Research Square

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Clinical Efficacy of the Mulligan Maneuver for Cervicogenic Headache: A Randomized Controlled Trial

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Abstract

Background

Cervicogenic headache is an often observed secondary headache in clinical settings, with patients who endure prolonged and persistent pain being particularly susceptible to mood changes.Currently, the Mulligan is one of the effective methods for CEH. However, there is a lack of evaluation about the strength and frequency of headaches, as well as the assessment of pain-induced emotions, in individuals with CEH using this particular procedure. Herein, we aimed to evaluate the effectiveness of the Mulligan maneuver from a multidimensional perspective of pain intensity and mood.

Methods

A total of forty patients diagnosed with CEH who satisfied the specified inclusion criteria were recruited and allocated randomly into two groups: the control group and the treatment group, with each group consisting of twenty cases. The control group received health education, while the treatment group received the Mulligan maneuver once daily over a course of 10 treatment sessions.The clinical outcome of patients with CEH in two groups was assessed using the Visual Analog Scale (VAS), Hamilton Anxiety Scale (HAMA), and Hamilton Depression Scale (HAMD). Resting-state functional magnetic resonance imaging (fMRI) was employed to examine variations in brain function activities between the two CEH groups. Brain regions showing differences were identified as regions of interest (ROI) and subsequently correlated with clinical behavioral measures using Pearson's correlation analysis.

Results

The differences in VAS, HAMA and HAMD between the two groups of CEH patients were also statistically significant ($P < 0.05$). The brain regions that showed differences in the ReHo scores between the two groups of CEH patients included the left cerebellum, the frontal gyrus, and the middle temporal gyrus. There was a positive correlation between the left frontal gyrus and VAS, HAMA and HAMD. ($R^2 = 0.48$, $P < 0.05$; $R^2 = 0.28$, $P < 0.05$; $R^2 = 0.26$, $P < 0.05$); the left middle temporal gyrus had a negative correlation with VAS, HAMA, and HAMD. ($R^2 = 0.44$, $P < 0.05$; $R^2 = 0.43$, $P < 0.05$; $R^2 = 0.25$, $P < 0.05$); and the left cerebellum had a positive correlation with VAS correlation ($R^2 = 0.27$, $P < 0.05$).

Conclusion

The Mulligan maneuver may improve pain levels and have a moderating effect on pain-related negative emotions by regulating the function of relevant brain regions in CEH patients.

Background

Cervicogenic headache (CEH) is one of the most common secondary headaches in clinical practice and is caused by bony, disc, or soft tissue disorders of the cervical spine.[1] Approximately 54% of CEH patients can develop chronic intractable pain. This can lead to anxiety or depression, seriously affecting the daily activities of patients.[2] Recent studies have shown that manipulation can positively affect headache intensity, frequency, and cervical spine dysfunction in CEH patients[3]. Based on a systematic review and meta-analysis, we found that manipulation can significantly improve the symptoms of head and neck pain in CEH patients and restore normal physiological function of the cervical spine without obvious side effects.[4] However, manipulation has not been reported to improve pain cognition and pain emotion in CEH patients. Recent studies have shown that the manipulation has a modulatory effect on the functional activity of certain regions of the brain. The manipulation can activate the function of the bilateral orbito gyrus, the middle frontal gyrus, the bilateral cuneate lobes, the bilateral inferior frontal gyrus, and the bilateral anterior cingulate gyrus. It increases connectivity between the sensory and executive cortex and inhibits its connection to the cognitive, visual, and memory cortex [5, 6].

The technique known as Mulligan manipulation was developed by Brian R. Mulligan, a physiotherapist from New Zealand. This approach is grounded in an understanding of the anatomical features of the cervical facet joints. Mulligan posited that by exerting pressure on the spinous processes in a weight-bearing stance, the facet joints would undergo a synchronized sliding motion in a parallel manner. After more than half a century of clinical practice and technical improvement, it has formed a safe and effective mature treatment for cervical and upper thoracic spine disorders. The Mulligan maneuver is highly effective in the manipulative treatment of CEH. Herein, we hypothesize that the Mulligan maneuver has an analgesic effect on head and neck pain in CEH patients and alleviates painful emotions.

Methods/design

This pilot study used a fully randomized, controlled, double-blinded, double-simulation research method. The study was registered in the China Clinical Trial Registration Center (registration number:ChiCTR2100054072 23/08/2021) and reviewed and approved by the Ethics Committee of the first affiliated hospital of Zhejiang Chinese Medical University with approval number (ethics number:2021-K-491-01 19/07/2021). All subjects signed an informed consent before the study. All methods were carried out in accordance with the tenets of the Declaration of Helsinki as well as the relevant guidelines and regulations.

Eligibility criteria: All participants were diagnosed with CEH according to the diagnostic criteria for CEH in the third edition of the International Classification of Headache Disorders (ICHD-3) in 2018. They were examined at the outpatient clinic of the first affiliated hospital of Zhejiang Chinese Medical University from January 2022 to December 2022

Inclusion criteria were as follows: Meet the diagnostic criteria; Age 18–70 years old, right-handed; Duration of disease ≥ 1 week; and VAS score ≥ 3/10.

Exclusion criteria: History of cervical spine surgery or history of severe cervical spine trauma; Combination of severe osteoporosis, bone tumor, and bone tuberculosis; Combination of cardiovascular, cerebrovascular, digestive, hematologic and other serious medical diseases; Combined with mental diseases, such as claustrophobia and mental retardation; Pregnant or lactating women; People with language comprehension and expression disorders; Contraindications to magnetic resonance, such as metal foreign bodies in the body; and pacemaker implantation.

Elimination criteria: Enrolled cases should be excluded if they meet any of the following criteria: those who are unable to complete the entire treatment and observation process; those who are unable to fully understand the forms and questionnaires provided as part of the research process or who require assistance from others to complete them; those who are receiving other therapies at the same time during the treatment process; and those who have poor adherence to the study.

