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Pilot Study of Cerebral Hemodynamics in Depressive Patient Under Electroconvulsive Therapy

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Background: Major depressive disorder (MDD) poses a significant treatment challenge, with some patients unresponsive to conventional therapies. Electroconvulsive therapy (ECT) can be effective but its mechanisms are not fully understood. This study employs functional Near-Infrared Spectroscopy (fNIRS) to explore the neurobiological changes induced by ECT in A MDD patient, aiming to shed light on its therapeutic effects.

Purpose: This study employs fNIRS to assess differences between MDD patient and controls, and examines changes in cerebral hemodynamics and brain network nodes post-ECT to elucidate treatment mechanisms.

Methods: 26 age and gender-matched controls and one MDD male patient underwent fNIRS during a verbal fluency task. The patient received ECT, with dynamic evaluation of beta, integral, and centroid values in regions of interest (ROIs) post-treatment. Resting-state fNIRS and functional connectivity assessments were also conducted post-ECT.

Results: MDD patient exhibited significantly lower hemodynamic metrics and functional connectivity compared to controls at baseline. Post-ECT, dynamic changes in these metrics were observed, trending towards normalization and showing no significant differences from controls.

Conclusion: ECT modifies cerebral hemodynamics and functional connectivity in depressive patients, as evidenced by fNIRS metrics. This study underscores the utility of fNIRS for objective neurobiological monitoring in ECT treatment.

Keywords: functional near-infrared spectroscopy, cerebral hemodynamics, major depressive disorder, electroconvulsive therapy

Introduction

Major Depressive Disorder (MDD) is a prevalent chronic condition in the majority of societies globally. It disrupts normal functioning, induces a state of depression, and significantly diminishes the quality of life.[1,2] Depressive symptoms can severely hinder daily activities, resulting in considerable societal and economic burdens.[1,3–5] Individuals diagnosed with MDD typically exhibit sustained feelings of sadness and a diminished ability to experience pleasure or interest over a period of at least two weeks, with symptoms that may fluctuate at different stages of life.[6]

Severe MDD often leads to suicidal thoughts, emphasizing the urgency for effective treatment.[4,7] While pharmaceutical intervention is the primary approach, its delayed onset and low response rates pose significant challenges.[8] Electroconvulsive Therapy (ECT) has historically proven highly effective for MDD, surpassing alternative treatments in rapidly reducing suicide risk.[9–11] Modified Electroconvulsive Therapy (MECT), a controlled procedure involving anesthesia and muscle relaxants, remains a gold standard in the treatment of resistant depression, providing rapid relief.[12,13] In this document, we have simplified the terminology, using ECT to describe it directly.

Despite its efficacy, varying clinical perspectives on ECT persist due to misconceptions about its mechanisms, concerns about memory impairment, and apprehensions about electricity.[14,15] Studies have highlighted decreased cerebral blood flow in the cerebral cortex as a biological marker of depressive episodes.[16–20] Investigating how this

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changes post-ECT treatment, especially after a single session, is a recent focus of research. Functional Near-Infrared Spectroscopy (fNIRS) provides a practical tool to study hemodynamics in MDD patients, offering insights into cognitive-related assessments.[21,22]

Currently, limited research exists on the combination of ECT and fNIRS, with inconsistent findings from studies on bilateral frontotemporal ECT.[17,23] This study aims to utilize fNIRS to explore the impact of a single session of ECT on cortical hemodynamic responses in MDD patient. Given the dynamic nature of activation changes induced by the Verbal Fluency Test (VFT) task during different sessions of ECT, we hypothesize varying responses within a single session.

Materials and Methods

Participants and Experimental Scheme

In this study, a 24-year-old male diagnosed with MDD was included, along with 26 healthy controls matched for age, gender, and educational level. All participants in the control group were male, right-handed, and their native language was Mandarin Chinese. All participants provided informed consent. Notably, they had no prior history of neurological disorders, epilepsy, substance abuse, or personality disorders. The healthy controls recruited from the university campus underwent assessments including the SCL-90 test, Zung Self-rating Depression Scale (SDS), and the Zung Self-rating Anxiety Scale (SAS) upon enrollment. Their scores fell within the normal reference range. Due to suboptimal data quality (as detailed in Section 2.3.1), four healthy controls were excluded from subsequent data analysis, leaving a total of 22 healthy controls (all male, mean age = 26.55±2.44).

The MDD patient was recruited from the Inpatient Department of the Third Hospital of Mianyang & Sichuan Mental Health Center, Sichuan Province, China. Diagnosis was conducted by two attending psychiatrists based on the criteria outlined in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5),[6] and comorbid psychiatric disorders were assessed through clinical interviews. The study received approval from the Ethics Committee of the Sichuan Mental Health Center, and informed consent was obtained from the participants. The MDD patient had a duration of illness of one year, presenting with clear depressive symptoms, suicidal ideation, and a history of suicide attempts. Prior to admission, the patient underwent two antidepressant treatments during outpatient care, lasting for a period of five months. These treatments included sertraline at 200 mg/day for 2 months and venlafaxine extended-release tablets at 225 mg/day for 2 months. However, there was no significant improvement in symptoms, meeting the criteria for treatment-resistant depression (TRD).[24] Neuroimaging revealed no abnormalities, and results for liver and kidney function, routine blood tests, and thyroid function were within normal range. The patient provided informed consent for receiving ECT treatment, and retained the right to decide whether to continue the ECT treatment during the course.

Study Design

To evaluate hemodynamic responses during cognitive tasks, participants underwent a VFT while concurrent fNIRS data was collected following a 5-minute period of eyes-closed resting state. The number of novel words generated during the VFT was recorded. Additionally, fNIRS detection was applied during the VFT. For detailed methodology, refer to Section 2.2.2. Healthy controls underwent these assessments once.

Following these initial tests, MDD patients received five sessions of right temporoparietal region stimulation via ECT, with a one-day rest period between each session. Within 8–24 hours after each ECT session, fNIRS measurements identical to the ones mentioned earlier were conducted to monitor hemodynamic changes.

To mitigate potential practice effects, assessments using the SDS and SAS were administered only after the 1st, 3rd, and 5th ECT treatments, as well as prior to the corresponding fNIRS assessments.

Modified Electroconvulsive Therapy (ECT)

Patients received ECT using the Somatics thymatron - system IV device (Somatics, Inc., Lake Bluff, IL, USA). The ECT procedure was conducted under general anesthesia with 100% oxygenation for one minute. Anesthesia induction was achieved by intravenous injection of etomidate at 0.3mg/Kg, followed by succinylcholine at 1mg/Kg for muscle relaxation. Electrode placement followed the right unilateral (RUL) protocol, with placement coordinates referenced

from d'elia's temporoparietal right unilateral (TP-RUL) placement. The current strength was set at 0.9A, with a pulse width of 0.5ms and a pulse frequency of 30Hz. Static resistance during ECT was controlled to be below 3000 ohms. The stimulus intensity was set in percentage mode, with the absolute energy value determined by multiplying the patient's age by 80%. The duration of the seizure activity was based on the recording from a dual-channel electroencephalogram. Stimulation parameters and patient medication remained consistent throughout a single ECT session.

