Altered Effective Connectivity in Migraine Patients During Emotional Stimuli: a Multi-frequency Magnetoencephalography Study.

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Abstract

Background: Migraine is a common and disabling primary headache associated with a wide range of psychiatric comorbidities. However, the mechanisms of emotion processing in migraine are not fully understood yet. The present study was designed to investigate the neural network during neutral, positive and negative emotional stimuli in migraine suffers.

Methods: We enrolled 24 migraine suffers and 24 age- and sex-matched controls in this study. Neuromagnetic brain activity was recorded by using a whole-head magnetoencephalography (MEG) system towards human faces expression pictures. MEG data were analyzed in the multi-frequency band of 1–100 Hz.

Results: Migraine patients exhibited significantly enhanced effective connectivity from the prefrontal lobe to the temporal cortex during negative emotional stimuli in the gamma band(30-90Hz). Graph theory analysis revealed that patients had (1) an increased degree and clustering coefficient of connectivity in the delta band(1-4Hz) during positive emotional stimuli; (2) an increased degree of connectivity in the delta band(1-4Hz) during negative emotional stimuli.

Conclusion: The results suggested individuals with migraine showed deviant effective connectivity when viewing human facial expressions in multi-frequency. The prefrontal-temporal pathway might be related to the altered negative emotion modulation in migraine. These findings may contribute to understanding the mechanism of the comorbidity of depression and anxiety in migraine and provide references for the comprehensive therapeutic plan.

1. Introduction

Migraine is a common primary headache which was characterized by moderate to severe pain and accompanied by vomiting, nausea, photophobia, and phonophobia[1]. Due to the high prevalence and social burden of migraine, it emerged as public health concern worldwide[2]. However, the neuropathological mechanisms and treatment strategies for migraine are far from satisfactory. Thus, it is imperative to explore the pathology of migraine for more effective therapeutic methods.

From previous studies, patients with migraine have shown hypersensitivity to sensory stimuli and abnormal processing of multiple sensory information during and between headache attacks[3, 4]. The technology of neuroimage provides a better understanding of the neural dysfunction of migraine. Brain image researches have demonstrated abnormal activation exposure to sensory stimuli, absence of the normal habituating response between attacks, and atypical functional connectivity of sensory processing brain areas[5]. Migraine suffers always complain uncomfortable emotional experience and meanwhile, headache attack frequency is associated with psychiatry comorbidities like depression and anxiety[6–8]. In these literatures, emotional stress is the most trigger for their headache, in turn, migraine attack may aggravate their stress symptom. Even there has been a study proposed that migraine with or without comorbid depression are different disorders at the gene level[9]. Therefore, early diagnosis and therapy of psychiatry comorbidities are necessary for migraineurs.

Human facial expression as a type of emotional stimuli has been used to investigate central nervous system processing. According to event-related potentials studies, the migraine group displayed more negative toward angry faces compared to neutral faces[10]. This phenomenon can be interpreted as a differential process of emotional facial contents preferentially and intensively towards unpleasant stimuli. Most recently, it has been proposed that patients with migraine showed altered brain activation under negative emotion stimuli using functional MRI (fMRI) and electroencephalogram (EEG)[11–13]. In these articles, migraineurs were found stronger activation in the visual cortex, cerebellum, and amygdala than healthy volunteers. Furthermore, the results of functional connectivity studies have also revealed that brain regions show atypical connectivity in migraine patients include those involved in affective emotion processing like the amygdala[14], anterior insula, and anterior cingulate cortex[15, 16].

Magnetoencephalography(MEG), a non-invasive device,has been used to investigate neurological disorders in multiple frequency bands. Equip with a high temporal resolution, MEG can detect the subtle difference in neuronal activity[17]. Previous analysis of migraine with MEG revealed intrinsic connectivity network at rest and under somatosensory stimulation[18, 19]. As far as we know no previous studies have applied MEG to examine neural networks to face expression stimuli in migraineurs.

The present study was designed to discover the whole-brain effective connectivity (EC) towards human emotional faces in migraine patients during the headache-free phase using MEG. To this end, we chose negative, positive, neutral facial expressions and record neuromagnetic signals from 1Hz to 100Hz band. Furthermore, we also aim to evaluate the impact of migraine characteristics. We hypothesis a significantly typical effective connectivity in response to negative emotional stimuli in the migraine group compared to controls. Moreover, the disruptions of whole-brain effective connectivity would be associated with neuropsychological scores of migraine patients.

2. Methods

2.1 Participants

We enrolled 24 migraine patients without aura and 24 controls in this study, and all patients were recruited from the outpatient clinic of Nanjing Brain Hospital. The study was approved by the medical ethics committee of Nanjing Brain Hospital, and each subject provided written informed consent. The inclusion criteria for migraine patients were based on the International Classification of Headache Disorders, 3rd edition (ICHD- beta) of 2013 (Headache Classification Subcommittee of the International Headache Society, 2013). All subjects were right-handed, and all systemic disorders and other neurological diseases were excluded based on both clinical interviews and structural MRI. Besides, migraineurs should stop using the drug within 1 week before MEG recording. The features of migraine clinical assessment included the onset age, headache frequency, duration of last headache attacks, accompanied symptoms, and pain intensity (VAS) were collected. The Hamilton Anxiety Scale (HAM-A) and Hamilton Depression Scale (HAM-D) were used to evaluate the subjects' anxiety and depression symptoms.