Dropout Criteria: Cases that have been enrolled but have not completed the clinical program should be considered to have dropped out in the following cases: The patient withdraws from the study on his/her own; Subjects with poor compliance cannot come for treatment as required, and the patient does not cooperate; The treatment is effective during treatment but cannot complete the entire observation program.; The treatment is effective during treatment, but the patient cannot complete the entire observation program; The subject does not withdraw from the study but no longer accepts the treatment and loses the visit; In the course of the study, other diseases occur, and the treatment is stopped for more than one week in the middle of the study.

Procedures

First, all participants signed an informed consent form and were randomly allocated to the Mulligan manipulative therapy group and the control group. The randomization method achieved allocation concealment using randomization envelopes that were opaque and sealed randomization envelopes. The allocation scheme of two groups was placed in envelopes with the serial number of the group on the outside and the group printed on the inside of the envelope. The envelopes with numerical identifiers were sequentially unsealed in accordance with the order of patients who were still not being attended to and the administration of treatment was carried out according to the specified interventions outlined within the envelopes and treatment was administered according to the interventions requested within the envelopes. The treatment regimen received by each subject was determined by the generated randomized sequence. The Clinical Evaluation Centre of the first affiliated hospital of Zhejiang Chinese Medical University was responsible for the efficacy evaluation to achieve blinding of patients and statistical evaluators. A sample expansion of 20% was proposed, given the possibility of attrition in the study (Fig. 1).

Before starting of the study, individuals in both experimental groups underwent the Visual Analogue Scale (VAS) in order to evaluate the perception of pain. Additionally, the Hamilton Anxiety Scale (HAMA) and the Hamilton Depression Scale (HAMD) were administered to assess the emotional aspects of pain.

Furthermore, resting-state magnetic resonance imaging (fMRI) was conducted on all participants to evaluate brain functional activity using the ReHo score, a specialized metric for measuring local brain functional activity. At the end of the study, VAS, HAMA, HAMD, and fMRI scans were repeated to assess efficacy.

Interventions

The manipulations used were carried out by a therapist possessing over six years of expertise who underwent training in both the subject matter of investigation and quality control before the beginning of the trial. The patients in the treatment group received one Mulligan maneuver per day, with each session lasting at least 20 min for ten sessions. The health promotion group delivered the health promotion content to all subjects via the WeChat group daily and answered questions about the promotion content for ten days.

The educational content encompasses various aspects such as the definition of CEH, the primary causes of diseases, daily preventive measures, lifestyle habits, and dietary recommendations. It emphasizes the importance of avoiding excessive strain, exposure to wind and cold, and prolonged usage of electronic devices such as computers and mobile phones. However, it does not encompass the treatment of cervical vertebrae or exercise methods for rehabilitation within the scope of health education.

Mulligan Manipulation:

Step 1: Assessment

CEH is associated with abnormal proprioceptive input in the upper cervical segment (C1-C2). Therefore, confirmation of the key site for treatment influences the outcome.To verify the primary stimulus of the provocation movement, if the occurrence of headache is triggered by flexion and extension, it is recommended to carefully manipulate the spinous process of the second cervical vertebra and engage in posterior extension in collaboration with the patient. Confirmation of cervical 2 as the primary location is established when the headache is relieved.Whenever the patient experiences a headache due to rotation, it is recommended to gently move the transverse process of the ipsilateral side of cervical 1 in a sliding motion from posterior to anterior, while also assisting the patient in performing rotational movements. In case that the headache persists, it is recommended to manipulate the transverse process of the contralateral side of cervical vertebra 1 in a sliding motion, while also engaging the patient in rotational movements. In the event that the headache persists, it is recommended to gently manipulate the ipsilateral spinous process of cervical 2 in a sliding motion, while concurrently engaging the patient in rotational movements(Fig. 2).

Step 2: Treatment

Flexion-extension headache: In the seated position, the operator applies a constant posterior-anterior thrust at the assessed site of application (posterior border of the C2 spinous process), This thrust is accompanied by a compressive force of approximately 50N, directed towards the patient's eyes. The

operator instructs the patient to perform a cervical lordosis maneuver while the remaining fingers of the therapist immobilize the patient's cheeks. This procedure is repeated three times.

Rotational headache: In the seated position, the operator applied a steady posterior-anterior thrust at the assessed site of application (left or right side of the C1 transverse process), maintaining a compressive force of approximately 50N and directed towards the patient's eyes. Simultaneously, the patient was instructed to turn his head to the same side, and the procedure was repeated three times.

Step 3: Exercise

Flexion-extension headache: The patient is seated, and the middle or index finger of patient is in contact with the posterior aspect of posterior border of C2, exerting and maintaining a posterior-anterior slide while actively extending the neck posteriorly.

Rotational headache: The patient takes a sitting position, the middle finger or index finger of patient touches the posterior aspect of C1 transverse process on the symptomatic side, and the finger continuously pushes the cervical vertebrae to slide forward while actively turning the head to the same side.

Image acquisition

A GE Discovery MR750 3.0T MRI scanner was used for imaging. The subjects underwent structural and BOLD functional imaging, and the scanning range was from the frontal-parietal to the base of skull, covering the entire brain. The scanning parameter settings: The structural image was acquired using the weighted fast scrambled phase gradient echo sequence technique. This allowed for acquiring the axial weighted images of T1W1 and T2W1. The scanning parameters were as follows: a repetition time of 1,900 ms, a field of view set to 256×256 cm, an echo time of 2.26 ms, a matrix size of 256×256, and a scanning time of 7 min. Additionally, BOLD functional imaging was performed using the gradient echo sequence technique with a single excitation planar echo to acquire the information function. Scanning parameters: The repetition time is 2000 ms, the time point is 240, the echo time is 30 ms, the number of layers is 30, the layer thickness is 5 mm, the matrix is set to 64×64, the field of view is set to 256×256 cm, the flip angle is 90°, and the scanning time is 8 min.

