEG Frequency Bands

The dynamic coupling among different MEG frequency bands was analyzed in schizophrenia patients and controls under different stimulus conditions. A two-factor ANOVA with group (patients with schizophrenia and controls) and stimulus condition (positive, negative, neutral and gray cross) was performed. The results of the two-factor ANOVA for dynamic coupling strength are shown in Table II. It is clear from Table I that there was no interaction between the two factors (Group and Stimulus condition). Table II also shows that the difference in dynamic coupling strength between the two groups mainly appeared in three frequency pairs (the theta-alpha 1, theta-gamma and delta-gamma pairs). The results of the post hoc independent sample t-tests in each

TABLE II
THE RESULTS OF TWO-FACTOR ANOVA FOR DYNAMIC COUPLING STRENGTH

Frequency pair	Group	Stimulus	Group & Stimulus
Delta-Theta	p=0.497	p=0.385	p=0.809
Delta-Alpha 1	p=0.850	p=0.352	p=0.804
Delta-Alpha 2	p=0.742	p=0.390	p=0.843
Delta-Beta	p=0.621	p=0.664	p=0.962
Delta-Gamma	p=0.043*	p=0.315	p=0.759
Theta-Alpha 1	p=0.005*	p=0.972	p=0.558
Theta-Alpha 2	p=0.221	p=0.997	p=0.742
Theta-beta	p=0.455	p=0.892	p=0.936
Theta-Gamma	p<0.001*	p=0.987	p=0.727
Alpha 1-Alpha 2	p=0.232	p=0.957	p=0.992
Alpha 1-Beta	p=0.056	p=0.850	p=0.900
Alpha 1-Gamma	p=0.055	p=0.979	p=0.977
Alpha 2-Beta	p=0.153	p=0.881	p=0.923
Alpha 2-Gamma	p=0.395	p=0.984	p=0.995
Beta-Gamma	p=0.486	p=0.914	p=0.952

* denotes that there is a significant difference.

stimulus condition were as follows. The coupling between different pairs of MEG frequency bands in schizophrenia patients and controls under different stimulus conditions are shown in Fig. 5.

Under the negative stimulus condition, the coupling between the theta and gamma bands (highlighted in Fig. 5(a)) in schizophrenia patients was significantly stronger than that in the controls. The results of the statistical analysis are shown in Fig. 6.

Fig. 5(b) clearly shows that under the positive stimulus condition, the coupling strength between the alpha 1 wave and theta wave, between the delta wave and gamma wave, and between the theta wave and gamma wave of the MEG signals (links highlighted in Fig. 5(b)) was significantly greater in patients with schizophrenia than in controls. The statistical analysis results are shown in Fig. 7. The results revealed that the coupling strength between the theta wave and gamma wave of the MEG signals significantly differed between schizophrenia patients and controls ($p = 0.001$).

As shown in Fig. 5(c), there were no significant differences in the coupling strength of different MEG frequency band pairs between schizophrenia patients and the controls under the neutral stimulus condition.

As clearly seen in Fig. 5(d), under the gray-cross stimulus condition, the coupling strengths between the alpha 1 wave and the theta wave as well as between the theta wave and the gamma wave (the links highlighted in Fig. 5(d)) in schizophrenia patients were significantly higher than those in controls. The statistical analysis results are shown in Fig. 8. Statistical analysis revealed that the greatest difference in the dynamic coupling strength between schizophrenia patients and the controls occurred in the theta-gamma pair ($p = 0.00063$).

Under the four different stimulus conditions, the dynamic coupling strength between the different MEG frequency bands of schizophrenia patients and the controls varied. The post hoc independent sample t-tests revealed significant differences in the coupling intensity of the different frequency band pairs in schizophrenia patients and controls for three pairs in the positive stimulus condition, two pairs in the gray-cross stimulus condition, and one pair in the negative stimulus condition. There were no significant group differences under the neutral stimulus condition.