2.2 Stimuli and procedure

We use human facial expression pictures as an emotion stimuli task to perform this research. In this task, pictures were categorized into fearful, happy, and neutral faces. Stimuli consist of 180 grey-scale photographs taken from the NimStim Set of Facial Expressions[20] and the Montreal Set of Facial Displays of Emotion[21]. Additionally, fixation cross targets were randomly inserted into 18 trials to ensure each subject focus on the pictures. Emotion pictures were displayed in a video by using BrainX software[22]. The pictures were randomly presented for 500ms followed by 2000–2500ms inter-trial intervals. All faces were set on the center of a black background. The experimental paradigm is shown in Fig. 1.

2.3 MEG Signals Recording

The MEG data were collected in a magnetic shielding room in the MEG center at Nanjing Brain Hospital using a whole-head 275-Channel MEG system (VSM Medical Technology Company, Canada). Patients were required no headache attacks for 72hs prior to testing and during or 24hs after recording. Before MEG signals recording, three electromagnetic coils were attached to reference landmarks on the left and right pre-auricular points and the nasion of each participant in order to check the head position. All subjects were instructed to lay comfortably in a positive supine gesture, remain still, and avoid moving head. During data scanning, each patient needed to keep gazing at the screen and press the button with their right hand when they saw a fixation cross in the video. The sampling rate of MEG recording was 6000Hz. Head positions were measured at the beginning and the end of the sampling. If the head move beyond 5mm, the data were excluded and sampling again. All recorded data were performed a noise cancellation of third-order gradients.

2.4 MRI Scanning

Structural T1 images of all subjects were collected using a 1.5T MRI (Singa, GE, USA). Three markers were placed on the nasion and bilateral pre-auricular points to identify the positions of the three coils used during the MEG data scanning to facilitate co-registration of the MRI and MEG data. All anatomical landmarks were subsequently digitized in the MEG study were identified on MRI.

2.5 Data Processing

The averaged data without no noise and other artifacts were marked "clean data", and were preprocessed by removing the direct current offset, then two main neuromagnetic components were obtained. We selected 90-180ms after triggering from MEG data as a time window to analysis. All data were filtered with band-pass filters at pre-defined bandwidths of delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), gamma (30–90 Hz), and we use a 50Hz notch filter to eliminate power-line noise. All data were proceeded additional analyses in these bands separately. A sample data is shown in Fig. 2.

Based on previous reports, the neural network was investigated at the source level[19]. Granger causality (GC) and covariance analysis were used to estimate EC. To analyze the EC network, we localized the significant neuromagnetic activity through real-time source imaging, which was defined as the volumetric source activity (or virtual sensor waveform) over each time point, and was specifically developed and optimized to analyze activities in multiple frequency bands[23, 24]. Source activity was computed by a two-step beamformed method. The detailed method was described in our earlier articles[17, 23]. The whole brain was scanned at 6mm resolution (around 17,160 voxels/source) in this study. We analyzed the correlation of all virtual sensor signals in time-windows corresponding to the event-related magnetic fields to estimate global connectivity[17, 25]. Next, we statistically analyzed the correlation of two virtual sensor signals between two source pairs by calculating the correlation coefficient based on the following mathematical formula:

$$R(X_a, X_b) = \frac{C(X_a, X_b)}{S_{X_a} S_{X_b}}$$

In this formula, R (X_a, X_b) represents the correlation between two source pairs in two positions (“a” and “b”). Xa and Xb indicate the MEG signals of two paired sources, used to calculate connections. C (Xa, Xb) and SxaSxb represent the mean and the standard deviation of the signals in the two sources, respectively. Moreover, to reduce bias, we also calculated every possible connection for each dual-source pair at the source level. Notably, any two voxels less than 10mm was recognized as one voxel.

Similar to recent reports, we use multivariate GC to analyze the directivity of connections[26, 27]. It can be interpreted that if one source activity could predict another source activity in a few milliseconds, we defined the two sources connected. Otherwise, the two sources were not connected. Then, neuromagnetic networks at the source level were overlapped onto structural MRIs of individual subjects. We visualized effective connectivity based on magnetic source imaging in three views (axial, coronal, and sagittal) to analyze the excitatory and inhibitory connections, which were shown in red and blue. An excitatory connection represents a positive connection where the amplitude of the signals in a source pair is positively correlated. An inhibitory connection represents a negative connection where the amplitude of the signals in two connected sources is negatively correlated[26].The yellow point indicates the node drive to other nodes while the pink point indicates the node were driven by other nodes.

Furthermore, we also perform graph theory analysis to quantify the characteristic of neural networks at the source level. In graph theory, a graph is a mathematical representation of a network and consists of a set of nodes and edges. To exactly define and compare the global EC networks properties, we calculated degree (D), strength (S), characteristic path length (L), and clustering coefficient (C) for each source pairs. The D of a node,often used to quantify centrality, indicates the number of connections between the node and the others. The L represents the number of edges in it[28]. The S parameter is defined as the measure of all possible links to all sources. The C refers to the probability that the neighbors of this node are also connected to each other and is considered to be a measure of the local connectivity of a graph. We set a threshold as a checkpoint to guarantee the data quality. All networks with EC values above the threshold could be shown. To define the threshold, we compute the t values for all source pairs.

$$T_P = R\sqrt{\frac{K-2}{1-R^2}}$$

In the equation above, Tp indicates the t value of a correlation; R indicates the correlation of a source pair; K represents the number of data points for connection. The Tp value used had a corresponding p-value < 0.01 as the thresholding for obtaining the EC network. All algorithms used above were performed using the MEG Processor software (Cincinnati, OH, USA).