Data preprocessing

Preprocessing was performed using the Statistical Paretric Mapping12 (SPM12) software package based on the MATLAB R2014a platform, which mainly includes removing time points, temporal layer correction and head movement correction, spatial normalization, de-linearization drift, and noise filtration. After preprocessing, the data were used to calculate the local consistency of each voxel with its neighboring 27 voxels in the same time series by applying Kendall's concordance coefficient. After preprocessing, Kendall's concordance coefficient was applied to calculate the local coherence between each voxel and its neighboring 27 voxels in the same time series. Subsequently, the whole-brain ReHo images of subjects' whole brains were generated. Finally, the whole-brain ReHo images were spatially smoothed using a smoothing kernel with a full-width and half-height of 6 mm to filter out the noise.

Sample size calculation

PASS26 software was used for sample size estimation. This study was a randomized controlled trial wherein two groups were established based on the pre-experiment outcomes. These groups were referred to as the experimental group and the control group. The treatment effectiveness of the two groups was expected to be 90% and 36.67%, respectively, with two-sided α = 0.05 and confidence level 1-α = 0.95 and the test efficacy 1-β not less than 0.8.The allocation of participants into the test and control groups followed a 1:1 ratio. Each group initially consisted of 16 cases, and the sample size was increased by 20% to account for potential factors including loss of visits and attrition. Consequently, a minimum of 20 cases per group was required for the study subjects. The sample size estimation formula for comparing the two sample rates is as follows:

$$n_1 = n_2 = \frac{\left[u_\alpha \sqrt{2p(1-p)} + u_\beta \sqrt{p_1(1-p_1)+p_2(1-p_2)}\right]^2}{(p_1-p_2)^2}$$

n is the required sample size for each group, Eq.p_1 andp_2 are the estimated two-sample frequencies, respectively, and$p$ the two-sample combined frequency.

Statistical analysis

Data were statistically analyzed using the SPSS26 software package (SPSS Inc. USA). Measurement data was described using $\bar{x}$±s and count data were described using constitutive ratios and frequencies. Independent samples t-test and paired rank sum test (Z-test) were used to compare the differences in indicators between the two groups of CEH patients. The RESTplusv1.24 software package was used for statistical analysis of the data. The smReHo plots of CEH patients in the two groups were subjected to paired samples t-test, corrected for multiple comparisons by the GRF method (P < 0.01 for voxel level, P < 0.05 for clusters). The ReHo values of different brain regions were extracted and analyzed by Pearson correlation analysis with clinical behavior indices (VAS, HAMA, HAMD), and the differences were considered statistically significant at P < 0.05.

Results

The clinical experiment involved a cohort of 40 patients, with 20 assigned to the Mulligan maneuver therapy group and the remaining 20 assigned to the health promotion intervention group. There were no statistically significant differences in the general age, sex, education level, disease duration, VAS score, HAMA score, and HAMD score of the patients in the two groups before the trial (P >0.05) (Table 1). The differences in VAS scores, HAMA scores, and HAMD scores between the two groups at the end of treatment were statistically significant (P < 0.05) (Table 2). Moreover, there were differences in the changes in ReHo scores of the left cerebellum, left middle frontal gyrus, and left middle temporal gyrus between the two groups (P < 0.01) (Fig. 3) (Table 3). Furthermore, we observed a positive correlation between the ReHo values of left frontal, middle gyrus and the VAS, HAMA, and HAMD scores in the

treatment group (R^2 = 0.48, P< 0.05; R^2 = 0.28, P< 0.05; R^2 = 0.26, P< 0.05) **(**Fig. 4**)**. Conversely, in the treatment group, we observed a negative correlation between the ReHo values of left temporal middle gyrus and the VAS score, HAMA score, and HAMD score (R^2 = 0. 44, P< 0.05; R^2 = 0.43, P< 0.05; R^2 = 0.25, P< 0.05) **(Fig. 5)**. The ReHo value of the cerebellum in the treatment group was positively correlated with the VAS score (R^2 = 0.27, P< 0.05). However, no significant correlations were found between HAMA and the HAMD scores (R^2 = 0.14, P> 0.05; R^2 = 0.04, P> 0.05) **(**Fig. 6**)**.

Discussion

CEH is one of the most common secondary headaches in clinical practice. Specifically 89.1% of calls made by patients seeking medical attention for headaches in an outpatient setting[1].Sjaastad [7] et al. suggested that CEH is associated with organic or functional cervical or soft tissue lesions or both. Bogduk [8] proposed that CEH is a form of entrapment pain and explained its pathogenesis with the congregation theory. According to this theory, lesions in the structures innervated by the high cervical nerves (the greater occipital, lesser occipital, and greater auricular nerves belong to the second and third cervical nerves) cause afferent injurious sensory messages from the high cervical nerves that are connected.These messages are then transmitted to the trigeminocervical fibers within the trigeminocervical complex (TCC) located in the grey columns of the posterior horn of the cervical medulla 1–3. These trigeminocervical fibers are also present in the cervical cord. TCC is located in the grey columns of posterior horn of the cervical medulla 1–3, causing errors in the central assessment of source of afferent noxious information, which in turn causes headache symptoms. Blake and Burstein [9] suggested that a headache caused by a cervical muscle spasm that compresses the greater occipital nerve, the lower occipital nerve, or the greater auricular nerve is one of the most common causes of CEH.

Chronic persistent pain can lead to cognitive abnormalities in pain, subsequently causing anxiety or depression. Several studies have shown that CEH patients suffer from the physical discomfort of pain, cognitive dysfunction, and psychological dysphoria [10]. A previous study has shown that CEH patients suffer from physical pain, cognitive dysfunction, and psychological distress. Moreover, an additional study has shown that CEH patients have synergistic increases or decreases in neuronal activity in localized brain tissue, suggesting that CEH involves pathological changes in multiple brain regions associated with regulating affective cognition.[11] Manipulative therapy is effective in CEH. Previous studies have demonstrated the effectiveness of manipulative therapy in terms of headache index, trigger point pressure pain, neck function assessment index, and range of motion in CEH [12], and the evaluation of pain-induced emotions is less involved.