NIRS Measurement

A 53 multi-channel instrument (BS-3000, Wuhan Znion Medical Technology Co., Wuhan, China) was used to measure the relative concentration changes of hemoglobin in prefrontal cortex. The sampling rate was 20Hz, and the wavelengths of near-infrared light were 690 and 830 nm. Each channel consists of a source-detector pair at a distance of 3 cm and were placed with reference to the 10–20 system (Source 9 is located at Fpz). 16 sources and 16 detectors constitute a total of 53 channels. The 53-channel placement is shown in Figure 1.

In order to normalize the fNIRS channels, we applied a 3D digitizer (NirMap, Wuhan Union Medical Technology Co., Wuhan, China) to record the exact spatial coordinates of 4 reference points (Nz, Cz, AL and RL) and 32 probes (16 sources and 16 detectors). Then the 53 channel were converted to an estimated Montreal Neurological Institute (MNI) space[25] by NIRS-SPM.[26] Based on the Broadmann probabilistic atlas, all 53 channels were then divided into the following five cortical regions: Pre-motor and supplementary motor area (PreM & SMA), frontal eye field (FEF), Broca's area (Broca), Dorsolateral prefrontal cortex (DLPFC) and frontal pole area (FPA) (See detail as Figure 1). Since numerous VFT-fNIRS studies[27] did not analysis the activity of PreM & SMA and FEF, they were excluded from the region of interest (ROI) level analysis.

The fNIRS experiment consisted of two distinct paradigms: a resting state and a verbal fluency task. The resting state was exclusively conducted with the patient and spanned a duration of 5 minutes. Throughout this period, the patient was instructed to sit comfortably in a softly lit room. They were advised to maintain stillness, keep their eyes closed, refrain from falling asleep, and attempt to keep their mind devoid of specific thoughts.

Following the resting state, a Chinese-language phonological VFT, as devised by Quan et al,[28] was administered. This test was administered to both the patient and the healthy controls. The task structure encompassed a 30-second pre-task baseline, a 60-second task phase, and a subsequent 60-second post-task baseline. In the pre-task and post-task baseline periods, participants were prompted to audibly count numbers, following the cues from the fNIRS device.

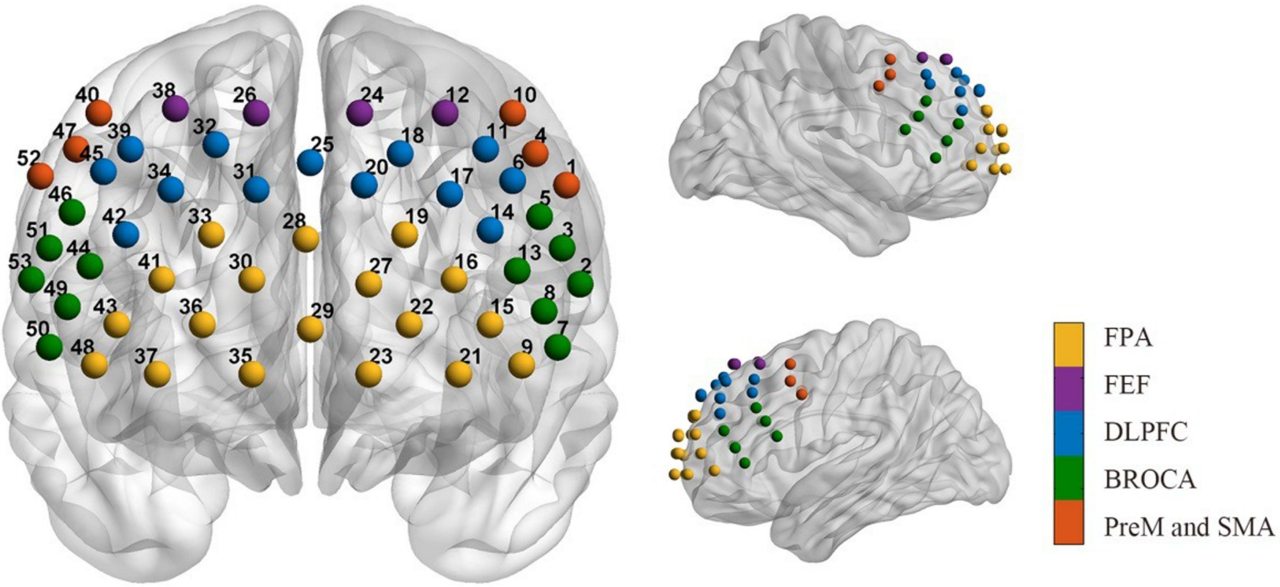

Figure 1 The 53-channel location on brain. The frontal pole area(FPA), The frontal eye field(FEF), The dorsolateral prefrontal cortex(DLPFC), Broca's area (BROCA), The Pre-motor and Supplementary motor area (PreM and SMA).

The 60-second task phase was divided into four consecutive 15-second blocks. In each block, one of the four common Chinese syllables - namely, "shang (上)", "shi (时)", "shuo (说)", and "jia (家)" - was audibly presented to the subjects. These syllables were selected due to their high frequency of use in daily life. Subsequently, participants were instructed to generate as many words as possible starting with the specified syllable. To mitigate potential practice effects resulting from multiple experiments, syllables were randomly selected from the thesaurus. Prior to the formal assessment, all participants underwent a training exercise to ensure their complete understanding of the task.

Throughout the task, a researcher closely monitored the participants' performance to guarantee their complete engagement in the assessment. The number of words uttered by each participant was meticulously recorded.

Data Analysis

Data Pre-Processing

Before data processing, we calculated the coefficient of variation (CV) values for each channel across the entire dataset to ensure signal quality.[29] Any channel with a CV value exceeding 15% was marked as a bad channel. If the number of bad channels exceeded 20% of the total, the participant was excluded. In this study, data from four healthy control participants were excluded. The patients' data remained within the acceptable CV range after each treatment. The fNIRS data underwent pre-processing following the method described by Takizawa et al.[30] Firstly, the raw optical intensity was converted to optical density (OD) using the MATLAB-based toolbox, Homer2.[31] Secondly, changes in relative concentration of oxygenated hemoglobin (oxy-Hb), deoxygenated hemoglobin (deoxy-Hb), and total hemoglobin (total-Hb) were calculated according to the modified Beer-Lambert Law.[32] We primarily used Oxy-Hb in subsequent analysis due to its better signal-to-noise ratio and stronger correlation with cerebral blood flow compared to Deoxy-Hb.[33,34] Thirdly, a moving average method with a window width of 5 seconds was applied to remove short-term motion artifacts and periodic physiological noise. Subsequently, we extracted the 125 seconds oxy-Hb signal for further analysis, encompassing the last 10 seconds of the pre-task period, 60 seconds of the task period, and the initial 55 seconds of the post-task period. Finally, the signals were normalized using linear fitting between a 10-second baseline in the last pre-task period and a 5-second baseline in the last post-task period.