IV. DISCUSSION

Compared with other methods of quantifying the coupling of time-series data [47], [64], mutual information was simple to acquire, easy to implement and could be used in quick calculations, which enabled better exploration of the coupling between two time series. Therefore, we used mutual information as a link indicator to construct a functional network. Besides, we also tried to estimate the functional connectivity network of MEG in schizophrenia patients using coherence and phase lag index, but the topological parameters of the functional connectivity network constructed by these two indices were hardly significantly different between the patients and controls on our dataset. This is because MEG has strong nonlinear properties, but the coherence describes the linear correlation in the frequency domain of the MEG signal, and can't explore the nonlinear correlation in the MEG signal [47], [64]. In addition, the phase lag index is sensitive to noise, and the noise signal in the MEG signal that is not processed cleanly will enhance the phase synchronization of the MEG signal leading to false connections [65].

Our study is the first to explore the nonlinear coupling between different pairs of MEG frequency bands in schizophrenia patients. The MEG acquisition equipment we used had 275 channels, so the MEG signals we collected consisted of 275 time series, which is equivalent to a 275-dimension time series. Because of the high dimensionality of the MEG data, the general algorithm describing the coupling between time-series data was not appropriate for exploring the dynamic network between different frequency bands of MEG signals in schizophrenia patients. Therefore, we utilized the nonlinear multidimensional cross-recurrence quantification analysis method to measure the dynamic coupling between the different pairs of frequency bands of MEG signals in schizophrenia patients. Multidimensional cross-recurrence quantification analysis directly calculates the nonlinear dynamic coupling between multidimensional time-series data. With this approach, it is not necessary to transform multidimensional time-series data into one-dimensional time-series data before calculating the nonlinear coupling between the two time series. Therefore, this approach is highly suitable for analyzing the MEG signals of patients with schizophrenia.

The results of the topological features of the functional network in schizophrenia patients and controls under four different stimulus conditions suggest that, compared to controls, schizophrenia patients have a higher speed of information transmission in the brain network and a more complex network structure. In other words, small changes in specific units of the brain network of patients with schizophrenia result in larger changes in the function of the entire brain network [5], [18], [23]. The presence of abnormal functional connectivity and structural abnormalities in the brain of schizophrenia patients may be the mechanisms underlying the above results. Regarding abnormal functional connectivity, previous

