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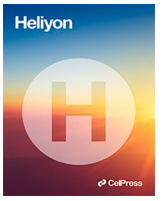

Research article

Altered functional brain activity in first-episode major depressive disorder treated with electro-acupuncture: A resting-state functional magnetic resonance imaging study

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ABSTRACT

Background: Previous studies have found electroacupuncture could improve the clinical symptoms of first-episode major depressive disorder (MDD), but the exact neural mechanism of action needs to be further elucidated.

Methods: Twenty-eight first-episode MDD patients were randomly divided into 14 electro-acupuncture stimulation (EAS) groups and 14 sham-acupuncture stimulation (SAS) groups, and clinical symptoms were assessed and functional magnetic resonance imaging (fMRI) scans were done in both groups. Amplitude of low-frequency fluctuations (ALFF) was used to observe the changes between the pre-treatment and post-treatment in the two groups, and the altered brain areas were selected as region of interest (ROI) to observe the FC changes. Meanwhile, the correlation between the altered clinical symptoms and the altered ALFF and FC of brain regions in the two groups was analyzed.

Results: The EAS significantly decreased the HAMD-24 and HAMA-14 scores of MDD than SAS group. The imaging results revealed that both groups were able to increase the ALFF of the left middle temporal gyrus and the left cerebellar posterior lobe. When using the left middle temporal gyrus and the left posterior cerebellar lobe as ROIs, EAS group increased the FC between the left middle temporal gyrus with the left superior frontal gyrus, the left middle frontal gyrus, and the left hippocampus, and decreased the FC between the left posterior cerebellar lobe and the left calcarine gyrus, while SAS group only increased the FC between the left middle temporal gyrus with the left superior frontal gyrus. The alternations in clinical symptoms after EAS treatment were positively correlated with the altered ALFF values in the left middle temporal gyrus and the altered FC values in the left middle temporal gyrus and the left middle frontal gyrus.

Conclusion: EA demonstrates modulation of functional activity in the default mode network (DMN), sensorimotor network (SMN), cognitive control network (CCN), limbic system, and visual network (VN) for the treatment of the first-episode MDD. Our findings contribute to the neuroimaging evidence for the efficacy of EAS.

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1. Introduction

Major Depressive Disorder (MDD) is a common and complex affective disorder characterized by persistent depression and pessimism, and even suicidal tendencies may occur [1,2]. Studies have shown that over 300 million people around the world suffer from MDD, which will play a vital role in the disease burden globally by 2030 [3,4]. Thus, effective and safe treatment for MDD remains a pressing research topic.

Currently, treatment for MDD consists of antidepressant medication, physical therapy and cognitive behavioral therapy [5–7]. However, most antidepressants cause tolerance and dependence in the body and are associated with a certain degree of side effects [8,9]. So far, cognitive behavioral therapy is promising for MDD. However, absence of compliance and demands of professional practitioners in this therapy have increased the difficulty in the clinical practice [10]. In addition, although physical therapy, including deep brain stimulation and vagus nerve stimulation, is effective for MDD, there are shortcomings such as invasiveness and high cost, which also limit its clinical use [11–13].

Electro-acupuncture and acupuncture are very important complementary therapies for MDD, acting as a multi-level, multi-target modulation by stimulating the patient's acupoints, thus serving to improve the clinical symptoms of MDD patients [14,15]. Although the efficacy and safety of electroacupuncture have been confirmed in previous studies [16,17], further elucidation is needed regarding the mechanism of therapeutic efficacy in MDD.

Resting-state functional magnetic resonance imaging (rs-fMRI) is an useful tool of explaining the complex brain activities, and it has been gradually applied to the field of psychiatric disorders in recent years [18,19]. In particular, there are studies on the brain mechanisms of MDD subtypes, including first-episode depression (FDE), recurrent depression and treatment-resistant depression (TRD), also applied to different age groups and different areas of sex differences [20–23]. The amplitude of low frequency fluctuation (ALFF), a common parameter of local brain function in rs-fMRI, reflects the level of spontaneous activity of each voxel in the brain by calculating the amplitude of blood oxygenation level-dependent (BOLD) signal relative to the baseline [24]. Functional connectivity (FC) is a hypothesis-driven analysis based on extracting time series of BOLD signals for each voxel in ROI and then calculating correlation studies with time series from other brain regions throughout the brain [25]. The combination of ALFF and FC in previous studies is helpful to explain the therapeutic mechanism more comprehensively [26,27].