Two visual indices, "Integral Value (IV)" and "Centroid Value (CV)", reflecting the time-course changes of fNIRS signal, were calculated based on previously reported results.[35] The IV describes the total size of the hemodynamic response during the 60-second activation task period, indicating the intensity of signal changes throughout the task. Higher values imply greater activity associated with the cognitive task. The CV is defined as the timepoint of the centroid of fNIRS signal change area across the task and post-task periods. Smaller CVs indicate a more prompt cortical response and relaxation following task completion.

General Linear Model Analysis

VFT task-evoked activation was analyzed using a general linear model (GLM) approach.[36,37] The GLM was performed using a MATLAB-based toolbox, NIRS-KIT.[38] The experimental design matrix included a constant and a task regressor. The task regressor was constructed by convolving a boxcar function (corresponding to onsets of VFT task) and canonical hemodynamic response function (HRF). The fNIRS signal in each channel was the explained variable in the GLM model. After GLM estimation, task beta values, reflecting the task-evoked activation, were obtained.

Resting-State Functional Connectivity

Only the HbO2 signal of the patient was used to calculate resting-state functional connectivity (RSFC) in this study. All RSFC analysis was performed using FC-NIRS.[39] As a conventional method, Pearson's correlation coefficient was calculated in any possible channel pair, which represented the strength of RSFC. This generated a correlation matrix for each treatment of the patient. We calculated the average FC matrix of patients per treatment. The number of network edges is used as a measure of RSFC strength. The network edge numbers were calculated as the connection numbers in the network within different threshold. Specifically, the channel was defined as "node" of network, and the correlation coefficient between any channel pair as the "edge" of network. The strength of RSFC is measured by the average number of edges.[40]

Statistical Analysis

Behavioral Performance

The number of words formed by the participants was recorded. To assess the performance of the participant with MDD in relation to the normal range at pre- and post-treatment, z-scores were calculated using the healthy controls' performance as the normative database.

Hemodynamic Response

A one-sample *t*-test was performed on the healthy control group for each channel task beta value to assess the task-induced activation in each channel to re-determine the region of interest (ROI). A Bonferroni correction was used to account for multiple comparisons. To determine the extent to which the MDD patient' hemodynamic responses fell within/outside the normal range during and after electroconvulsive therapy, z-scores were calculated for the corresponding indexes based on healthy control data. In describing the hemodynamic responses of patients with MDD, standardized norm referenced z-scores for changes in HbO2 were first calculated using the ROIs derived from the control group to determine the extent to which the hemodynamic response for the MDD participants were similar/differed from that of the healthy control group. Since the integral value reflects the strength and persistence of the neural activity response during the VFT task period (60 s), we judged the z-score threshold for the integral value to be (>-1 SD).The centroid value reflect the temporal characteristics of the intensity of neural response activity during the VFT task (0–125 s), so we judged the centroid value z-score threshold to be (<1 SD).In addition, we counted the number of channels with beta-value z-scores in the ±1 SD range before and after multiple treatments for depression, rather than beta-value. We calculated the beta values of depressed patients before and after multiple treatments. Then, the number of beta values under the region of interest that were within the normal range (±1 SD) was determined. Finally, we calculated the ratio of the number of channels under the region of interest in depressed patients to the number of channels in the normal group.

We calculated a laterality index with the formula (L-R)/(L+R) for each ROI.[41] L is the hemodynamic response of the left ROIs, R the hemodynamic response of the right ROIs. A left lateralization is indicated by a positive value and a right lateralization is indicated by a positive value for each index. We compared the lateralization index per treatment in MDD patients with the lateralization index in healthy controls(mean±SD).

Because the number of resting-state data and task-state data for normal controls did not match, we only counted the number of functionally connected edges of MDD patients' resting-state data at the ROI identified in the task state to observe their treatment trends.

Result

Number of VFT Words and Scale Scores

Following ECT, the number of word associations in the VFT as well as the scores on the SDS and SAS scales for MDD patient are presented in Table 1.

Healthy Controls -GLM Analysis

To examine the extent to which MDD participant's hemodynamic response differed from that of the healthy controls, we calculated activated channels in the GLM analysis of healthy controls. After Bonferroni correction, there were 27 channels in the healthy control group with significantly different hemodynamic responses. This hemodynamic response

Table 1 The Number of Word Associations in the VFT as Well as the Scores on the SDS and SAS Scales for MDD Patient

	Pre-ECT	First-ECT	Second-ECT	Third-ECT	Fourth-ECT	Fifth-ECT
Number of words	20	20	16	22	16	23
z-scores	1.449	1.449	0.504	1.921	0.504	2.157
SDS	75	71		56		43
SAS	39	35		27		31

was characterized specifically by a significant increase in HbO2 response in broca region (ROI1 from left channels 2,5,7,8,13,14;ROI4 from right channels 42,44,49,50,53) and frontal pole region (ROI2 from left channels 9,15,16,21,22,23,27,29;ROI3 from right channels 30, 33, 35, 36, 37, 41, 43, 48; see Figure 2a). The mean HbO and HbR waveforms for the four ROIs in the healthy control group are shown in Figure 2b.

MDD Patient

The mean values of HbO and HbR waveforms per ECT treatment in patients with MDD at the four ROIs are shown in Figure 3. To the naked eye, the waveforms of depressed patients before treatment were different from those of normal people. With the number of treatments, the waveform characteristics have a tendency to shift towards the waveform characteristics of normal people, especially the fourth waveform characteristics are closest to normal people.

GLM Analysis

After GLM analysis, we found that the results were consistent with the waveform characteristics. As shown in Table 2 and Figure 4a, ROI 1/2/4 had the same trend, the number of channels activated in the normal range tended to decrease after the third treatment, and rose to the highest value after the fourth treatment. However ROI 3 showed a decreasing trend in the number of channels activated in the normal range after the third treatment and rose to the highest value after the fifth treatment.

Hemodynamic Response

Table 3 shows the z-scores of integral values and Figure 4b shows the trend of integral values, the trend of patients' integral value results is consistent with the trend of beta value results. The results of z-scores of integral values indicate that at the fourth ECT treatment, the integral values of ROI 1 and ROI 4 fell within the normal range.

