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OBM Neurobiology

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Review

Dynamic Resting-State Functional Connectivity in Migraineurs

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Academic Editor: Yasushi Shibata

Special Issue: The Pathophysiology and Treatment for Migraine

OBM Neurobiology
2022, volume 6, issue 4
doi:10.21926/obm.neurobiol.2204143

Received: July 19, 2022
Accepted: October 18, 2022
Published: October 26, 2022

Abstract

Functional magnetic resonance imaging (fMRI) is widely used to detect changes in the resting-state brain networks of migraine patients. Functional connectivity fMRI analysis examines the functional organization of the brain based on temporal correlations of blood oxygen level-dependent signal changes in different brain regions. Most previous resting-state fMRI studies have assumed that functional connectivity between brain regions remains relatively stable over time. However, it is now known that the brain is a complex system that undergoes time-dependent dynamics. Therefore, functional connectivity may change over time. In recent years, resting-state fMRI analysis has evolved from the detection of static coupling to the study of dynamic connectivity. However, studies of dynamic functional connectivity in migraine patients are limited. Related studies have shown that dynamic functional connectivity analysis reveals significant changes in connectivity and abnormal networks not found in static functional connectivity analysis.

Keywords

Migraine; dynamic functional connectivity; network; MRI

1. Introduction

Migraine is a clinical syndrome characterized by headache with specific features and accompanying symptoms such as nausea, vomiting, photophobia, and phonophobia [1].

Functional MRI (fMRI) investigates the mechanisms lead to sensory hypersensitivity in migraine by measuring brain's response to sensory stimuli, while resting-state functional MRI analysis (rs-fMRI) investigates the functional connectivity of specific brain regions and networks responsible for sensory processing [2].

The rs-fMRI analysis methods can be classified into model-dependent and model-free methods [3]. Model-dependent methods examine functional connectivity by correlating the resting time series of a known region of interest (ROI) with the time series of all other regions, which clearly shows which regions' ROI is functionally connected. The model-free methods aim to search for general patterns of unique functional connectivity. Independent component analysis (ICA) is the most popular model-free method. ICA is applicable to whole brain voxel unit data, easily selects the time signals of resting-state independent components (ICs), and shows a high degree of consistency.

Conventionally, rs-fMRI analysis implicitly assumes that the statistical interdependence of signals between different brain regions is constant during the recording of a task-free experiment [4, 5]. However, by dividing the time series into short time segments, it is possible to detect time-varying patterns in network strength and components on the basis of sliding time window correlation [4, 5]. This method is known as dynamic connectivity analysis, and the functional connectivity for obtaining dynamic connectivity analysis is called dynamic functional connectivity (d-FC). Contrary to dynamic functional connectivity, conventional functional connectivity is called static functional connectivity (s-FC). Dynamic connectivity analysis better reflects fluctuations in neuronal activity and helps identify networks that cannot be detected by static functional analysis [4, 5]. We have described previous studies using dynamic connectivity analysis in migraine patients, including our previous study [6-11]. In this review, we provided insight into resting-state dynamic functional analysis in migraine patients.

2. Overview of Previous Dynamic rs-fMRI Studies

2.1 Characteristics of Participants

All 6 studies were conducted in migraine patients [6-11]. The diagnosis of migraine differed according to the purpose of the study and included migraine [7], migraine without aura (MwoA) [6, 10, 11], episodic migraine (EM) [8], and chronic migraine (CM) [9, 11]. The number of participants, including controls, ranged from 37 to 159 [6-11].

2.2 Migraine Phase in MRI

Migraine is divided into five phases: prodromal, aura, ictal, postictal, and interictal phases [1]. Of these, the prodromal, aura, and postictal phases are together referred to as the peri-ictal phase. MRI images were acquired during the interictal phase in three studies [6, 10, 11], and one study [9] assumed an interictal phase. Two studies [7, 8] acquired images of all phases, one of which [8] classified the images into the preictal phase and ictal/peri-ictal phases.

2.3 The Methods of d-FC Analysis

All studies performed d-FC analyses using the sliding window method [6-11]. However, the analyzed data using the sliding window method differed from study to study: three studies used ICs obtained from group ICA (GICA) [6, 8, 9], two studies used predefined ROIs [7, 11] and one study used the seed obtained from regional homogeneity (ReHo) and amplitude of low frequency fluctuations (ALFF) analyses [9]. Of these, two tools were used in GICA; two studies [6, 9] used the GIFT (https://trendscenter.org/software/gift/) [12, 13] and one study [8] used the FSL MELODIC software [14-17]. For predefined ROIs: one was 59 ROIs related to pain processing [7] and the other was 132 ROIs for the whole brain [11].