Herein, we found statistically significant changes in the function of frontal, middle gyrus, and middle temporal gyrus brain regions in CEH patients using the Mulligan maneuver. Furthermore, we identified correlations between these changes and clinical behavioral indicators. The middle frontal gyrus is a part of the frontal lobe that is thought to play a crucial role in regulating affective cognition, including memory and executive function. It is important to reduce pain sensitivity through affective cognitive modulation

[13]. In conjunction with the results of this project, we believe that CEH patients exposed to repeated painful stimuli who are subjected to recurrent noxious stimuli experience specific aberrations in the perception and modulation of pain-related data. Several below-threshold pain tends to be amplified and processed. This is related to the fact that long-term chronic pain tends to cause damage to the frontal gyrus and emotional cognitive decline in patients with CEH. The Mulligan Manipulation can somewhat improve the functional changes in the frontal gyrus and other brain regions and alleviate pain sensitivity due to cognitive decline.

The middle temporal gyrus is also a target of the Mulligan maneuver. Several studies have reported that the middle temporal gyrus is associated with emotional and sensory processing, including depression, anxiety, and pain ratings. Furthermore, it has been observed that enduring unpleasant emotional experiences resulting from pain can potentially create alterations in brain functionality. Herein, ReHo scores in the middle temporal gyrus were reduced and negatively correlated with VAS, HAMA, and HAMD, possibly due to the Mulligan maneuver's protective inhibitory effect on the middle temporal gyrus. MEDINA[14] study has found that cerebral blood flow in the middle temporal gyrus was reduced after treating CEH patients, which is consistent with our findings. However, the protective inhibitory effect of maneuver on the middle temporal gyrus remains to be verified. In conjunction with our results, we believe that the Mulligan maneuver can regulate the pain level and play a significant role in pain-induced emotions.

Additionally, we found that the manipulation had a benign moderating effect on changes in cerebellar function and a positive correlation between this change and VAS scores. Previous studies have focused on the cerebral cortex at the expense of cerebellar function. In a rat model of neuropathic pain, cerebellar activity was positively correlated with the development of neuropathic pain and prognosis[15]. The cerebellum plays an important role in processing pain sensations, as signal inputs from the A-fibre and C-fibre nociceptors reach the Purkinje cells of cerebellum[16]. The cerebellum is closely connected to the brain's limbic system, amygdala, hippocampus, anterior cingulate gyrus, and frontal and temporal lobes. According to our findings, we believe that the Mulligan maneuver adjusts the neural circuits between the cerebellum and the brain by modulating the functional areas of cerebellum, thereby activating the corresponding functional areas of brain and ultimately realizing the intervention of pain emotion.

Conclusions

Herein, we found that the Mulligan maneuver can improve pain levels and regulate pain-induced negative emotions by modulating the function of relevant brain regions in CEH patients. Nevertheless, it is important to acknowledge the constraints of this investigation, namely the relatively small sample size and the utilization of imaging data solely for the purpose of examining alterations in regional brain functionality among CEH patients. Consequently, further investigations need to be conducted to increase the sample size and explore the underlying mechanisms pertaining to the network connectivity of local cerebral activity.

Declarations

Data availability

The data sets that were used and/or analysed in the current study are available from the corresponding author upon reasonable request..

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Tables

Tab1:The demographics and characteristics of study patients before treatment were compared between the two groups.

Characteristics	Mulligan manoeuvre treatment group n=20 Mean ± SD	the health promotion intervention group n=20 Mean ± SD	*P* value
Age years	30.05±6.75	27.19±4.67	0.19
Gender			0.56
Male	15	7	
Female	5	13	
Education years	7.84±1.06	8.91±1.81	0.06
Course of disease years	4.53±2.65	4.99±2.62	0.63
VAS scores	4.96±0.89	5.31±0.6	0.15
HAMA scores	21.64±1.69	22.44±1.56	0.13
HAMD scores	24.23±1.58	23.64±1.67	0.26

A *p*-value < 0.05 indicates statistical significance.

Tab2:Comparison of VAS, HAMA and HAMD scores of CEH patients in the two groups before and after treatment

Clinical variables	Mulligan manoeuvre treatment group n=20 Mean ± SD	the health promotion intervention group n=20 Mean ± SD	*P* value
VAS scores			
Before	4.96±0.89	5.31±0.60	0.15
After	3.42±0.89	4.58±1.18	< 0.05
HAMA scores			
Before	21.64±1.69	22.44±1.56	0.13
Aftter	20.17±1.37	21.25±1.71	< 0.05
HAMD scores			
Before	24.23±1.58	23.64±1.67	0.26
Aftter	20.79±2.24	22.41±1.65	< 0.05

A *p*-value < 0.05 indicates statistical significance.

Tab3:Regions with abnormal ReHo scores in CEH patients in comparison between two groups after treatment.