Therefore, we observed the altered value of ALFF and FC of EA treatment in first-episode MDD by rs-fMRI technique, and the correlation between alteration and clinical scores. This study will demonstrate some implications and reference value for EAS to modulate the neuropathologic mechanism of MDD.

2. Methods

2.1. Subjects

The 28 right-handed first-episode MDD with were enrolled from Guang' anmen Hospital, China Academy of Chinese Medical Sciences. The experienced psychiatrists assessed patients' eligibility with the Diagnostic and Statistical Manual of Mental Disorders-fifth criteria (DSM-V) and 24-item Hamilton Depression Rating Scale (HAMD-24)$\geq$20. And patients' age was 18–60 years. Patients with severe chronic medical or neurological diseases, bipolar disorder, anxiety disorder or other mental disorders, risk of suicide, drug or alcohol addicts, and contraindications to MRI scanning were excluded.

During the treatment, it was not allowed to take psychiatric drugs , cognitive behavioral therapy and other complementary and alternative treatments. In addition, all patients were required to undergo assessment on the 14-item Hamilton Anxiety Scale (HAMA-14). The study protocol was approved by the Ethics Committee of Guang' anmen Hospital, China Academy of Chinese Medical Sciences (NO. 2014EC084-01).

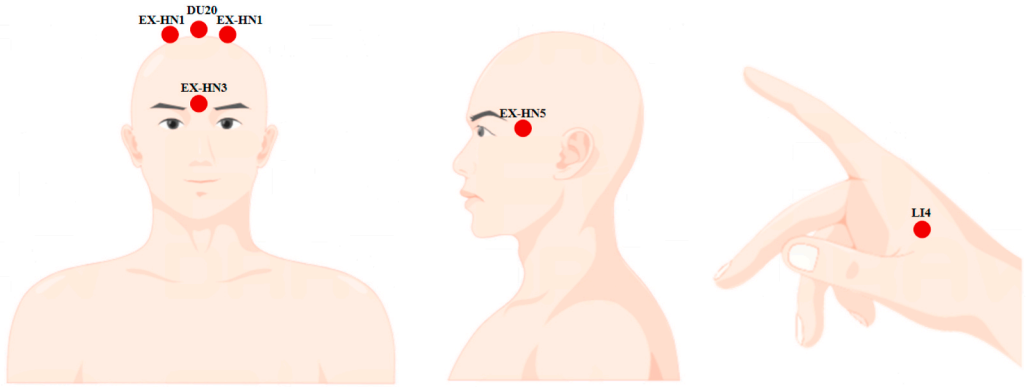

Fig. 1. |Location of Baihui acupoint (DU20), Si Shen Cong acupoint (EX-HN1), Tai Yang acupoint (EX-HN5), Yin Tang acupoint (EX-HN3), and He Gu acupoint (LI4).

2.2. Experiment paradigm

We divided 28 patients with first-episode MDD into 14 each in the electro-acupuncture stimulation (EAS) group and the sham-acupuncture stimulation (SAS) groups. The acupuncture points for depression were based on the meridian theory of traditional Chinese medicine and clinical practice. In the EAS group, acupuncture points were Bai hui (DU20), Si Shen Cong (EX-HN1), Tai Yang (EX-HN5), Yin Tang (EX-HN3), and He Gu (LI4). Electrodes were connected to the needle handles of the four acupuncture points after acupuncture (the EAS instrument was selected from the Hua Tuo brand electronic acupuncture instrument SDZ-V), and the waveform was selected as continuous wave with a pulse frequency of 1HZ, and the amplitude was based on the patient's feeling of jumping at the needle tip and tolerable. In the SAS group, the needles were put in the superficial area of the same five acupoints in each patient. No manipulation was performed during the entire treatment, thus not DE Qi was obtained from the acupuncture points. Patients in both groups were stimulated 3 times one week (every other day) for 30 min/time for 6 weeks (18 times in total) , (Fig. 1).

