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Research article

Depression-induced changes in directed functional brain networks: A source-space resting-state EEG study

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Abstract: Current research confirms abnormalities in resting-state electroencephalogram (EEG) power and functional connectivity (FC) patterns in specific brain regions of individuals with depression. To study changes in the flow of information between cortical regions of the brain in patients with depression, we used 64-channel EEG to record neural oscillatory activity in 68 relevant cortical regions in 22 depressed patients and 22 healthy adolescents using source-space EEG. The direction and strength of information flow between brain regions was investigated using directional phase transfer entropy (PTE). Compared to healthy controls, we observed an increased intensity of PTE information flow between the left and right hemispheres in the theta and alpha frequency bands in depressed subjects. The intensity of information flow between anterior and posterior regions within each hemisphere was reduced. Significant differences were found in the left supramarginal gyrus, right delta in the theta frequency band and bilateral lateral occipital lobe, and paracentral gyrus and parahippocampal gyrus in the alpha frequency band. The accuracy of cross-classification of directed PTE values with significant differences between groups was 91%. These findings suggest that altered information flow in the brains of depressed patients is related to the pathogenesis of depression, providing insights for patient identification and pathological studies.

Keywords: depression; electroencephalogram; directed connectivity; depressive symptoms

1. Introduction

Depression is a serious mental health problem that can be very harmful to individuals and society. Depression can seriously affect the emotional and psychological state of patients, causing them to feel sad, hopeless, and disinterested for long periods of time. This persistent low mood can cause a person to lose enthusiasm and motivation for life, affecting work, school and relationships. The World Health Organization (WHO) [1] highlights that depression is one of the most common mental illnesses in the world, with approximately 340 million people worldwide suffering from depression. This means that about one in 20 people are affected by depression. Early and accurate diagnosis and timely and effective treatment are essential to minimizing the harm caused by depression.

The treatment of depression continues to pose challenges despite years of development. Antidepressant drugs exert their therapeutic effects by modulating the interaction of neurotransmitter systems across multiple brain regions. Different types of antidepressants use different principles and mechanisms to treat depression. Healthy subjects receiving venlafaxine showed a decrease in theta-band rhythms in the midline-and-right-frontal (MRF) region at 48 hours and at 1 week after randomization [2]. Selective serotonin reuptake inhibitors may restore abnormal brain activity in the inferior frontal cortex of patients [3]. However, successive empirical attempts to identify initial resistance to antidepressant treatment can complicate clinical drug therapy progressively [4]. Thus, the exact medication regimen to be used needs to be carefully considered.

Like medication, transcranial magnetic stimulation (TMS) is a commonly used clinical treatment for depression. TMS is a non-invasive technique that utilizes a magnetic field to induce electrical currents that stimulate specific areas of the brain under an applied coil. Noda et al. used TMS to repetitively stimulate the right prefrontal cortex of depressed patients. This resulted in rapid modulation of EEG activity in depressed patients [5]. Hutton et al. found that stimulation of the left dorsolateral prefrontal lobe of the brain using high-frequency TMS was effective in alleviating depressive symptoms [6]. They concluded that different TMS stimulation programs have different therapeutic effects on depressed patients. Therefore, studying the functional abnormalities of brain regions in patients with depression is crucial for the development and improvement of clinical treatment programs. Neuroimaging techniques are widely used in depression research. Electroencephalography and functional magnetic resonance imaging (fMRI) techniques have been shown to be effective and reliable in studying functional brain abnormalities in patients.

Functional connectivity is the statistical correlation between different regions within the brain, which reflects the functional collaboration and communication between brain regions. Changes in functional connectivity may indicate the neurobiological basis of disease and can serve as a biomarker for diagnosis and assessment of therapeutic efficacy. Naho et al. [7] found that antidepressants had a heterogeneous effect on the identified FCs of 25 melancholic MDDs. They suggested that regions with abnormal functional connectivity such as the left dorsolateral prefrontal cortex, inferior frontal gyrus, and others could be targets for future optimization of depression treatment regimens. Hui et al. [8] found that mindfulness-based cognitive therapy strengthened functional connections between the amygdala and middle frontal gyrus, and this increase in communication correlated with improvements in clinical symptoms.

Effective connectivity is one of the common EEG indicators of functional networks. It describes

the causal relationships between different brain regions and the way information is transmitted and interacts in the brain [9]. By inferring the directionality and strength of information transfer, researchers can construct a more accurate brain connectivity map that reveals the functional connectivity patterns between different brain regions. For instance, Alena et al. utilized partial directed coherence (PDC) to evaluate the overall efficiency of the entire brain and graph-theoretic metrics of specific structures, identifying the significant role of the amygdala in depression [10]. In another study, Olejarczyk et al. employed direct transfer function (DTF) to assess the therapeutic effects of transcranial magnetic stimulation and determine the most suitable stimulation protocol [11].