Table 4 shows the z-scores of the centroid value, and Figure 4c shows the trend of the centroid value, which shows that the z-scores of the centroid value of ROI 2 and ROI 3 were within the normal range after each ECT treatment compared to the pre-treatment period, showing an anterior trend; ROI 2 had the smallest z-score of centroid value at the fourth ECT treatment. The z-scores of the centroid value of ROI 1 were within the normal range after each ECT treatment compared to the pre-treatment period, showing an anterior trend; ROI 2 had the smallest z-score of centroid value at the fourth ECT

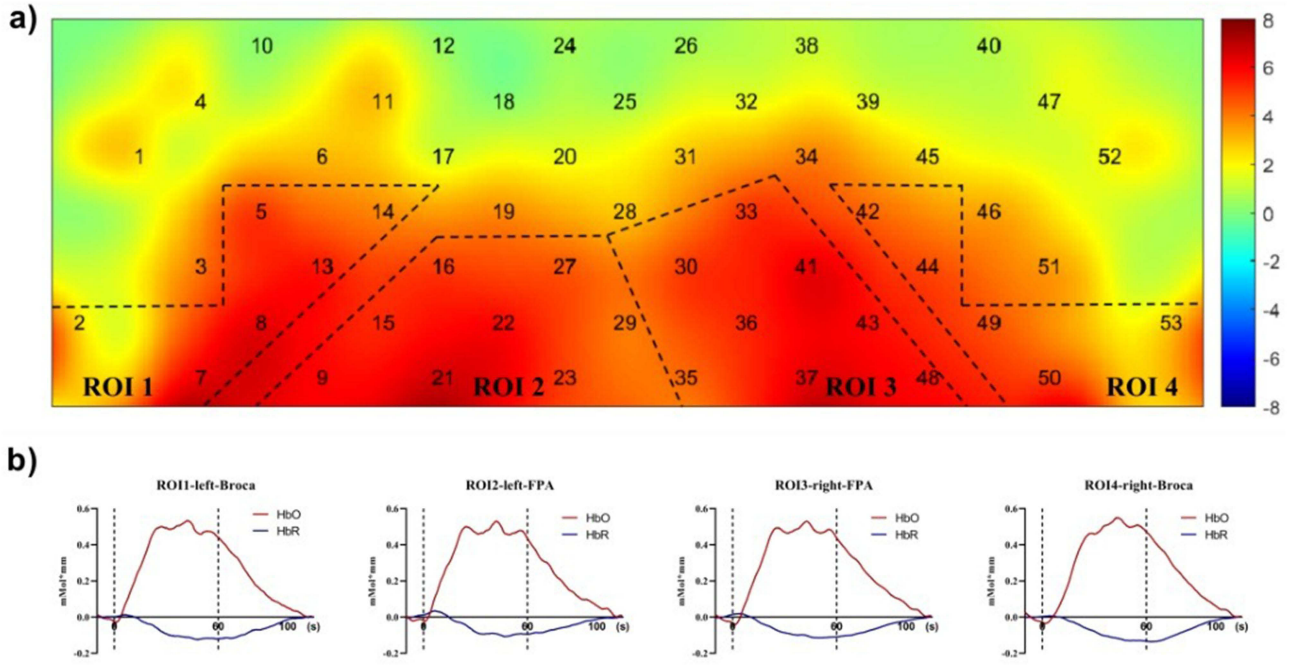

Figure 2 (**a**) Hemodynamic topography of activation for healthy controls, including ROIs outlined in black dotted line. (**b**) Mean hemodynamic response for HbO as well as HbR over our predefined ROI for the healthy group during the VFT.

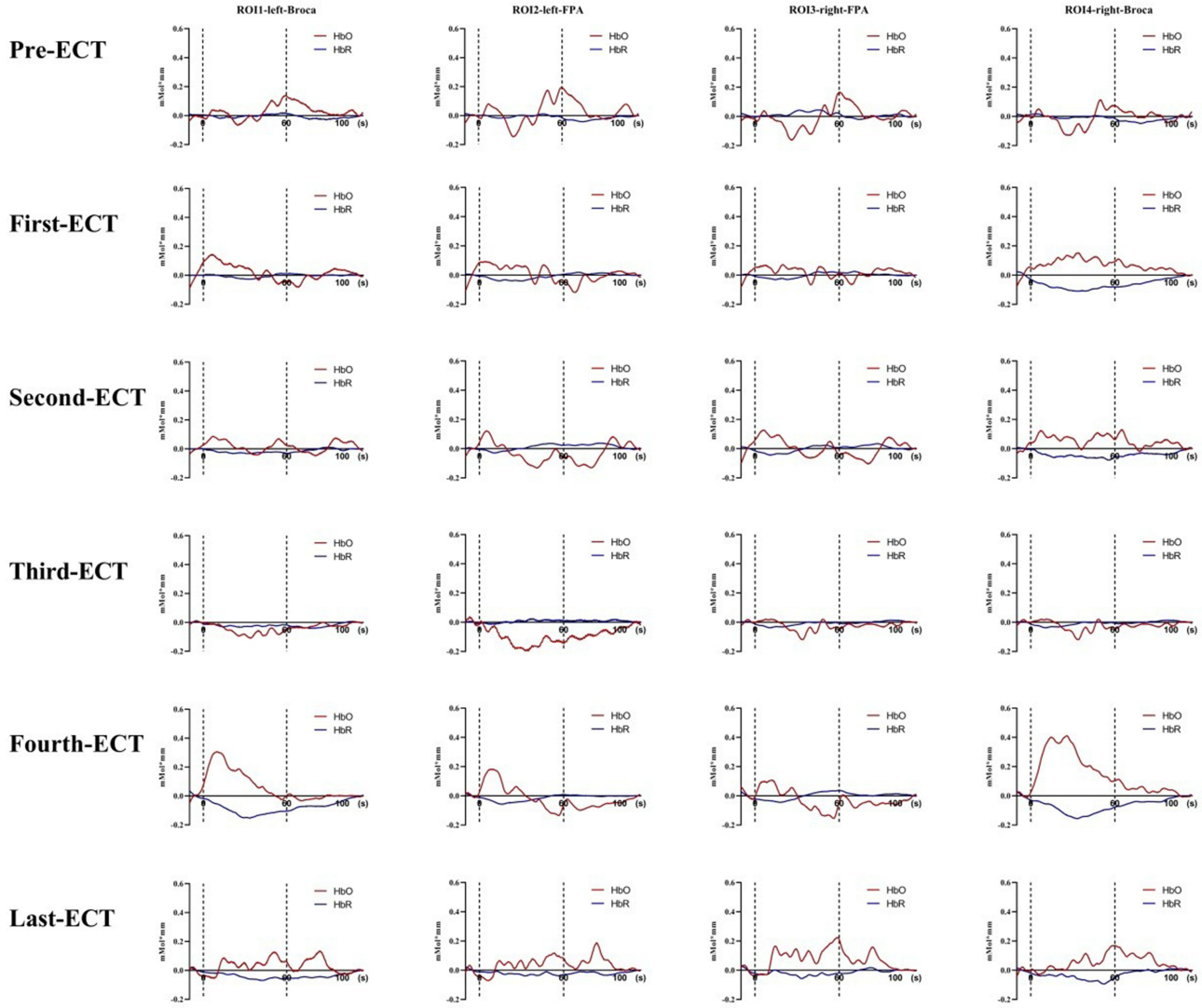

Figure 3 Mean hemodynamic response of MDD patients to HbO and HbR per-treatment at our predefined ROIs during VFT.

treatment. Compared to pre-treatment, the z-scores of the centroid value in ROI 1 was within the normal range after each ECT treatment except the second ECT treatment; the z-scores of the centroid value was the smallest during the fourth treatment. Compared to pre-treatment, the z-scores of the centroid value in ROI 4 was within the normal range after each ECT treatment except the last ECT treatment; the z-scores of the centroid value was the smallest during the fourth treatment.