Brain area	Voxel size	Peak t-value	MNI coordinates		
			Xvalue	Yvalue	Zvalue
ReHo scores					
Cerebellum	714	3.93	-3	-39	-15
middle temporal gyrus	1407	-3.99	-54	-30	0
middle frontal gyrus	943	3.92	-27	21	57

Figures

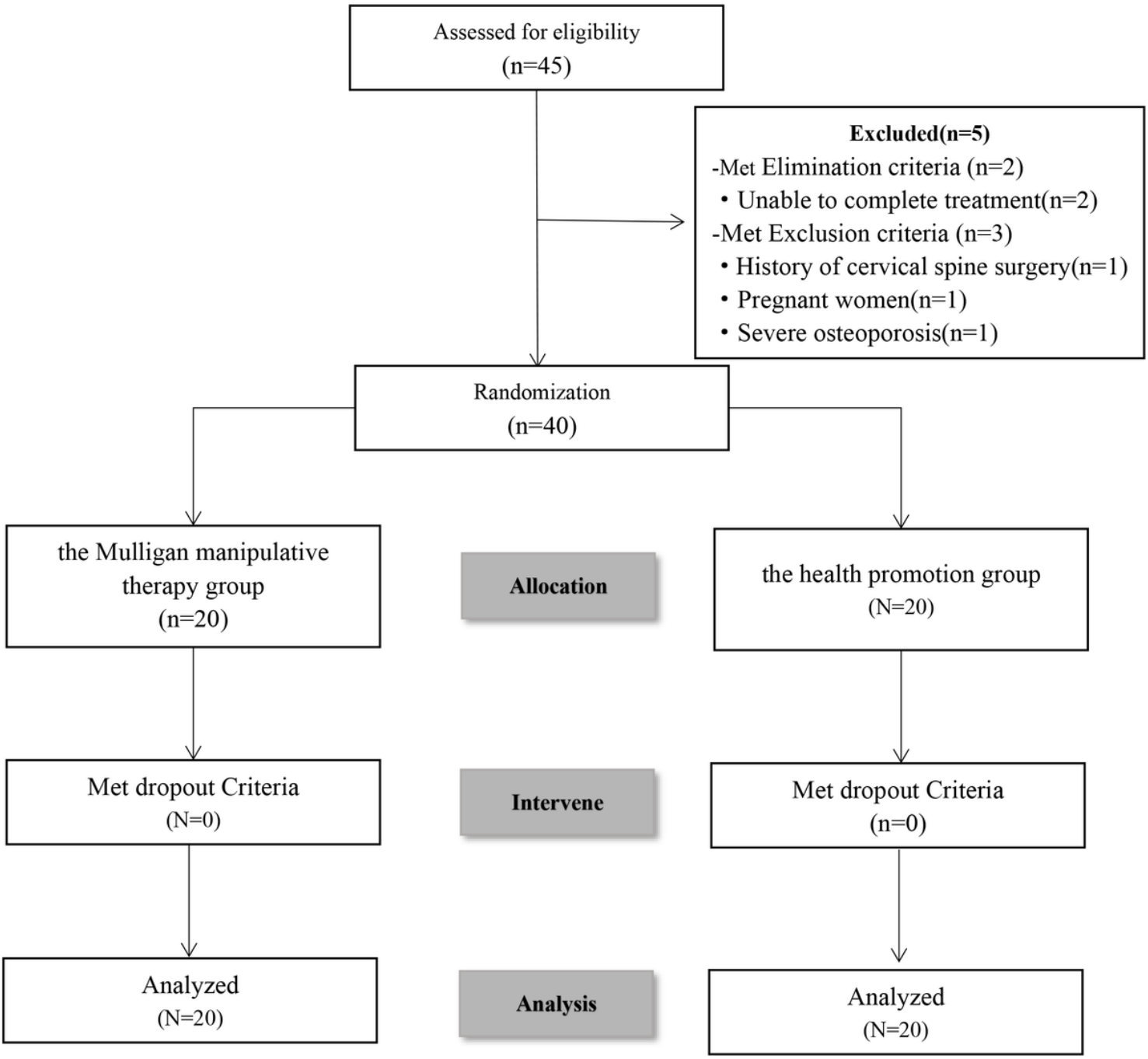


Figure 1

Consolidated Standards of Reporting Trials (CONSORT) diagram showing the enrollment patients in this study