2.6 Statistical analyses

We used the software package SPSS version 19.0 (IBM, Inc.) to perform statistical analyses. The EC network patterns of migraine patients and controls were visually inspected and analyzed by Fisher's exact test. A two-tailed student's t-test was applied to access the network properties between the case group and control group. Correlation analyses were estimated using Spearman correlation coefficients. P < 0.05 was set to be a threshold of significant difference, and the Bonferroni correction was used to correct for multiple comparisons. False discovery rate (FDR) was applied to reduce type I errors.

3. Results

3.1 Demographics and Clinical characteristics

Compare with healthy subjects, migraine patients showed no difference in age, gender as shown in Table 1. In addition, the migraine group demonstrated a detailed score on the headache and neuropsychology scale.

3.2 Network pattern

We found that the majority of migraineurs (19/24) showed increased effective connectivity from the prefrontal cortex (PFC) to the temporal lobe (TL) during negative emotional stimuli in the gamma band(30-90Hz), while controls show dominant connectivity between PFC and visual cortex in response to positive and neutral human faces.

In some frequency ranges (1–4Hz, 4–8Hz, 8–12 Hz, 13–30 Hz), the migraine patients and controls mostly displayed excitatory connections between the sources in the frontal cortex and occipital cortex, although their topographic patterns vary between individuals. No significant difference was shown between patients and controls under positive, neutral, and negative emotional stimulus in the above four bands. The details are shown in Fig. 3.4.

3.3 Graph Theory

The analysis of graph theory shows a significant difference in graph theory parameters in patients with migraine compared to those of the control group.

In the migraine group, the D and C significantly increased in the delta (1-4 Hz) band during the viewing of happy facial expressions. We also found a tendency towards an increased L and an increased D in delta (1-4Hz) and theta band (4-8Hz) respectively, although the differences were not significant. When viewing sad or angry facial expressions, migraine suffers showed a significantly increased D and a tendency of increased C in the delta band (1-4Hz). Besides a tendency towards an increased L, no significant differences were observed during the viewing of neutral human facial expressions. The details are shown in Fig. 5.

3.4 Clinical Association

Correlation analysis shows there was no significant correlation between network properties and neuropsychology scales in migraine under neutral emotional stimulation. In response to positive emotional stimuli, we found HAM-A and HAM-D had a significant correlation with graph theory characteristics in some frequency ranges respectively. In detail, we found HAM-D negatively correlated with D ($p=0.039$, $r=-0.425$) and C ($p=0.014$, $r=-0.495$) in the delta band. Additionally, HAM-D ratings have negative correlation with D ($p=0.027$, $r=-0.451$) and S ($p=0.014$ $r=-0.493$) in alpha band as well as D ($p=0.007$, $r=-0.537$) in the beta band. We also found HAM-A had a negative correlation with L ($p=0.028$, $r=-0.447$) in the beta band. As for negative emotional stimuli, we found migraineurs' HAM-D score showed a negative correlation with D($p=0.027$, $r=-0.452$) in the alpha band. No significant correlation was found between the rest of the parameters in other frequency ranges. Details are shown in Fig. 6.

4. Discussion

In this study, we investigate the effective connectivity from low to high frequency from all participants. The migraine group showed altered neural network characteristics during the headache-free phase exposure to human facial expressions stimulation in distinct frequency ranges, including network patterns and brain topology measurements.

The main findings in the present study were the significant activation in migraine patients for the fearful facial expression. Human facial pictures are important stimuli in social communications and the facial emotional faces may be noticed in advance. This sensitivity might be related to the prioritized automatically perception of threaten detection[29, 30]. Several pieces of research provided evidence the migraineurs show abnormal neural in response to negative facial expressions[12, 13]. This suggests that migraineurs might process negative emotional perceptions abnormally during the interictal phase.

Notably, the abnormal network pattern of effectivity connectivity was identified for the patients with migraine from the whole-brain analysis. The prefrontal cortex (PFC) was significantly activated in the migraine group while viewing negative pictures. As mentioned before, the fronto-temporal pathway plays a crucial role in visually presented emotion recognition, and these regions may sustain over-activation through hyper-perfusion during emotion modulation in bipolar illness patients[31, 32]. The PFC is mainly responsible for attention, working memory, executive functions, and emotional regulation[33]. Consist with our study, PFC of migraineur exhibited stronger functional connectivity with other brain areas in resting-state, which indicates that the brain regions participated in emotion regulation may be active even without extra emotional stimulus in individuals with migraine[34]. A review illustrated the functional neuroimage studies of emotional regulation in detail and proposed PFC acts a key part in regulating emotion via cognitive reappraisal[35]. The comorbidity between migraine and major depressive disorder (MDD) has been widely admitted, and dorsolateral prefrontal cortex (DLPFC) as a dysfunctional region might be related to the co-occurrence of these two diseases[36]. Moreover, the DLPFC was a main therapeutic target in repetitive transcranial magnetic stimulation(rTMS) for the treatment of migraine and depression[37, 38]. Combine with previous studies, our observations suggest the increased PFC might result from greater efforts to regulate emotion.

