Magnetoencephalogram analysis of depression based on multivariable sign transfer entropy

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Abstract. In this paper, multivariable sign transfer entropy algorithm is used to calculate the multivariable sign transfer entropy values of the same brain region and different brain regions stimulated by different emotional images in patients with depression and healthy control group. The connectivity of the magnetic channels in the brain region and between brain regions is studied. And the conclusions of negative cognitive bias in depressed patients [1] and functional asymmetry of emotion of cerebral hemispheres are verified [2]. The results showed that: For different brain regions, the left occipital region →frontal region under positive emotional picture stimulation and neutral emotional picture stimulation can significantly distinguish the depressed patients’ group from the healthy control group, the corresponding connection strength of depressed patients was significantly weaker than that of healthy control group.

1. Introduction

The brain is a complex organic whole, and different brain functional regions often interact each other. MEG [3] technology has super high temporal and spatial resolution, which can accurately locate the brain function and explore the internal structure of the brain. The human brain is a complex nonlinear system whose left and right hemispheres are asymmetric. While the transfer entropy [4] can not only obtain the dynamic characteristics of the nonlinear system but also obtain its direction. Therefore, the transfer entropy algorithm just can satisfy the study of asymmetric characteristics of the brain. The traditional transfer entropy algorithm is only for the study of binary connectivity, that is, connectivity between two variables. And for MEG signal in depressed disease, the magnetic channel signals within the same functional area and between different functional areas may affect each other. So, based on the traditional transfer entropy, we take the multivariate transfer entropy algorithm to study the connectivity among multiple magnetic channels of the same brain region and different brain regions [5]. Because the transfer entropy is easily affected by noise, the original data is processed into symbol sequence by symbolization algorithm, and then the value multivariable symbolic transfer entropy is calculated [6].
We mainly selected occipital region → frontal region channel combinations and occipital region → central region channel combinations to calculate the corresponding improved multivariable sign transfer entropy.

2. Multivariable sign transfer entropy

2.1. Multivariable transfer entropy

Transfer entropy is a model method to detect causality in multiple time series. It can distinguish between direct and indirect causation and common drivers without assuming any underlying model [7]. However, it applies primarily to binary system connectivity because its definition in higher dimensions involves an infinite number of vectors that are difficult to estimate. To overcome this limitation, Runge proposed to embed the multivariate into the framework of the graphical model, and gave a formula to decompose it into the sum of the finite dimensions of its parts, also known as decomposition transfer entropy. Transfer entropy can be used to research the mutual information [8] about directional and dynamic characteristics contained by two systems. While it is a complex nonlinear system inside human brain, so, transfer entropy is suitable for the analysis of coupling strength and direction of complex nonlinear system.

Based on the above decomposition transfer entropy, the following definition of multivariable transfer entropy is introduced. Let's say we have a stationary multivariate discrete time random process, $\mathbf{X}$, with a value of $\mathbf{X}_t$ at time $t$. The corresponding sub-processes are represented by $X$, $Y$, $Z$, $W$, etc. Their past moments are defined as $\mathbf{X}_t^{\tau} = (\mathbf{X}_{t-\tau}, \mathbf{X}_{t-2\tau}, \ldots)$ and $\mathbf{X}_t^{\tau} = (X_{t-\tau}, X_{t-2\tau}, \ldots)$ where $X_t^{\tau}$ is a subset of $\mathbf{X}_t^{\tau}$. The transfer entropy:

$$I_{\mathbf{X} \rightarrow \mathbf{Y}} = I(X_t; Y_t | X_{t-\tau}^{\tau})$$

(1)

indicates the uncertainty of $X_t^{\tau}$ to $Y_t$ under the condition of $X_{t-\tau}^{\tau}$. The infinite dimensions in the above definition are $X_t^{\tau}$ and $X_{t-\tau}^{\tau}$.