2.3. MRI data acquisition

All MDD patients in this study acquired MRI (Siemens Medical, Erlangen, Germany) data at the Department of Radiology, Guang' anmen Hospital, China Academy of Chinese Medical Sciences. Patients lie on the examination bed and put on noise-cancelling headphones during the fMRI examination. The scan sequence was first performed in T1WI and then in the same plane as the T1WI image using a planar echo imaging (EPI) sequence. The parameters included time repetition (TR) 5000 ms, echo time (TE) TE 2.98 ms, layer thickness 1 mm, layer interval 0.6 mm, 32 layers, field of view (FOV) 240 mm × 256 mm, flip angle (FA) 4°and scan time 8 min 22 s. Blood oxygenation level dependent (BOLD) imaging parameters included TR 2000 ms, TE 30 ms, FA 90°, layer interval 0.6 mm, 32 layers, matrix 64 × 64, FOV 224 mm × 224 mm, and scan time 6 min 46 s.

2.4. Image preprocessing

The DPARSF 6.0 toolkit of Matlab 2021a platform was used to process the image data with the following procedure: (1) the DICOM format to NIFTI format; (2) removing the first 10 time points data; (3) slice timing; (4) head movement correction (movement≥2 mm in any direction and 2°were removed); (5) spatial normalization, transforming subjects' functional images into Montreal Neurological Institute (MNI) space, resampling to 3 mm × 3 mm × 3 mm spatial resolution; (6) spatial smoothing using a 6 mm smoothing kernel (7) linear detrending; (8) regression covariance to remove white matter brain signal, 24 head movement parameters, and cerebrospinal fluid signal; (9) 0.01–0.08 Hz filtering of the preprocessed images.

2.5. Amplitude of low frequency fluctuation analysis

Before Amplitude of low frequency fluctuation (ALFF) data processing, we conducted a 6 mm × 6 mm × 6 mm smoothing kernel, and then got the power spectrum by Fourier transforming the voxel-by-voxel time series using fast Fourier transform. Next, we calculated the square root of each power spectrum at frequency, and obtained the ALFF by squaring and homogenizing the frequency power spectra in the 0.01–0.08 Hz filter band, and then averaged the voxel-by-voxel ALFF values with the whole-brain ALFF and performed Z-transformation to obtain the normalized zALFF values.

2.6. Functional connectivity analysis

We selected the difference brain regions after ALFF statistics as regions of interest (ROI) to perform the Functional connectivity (FC) analysis. We calculated the correlation coefficient (r) between the mean time series of the difference brain regions and the time series of other voxels in the whole brain, and then used Fisher Z-transformation to transform into Z-values, further got the FC intensity values.

2.7. Statistical analysis

The comparisons were performed using SPSS 23.0 software. T-tests or the chi-square test were applied to compare clinical basic information between the two groups at baseline. Analysis of covariance was utilized to compare the differences in longitudinal alternations of clinical scores between the two groups pre-treatment and post-treatment. The threshold for these differences was set at $P < 0.05$.

Image data processing was analyzed using the DPARSF 5.0 toolkit. Repeated measures of ANCOVA were used to reflect the treatment effect as an interaction effect of group (EAS group, SAS group) × time (pre-treatment, aft-treatment). The parameters including sex, age, education level and head movement were also used as covariates. Gaussian random fields (GRF) were used for multiple comparison correction, with threshold voxel levels set as $P < 0.005$ and cluster levels set as $P < 0.05$, considered statistically significant, and a minimum nuclear voxel number threshold set at 15.

DPARSF 6.0 software was applied to extract ALFF values and FC values for the four groups of differential brain regions. We utilized a post hoc two-sample t-test analysis between groups with SPSS 23.0, with a threshold set at $P < 0.05$ as statistically significant. Then, we further analyzed the correlation between the altered brain regions in ALFF values and FC values in abnormal brain and decreased clinical scores in the two groups, respectively, controlling for age, sex, head movement parameters and education level, and $P < 0.05$ was set statistically significant.

3. Results

3.1. Demographic characteristics and clinical symptoms

No statistical differences was found between the two groups for age, sex, education level, HAMD-24 scores and HAMA-14 scores (Table 1).

3.2. Clinical outcomes

For the HAMD-24 score, analysis of covariance displayed that the group main effect was significant ($F = 3.829$, $P = 0.047$). The group × time interaction effect was significant ($F = 4.732$, $P = 0.040$), and post hoc analyses showed a more significant improvement in the EAS group than in the SAS group post-treatment.

For the HAMA-14 score, analysis of covariance displayed that the group main effect was significant ($F = 4.327$, $P = 0.043$). The group × time interaction effect was significant ($F = 5.103$, $P = 0.032$), and post hoc analyses showed a more significant improvement in the EAS group than in the SAS group post-treatment. (Table 2).