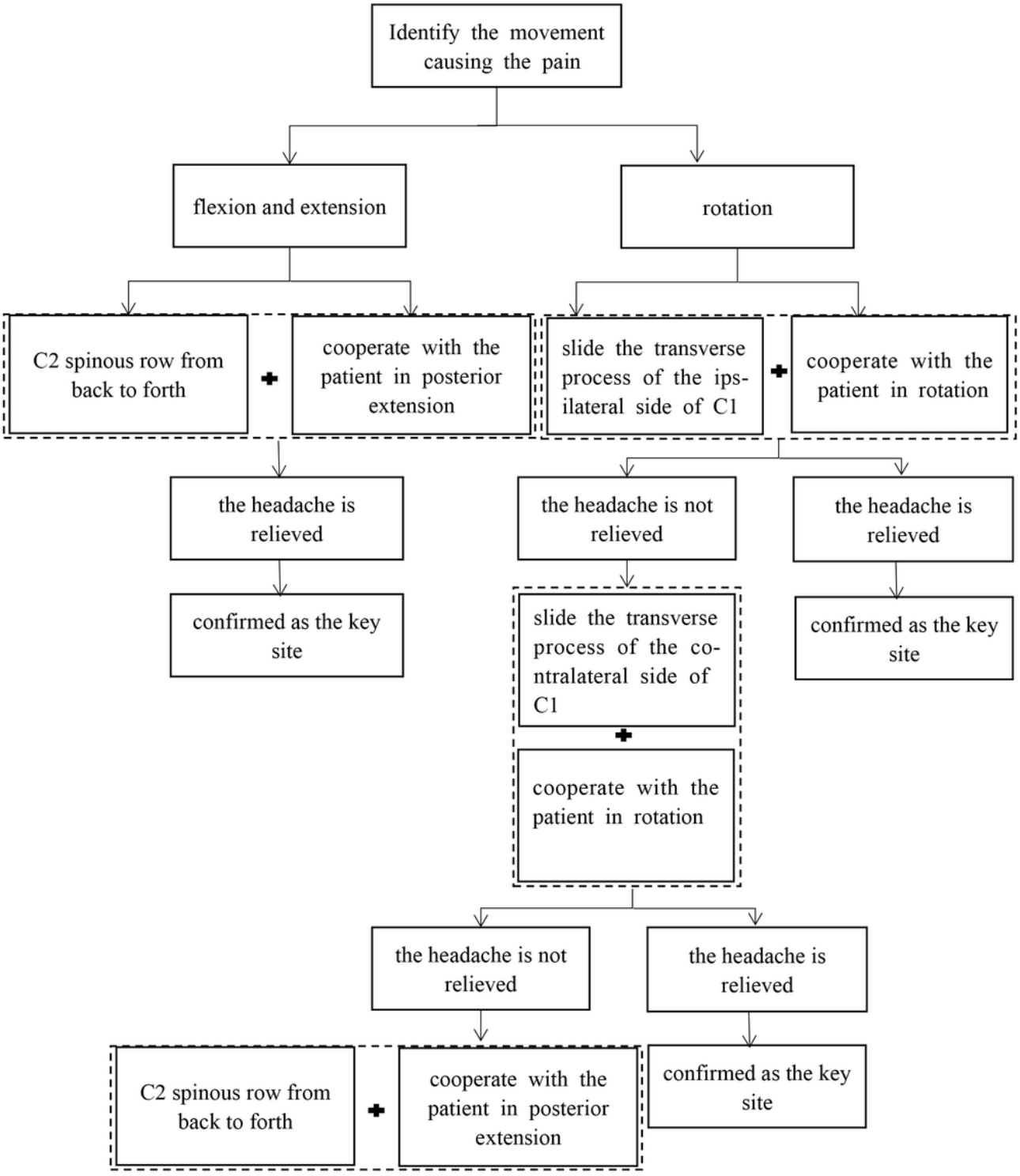


Figure 2

confirm the key site flowchart

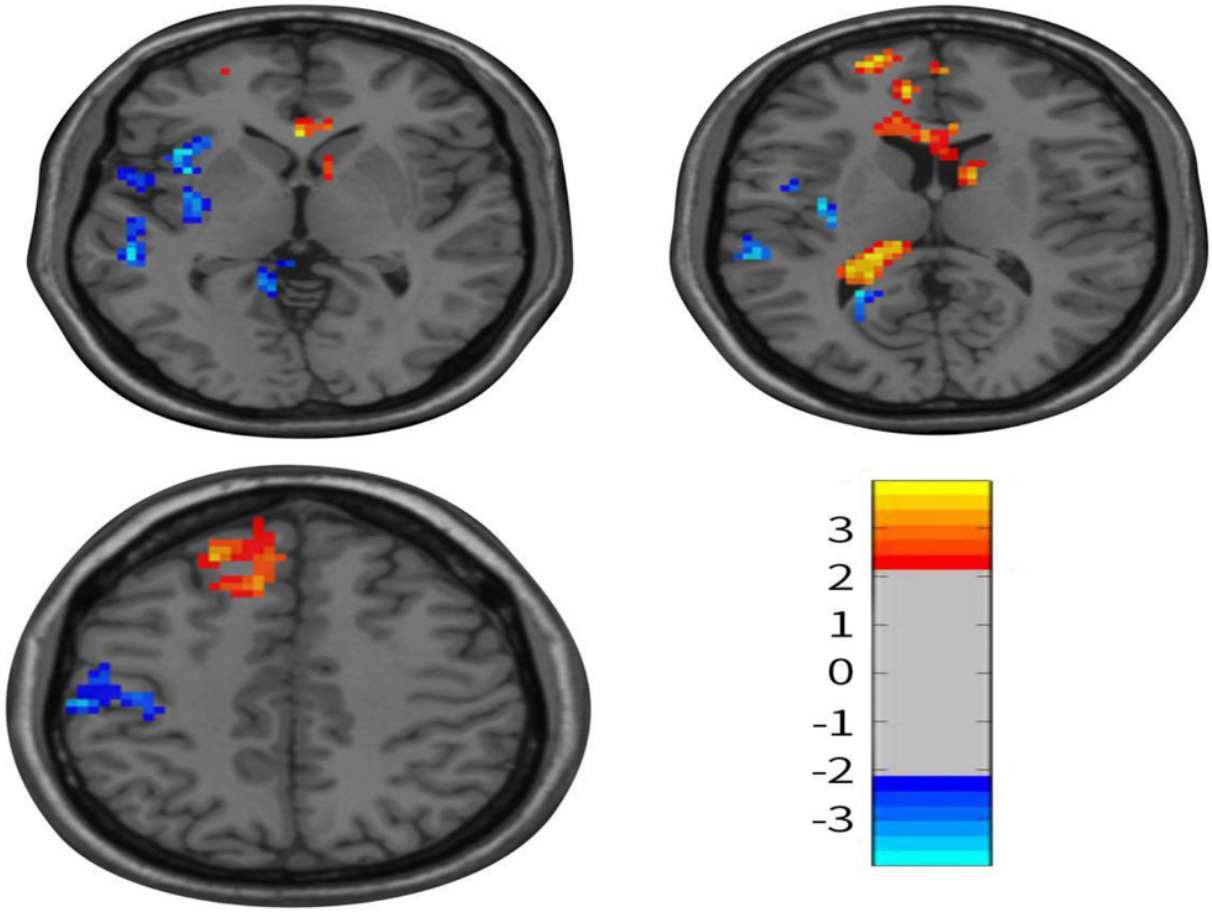


Figure 3

Axis of change in ReHo values in CEH patients after treatment in the Mulligan manoeuvre treatment group compared to the health promotion intervention group

Note: Areas of decreased ReHo in CEH patients in the Mulligan manoeuvre treatment group compared to the health promotion intervention group include middle temporal gyrus (blue areas); areas of increased ReHo include cerebellum, middle frontal gyrus (red areas).