However, the prediction models based on PDC and DTF have certain limitations and lack flexibility in capturing the frequency domain characteristics of nonlinear systems. These models are applicable to lengthy low-latitude data series. Otherwise, the problem of data interference and dimension explosion will occur. Thus, it is difficult to handle multivariate systems like EEG signals.

PTE is an information-theoretic method that provides insights into the direction of information transfer, indicating which variable exerts a greater influence on another variable [12]. This is crucial for understanding causality and information flow within complex systems. Unlike other methods, PTE can detect nonlinear causality and information transfer without relying on a specific model of the input data. It is particularly well-suited for estimating directional connectivity in brain networks based on phase information. In the context of resting-state functional networks, the directional changes in preferred information flow between sources can be effectively studied using directional phase transfer entropy (dPTE) [13]. As a result, PTE offers significant advantages in analyzing information flow within brain networks and resting-state functional networks. It not only indicates the strength of connectivity between brain regions in the same way as conventional functional connectivity metrics, but also indicates the directionality of that connectivity in the same way as the PDC predictive model.

We used standard low-resolution electromagnetic tomography (sLORETA) [14] to calculate current density distributions in various regions of the brain. In this way, an adaptive spatial model of the scalp source was constructed. EEG signals based on lead orientation can be converted to anatomically based time series so that the time series correspond to the scalp spatial model signal sources. Compared to the lead position method, the signal source localization method is more suitable for brain partitioning. This makes the processed data more interpretable.

We also calculated the partial transfer entropy (PTE) index between each pair of time series and considered not only the strength of functional connectivity, but also the ability to determine the specific direction of information flow. dPTE requires no input model data and is well suited to estimating the connectivity of large-scale human brain networks. Statistical analyses of dPTE feature matrices of different dimensions were performed for depressed and healthy individuals. We analyzed depression EEG in different frequency bands, lobes, brain regions with abnormal connectivity and characteristics of information flow between brain regions. These findings can provide excellent support and a reliable basis for the implementation of clinical treatment protocols for depression.

The organization of the paper is as follows: In the second section, we describe our research methodology and experimental design as well as demographic data statistics of the subjects. In the third section, we present the results of the experiment, including the statistical analysis of the data and the analysis of the indicators. In the fourth section, we provide an in-depth discussion of these results, explore their additions to the literature and their implications at the theoretical and applied levels,

summarize our major findings, and propose directions for future research.

2. Materials and methods

2.1. Environment and participants

We recruited 22 depressed adolescents and 22 healthy adolescents, and the difference in age between the two groups was not statistically significant ($p>0.05$). The subjects were right-handed, with normal or corrected vision, no history of mental illness, drug addiction, or alcoholism, and were all tested and diagnosed by a professional doctor using the Hamilton Depression Scale in a hospital in Changzhou City. Normal subjects had HAMD scores around 3, while depressed subjects had scores as high as around 20.

Before the experiment, all were informed of the details of the experiment and signed an informed consent form with the subjects and their guardians to participate in this experiment voluntarily. EEG signals were collected from subjects in the resting state with eyes open for 5 minutes and eyes closed for 5 minutes. The experimental environment was quiet, had a comfortable temperature, there was no noise and visual interference, and the subjects were asked to sit still and stay awake, avoiding large movements as much as possible.

Table 1. Demographic and clinical data for patients with depression and controls groups.

Variables	Healthy group	Depressed patients	P-value
Sex ratio , male/female	11/11	12/10	NA
Age (years)	16.25±1.4	16.17±0.96	0.91
Education(years)	9.2±1.52	9±1.71	0.54
Observer-rated depression scale (HAMD-17)	3.2±1.64	20.3±4.7	< 0.001
Handedness (left/right)	0/22	0/22	NA

The Mann-Whitney U test was used for age, age at education, and HAME scale scores.

2.2. Acquisition system and settings

EEG data acquisition was performed using a 64-lead EEG acquisition system from EGI with Net Station software, with the electrode position distribution based on the 10-10 international standard, the reference electrode being the Cz electrode, the sampling frequency being 500 Hz, and the upper limit of the electrode impedance being set to 50 kΩ.

2.3. EEG data preprocessing

The raw data collected were processed to make it compatible with MATLAB software by converting it into a raw format using Net Station software. Subsequently, the data underwent

preprocessing using the EEGLAB toolbox (version 2022), following these specific steps: band-pass filtering from 0.5 Hz to 45 Hz, reconversion of the reference point to an average reference, removal of artifacts such as blinks and head movements using independent component analysis (ICA), and replacement of bad leads with signal drift by averaging the data overlay with neighboring leads. Finally, a 3-minute clean data segment was selected for further analysis.