In addition, compared with the healthy subjects, the migraineurs showed enhanced activation in the temporal lobe. The previous reports have suggested the human temporal cortex is an essential element in face and emotion perception[39]. A meta-analysis of emotion viewing task in healthy subjects also revealed the bilateral fusiform and middle temporal gyrus were activated, which indicate these subregions of the temporal lobe were involved in the process of emotion[40]. Several studies revealed structural and functional abnormalities of TL in migraine, which may be related to long-term stressful and chronic pain state in migraine suffers[41, 42]. A few neuroimage studies have proposed migraineurs show hyperexcitability in the temporal cortex in response to aversive stimuli, which line with our findings[42]. Unpleasant human facial expressions and painful heat stimuli both are aversive stimuli, and they both can cause TL activation. Altered gray matter architecture has previously been identified in patients with migraine[43, 44]. A Structural neuroimage study has demonstrated that the temporal pole cortical thickness correlation can be used to differentiate the migraine brain from the healthy brain[41]. Genetic studies pointed that migraine and MDD are comorbid influenced by the same genes, to a degree[9]. Likewise, MDD patients displayed greater recruitment of the right middle temporal gyrus and early increased gamma activity at the anterior temporal region during a visual emotion task[45, 46]. The above-referred TL dysfunction was attributed to the unequal distribution between bottom-up hyperactive emotional processing and top-down hypoactive attention function. Taken together, the TL appears to correspond with the capability to integrate emotionally related facial features.

Another major finding was that the global effectivity connectivity of graph theory analysis shows the altered brain network of organization in the migraine suffers, which indicates significantly increased D and C in 1-4Hz and 4-8Hz under negative emotional stimulation. In several aforementioned MEG reports, different topological properties in the neural network of migraine patients were demonstrated not only in resting state but also in specific tasks[18, 19]. The D is a powerful metric to measure the centrality of a network, and it emphasized the effect and significance of a brain network at the voxel level. Increased D in the patients' group suggests high integration ability of a migraineur’s brain region within cortical networks. The phenomenon of over-connectivity in migraine may be related to hyperexcitability in the brain network. The C defines the possibility that neighboring nodes will be connected. According to a report from Watts and Strogatz, the small-world network is the most efficient network which was characterized by highly clustered and small characteristic path length, compared to random network and regular network[47]. We concluded that enhanced D and C in patients with migraine reveal an inefficient brain network. These findings provide evidence that long-term repeated migraine attacks affect the emotion process in migraine suffers.

The results of correlation analysis demonstrated the parameters of graph theory in migraine patients had a negative correlation with neuropsychological assessments in multi-frequency following by positive and negative emotional stimuli. Migraine patients with high anxiety scores and depression scores have been related to the high degree of migraine disability. Moreover, migraine can induce negative emotions, and negative events can aggravate migraine. Our findings reveal that the migraine suffers showed more deficits in the processing of emotional stimuli than did the healthy control group, which consists with the conclusion from a previous study[12].

We have recognized there are some limitations in current study. We enrolled several migraine patients with mild anxiety or depression from the neuropsychology scale, which may affect our results. To solve the problems, further studies need to recruit a large sample size of migraineurs to divide into with or without obvious stress problems. Additionally, not all migraineurs in the present study experienced headache in the same part of the brain, even not all of those experienced bilateral headache. Further research should avoid all the above bias.

5. Conclusion

In summary, the study demonstrates that individuals with migraine showed deviant effective connectivity when viewing human facial expressions in multi-frequency. The prefrontal-temporal pathway might be related to the altered negative emotion modulation in migraine. Furthermore, the aberrant neural network showed a negative correlation with depressive symptom severity. The emotion dysregulation was possibly correlated with morbidity and pathogenesis of migraine. These findings may contribute to understanding the mechanism of the comorbidity of depression and anxiety in migraine and provide a reference for clinical treatment.

Abbreviations

MEG: magnetoencephalography; EC: effective connectivity; EEG: electroencephalogram; fMRI: functional magnetic resonance imaging; ICHD: International Classification of Headache Disorders; FDR: false discovery rate; VAS: visual analog scale; HAM-A, The Hamilton Anxiety Scale; HAM-D, Hamilton Depression Scale; GC, granger causality; D, degree; S, strength; L, path length; C, clustering coefficient; PFC, prefrontal cortex; MDD, major depressive disorder; DLPFC, dorsolateral prefrontal cortex; rTMS: repetitive Transcranial magnetic stimulation; TL, temporal lobe.

Declarations

Ethics approval and consent to participate

The study was approved by the medical ethics committee of The Affiliated Brain Hospital of Nanjing Medical University. Written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JR, QY, and JPS conceived and designed the experiments. JR, YQC, FL, QQC performed the experiments. JR, QY, MJT, JX analyzed the data. JR and JPS wrote the paper. All authors read and approved the final manuscript.

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Table

Table 1 Clinical features and neuropsychological evaluation of patients.