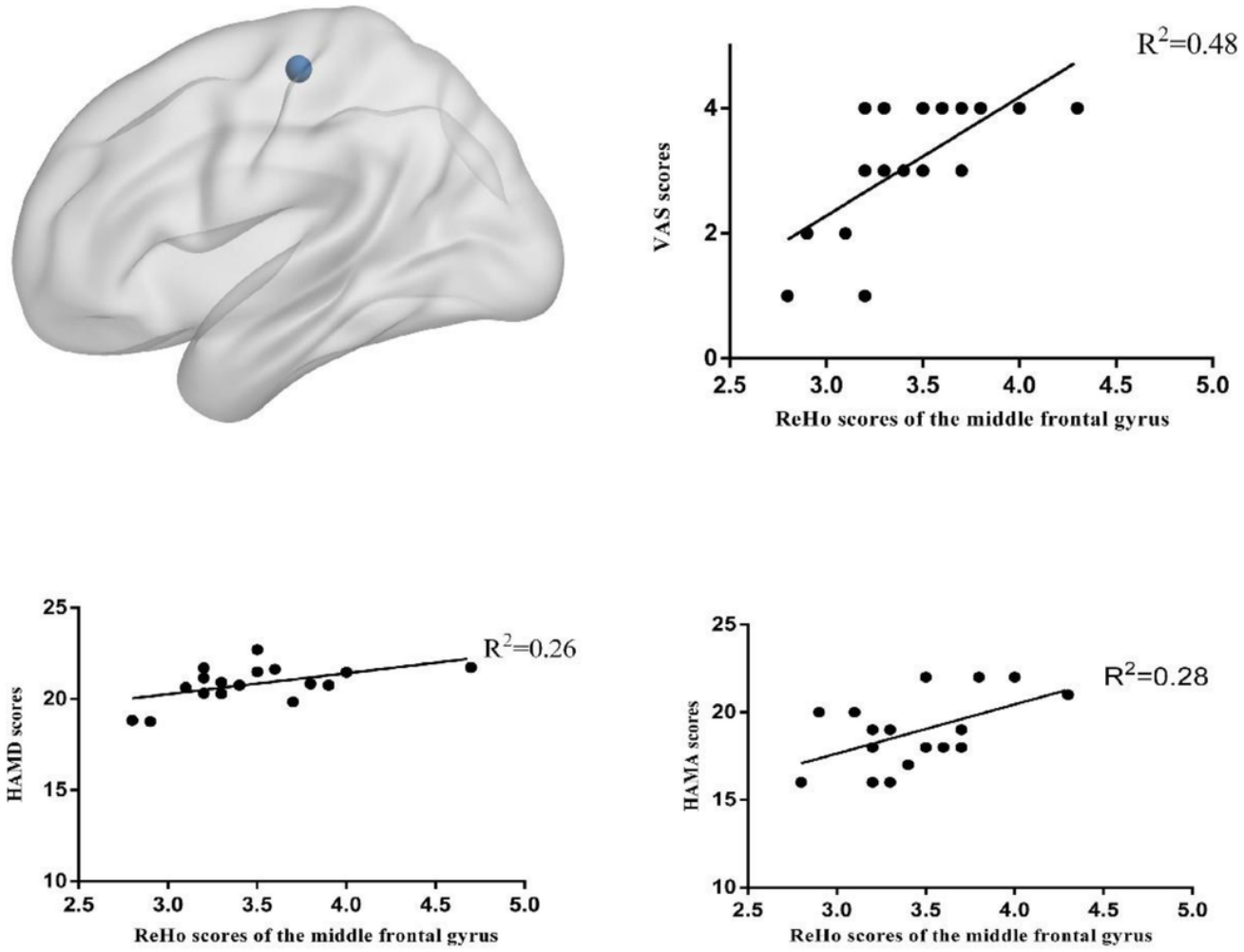


Figure 4

Pearson's Correlation Analysis of the Frontal Middle Gyrus with VAS scores HAMD scores HAMA scores in Patients with CEH after Mulligan manoeuvre treatment