2.4. EEG analysis

2.4.1. Source estimation

We employed a rigorous approach to map cortical current source density (CSD) utilizing a distributed model comprising 15,000 current dipoles. The spatial distribution and orientations of these dipoles were determined based on cortical regions defined in the brain neurological institute (MNI) standard brain model [15]. To ensure compatibility with the sensor network's geometry, the MNI model was suitably adapted. The cortical model for EEG analysis was generated using the openMEEG boundary element method [16], which calculated a source space model of the cortical surface in a block-by-block fashion. In order to mitigate the impact of slow bias in the data, the noise covariance was diligently computed.

The standard MNLS solution is given by the following equation:

$$\mathrm{j} = \arg\min \| \mathrm{m} - \mathrm{Lj} \| + \lambda \| \mathrm{j} \| = \mathrm{Tm} \text{ with } \mathrm{T} = \mathrm{L}^{\mathrm{T}}[\mathrm{LL}^{\mathrm{T}} + \lambda 1]^{\dagger} \tag{1}$$

where j is the unknown current density vector, m is the measured data vector, L is the leading field matrix, † denotes the Moore-Penrose pseudo-inverse matrix, and 1 is the unit matrix.

In the Bayesian view, the potential variance $\mathrm{S_m}$ is a function of the noise variance $\mathrm{S_{m,\ noise}} = \lambda 1$ and the prior source variance $\mathrm{S_{j,prior}} = 1$:

$$\mathrm{S_m} = \mathrm{LS_{j,prior}L^T} + \mathrm{S_{m,\ noise}} = \mathrm{LL^T} + \lambda 1 \tag{2}$$

The variance $\mathrm{S_j}$ of the estimated current density j is given by the following equation:

$$\mathrm{S_j} = \mathrm{TS_m T^{T=} L^T}\left[\mathrm{LS_{j,prior}L^T} + \lambda 1\right]^{\dagger} \tag{3}$$

The sLORETA metric of the source location k is computed as based on its corresponding 3-dimensional subvector jk and the 3 × 3 block diagonal elements $\mathrm{S_{j,k}}$ of the covariance matrix $\mathrm{S_j}$:

$$\mathrm{j_k}^{\mathrm{T}}\left[\mathrm{S_{j,k}}\right]^{-1}\mathrm{j_k} \tag{4}$$

sLORETA can be written as a linear operator applied to the data vector m:

$$\left[\mathrm{S_{j,k}}\right]^{-0.5}\mathrm{j_k} = \left[\mathrm{S_{j,k}}\right]^{-0.5}\mathrm{T_k m} \tag{5}$$

where Tk denotes the row in T associated with k. The activation of 15,000 dipoles was computed from the EEG time series using a weighted minimum-paradigm estimator.

Finally, according to the Desikan-Killiany (DK) Brain Atlas [17], dipoles were categorized into 68 regions of interest (ROIs). The activity of each ROI was generated by averaging the CSDs of all voxels within that region. The 68 ROIs were further categorized into 14 regions based on their anatomical location on the cortex: LPF, RPF, LF, RF, LC, RC, LP, RP, LO, RO, LT, RT, LL, and RL.

2.4.2 Directed connectivity: directed phase transfer entropy

PTE is a transfer entropy of signal phase time series based on the transfer entropy (TE) principle, which is suitable to study information transfer in high-lead EEG signals.

TE is a metric that measures the transfer of information between stochastic processes. It is based on the comparison of conditional and joint probabilities and is used to describe the degree of causal influence of one random variable on another. Transfer entropy measures the flow of information from one random variable X to another random variable Y. The formula for transfer entropy is:

$$TE(X \to Y) = H(Y|Y') - H(Y|Y', X') \tag{6}$$

where H(Y|Y') is the conditional entropy of the Y value at the current moment given the Y value Y' at the past moment; H(Y|Y', X') is the conditional entropy of the Y value at the current moment given the Y value Y' and X value X' at the past moment. A positive transfer entropy indicates that X has a causal effect on Y, and a zero or negative entropy indicates that X has no causal effect on Y.

PTE estimates the strength of the causal relationship between two signals based on the instantaneous phase difference computed using the Hilbert transform and controls for possible causal effects of other signals. It is often used to assess causal relationships between a wider range of variables:

$$PTE(X \to Y) = I\left(\theta_y(t), \theta_x(t') \middle| \theta_y(t')\right) \tag{7}$$

where θx(t′) and θy(t′) are the past states of the instantaneous phase time series of X(t) and Y(t) at $t' = t - \delta t$, respectively. There is no specific upper limit on the PTE; thus, we normalize the PTE using the dPTE:

$$\mathrm{dPTE}_{x \to y} = PTE_{x \to y} / \left(PTE_{x \to y} + PTE_{y \to x}\right) \tag{8}$$

The value of dPTExy ranges from 0 to 1. For dPTExy>0.5, the signal flows preferentially from X to Y, and for dPTExy<0.5, the signal flows from Y to X. Subtracting 0.5 for all dPTExy, the information flow direction is defined in terms of positive and negative.