Parameter	Migraine	Control
Gender (women/men)	18F/6M	16F/8M
Age (years)	29.25±9.32	29.71±7.46
Disease history (years)	11.17±6.62	
Frequency (times/month)	4.67±4.40	
Durations of migraine attacks (hours)	20.76±17.71	
Accompanied symptoms with attack N		
Phonophobia	20	
Photophobia	18	
Nausea/Vomiting	17	
Locus of headache N		
Bilateral	7	
Unilateral	17	
Pain type (number of subjects)		
Throbbing	18	
Pressure	3	
Sharp	2	
Stabbing	1	
VAS of attack intensity (0–10)	7.42±1.44	
HAM-A Rating	9.67±4.63	
HAM-D Rating	10.33±5.11	

N, number; VAS, visual analog scale; HAM-A, The Hamilton Anxiety Scale; HAM-D Hamilton Depression Scale.

Figures

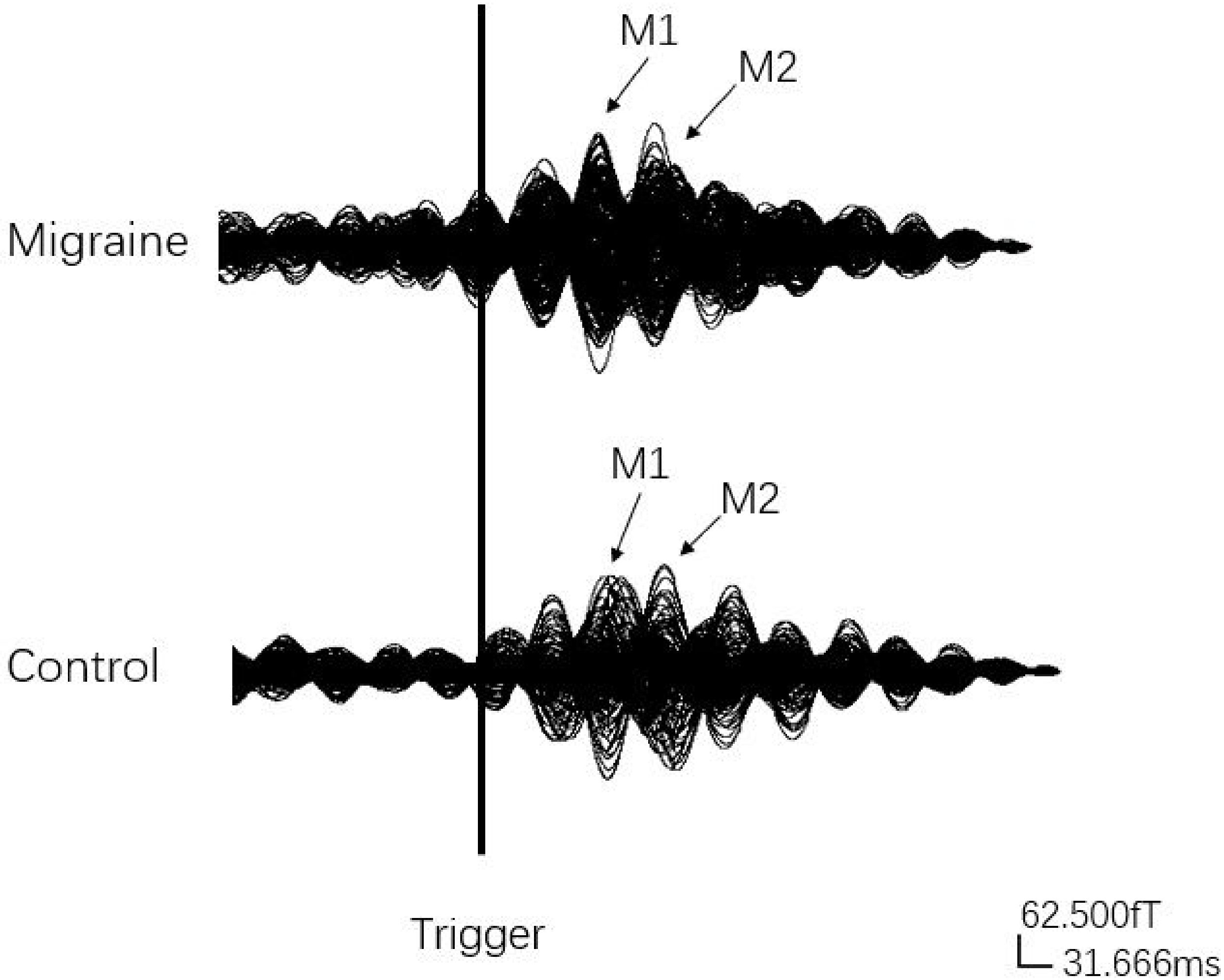

Figure 1

Emotional task paradigm.