Laterality Analysis

As shown in Figure 5, the laterality index of beta and integral values shows that the lateralization indices of the MDD patient exceeded the M±SD range of the healthy controls only at the third treatment and were negative. The laterality index of centroid value showed that the Broca brain region's laterality index at the first and the second ECT treatment were outside the M±SD range of the healthy control group. FPA brain regions at the first\second and fourth ECT treatments had laterality index outside the M±SD range of healthy controls. Our results suggest that the MDD patient was affected by lateralization at the third treatment compared to healthy controls.

Functional Connectivity

Figure 6 shows the functional connectivity matrix of MDD patient before treatment versus each ECT treatment. The trend of functional connectivity strength after ECT therapy in MDD patient was consistent with the trend of task state

Table 2 Ratio of the Number of Channels with z-Scores of Beta Values Within the Normal Range (±1 SD) to the Number of Channels in the Control Group Before and After Multiple Treatments in Patients with MDD in the Four ROI (The Number in Parentheses Indicates the Number of Channels). (Bolding Indicates That the z-Scores Fall Within the Normal Range)

	ROI 1	ROI 2	ROI 3	ROI 4
Pre-ECT	0.17(1)	0.13(1)	0.00(0)	0.20(1)
First-ECT	0.33(2)	0.38(3)	0.13(1)	0.25(2)
Second-ECT	0.33(2)	0.13(1)	0.25(2)	0.80(4)
Third-ECT	0.17(1)	0.25(2)	0.00(0)	0.25(2)
Fourth-ECT	**0.67(4)**	**0.63(5)**	0.13(1)	**1.00(5)**
Last-ECT	0.33(2)	0.25(2)	**0.63(5)**	0.13(1)

data. As shown in Figure 7, the functional connectivity results indicated that the number of functional connectivity edges in MDD patient was the lowest after the third treatment and the highest after the fourth ECT treatment.

Discussion

This study shows that ECT treatment effectively restores abnormal brain indices, including β value, integral value, centroid value, and functional connection edges, in MDD patients. It should be noted that, compared to the normal control group, this study did not find any statistically significant differences. The dynamic changes in these metrics were consistently supported by fNIRS.

In examining hemodynamic changes in the frontotemporal cortical region, we utilized fNIRS technology. Regions of Interest (ROIs) provided spatial location information within the result metrics. The β value and integral value of oxygenated hemoglobin described spatial characteristics, while the centroid value depicted temporal features. Additionally, functional connectivity edges offered insights into the brain network's structure. Results showed consistent trends across all four ROIs in terms of channel activation, integral values, centroid values, and functional connectivity edges after ECT administration. These findings further validate the impact of ECT on cortical activation and hemodynamics.

The centroid value, representing temporal changes during the task, indicates the time for the fNIRS signal to reach half of its change. A smaller value suggests a quicker cortical response post-task. The integral value signifies the magnitude of hemodynamic response during the activation task, indicating intensity. A higher value suggests increased neural activity associated with the cognitive task.

Previous studies have shown the significance of centroid values in distinguishing between depression and schizophrenia within the frontal lobe region.[35] Our study demonstrated abnormal centroid values in MDD patients pre-ECT treatment, which normalized post-treatment, aligning with changes in integral values. These consistent results highlight the reliability, stability, and robustness of the current findings.

Additionally, the clinical scale results indicate a gradual improvement in the course of the disease. However, the fNIRS results demonstrate a spiraling upward trend, indicating some inconsistency between the two metrics. While fNIRS may prove to be a more sensitive metric, the upward trend observed could reflect variations in the effectiveness of treatments across different sessions. This observation sheds light on the discrepancies observed in prior studies.[17,23] It is important to note that the present findings, based on a single patient, suggest that the fourth session may have yielded the most favorable outcomes. However, this does not provide conclusive evidence that additional sessions beyond this point would not lead to further improvements. Given the individual nature of treatment response and the lack of a clear plateau in clinical depression scores, it is premature to suggest that more sessions do not necessarily equate to better results. Future research with a larger sample size and a focus on clinical outcomes is needed to determine the optimal number of treatments within a course and to provide valuable insights for clinical treatment planning.