We apply dPTE to high-lead EEG and using dPTE in the 0.5-48 Hz frequency range to estimate the directional FC between all combinations of the corresponding source time series and extracting significant network connections using alignment tests. In order to ascertain the clear directionality of information flow between two regions of interest (ROIs), a nonparametric alignment test was employed. To validate the strength of the information flow, 5,000 random permutations were conducted for each dPTE value. This procedure determined whether the observed information flow was significantly different from zero. The null distribution was symmetrically generated around the mean of the null hypothesis. Subsequently, p-values were obtained for each state of consciousness, and these p-values were adjusted for multiple comparisons using the tmax method to effectively control

for family-wise error rates.

In this study, a second-order Butterworth bandpass filter was used to divide the signal into four frequency bands: delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (13-30 Hz). For each band, we split the backtracked time series into smaller windows (5 seconds long) to generate the dPTE matrix and average it.

2.5. Statistical analysis

To assess the differences between groups, Friedman's test was employed to determine the number of information flows exhibiting significant disparities across various brain regions. Regions of interest (ROIs) displaying significant differences between groups were further analyzed, and their corresponding directed Partial Transfer Entropy (dPTE) values were extracted as feature datasets for classification validation. To investigate the discriminative capacity of the depression detection indices under investigation, a SVM classifier was selected for 5-fold cross-validation. The performance of the classifier was evaluated based on criteria such as specificity, sensitivity, and accuracy.

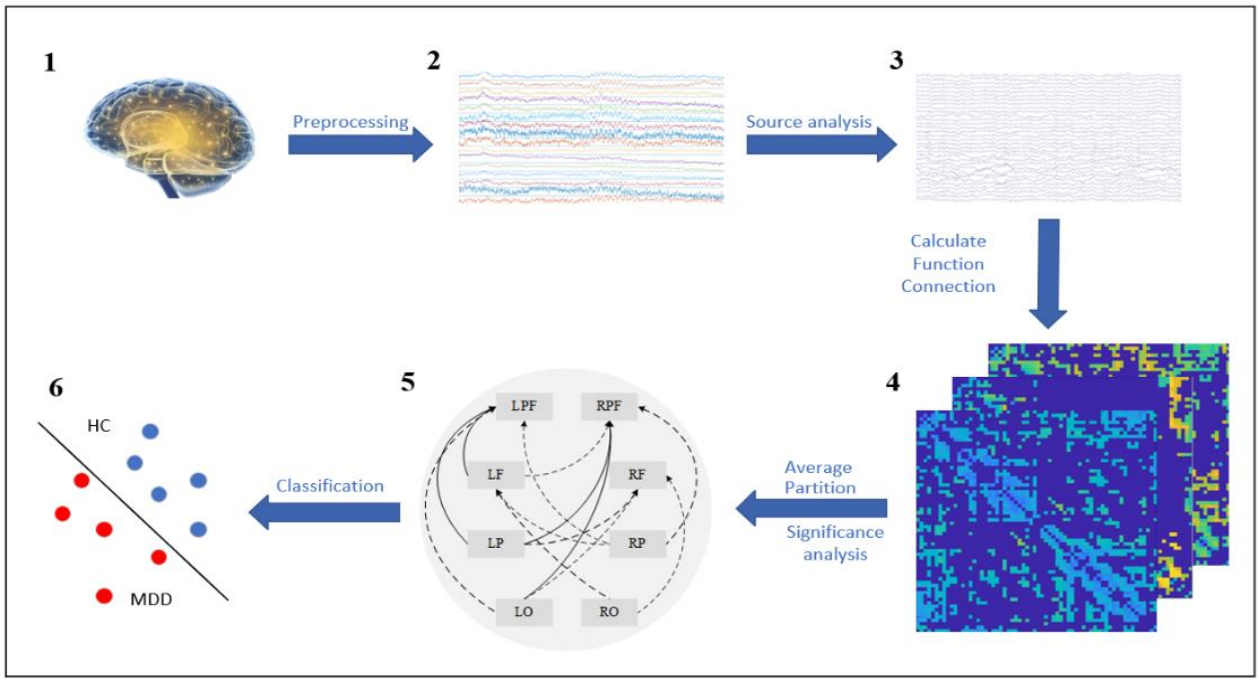

Figure 1. Flow chart of depression brain information flow analysis technique.

3. Results

The PTE data were subjected to normalization, resulting in a dPTE matrix with values ranging from 0 to 1. Since the distribution of dPTE values did not conform to a normal distribution, we use the nonparametric permutation test to confirm that the information flow between two ROIs has a clear directionality. The permutation test involved creating a dataset comprising information flow intensities from all subjects, followed by 5,000 random permutations to assess whether the information flow intensities significantly deviated from zero. The null distribution was symmetrically centered around

the mean of the null hypothesis. A p-value was obtained for each state of consciousness, and multiple corrections using the "tmax" method were applied to control for family-wise error rates.