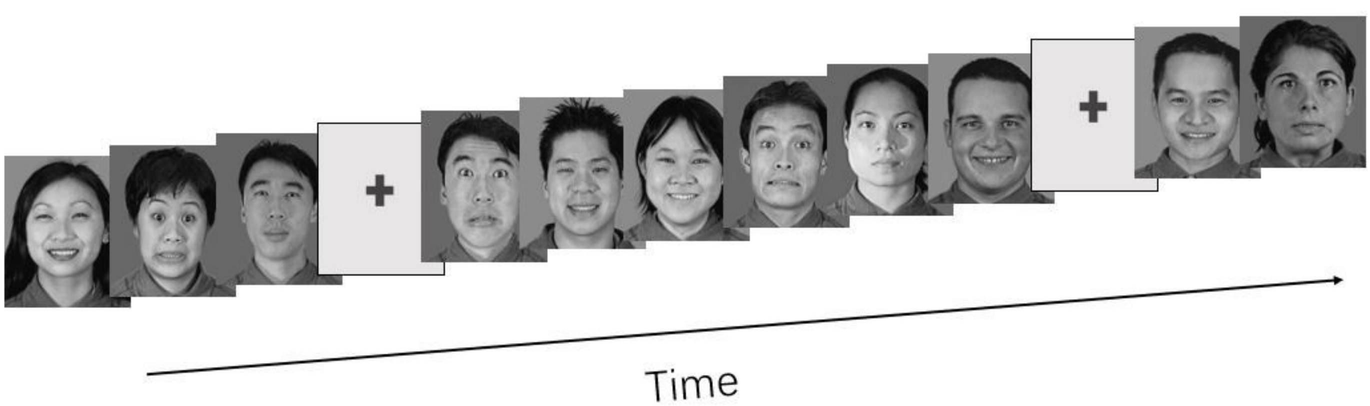

Figure 2

Magnetoencephalography (MEG) waveforms showing neuromagnetic activation following by emotional stimuli in a migraine subject and a healthy subject in the 8-12Hz range. The ”M1” and ”M2” are two main components evoked by human facial expressions. The “Trigger” indicates the start of emotional stimuli.

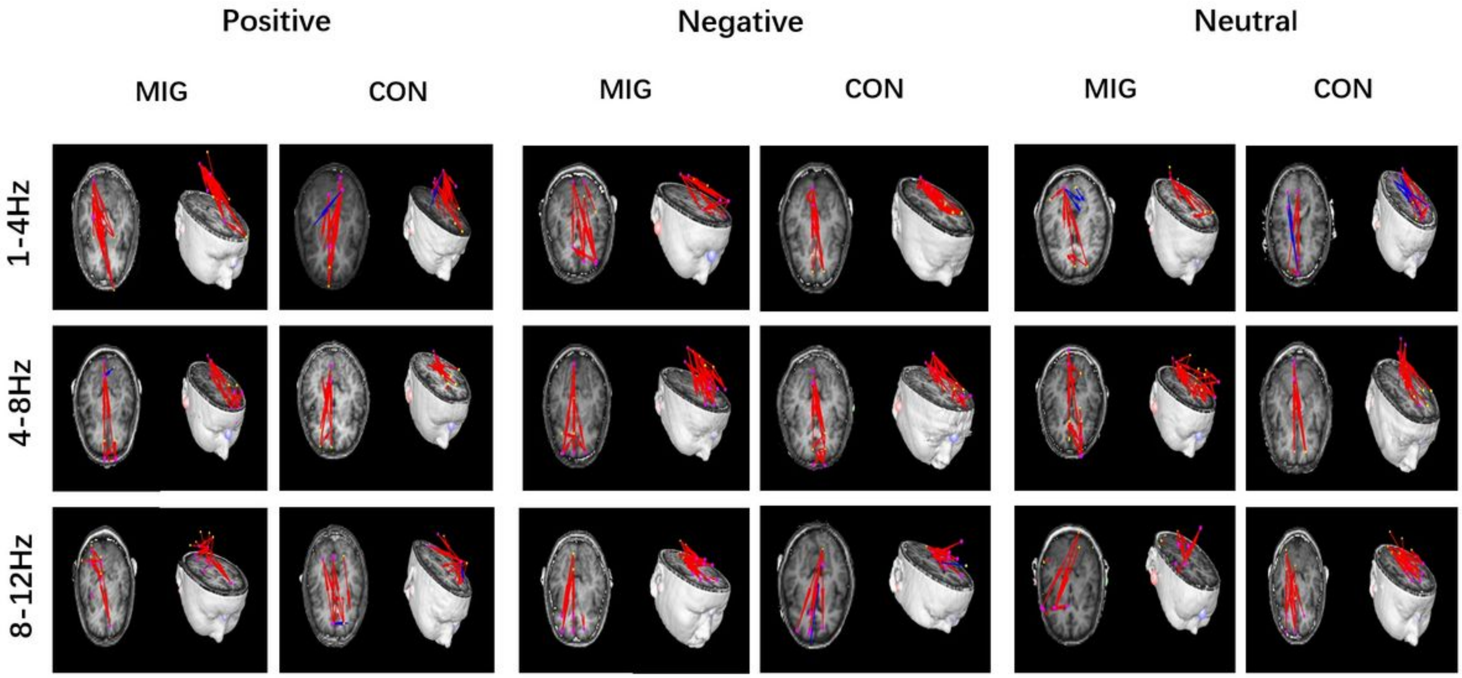

Figure 3

Typical predominant EC networks in the 1–13 Hz frequency range in migraine patients and controls, visualized from the axial (left column) and lateral (right column) views. No significant differences were observed between the two groups when exposure to emotional stimuli. (Color figure online)