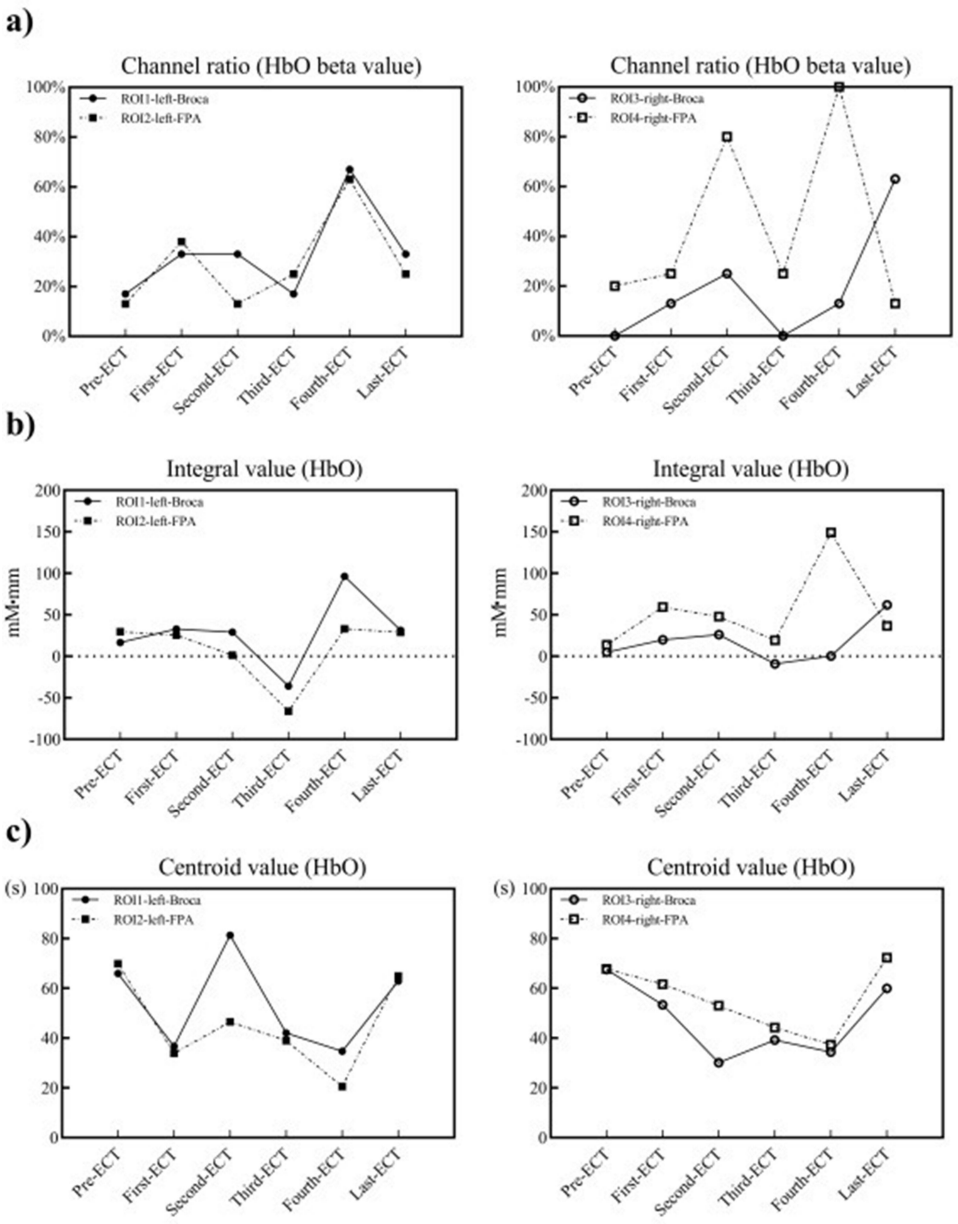

Figure 4 (**a**) Trends in the ratio of the number of channels with z-scores of beta values within the normal range (±1 SD) to the number of channels in the control group before and after multiple ECT treatments in patients with MDD in the four ROI. (**b**) Trends in integral value for MDD patients before and after multiple ECT treatments at the four ROIs. (**c**) Trends in centroid value for MDD patients before and after multiple ECT treatments at the four ROIs.

In terms of cognitive tasks, we opted for the VFT. Previous studies have demonstrated high sensitivity and specificity in screening for depression using versions of the VFT in Chinese, English, and Japanese populations.[28,42,43] Behaviorally, consistent with previous research, our study did not find a statistical difference in VFT word generation between depressed patients and normal controls at baseline.[44] While past studies observed a significant decline in VFT scores after ECT treatment,[45] we found that there were no significant behavioral changes in word generation during the VFT task after receiving ECT stimulation. This may be related to the placement of the ECT electrodes, as bilateral placement is associated with greater cognitive impairment.[46]

Some scholars have reported a heterogeneous pattern in individual subjects during the completion of the VFT in normal controls, but no hemispheric dominance was observed at the group level.[47] We did not find language lateralization in normal subjects using the Chinese version of VFT either. VFT comprises two modes: phonemic language fluency task

Table 3 Z-Score for the Integral Value Before and After Multiple Treatments for MDD (Bolding Indicates That the Z-Score is Within the Normal Range)

	ROI 1	ROI 2	ROI 3	ROI 4
Pre-ECT	−1.406	−1.278	−1.735	−1.315
First-ECT	−1.300	−1.304	−1.619	−1.027
Second-ECT	−1.324	−1.455	−1.570	−1.101
Third-ECT	−1.750	−1.879	−1.843	−1.280
Fourth-ECT	**−0.884**	−1.257	−1.770	**−0.457**
Last-ECT	−1.310	−1.284	−1.291	−1.171

Table 4 Z-Score for the Centroid Value Before and After Multiple Treatments for MDD (Bolding Indicates That the Z-Score is Within the Normal Range)

	ROI 1	ROI 2	ROI 3	ROI 4
Pre-ECT	1.256	1.159	1.144	1.116
First-ECT	**−2.061**	**−1.978**	**−0.319**	**0.453**
Second-ECT	3.007	**−0.875**	**−2.730**	**−0.474**
Third-ECT	**−1.462**	**−1.538**	**−1.790**	**−1.432**
Fourth-ECT	**−2.292**	**−3.144**	**−2.293**	**−2.165**
Last-ECT	**0.908**	**0.727**	**0.356**	1.604

(phonemic VFT) and semantic language fluency task (semantic VFT). In our study, we utilized the phonemic language fluency task, which has been previously associated with the prefrontal cortex (PFC),[48] an area closely linked with cognition. In MDD patients, we observed rightward lateralization during VFT after the third ECT treatment. This marks the first use of fNIRS to discover the impact of ECT on language lateralization in MDD patients. It's worth noting that our study is the first to report on lateralization in the Chinese version of the VFT task. Previous literature has also shown lateralization in depressive patients and suggested its association with patient prognosis.[49]

Describing the ECT treatment protocol is crucial, as different settings and parameters can lead to varied outcomes. Currently, the most commonly used methods internationally are unilateral and bilateral stimulation. Although bilateral stimulation is more prevalent in Europe, our region tends to favor unilateral stimulation.[50] Previous research indicates that unilateral and bilateral stimulation have similar efficacy, but unilateral stimulation is associated with fewer cognitive side effects.[51] In our ECT treatment, we opt for a pulse width of 0.5 milliseconds and a stimulus intensity based on 80% of the age-based method (ABM). Pulse width and stimulus dosage are relevant to the efficacy of ECT; a narrower pulse width requires a higher energy dose to achieve the same therapeutic effect. The electrodes are placed in the right temporoparietal region. We opted for unilateral stimulation due to its similar efficacy and lower cognitive impairment compared to bilateral stimulation.

Given the cognitive impairment often reported by patients during ECT treatment, we attempted to correlate the lateralization phenomenon with subjective cognitive decline. In our results, we did not observe a clear activation in the right hemisphere after the third ECT treatment. Instead, we observed a more significant decrease in cortical hemodynamics on the left side. Therefore, we believe that the emergence of rightward lateralization in VFT is associated with cognitive decline after ECT. However, we also found that this lateralization is not persistent, as it disappears after the fourth ECT treatment. This could explain the transient cognitive decline observed after ECT treatment.

Regarding activation in brain regions, consistent with previous studies using perfusion MRI,[52] we found that the activation trend was most pronounced in ROI-4 under the right temporal electrode when the CFB increased in the cortex.