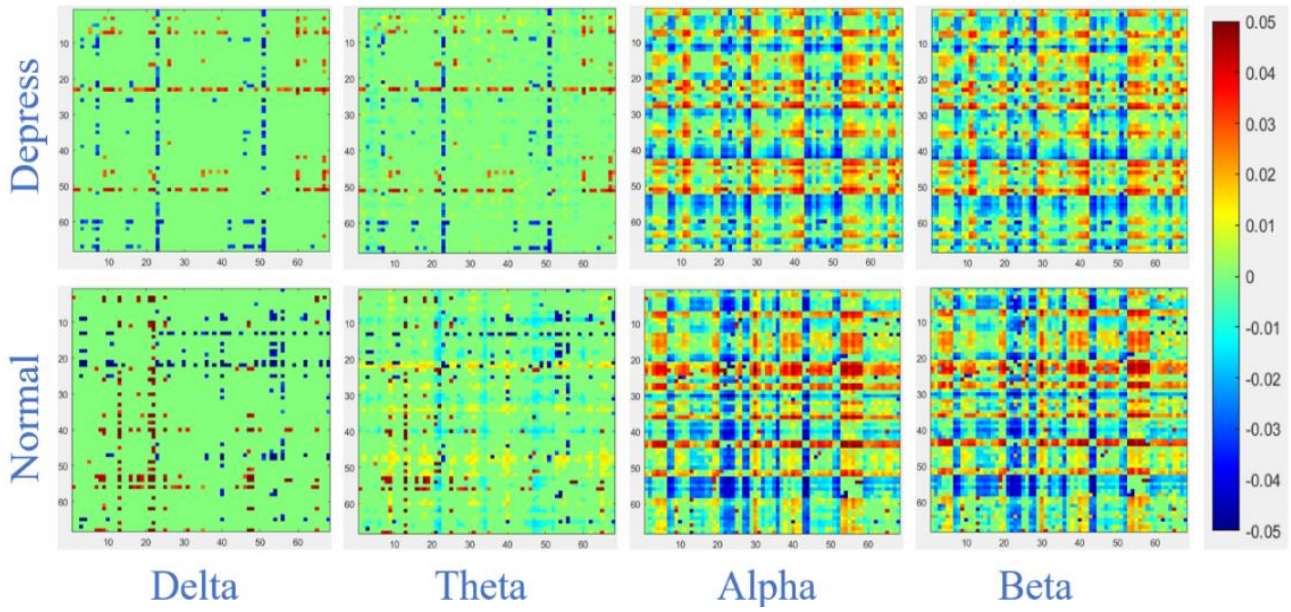

Figure 2. Significant directional connectivity matrices in four frequency bands for depressed patients and controls. The color blocks in the xth row and yth column of each connection matrix indicate the dPTE values of the xth ROI flowing to the yth ROI: dPTExy.

The $dPTE_{xy}$ value is between 0 and 1. When $0.5< dPTE_{xy} <1$, it means that the information flow is prioritized from x to y; When $0< dPTE_{xy} <0.5$, it means that the information flow is from y to x; When $dPTE_{xy}, = 0$ it indicates that the information flow between signal x and signal y is in equilibrium.

Among them, delta and theta frequency bands had less significant information flow, and alpha and beta significant information flow was more. Moreover, in all frequency bands, the intensity of information flow was higher in the healthy group of subjects than in the depressed group.

The 68 time series were reordered according to brain partitioning and a Friedman test was performed between groups. As shown in Figure 3, the between-group differences between the depressed and subject groups were concentrated in the theta and alpha bands, and the regions presenting differences were relatively concentrated. For this reason, the amount of information flow from each region to the other regions was counted. Brain regions were divided into LPF, RPF, LF, RF, LC, RC, LP, RP, LO, RO, LT, RT, LL, and RL according to the DK partitioning. The number of information streams generated by ROIs within each region was averaged after summation, and the results are shown in Figure 4.

Significant differences in brain connectivity were observed between the depressed and healthy groups. Specifically, these differences were found to be more prominent in the right hemisphere regions compared to the left hemisphere regions. The occipital regions exhibited greater disparities in connectivity compared to other brain regions. Notably, the differences in connectivity within the right central hook region were particularly pronounced in the alpha frequency band.