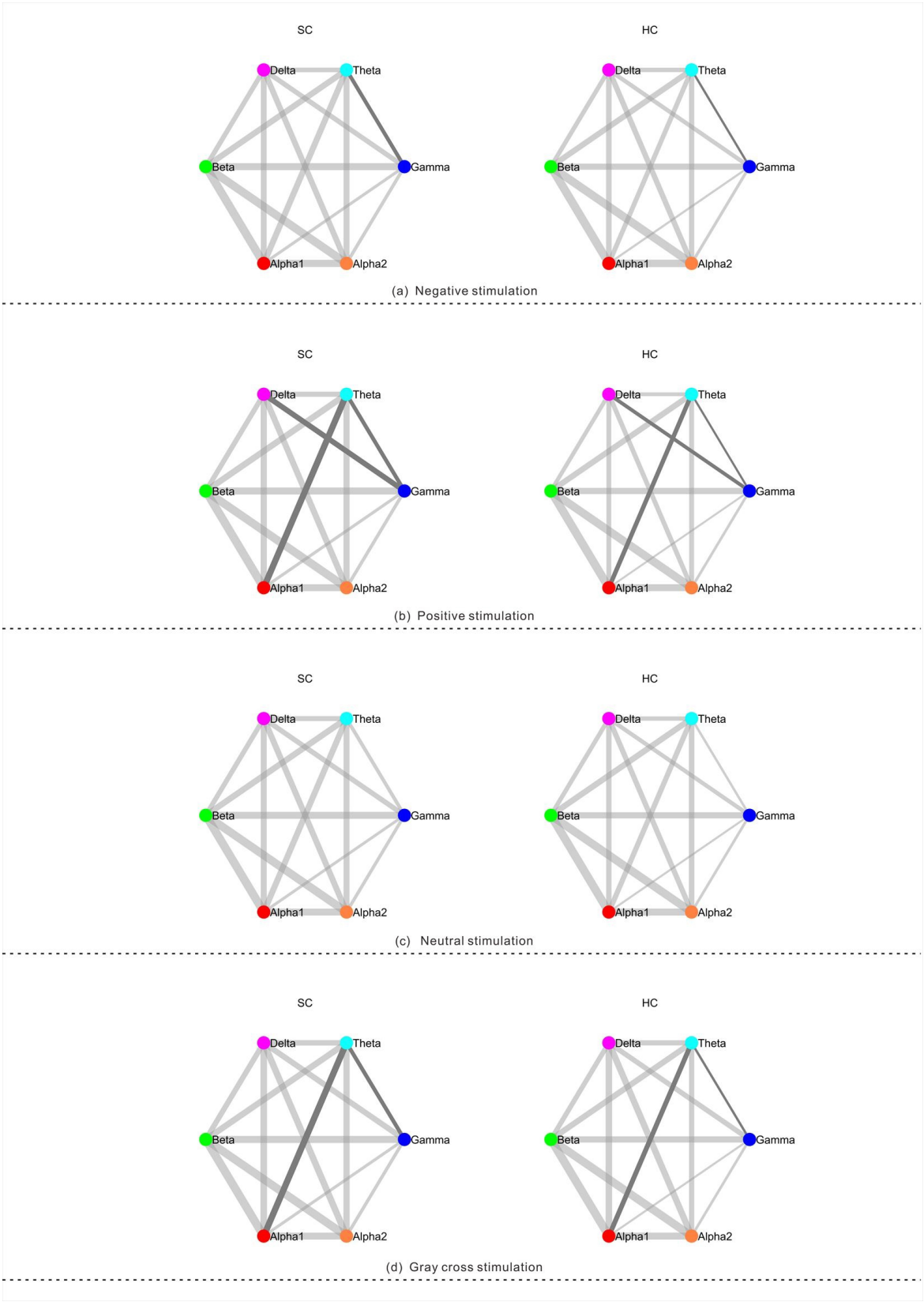

Fig. 5. The dynamic coupling among different MEG frequency bands in schizophrenia patients and controls under different stimulus conditions. The colored nodes in the figure represent MEG signals of different frequency bands, and the width of the connection indicates the coupling strength. The links highlighted in the figure represent those with statistically significant differences. HC indicates the MEG signals of healthy controls, and SC represents the MEG signals of patients with schizophrenia.

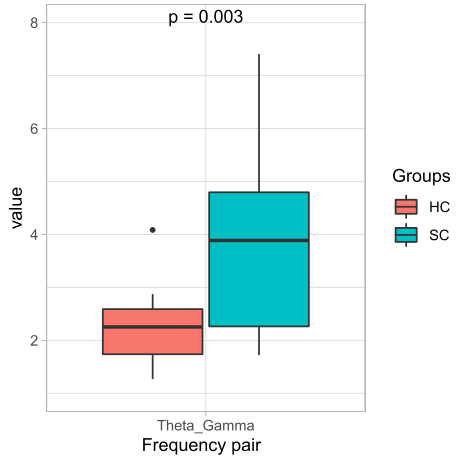

Fig. 6. Statistical analysis of the theta wave and gamma wave link strengths of MEG signals in patients with schizophrenia and controls under the negative stimulus condition. HC indicates the MEG signals of healthy controls, and SC represents the MEG signals of patients with schizophrenia.

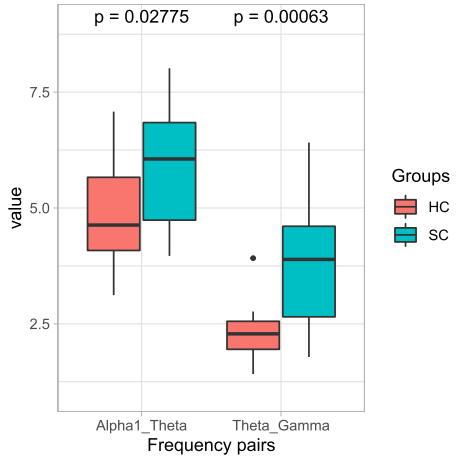

Fig. 8. Statistical analysis of link intensities between the alpha 1 wave and theta wave and between the theta wave and gamma wave in patients with schizophrenia and controls under gray cross stimulus condition. HC indicates the MEG signals of healthy controls, and SC represents the MEG signals of patients with schizophrenia.