3.3. The group × time interaction effect in ALFF among the four groups

The group × time interaction effect in ALFF among the four groups was located in the left middle temporal gyrus (MTG) and left cerebellar posterior lobe (CPL). We did not find the difference in the main effect. (Table 3,Fig. 2).

3.4. Post hoc analyses in ALFF among the four groups

In both groups, ALFF was increased in the left MTG and the left CPL compared to the pre-treatment group. When compared between the two groups aft-treatment, the increase in ALFF in the left CPL was more significant in the EAS group than the SAS group (Fig. 3).

3.5. The group × time interaction effects in seed-based FC among the four groups

When the left MTG was the seed, the group × time interaction effects in FC among the four groups was located in the left superior frontal gyrus (SFG), left middle frontal gyrus (MFG)and left hippocampus. When the left CPL was the seed, the group × time interaction effects in FC among the four groups was located in the left calcarine. No significant difference was found in the main effect (Table 4, Fig. 4).

3.6. Post hoc analyses in FC among the four groups

When the left MTG was used as the seed, the post-EAS group increased FC in the left SFG, left MFG and left hippocampus than pre-EAS group, while the post-SAS group increased FC in the left SFG, than pre-SAS group. When the left CPL was used as the seed, the post-EAS group decreased FC in the left calcarine compared to the pre-EAS group, and more significant decreases was found in the post-EAS group compared to the post-SAS group (Fig. 5).

3.7. Correlation with clinical scores

In the EAS group, we observed a negative correlation between the change in ALFF of the left MTG and the change in HAMD-24 score ($r = -0.646$, $P = 0.013$), and a positive correlation between the change in FC of the left MTG and left MFG and the change in HAMD-24 score ($r = 0.539$, $P = 0.047$) [Fig. 6(A and B)]. However, no significant correlation between the changes in clinical scores and changes in brain function in the ASA group.

Table 1
Clinical and demographic features.

Items	electro-acupuncture	sham-acupuncture	t/X^2	*P*-value
Age (Years)	36.28 ± 6.88	39.64 ± 7.06	−1.273	0.214[a]
Sex (M/F)	4/10	5/9	0.164	0.686[b]
Education (years)	13.42 ± 3.43	14.21 ± 3.01	−0.643	0.526[a]
HAMD-24	23.00 ± 3.01	23.85 ± 3.57	−0.687	0.498[a]
HAMA-14	19.28 ± 3.58	19.42 ± 4.44	−0.094	0.926[a]

[a] *P*-value from a two-sample *t*-test.
[b] *P*-values from a chi-square test.

Table 2
Longitudinal changes of clinical outcomes (Mean ± SD).

Items	electro-acupuncture	sham-acupuncture	*F*	*P*
HAMD-24_pre	23.00 ± 3.01	23.85 ± 3.57	4.732	0.040
HAMD-24_post	9.28 ± 4.59[a]	15.42 ± 6.40		
HAMA-14_pre	19.28 ± 3.58	19.42 ± 4.44	5.103	0.023
HAMA-14_post	8.64 ± 4.74[a]	12.71 ± 4.89		

[a] Post hoc analyses compared between the two groups post-treatment , $P < 0.05$.

Table 3
The group × time interaction effect in ALFF among the four groups.

Clusters	Brain Regions	Peak Coordinates (MNI)			Cluster Size	*F*-Values
		X	Y	Z		
1	left middle temporal gyrus	−51	−12	−15	21	26.430
2	left posterior cerebellar lobe	−39	−81	−30	24	25.122