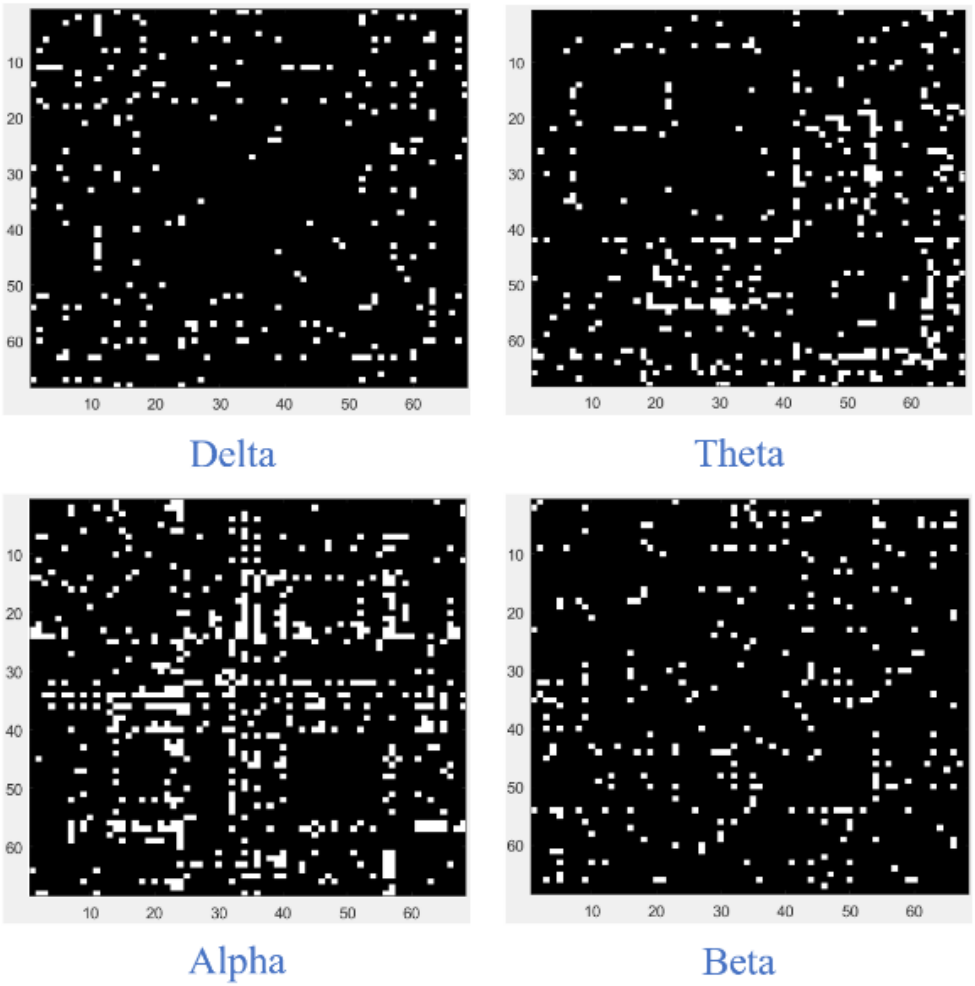

Figure 3. Results of Friedman's test between groups.

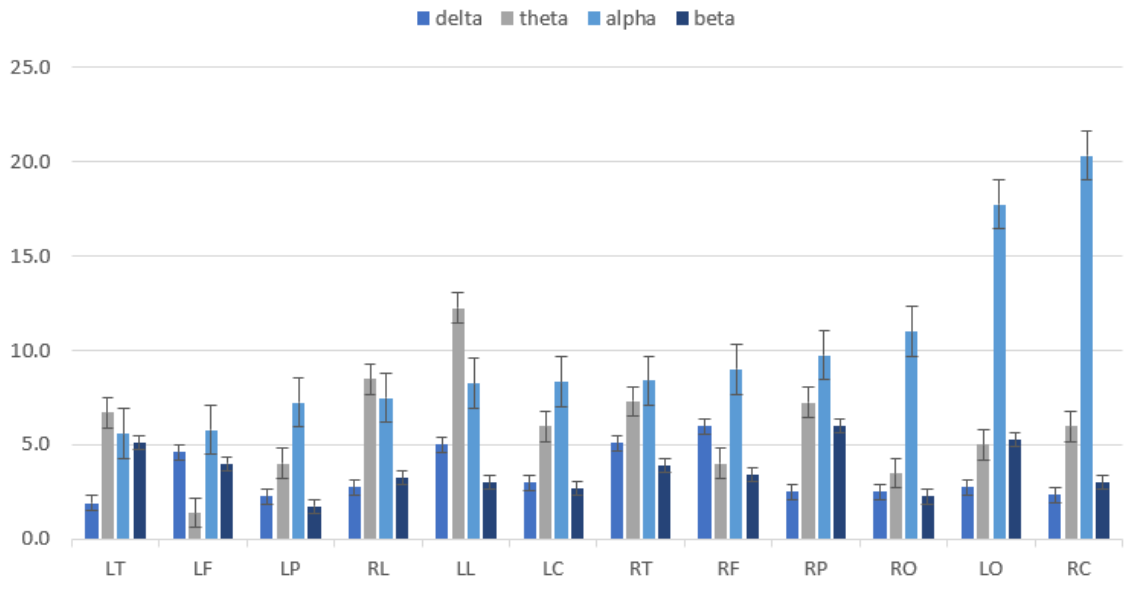

Figure 4. Number of information flows in brain regions.