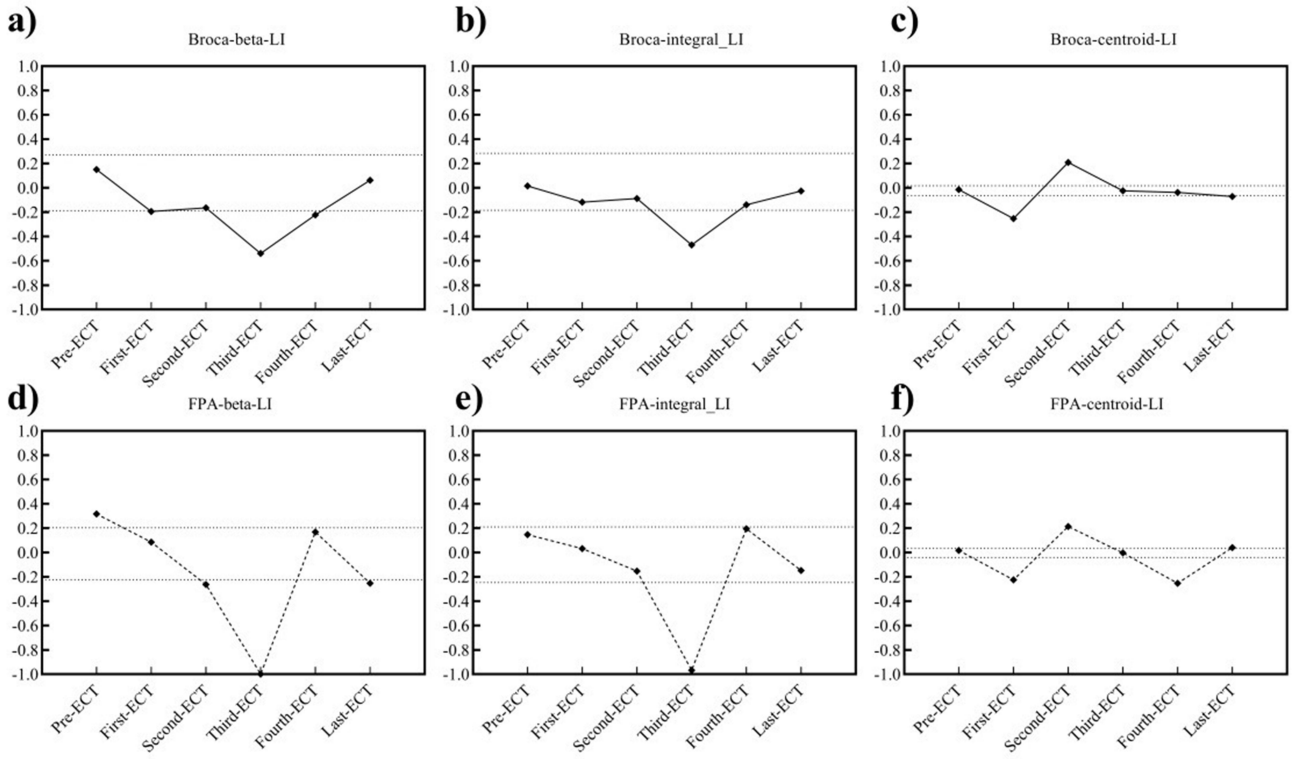

Figure 5 (**a**) Lateralized values of beta value in Broca's area before and after multiple ECT treatments in MDD patient. (**b**) Lateralized values of integral value in Broca's area before and after multiple ECT treatments in MDD patient. (**c**) Lateralized values of centroid value in Broca's area before and after multiple ECT treatments in MDD patient. (**d**) Lateralized values of beta value in FPA before and after multiple ECT treatments in MDD patient. (**e**) Lateralized values of integral value in FPA before and after multiple ECT treatments in MDD patient. (**f**) Lateralized values of centroid value in FPA before and after multiple ECT treatments in MDD patient.

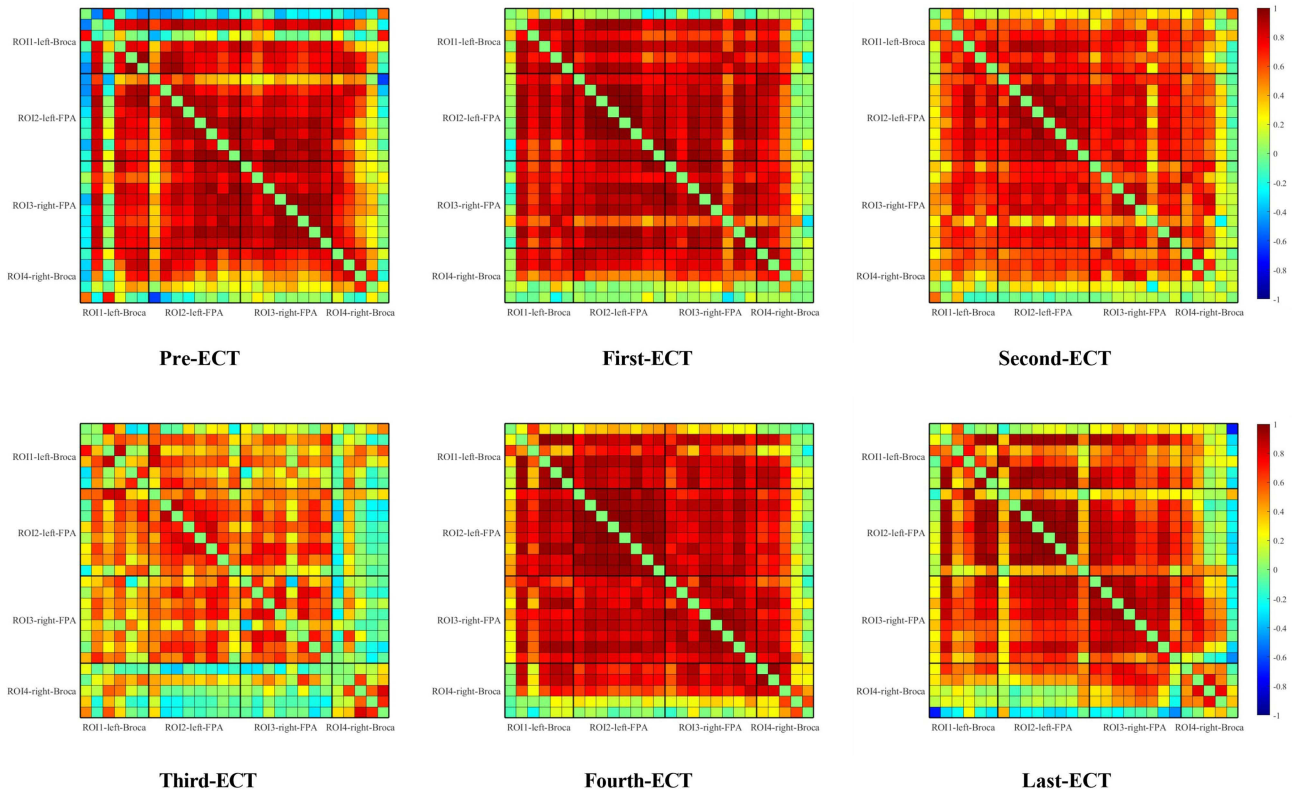

Figure 6 Functional connectivity of MDD patients before and after multiple ECT treatments.