The decomposition of high dimensional transfer entropy by time delay is introduced through the chain rule, namely:

$$I(X_t; Y_t | X_{t-\tau}^{\tau}) = \sum_{\tau=1}^{\infty} I(X_{t-\tau}; Y_t | X_{t-\tau}^{\tau}, X_{t-2\tau}^{\tau})$$

(2)

Then, the theoretical graph model is used to solve the infinite dimension problem in the estimation. According to the Markov properties in the independent process, as shown in Figure 1, The transferring entropy can be represented as:

$$I(X_{t-\tau}; Y_t | X_{t-\tau}^{\tau}, X_{t-2\tau}^{\tau}) = I(X_{t-\tau}; Y_t | S_{Y,X_{t-\tau}}^{\tau})$$

(3)

Among this, $S_{Y,X_{t-\tau}}^{\tau} \subset X_{t-\tau}^{\tau} \cup X_{t-2\tau}^{\tau}$ is a limited subset of $X_{t-\tau}^{\tau} \cup X_{t-2\tau}^{\tau}$ which is determined by the time sequence graph. Because the formula tends to decay with exponent $\tau$, the rest of the infinity can be truncated at specified $\tau^*$, namely:

$$I_{\mathbf{X} \rightarrow \mathbf{Y}}^{\tau^*} \approx I_{\mathbf{X} \rightarrow \mathbf{Y}}^{\tau^*} = \sum_{\tau=1}^{\tau^*} I(X_{t-\tau}; Y_t | S_{Y,X_{t-\tau}}^{\tau})$$

(4)
2.2. Signifying
Symbolization mainly takes the means of "Coarse granulation" to transform the original time series into the specified symbol sequences according to certain mapping rules.

The symbolized time series can remove a lot of redundant information on the basis of retaining the nonlinear dynamic characteristics. Then, the key information needed is obtained by studying the dynamic characteristics of the symbol sequence. The symbolization algorithm adopted in this chapter is the static scale symbolization method in symbolic dynamics. For the study of static symbolization, Wessel [9] et al. proposed the time series four-symbol static scale symbol method in the study of heart rate of patients with chronic heart failure, and its mapping rules are as follows:

$$s_i(x_i) = \begin{cases} 
0: & \mu_1 < x_i \leq (1 + a)\mu_1 \quad \text{or} \quad (1 + a)\mu_2 \leq x_i < \mu_2 \\
1: & (1 + a)\mu_1 < x_i < \infty \quad \text{or} \quad -\infty < x_i < (1 + a) \\
2: & (1 - a)\mu_1 < x_i \leq \mu_1 \quad \text{or} \quad \mu_2 \leq x_i < (1 - a)\mu_2 \\
3: & (1 - a)\mu_2 \leq x_i \leq (1 - a)\mu_1 \\
\end{cases} \quad (5)$$

$i = 1,2,\ldots,N$

N stands for the position of signs corresponding to the symbolized original time series. Set $\mu_1$ as the mean value of data that is less than zero in the time series, $\mu_2$ as the mean value of data that is greater than zero. $\alpha$ is a static scale factor, and if the value is too high, the dynamic characteristics of the original data may be missing, and if the value is too small, the correlation will be large, and there will be more redundant information, which will increase the influence of noise. Therefore, the $\alpha$ is generally set as 0.03-0.07, and the time series tend to be similar after symbolization. The $\alpha$ for this experiment is set as 0.05.

2.3. Multivariable sign transfer entropy
For the study of EEG, the nonlinear dynamics methods mainly include correlation dimension [10], Lyapunov index [11], Kolmogorov entropy, approximate entropy [12], sample entropy [13], etc. However, there are few studies on nonlinear dynamic methods of magnetoencephalogram signals at home and abroad. At present, the relevant nonlinear dynamics methods applied in the study of magnetoencephalography mainly include Lempel-Ziv, correlation dimension and entropy statistics.

The human brain is a complex nonlinear system with asymmetry in the left and right hemispheres. The transfer entropy can not only obtain the dynamic characteristics of the nonlinear system but also its direction. Therefore, the transfer entropy algorithm can exactly satisfy the study of asymmetric characteristics of the brain. The traditional transfer entropy algorithm is only for the study of bivariate connectivity, that is, the study of the connectivity between two variables. For the signal of depression magnetoencephalogram, the signals of magnetoencephalography channel in the same functional area and between different functional areas may affect each other. Based on the information on multivariable transferring entropy and signifying stated before, we can give out the definition of multivariable sign transfer entropy. That is:

Map the sequence $X$ to a symbolic sequence according to symbolic rules, $S = \{s_1, s_2, \ldots, s_i, \ldots, s_n\}$, mapping $Y$ as symbolic sequences $J = \{j_1, j_2, \ldots, j_i, \ldots, j_n\}$, $j_i \in$
$A(A = 0,1,2,3)$ mapping $Z$ for the corresponding symbol sequence $K = \{k_1, k_2, \ldots, k_i, \ldots, k_n\}$, $k_i \in A(A = 0,1,2,3)$. The transfer entropy of multivariable symbols can be defined as:

\[
I_{S_j \rightarrow S_i}^{TE} \approx I_{S_j \rightarrow S_i}^{DTE} = \sum p(s_{n-\tau}, j_n, s_{n-\tau-1}, j_{n-\tau}, s_{n-\tau+1}, j_{n-\tau+1}, k_{n-\tau}, k_{n-\tau-1}) \cdot \log \frac{p(s_{n-\tau}, j_n, s_{n-\tau-1}, j_{n-\tau}, s_{n-\tau+1}, j_{n-\tau+1}, k_{n-\tau}, k_{n-\tau-1})}{p(j_n, s_{n-\tau}, j_{n-\tau}, s_{n-\tau-1}, j_{n-\tau+1}, k_{n-\tau}, k_{n-\tau-1})} \cdot \log \frac{p(s_{n-\tau}, j_n, s_{n-\tau-1}, j_{n-\tau}, s_{n-\tau+1}, j_{n-\tau+1}, k_{n-\tau}, k_{n-\tau-1})}{p(s_{n-\tau}, j_n, s_{n-\tau-1}, j_{n-\tau}, s_{n-\tau+1}, j_{n-\tau+1}, k_{n-\tau}, k_{n-\tau-1})}
\]

(6)

3. Experimental data source

In this study, the multivariate sign transfer entropy algorithm was used to analyze the connectivity differences in the same brain region and different brain regions between the depressed patients’ group and the healthy control group. The magnetoencephalogram data of the experimental study were obtained from 13 groups of magnetoencephalogram data collected by the magnetoencephalogram center of the affiliated brain hospital of Nanjing Medical University, including 8 groups of healthy subjects and 5 groups of depressed patients.

The depression sample included 3 male and 2 female patients with depression in the inpatient department of the hospital. They ranged in age from 18 to 35, with an average age of 25±4 years. The healthy samples were from the interns and medical graduate students in the hospital of Nanjing Medical University. Their ages ranged from 20 to 28 years old, with an average age of 23±2 years old. All the subjects had normal sensory stimulation, no history of infectious diseases, no contraindications of other mental diseases, no contraindications of brain magnetic resonance examination, no recent use of psycho-suppressive drugs, and were informed of the experimental situation and related matters by the ethics committee of Nanjing Medical University. The emotional picture stimulation used in this experiment was selected from the International Affective Pictures System (IAPS).

There were 80 positive emotional stimulus pictures, 80 negative emotional stimulus pictures and 80 neutral emotional stimulus pictures. Keep each image in the same pixel size and brightness. The three emotional images were randomly grouped, and each group was randomly inserted with 10 images of the gray cross and white base as the target stimulus. These data were filtered out during the actual experimental analysis. Each image was updated at an interval of 1000ms, and the target stimulation interval was 300ms. In order to reduce the experimental error of the predicted images, the stimulus interval was adjusted randomly between 1500-2000ms. The Canadian CTF275 channel system was used to collect the magnetoencephalogram data of the subjects, with a sampling frequency of 1200Hz and a bandwidth of 300Hz. Subjects entered the magnetic shielding room and used projection equipment and specular reflection outside the shielding room to project the emotionally stimulating pictures to the center of the subject’s viewing screen. During the test, the subjects were asked to relax physically and mentally, keep their heads and eyes still, and watch the pictures patiently to feel the emotional significance of the pictures. The original data collected by magnetoencephalogram is .Meg4 file, and SPM8 software is used to adjust the time delay accordingly. The data in the time interval of -200ms-600ms are converted into MATLAB for calculation and processing. The processed data structure is the data dimension.

4. Data processing and analysis

4.1. Multivariable sign transfer entropy in occipital region →frontal region

The study on the connectivity of the occipital region →frontal region can be divided into four channel combinations, namely the left region of the occipital region →left frontal region, left region of the occipital region →right frontal region, right region of the occipital region →left frontal region, right region of the occipital region →right frontal region.