There was a significant increase in information flow between the two halves of the brain in depressed subjects, but there is a lack of information flow between more distant brain regions. The brain regions corresponding to the DK template are shown in Table 2. Using the values of information flow with significant differences between alpha and theta in Figure 5 as a dataset, the model performance achieves 91% correctness using an SVM classifier with a five-fold cross-validation.

Table 2. Brain regions showing significant differences in information flow.

Delta	Theta	Alpha	Beta
LO 0.037*	LP 0.029*	RC 0.007**	LF 0.14*
cuneus	supramarginal	paracentral	caudal middle frontal
RPF 0.009**	RF 0.005**	RT 0.004**	RT 0.17*
frontal pole	Pars triangularis	parahippocampal	entorhinal
RT 0.025*	RL 0.036*	RO 0.004**	T 0.43*
entorhinal	rostral anterior cingulate	Lateral occipital	middle temporal
LT 0.046*		LF 0.028*	LT 0.004**
superior temporal		superior frontal	parahippocampal
RP 0.041*		RT 0.045*	RO 0.007**
supramarginal		middle temporal	pericalcarine
		RPF 0.014*	RC 0.002**
		pars orbitalis	precentral
		LO 0.038**	RP 0.006**
		lateral occipital	inferior parietal
			RT 0.029*
			temporal pole

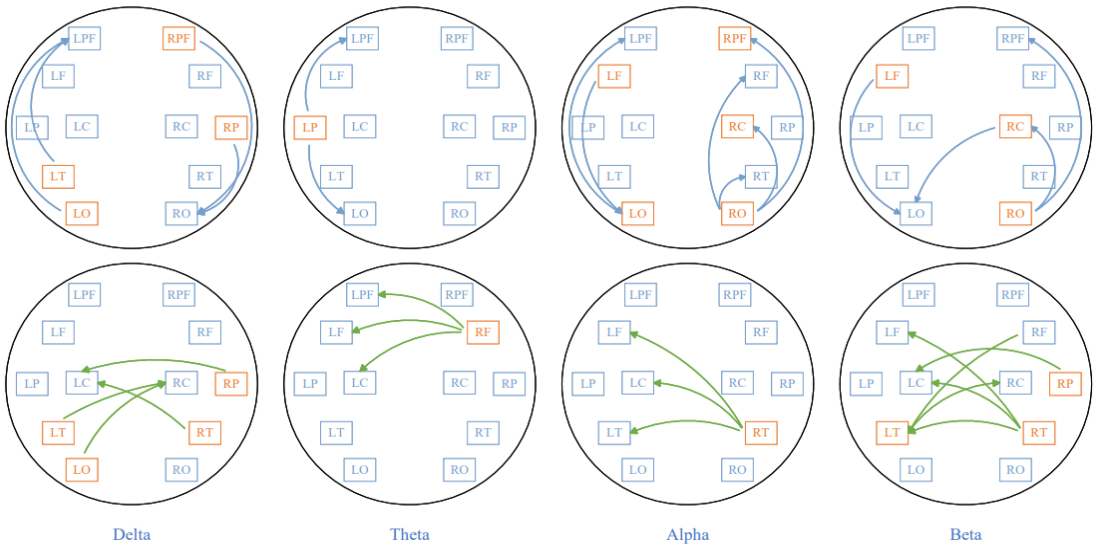

Figure 5. Information flow loops. The solid lines indicate significant directed information flow between the two ROIs (permutation test, P<0.05), blue lines indicate stronger

information flow in the healthy group than in the depressed group, and green lines indicate stronger information flow in the depressed group than in the healthy group.

4. Discussion

To mitigate the negative effects of depression on patients and to aid in the development of a drug or TMS programs, it would be useful to study abnormalities in the areas of brain function associated with depression and abnormalities in the connections between brain regions. Researchers using functional magnetic resonance imaging have successfully identified different areas of the brain with impaired function in patients with different subtypes of depression [18]. Although fMRI provides valuable information, the equipment is expensive and not easy to use. In contrast, EEG technology is inexpensive, easy to administer, and is an important tool for clinical assessment and community screening.