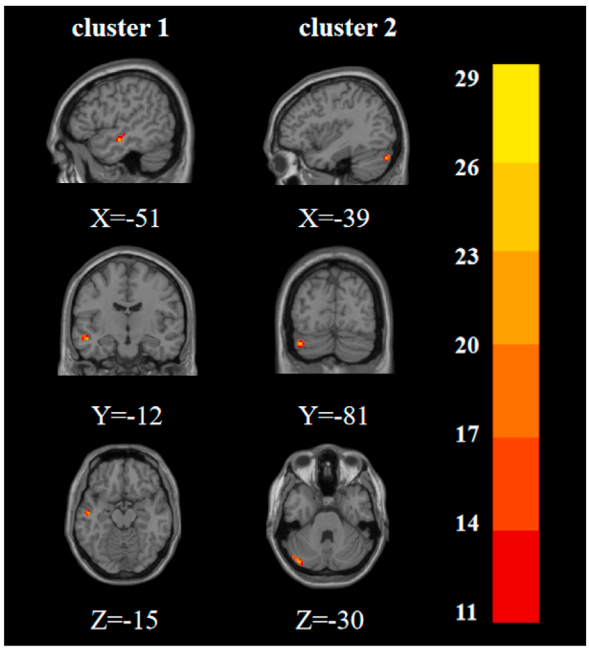

Fig. 2. The group × time interaction effect in ALFF among the four groups.

4. Discussion

To our knowledge, this is the first study to investigate the brain effect mechanisms of EAS treatment for 6 weeks as compared with SAS in MDD patients. This research reflexed the clinical cumulative effect based on the 6 weeks' EAS treatment instead of the immediate modulation. This study showed EAS treatment induced brain functional activity changes in ALFF and FC value, and we observed the correlation between the changes and clinical symptom. This research provides new insights into the neural mechanism of EAS in treating MDD.

In this research, we observed that both EAS and SAS groups were able to increase ALFF in the left MTG of MDD patients. The MTG mainly participates in human memory, emotion regulation, self-reference, and semantic processing, and is also an important region of the DMN [28–30]. Previous studies have shown that ALFF was lower in the left MTG in the FDE compared with the healthy controls [31]. Another TRD study showed that ALFF in the left MTG was decreased comparing with the non-TRD group, suggesting that impaired function of the left MTG may play an important role in the pathological mechanism of MDD [32]. Moreover, previous study also found the vortioxetine could increase ALFF values of the MTG in MDD [33]. In this study, we also observed the relationship between ALFF changes in the left MTG and HAMD-24 changes after EAS, indicating that modulation of the MTG is an important target for EAS treatment.

We found that both the EAS and SAS groups were able to increase ALFF in the left CPL, and the increase was more significant in EAS

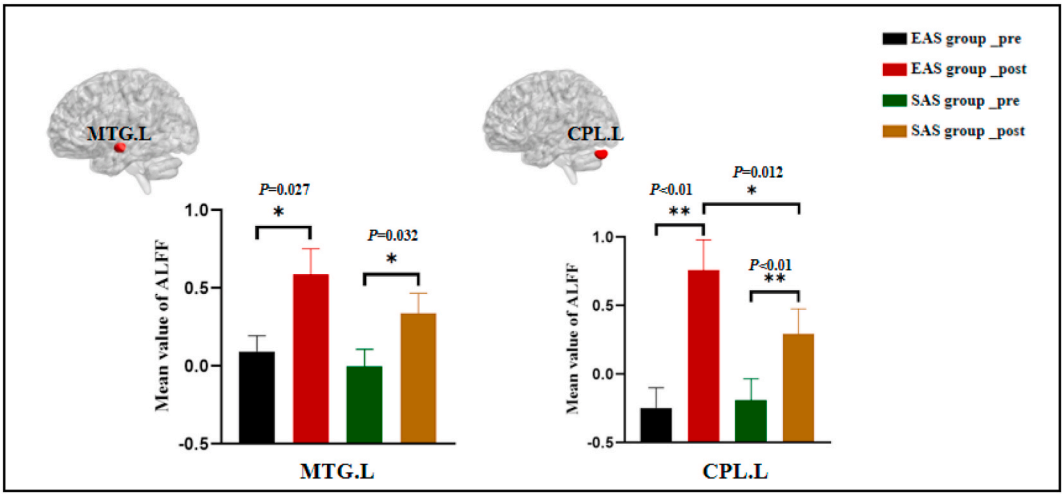

Fig. 3. Post hoc analyses in ALFF among the four groups. MTG. L, left middle temporal gyrus; CPL,left cerebellumposterior lobe; EAS group,electro-acupuncture stimulation group; SAS group, sham-acupuncture stimulation group; *, $P < 0.05$; **, $P < 0.01$.

Table 4
The group × time interaction effect in seed-based FC among the four groups.