4.2. Results of MSTE under negative, positive and neutral stimulation

Figure 2, Figure 3 and Figure 4 show the comparison of multivariable sign transfer entropy between depressed patients and healthy control group for the combination of occipital to frontal channels under the stimulation of three types of emotional images. Select all left channel of the occipital
region (MLO11-MLO53), all right channel of the occipital region (MLR11-MLR53), left channel of the frontal region (MLF11-MLF45), right channel of the frontal region (MRF11-MRF45), and MZO1 of the central channel of the occipital region as the known variable channel, and the corresponding horizontal axis coordinates are different channel combinations.

Figure 2 corresponds the multivariable sign transfer entropy of the channel from the left occipital area to the frontal area of the two sample groups under the stimuli of negative emotional pictures. The difference of the multivariable sign transfer entropy between the depression patients and healthy controls is significant, and the entropy value of the depressed patients is greater than that of the healthy group.

Figure 3 shows the multivariate sign transfer entropy of the two groups of samples from the occipital region to the frontal region under positive emotional picture stimulation. In addition to the individual channel combinations, the transfer entropy of multivariable signs in the occipital region → frontal region corresponding to the healthy control group was greater than that in the depressed group, among which the left occipital region → left frontal region and the left occipital region → right frontal region. The difference between the depressed patient group and the healthy control group was obvious.

Figure 4 shows the multivariate sign transfer entropy of the two groups of samples from the occipital region to the frontal region under the stimulation of a neutral emotional picture. In addition to the individual channel combinations, the entropy of multivariable sign transfer in the occipital region → frontal region corresponding to the healthy control group was larger than that in the depressed group. And all four combinations of neutral stimuli can distinguish between the depressed group and the healthy control group. However, under the combination of the left occipital region → left frontal region, left occipital region → right frontal region, the difference between depressed patients and healthy

![Figure 2. MSTE under negative stimuli.](image-url)
control group was more obvious. As for the channel combinations that satisfy the differences in the above analysis, the multivariable sign transfer entropy of the healthy control group is quite different from that of the depressed group, but the existence of individual cases of individual channel combinations cannot be excluded. SPSS software was used to conduct independent sample T test on individual sample data of each channel combination to verify the significance of the multi-variable sign transfer entropy algorithm in distinguishing the depressed patients’ group from the healthy control group. Due to the large number of T-test results in the combination channel of the occipital region →frontal region, two groups of T-test results were randomly selected as examples. The independent sample T-test results of the left occipital region to the right frontal region channel combination (MLO12→MRF12|MZO01) were 0.015<0.05, which could significantly distinguish the healthy control group samples from the depressed patients group samples. The independent sample T-test results of the left occipital region to the left frontal region channel combination (MLO21→MLF21|MZO01) under the stimulation of neutral emotional pictures showed a P value of 0.029, which could significantly distinguish the depressed patients’ group from the healthy control group.

Figure 3. MSTE under positive stimuli.
According to the analysis of the experimental results of the above different brain regions, it can be found that under the stimulation of different emotional pictures, for the combination of the left occipital region to the frontal region channel, there was a significant difference in the entropy of multivariable sign transfer between the depressed patients group and the healthy control group, which could distinguish the depressed patients group from the healthy control group. Under the stimulation of negative emotional pictures, the left occipital region → the left frontal region channel combination can significantly distinguish the depressed group from the healthy control group. The brain connectivity of depressed patients is significantly higher than that of the healthy control group. Under the stimulation of positive emotional pictures, the brain connectivity of depressed patients was significantly lower than that of healthy control group under the combination of the left occipital region → left frontal region and left occipital region → right frontal region. Under the stimulation of neutral emotional picture, for the combination of left occipital region → left frontal region, left occipital region → right frontal region, the corresponding connection strength of depressed patients was significantly weaker than that of healthy control group.

5. Conclusions
For different brain regions (pillow to frontal area, occipital region, central region) experimental results analysis found that positive emotional stimulation and neutral emotional pictures, left occipital area to the frontal area (left frontal area and right frontal area) is especially significant to the distinction between a group of patients with depression and the multivariable sign transfer entropy value of healthy control group was greater than patients with depression. However, the effect of channel
combination between right occipital region → frontal region was not significant, which just verified the asymmetry of emotion building in the cerebral hemisphere.

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