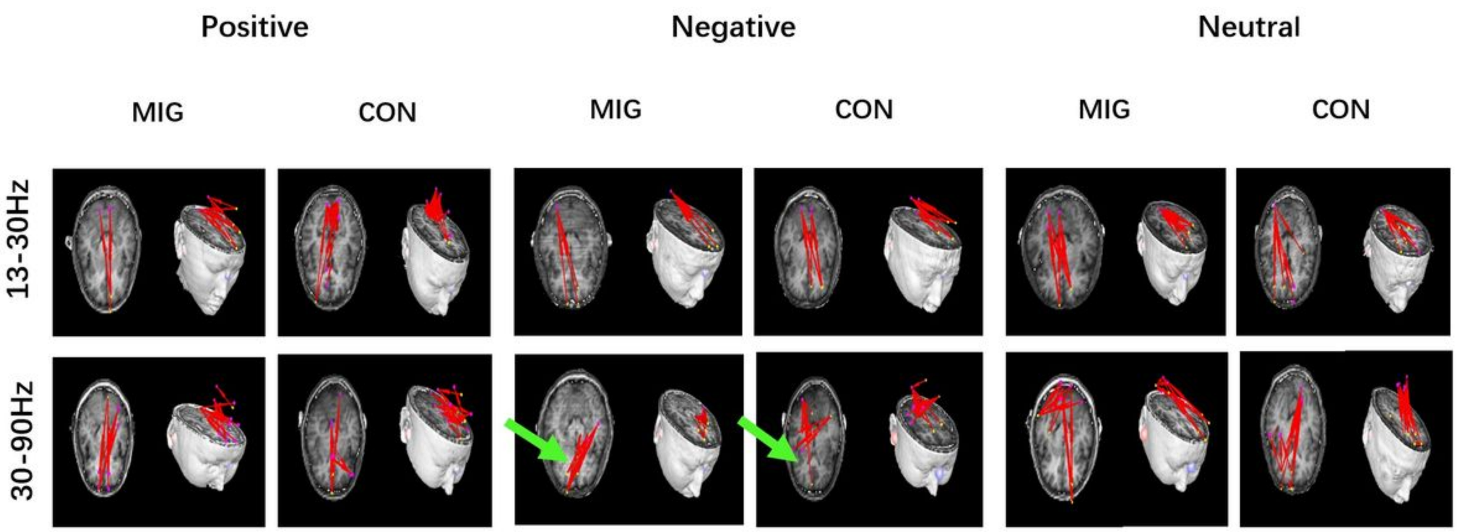

Figure 4

Typical EC network patterns in the 13–90 Hz frequency range in migraine patients and controls in response to positive, negative and neutral human expressions respectively, visualized from the lateral (left column) and axial (right column) views. Migraineurs show a significantly altered pattern of EC network at 30-90 Hz in face of negative emotional stimuli compared with the controls, showing more connections from the prefrontal lobe to the temporal lobe, which are indicated by green arrows. No significant differences were observed between the two groups exposure to positive and neutral stimuli. (Color figure online)