Seed	Clusters	Brain Regions	Peak Coordinates (MNI)			Cluster Size	*F*-Values
			X	Y	Z		
left middle temporal gyrus	1	left superior frontal gyrus	−18	48	30	19	27.523
	2	left middle frontal gyrus	−30	54	6	16	25.989
	3	left hippocampus	−24	−12	−24	17	13.177
left posterior cerebellar lobe	1	left calcarine	−15	−78	6	23	22.513

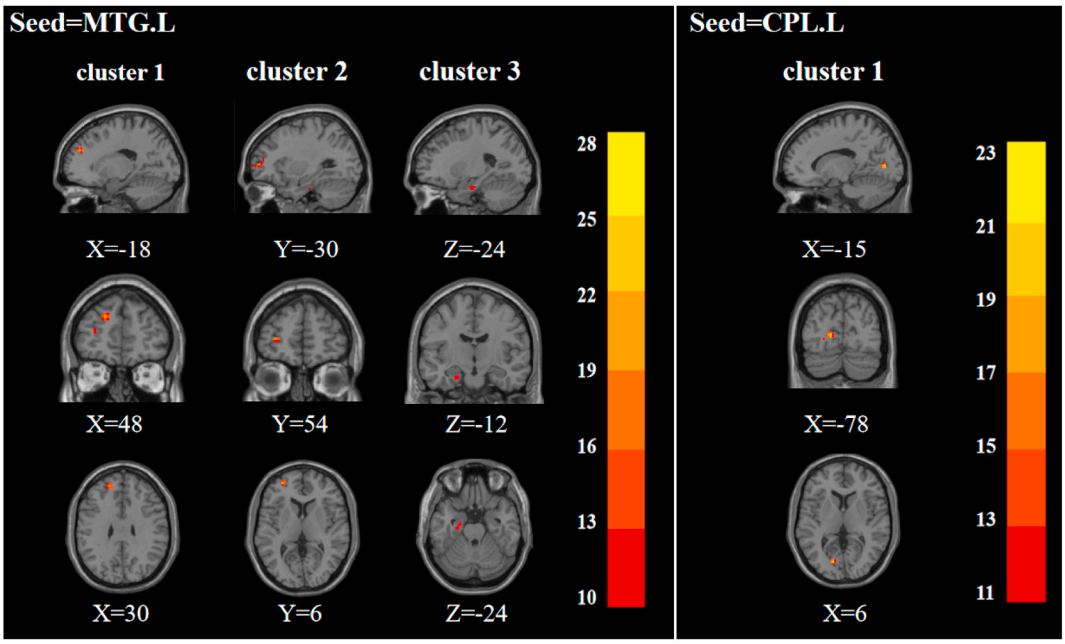

Fig. 4. The group × time interaction effect in FC among the four group. MTG, middle temporal gyrus; CPL, cerebellum posterior lobe; L, left.