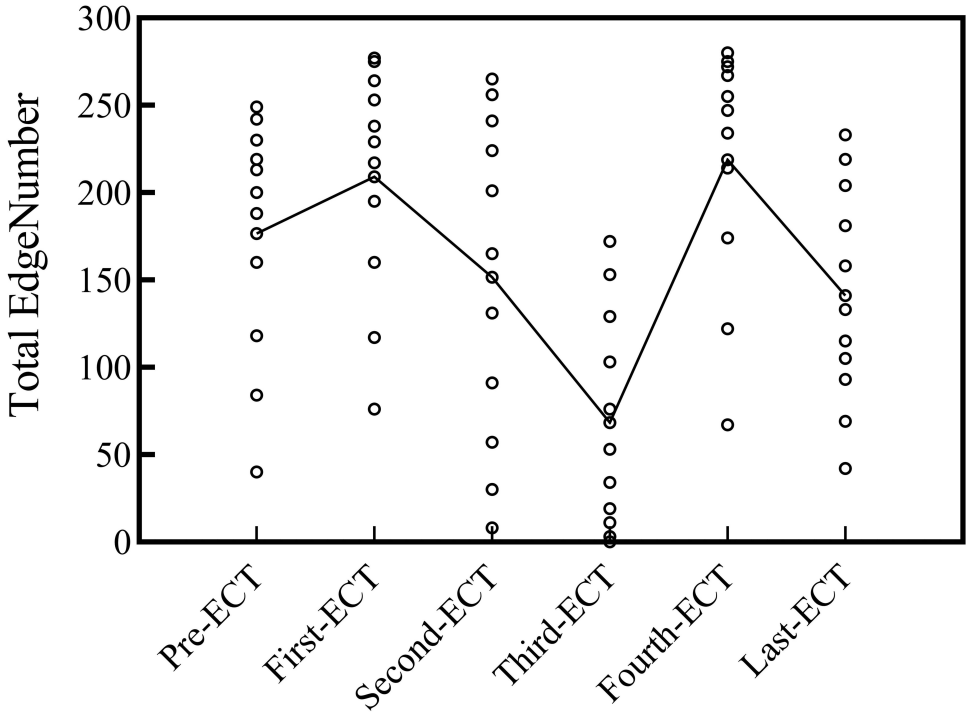

Figure 7 Number of functionally connected edges in MDD patients before and after multiple ECT treatments.

This area is close to the location of the right temporal ECT electrode, indicating a close relationship between the neuroplasticity of this brain region and the effect of right unilateral ECT.[52]

In terms of functional connectivity, we conducted a preliminary exploration using node metrics, which exhibited trends consistent with task-related metrics. This confirms the feasibility of combining resting-state and task-related metrics in fNIRS.

Compared to previous studies, our research distinguished itself through the delineation of ROIs, emphasis on ECT parameter configuration, diverse outcome metrics, and dynamic assessments after each ECT session.

Limitations and Implications

While our study represents the inaugural exploration of dynamic cerebral blood flow changes in ECT using fNIRS, it is important to acknowledge certain limitations. The sample size was small, and deviations from the recommended 8–12 ECT sessions, as outlined in the guidelines, occurred due to patients' perceived symptom improvement and subsequent reluctance to undergo additional treatments. Furthermore, the absence of long-term follow-ups constitutes a notable deficiency in our study.

These limitations underscore the need for comprehensive investigation in future research endeavors. The commonality and heterogeneity observed in depressive disorders, combined with the existing constraints in treatment modalities, emphasize the urgency of in-depth exploration in forthcoming studies.

Conclusion

In summary, our findings suggest that changes in cerebral blood flow during a single session of ECT are dynamic, not static. The use of fNIRS for monitoring these dynamic cortical activity changes proves to be a viable method. The consistency observed in fNIRS outcome measures validates its stability as a metric.

While the overall effectiveness of ECT is established, there remain uncertainties regarding individual-level variations in cognitive function and therapeutic efficacy. Compared to MRI, fNIRS technology offers advantages like high ecological validity, low noise interference, high temporal resolution, and insensitivity to motion artifacts. Given the preliminary findings from this single-patient study, fNIRS shows promise as a tool for monitoring dynamic cerebral

blood flow changes during ECT treatment. This suggests potential for fNIRS to offer valuable insights into treatment response and brain function, although further research with larger patient cohorts is needed to substantiate these preliminary observations and explore its full utility in clinical settings. By assessing CBF changes after each ECT session at an individual level, implementing closed-loop control, and making timely adjustments, we can optimize treatment frequency and customize ECT protocols. This offers a practical and feasible avenue for precision treatment of depressive disorders.

Abbreviations

BROCA, Broca's area; CV, coefficient of variation/ Centroid Value; deoxy-Hb, deoxygenated hemoglobin; DLPFC, dorsolateral prefrontal cortex; DSM-5, the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders; ECT, Electroconvulsive Therapy; FEF, frontal eye field; fNIRS, functional Near-Infrared Spectroscopy; FPA, frontal pole area; GLM, general linear model; HRF, hemodynamic response function; IV, Integral Value; MDD, Major Depressive Disorder; ECT, Modified Electroconvulsive Therapy; OD, optical density; oxy-Hb, oxygenated hemoglobin; PFC, prefrontal cortex; PreM, Pre-motor area; ROIs, regions of interest; RSFC, resting-state functional connectivity; RUL, right unilateral; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; SMA, Supplementary motor area; total-Hb, total hemoglobin; TP-RUL, temporoparietal right unilateral; TRD, Treatment-Resistant Depression; VFT, Verbal Fluency Task.

Data Sharing Statement

All the Functional Near-Infrared Spectroscopy (fNIRS) data of participants in the study are accessible at https://figshare.com/s/20438fed9a5f2de9b235.

Ethical Approval

This study was granted ethical approval by the Ethics Committee of the Sichuan Mental Health Center. Compliance with the Declaration of Helsinki was strictly observed throughout the research process. Written informed consent, including consent for publication, was obtained from all participants prior to their involvement in the study. This statement confirms that each participant, or their legal guardian if the participant is unable to provide consent, was fully informed about the study's purpose, procedures, potential risks, and benefits, and voluntarily agreed to participate and have their data published.

Informed Consent

Consent to participate in the study was obtained in writing from the legal guardians or next of kin of each participant involved.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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