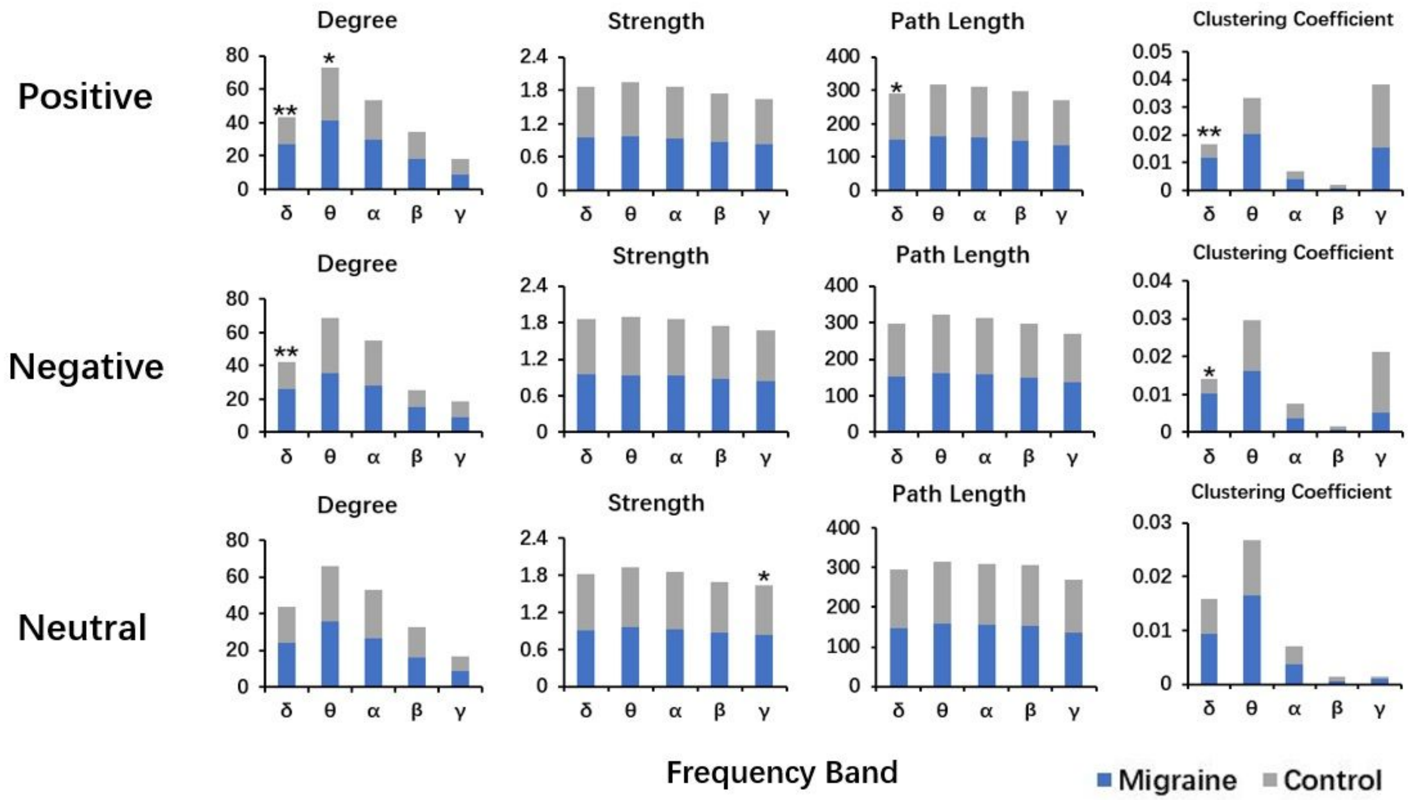

Figure 5

Comparison in the organization of the EC networks measured by four parameters (degree, strength, path length, and clustering coefficient) between migraine patients and healthy controls. *p represents p<0.05, **p represents p< 0.05 and the result is still significant after correction for multiple comparisons using the FDR controlling procedure (corrected for 5 × 4 tests). (Color figure online)

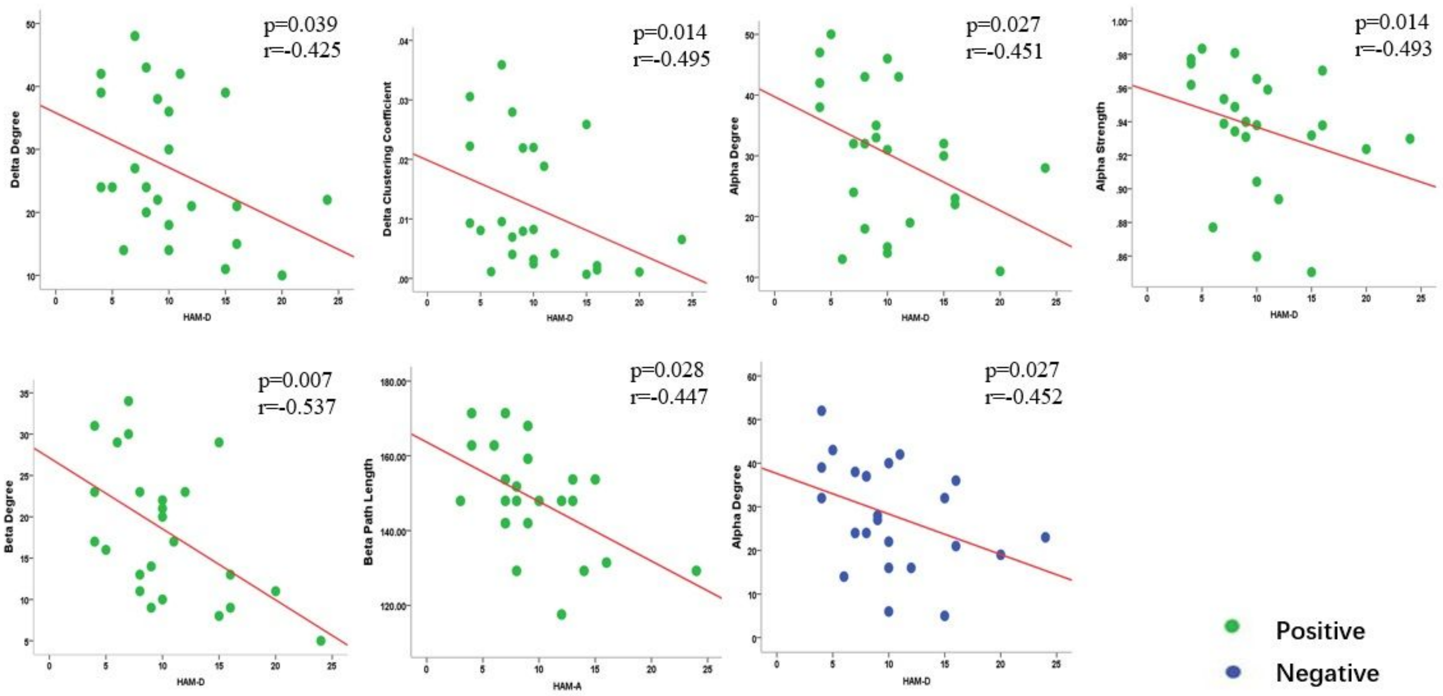

Figure 6

Correlation between the parameters of graph theory and neuropsychological scales in migraineurs when viewing positive emotional stimuli (green point) and negative emotional stimuli (blue point). In positive emotional stimuli, HAM-D shows a negative correlation with D and C in the delta band, a negative correlation with D and S in the alpha band as well as D in the beta band. HAM-A shows a negative correlation with L in the beta band. In negative emotional stimuli, migraineurs' HAM-D score showed a negative correlation with D in the alpha band.