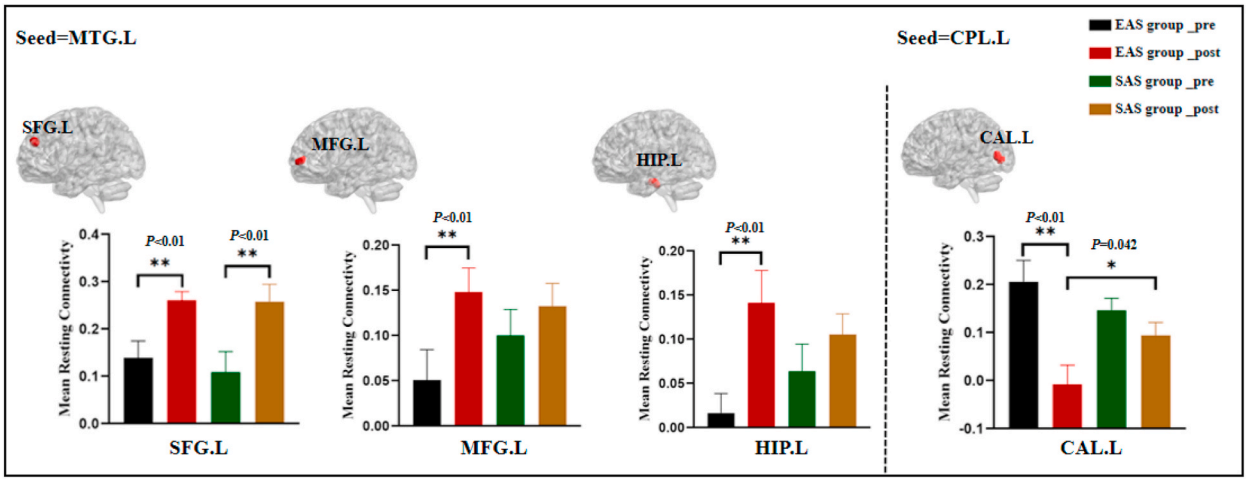

Fig. 5. Post hoc analyses in FC among the four groups. MTG, middle temporal gyrus; CPL,cerebellum posterior lobe; SFG, superior frontal gyrus; MFG, middle frontal gyrus; HIP, hippocampus; CAL. calcarine; L, left. EAS group, electro-acupuncture stimulation group; SAS group, sham-acupuncture stimulation group; *, $P < 0.05$; **, $P < 0.01$.

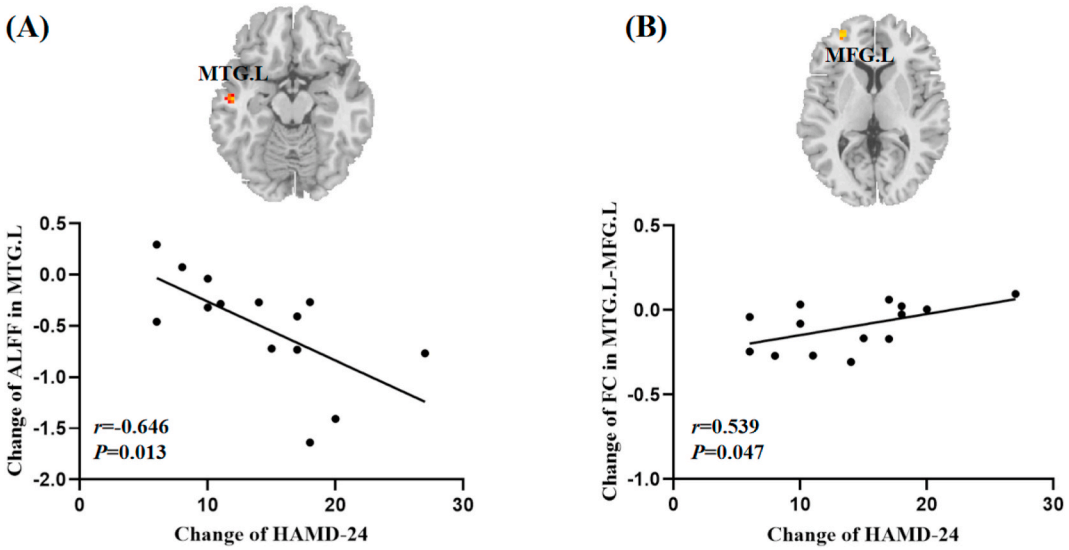

Fig. 6. Correlation with clinical scores. (A)negative correlation between the value of change in ALFF in the left MTG and the value of change in HAMD-24 score; (B)positive correlation between the value of change in FC in the left MTG and left MFG and the value of change in HAMD-24; MTG, middle temporal gyrus; MFG, middle frontal gyrus.

than in SAS group. The left CPL belongs to the SMN and is involved in sensory, motor functions, emotional and cognitive processing activities [34–36]. A previous study found the TRD group had lower ALFF in CPL compared to the nTRD group, and the ALFF in the CPL was also correlated with depression severity, suggesting that the cerebellum also plays a part in MDD [32]. A study also observed that ketamine can alleviate MDD by modulating the FC of the salience network and the cerebellum [37]. Another study found that improved clinical efficacy of duloxetine in MDD was associated with reversal of the FC between the striatum and the left cerebellum [38]. A review suggests that acupuncture for the treatment of disease requires particular attention to the action of cerebellum in executive, emotional and motor aspects [39]. Thus, our findings indicate that the regulation of cerebellar functional activity plays the key role in EAS treatment for MDD patients.

In this study, the EAS group increased the FC of the left MTG with the left SFG and the left MFG after treatment in MDD patients, while the SAS group only increased the FC of the left MTG with the left SFG. The left SFG and left MFG are located in the dorsolateral prefrontal cortex (DLPFC) and are important components of the cognitive control network (CCN), mainly participate in situational memory, task switching, attention, and top-down executive control [40–42]. A meta-analysis demonstrated that MDD decreased FC in the right MFG and left precuneus compared to the HC group, indicating that FC abnormalities in CCN and DMN are strongly associated with MDD onset [43]. Several previous physical therapies using DLPFC as a target for the treatment of MDD were able to significantly

improve the clinical symptoms of MDD [44–46], and the treatment might be effective by modulating the FC between DLPFC and DMN and affective network [45,47]. Therefore, we speculate that the mechanism of the efficacy of the EAS group might correlated with the modulation of FC between DMN and CCN.