Most EEG studies rely to some extent on graph theory to categorize and identify subjects through functional connectivity matrices. Hasanzadeh et al. [12] reported that depressed individuals have stronger than normal brain functional connectivity and a more randomized brain network structure. Although these biomarkers achieved high classification accuracy, graph theoretic results are difficult to interpret physiologically. However, Orgo et al. [19] found that the inclusion of graph theory metrics did not significantly improve the accuracy of functional connectivity metrics in distinguishing between depressed and control groups. Therefore, it remains a challenge to study the effects between depressive foci and brain regions to complement clinical medication and therapeutic modalities such as transcranial magnetic stimulation.

In this study, we investigated whether the functional connectivity between certain brain regions in the EEG signals of depressed patients is abnormal in the resting state and whether there are differences in the direction of information flow compared to the healthy group. We tracked EEG signals using sLORETA and then calculated the PTE effective connectivity matrix. By performing a permutation test on the data from all subjects, we found that the overall information flow in resting-state EEG occurs predominantly in the alpha and beta frequency bands. Notably, the healthy group showed a higher intensity of overall information flow compared to the depressed group. This observation may be due to the inverse relationship between alpha power and cortical activity. That is, a decrease in alpha power in the posterior regions of the brain may indicate an increase in neuronal excitability.

We performed Friedman's test on the PTE matrix to compare the healthy and depressed groups and found significant differences in the alpha and beta frequency bands. Specifically, the depressed group showed increased interhemispheric connectivity and decreased teleconnection. This increased interhemispheric functional connectivity may be due to the disruption of corpus callosum integrity [20], resulting in imbalances in hemispheric functional coordination. In addition, depressed patients showed reduced grey matter volume in the left precentral gyrus and increased grey matter volume in the right thalamus [21]. These abnormal grey matter volumes and connectivity patterns reflect abnormal intrinsic wiring costs of brain structures, resulting in atypical topological properties of functional connectivity.

Comparing the two groups of subjects, we observed greater differences in the right than in the left

brain regions, especially in the right central lobe region, where the differences in the alpha band were most pronounced. theta and beta bands in the left occipital and right frontal lobes showed similar characteristics. In addition, the intensity of information flow was consistent with depression scores. Similarly, Carola et al. found increased functional connectivity in the right frontal and central regions of the brain in depressed patients [22]. A study of transcranial magnetic stimulation targeting isolated cerebral hemispheres showed the potential to alleviate cerebral hemispheric imbalances and was effective in improving core depressive factors and anxiety symptoms in patients [23].

Other researchers looked at lesions in the occipital and right frontal lobes and found that occipital curvature was more common in depressed people than in healthy people. Occipital asymmetry and occipital curvature, although different phenomena, may be due to incomplete neural pruning, limited cranial space for brain growth, or ventricular enlargement exacerbating the natural occipital curvature pattern, resulting in brain compression and the need to 'wrap' the other occipital lobe [24]. A recent meta-analysis showed that hyperconnectivity in the prefrontal and anterior cingulate regions of the default mode network (DMN) is primarily associated with rumination, highlighting the critical role of prefrontal regions in this process [25]. In contrast, hemodynamic activation in the right dorsolateral prefrontal cortex (DLPFC) and right frontal pole cortex (FPC) was significantly increased in the anxious-depressed group compared to the non-anxious-depressed and healthy groups [26].

There was also a significant increase in the strength of information flow from the parahippocampal gyrus and middle temporal gyrus in the temporal lobe. Researchers using functional magnetic resonance imaging found a higher prevalence of hippocampal structural abnormalities in depressed patients, accompanied by increased activity within the brain's default mode network and increased extratemporal activation compared to the non-depressed group [27]. In particular, abnormal and excessive functional connectivity was observed in the right parietal lobe across both the delta and beta frequency bands, particularly in relation to the left central hook. Hou et al. targeted the parietal lobe and observed significant rehabilitative outcomes following four weeks of neurofeedback training [28].

In summary, extensive research has consistently shown significant inter-individual variability in the neurophysiological features associated with depressive symptoms. Rather than being limited to specific local changes, pathophysiological changes in depression appear to involve multiple brain regions [29]. We found that depression is associated with abnormalities in information flow within regions such as the occipital lobe, right frontal lobe, right temporal lobe and central sulcus. The depressed patients generally showed a decrease in long-range information flow between the ipsilateral anterior and posterior regions of the brain, and an increase in information flow between hemispheres. Notably, these connectivity differences were more pronounced in the right side of the brain compared to the left side. The data set used in this study consisted of dPTE values representing information flow and showed statistically significant differences in the alpha and theta bands, with a classification accuracy of 91%. These findings suggest that these abnormalities may contribute to depressive episodes. Given the variability between patients and the potential differences in underlying pathogenesis, future treatment protocols for depression should take these factors into account. Our approach may help clinicians to develop individualized treatment plans tailored to the specific needs of each depressed individual.

Conflict of interest

The authors declared that they have no conflicts of interest to this work.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Data Availability

Please contact the correspondence authors for data request.

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