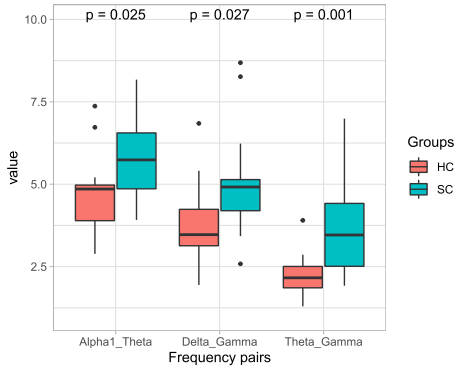

Fig. 7. Statistical analysis of the link intensity of alpha 1 and theta waves, delta and gamma waves, and theta and gamma waves in patients with schizophrenia and controls under the positive stimulus condition. HC indicates the MEG signals of healthy controls, and SC represents the MEG signals of patients with schizophrenia.

studies have proven that glutamatergic N-methyl-D-aspartate (NMDA) receptor function is abnormal in schizophrenia patients, impairing the feedback loop that regulates neuronal activity and leading to abnormal firing of neurons in the brain of schizophrenia patients, resulting in a disruption of the excitatory-inhibitory balance of nerve cells [66], [67], [68]. The change in the excitatory-inhibitory balance leads to desynchronization of the nervous system, which leads to the abnormal connectivity of the brain observed in schizophrenia patients [69], [70]. Due to the abnormal connections among neurons in the brains of patients with schizophrenia [46], [48], [49], [50], the whole-brain networks of these patients undergo large changes in performance [71]. Regarding structural abnormalities, studies have demonstrated abnormalities in the white and gray matter of the brain in schizophrenia patients, leading to changes in brain activity [72], [73], [74]. Overall, these changes result in increased complexity and disorder of the entire nervous system in schizophrenia patients, leading to clinical symptoms. These changes may be the main reason for the onset of schizophrenia.

The strength of dynamic coupling between different MEG frequency bands in schizophrenia patients and the controls differed under different stimulus conditions. We found that positive stimuli influenced the coupling strength between three different pairs of MEG frequency bands (theta-alpha 1, theta-gamma and delta-gamma) in schizophrenia patients. However, neutral stimuli had almost no effect on the link between the different pairs of MEG frequency bands in patients with schizophrenia. Thus, positive stimuli resulted in prominent brain activity differences in schizophrenia patients. Similar results were found in previous studies. Aydin et al. [75] had shown that positive stimulation induces higher activation of the cerebral cortex. Hempel et al. [13] found that schizophrenia patients had increased activation of physiological activities when viewing positive emotional stimuli. Martin et al. [76] demonstrated that the activity in the gamma band of schizophrenia patients was significantly increased by positive stimuli. Martin also revealed that the LPP of schizophrenia patients significantly increased in the positive stimulus condition [16], [17]. The above findings suggest that the changes in brain features are greater in schizophrenia patients than in controls under the positive stimulus condition; these differences may be a potential biomarker for schizophrenia. Therefore, we speculate that in the early diagnosis of schizophrenia, using positive stimuli may facilitate the identification of patients with schizophrenia in the early stages. This early identification may improve clinical interventions and thereby reduce the incidence of the disease.

This paper investigated the topological characteristics of the brain network of patients with schizophrenia and the dynamic coupling between different MEG frequency bands. Although this study provided a more comprehensive perspective for the study of brain signals in schizophrenia, there were still some limitations. First and most importantly, this study had a small sample size, the conclusions of this study need to

be further validated on a larger sample dataset. Second, the functional network of patients with schizophrenia remained at the sensor level, not at the source-space level. Finally, we assessed only the dynamic coupling strength between pairs of MEG frequency bands; thus, the causal relationship of this coupling was not assessed. Therefore, our future studies will focus on the functional brain network of patients with schizophrenia and the causality of the MEG frequency band coupling in source space.

V. Conclusion

This study explored the functional networks of MEG signals in six different frequency bands under four different stimulation conditions at the sensor level in schizophrenia patients. We are the first to explore the dynamic coupling between pairs of MEG frequency bands in schizophrenia patients under four different stimulus conditions. In particular, the nonlinear dynamic coupling between MEG frequency bands of schizophrenia patients provides a new direction for schizophrenia research. Our approach revealed important information about the brain activity of schizophrenia patients. Abnormal network feature information in MEG data of schizophrenia patients can be used as a marker for the diagnosis of schizophrenia and may be able to successfully distinguish schizophrenia patients from controls. Our results have practical applications to enhance patient diagnosis and expand schizophrenia research.

Conflict of Interest

All authors have no conflicting interests with each other.

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