We also found an increased FC between the left MTG and left hippocampus after EA treatment. The hippocampus belongs to the limbic system, which participates in cognitive memory, emotional processing and other functions, and is an important part of the limbic system [48,49]. Abnormal hippocampal function may lead to various depressive symptoms [50,51]. More importantly, the hippocampus has a high level of neuroplasticity and is often used as an observational target for antidepressant drug therapy [52]. Previous studies found that the acupuncture was able to increase FC between the left temporal lobe and hippocampus in the anxious patients compared to the sham-needle [53]. Another study showed that EAS can modulate the FC between hippocampus and DMN in MDD [54]. Thus, our findings demonstrate that the clinical effectiveness of EAS for MDD might be closely related to the modulation of FC between the MTG and hippocampus.

In addition, FC was decreased between the left CPL and left calcarine after EAS treatment, and was more significantly decreased than in the SAS group. The calcarine gyrus locates in the medial occipital lobe and is closely correlated with visual memory (VN), emotional attention, and other psychosomatic activities [55,56]. Previous studies have found increased FC between the anterior cingulate gyrus and VN in MDD patients, indicating functional impairment in the visual processing cortex [57]. Another machine learning study showed that abnormalities in the cerebellum, visual cortical areas and emotional networks may take effect in identifying MDD [58]. Recent studies showed that transcutaneous auricular vagus nerve stimulation improves clinical symptoms of MDD in relation to modulation of the VN [59]. Therefore, we speculate that the VN modulation of MDD by the EAS group may be an important mechanism for its efficacy.

In this study, EAS group had the more significant clinical improvement after treatment compared with SAS group. In addition, we found both EAS and SAS were able to reverse abnormal functional activity in some brain regions in MDD patients. This is partly because of the patients selected in this study were the first episode and mild MDD. However, EAS treatment had a broader range of effects, mainly distributed in the default mode network (DMN), sensorimotor network (SMN), cognitive control network (CCN), limbic system, and visual network (VN). Moreover, some brain functional activity changes elicited by EAS were correlated with clinical symptom.

There are several limitations in this study. First, our sample size is small, which might cause false positive results to some extent. Further expansion of the sample size is needed in the future to validate the our findings. Secondly, this study focused less on clinical scales, and the effects of EAS and SAS on differences in cognition, insomnia, and somatic symptoms in patients with FDE should be further observed in the future. Third, this study only focuses on ALFF and FC indicators, and further observation of graph theory, structural image and other indicators are needed in the future to display the neural mechanism.

5. Conclusions

In conclusion, our findings showed that the EA treatment increased ALFF in the left MTG, and also increased FC between the left MTG and left MFG. The changes in the ALFF and FC were also related to clinical symptom in MDD. The EA demonstrates modulation of functional activity in DMN, SMN, CCN, limbic system, and VN for the treatment of the first-episode MDD. This research contributes to the neuroimaging evidence for the efficacy of EAS.

Data availability statement

Raw data is available upon reasonable request.

Trial status

This study has been registered on the Chinese Clinical Trial Registry (registration number: ChiCTR-IOR-15006418, website: https://www.chictr.org.cn). The date was May 6, 2015.

Ethics and consent

The experimental study protocol was approved by the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences on Oct 23 , 2014 (NO. 2014EC084-01).

All the patients signed Written Informed Consent before enrollment.

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CRediT authorship contribution statement

XiaoLing Wang: Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition.

Ping Luo: Project administration, Formal analysis, Data curation. **Ling Zhang:** Formal analysis. **JiFei Sun:** Data curation. **JiuDong Cao:** Data curation. **Zhang Lei:** Data curation. **Hong Yang:** Data curation. **XueYu Lv:** Formal analysis, Data curation. **Jun Liu:** Methodology, Data curation. **XiaoYan Yao:** Data curation. **ShanShan Li:** Data curation. **JiLiang Fang:** Methodology, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank all patients who participated in this study for their cooperation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29613.

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