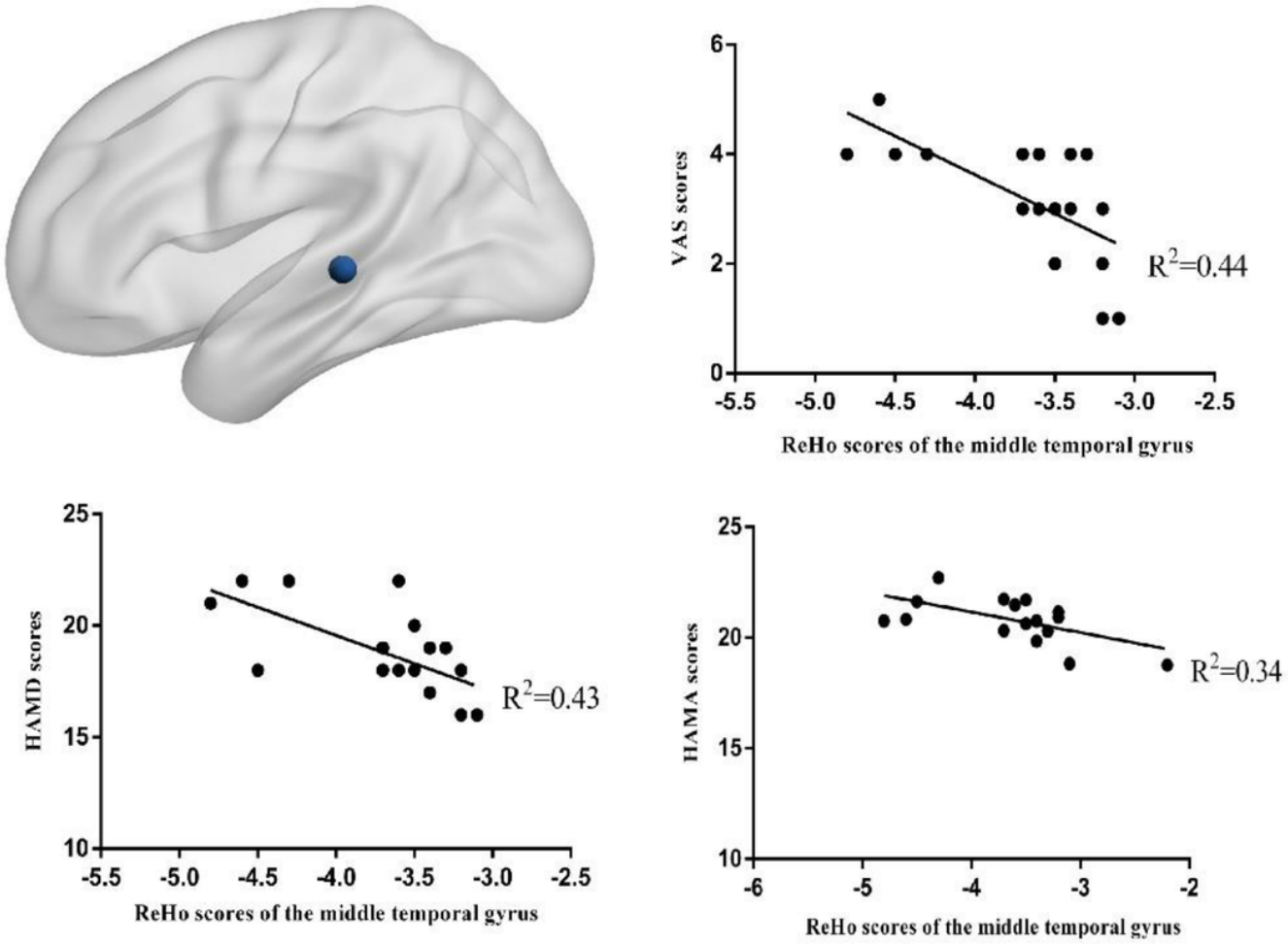


Figure 5

Pearson's Correlation Analysis of the left temporal middle gyrus with VAS scores HAMD scores HAMA scores in Patients with CEH after Mulligan manoeuvre treatment

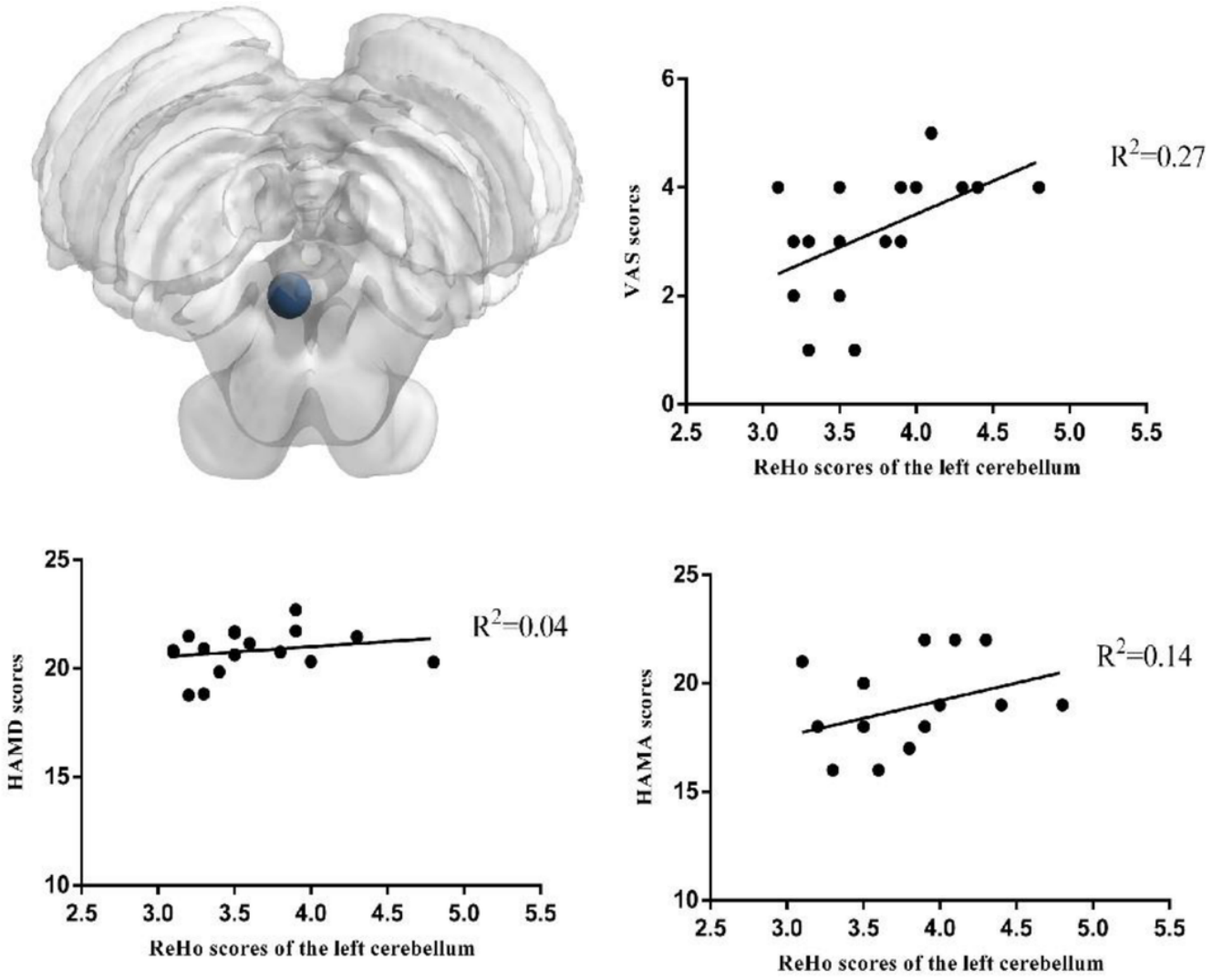


Figure 6

Pearson's Correlation Analysis of the the left cerebellum with VAS scores HAMD scores HAMA scores in Patients with CEH after Mulligan manoeuvre treatment