2.4 Comparison of d-FC with s-FC

Dynamic connectivity analysis can detect more fluctuations in neuronal activity than static functional analysis [4, 5]. Four of the six studies compared d-FC with s-FC to determine whether the advantage of dynamic connectivity analysis can be detected in migraine patients [7-9, 11]. Dumkrieger et al. reported that the significantly different FC between migraine and persistent posttraumatic headache (PPTH) were 17 region pairs in s-FC and 10 region pairs in d-FC [7]. Likewise, the ROI pairs with significant differences in migraine and PPTH in s-FC and d-FC were different. Lee et al. showed a single significant different network between interictal migraine patients and controls, whereas there were no significantly different networks between ictal/peri-ictal migraine patients and controls in static connectivity analysis [8]. In dynamic connectivity analysis, however, there were seven significant different networks each between interictal and ictal/peri-ictal migraine patients and their respective controls. Also, four ICs had significantly different connectivity in both interictal and ictal/peri-ictal migraine patients compared to controls. In addition, Zuo et al. demonstrated that there were no significantly different networks in static functional network connectivity (s-FNC) while five significantly different networks in dynamic functional network connectivity (d-FNC) were indicated [9]. Our previous study showed that there were 18 significantly different connectivity pairs between photophobic and non-photophobic patients, 15 significantly different connectivity pairs between phonophobic and non-phonophobic patients, and one significant different connectivity pair between patients with and without osmophobia in s-FC analysis [11]. While in d-FC analysis, there were 16 significantly different connectivity pairs between photophobic and non-photophobic patients, 8 significantly different connectivity pairs between phonophobic and non-phonophobic patients, and 14 significantly different connectivity pairs between osmophobic and non-osmophobic patients. Thus, in both s-FC and d-FC analysis, there were significantly different connectivity pairs between patients with and without photophobia, while no common significant connectivity pairs were observed between patients with and without phonophobia and between patients with and without osmophobia. The results of the above 4 studies showed that dynamic connectivity analysis can detect more significant networks and different connectivity pairs than static connectivity analysis.

3. The Details of Each Study

3.1 Abnormal Thalamocortical Network Dynamics in Migraine

Functional and morphological studies have suggested that the thalamocortical pathway plays an important role in the pathogenesis of migraine [18-20]. Tu et al. in 2019 reported abnormal thalamocortical network dynamics in migraine [6]. In this study, the authors investigated the d-FNC of thalamocortical networks in 89 interictal migraine patients and 70 healthy controls (HCs), and whether clinical features were associated with abnormal connectivity.

In detail, they performed 4 major steps within the framework of characterizing dynamic d-FNC to detect atypical functional dynamics in migraine. In step 1, GICA was conducted to decompose the whole brain resting-state fMRI data into multiple ICs using the GIFT toolbox [12, 13]. Following GICA, intrinsic component networks (ICNs) were selected from the ICs according to spatial activation maps [21]. In step 2, the d-FNC in ICNs was calculated using a sliding window approach with graphical lasso (least absolute shrinkage and selection operator), the graphical lasso was a remarkably fast simple algorithm that used a coordinate descent procedure for the lasso [4, 5, 22]. In step 3, the d-FNC estimates were hard clustered, i.e., the data items were grouped so that each item was assigned to only one cluster to assess the recurring d-FNC patterns over time [23]. Next, whether MwoA and HCs presented different occurrences of different functional d-FNC states during rs-fMRI was investigated. A 2-sample t-test was performed to examine the group difference in occurrence between MwoA and HCs for each d-FNC state, thereby, the presence of abnormal transient d-FNC was further investigated. In step 4, the efficiency of information transfer in dynamic brain networks is demonstrated to be variable by applying graph theory measures on different d-FNC states [24-29]. Specifically, ICNs were defined as nodes and the d-FNC between them was defined as edges, and efficiency was inversely proportional to the harmonic mean of the shortest distance (number of edges) between all possible pairs of nodes. The global efficiency was the average efficiency across all node pairs, while the local efficiency was the average of the nodal local efficiency within neighbors of the node.

The results identified 52 ICNs which were categorized into 5 d-FNC brain states to characterize and compare dynamic functional connectivity patterns. Group differences of occurrences and dFNC patterns showed migraineurs had a significantly higher occurrence rate in state 1 with strong positive connectivity within the somatomotor domain and visual domain, and a significantly lower occurrence rate in state 2 with sparsely connected. In addition, abnormalities in d-FNC with visual cortex and the precuneus of the posterior thalamus (nucleus pulvinar) were significantly correlated with migraine frequency. The posterior nucleus of the thalamus receives projections from the brainstem and transmits them to the primary and secondary somatosensory cortices, insula, primary and secondary visual cortices, primary auditory cortex, and anterior cingulate cortex [30]. It has been suggested that abnormal connections between the posterior nucleus of the thalamus and visual cortex may be implicated in clinical features of migraine, such as photophobia and allodynia. In addition, topological measurements revealed that migraine patients had significantly reduced information transfer efficiency in the global and local d-FNC.

3.2 Differences in Static and Dynamic Functional Connectivity Between Migraine and Persistent Posttraumatic Headache

Migraine and PPTH often share common phenotypic features. The main factor distinguishing PPTH from migraine is the head injury itself [31]. The structure of migraine and PPTH differ in regions within the right lateral orbitofrontal lobe, left caudal middle frontal lobe, left superior frontal lobe, left precuneus and right supramarginal gyrus. [31]. Dumkrieger et al. investigated the differences in brain function between migraine and PPTH in terms of s-FC and d-FC patterns in 59 preselected regions involved in pain processing [7].

The study explored functional connectivity using an ROI approach. Fifty-nine ROIs (29 bilateral regions and one midline area) were predetermined according to prior literature [32-39]. For each pair of ROIs, a sliding window correlation analysis was performed and the standard deviation of the obtained time course values was calculated. Resting-state data in 10 minutes was collected, and 60 seconds window lengths were selected to increase confidence in capturing time-varying fluctuations that can be missed using shorter window lengths. The d-FC values were compared between groups using ANOVA followed by t-tests adjusting for gender and age. And the Benjamini-Hochberg procedure was used to correct for multiple comparisons [40]

The results showed that significant differences in s-FC between migraine and PPTH were found in 17 pairs of regions and the major connections regions were the left ventral medial prefrontal cortex and left secondary somatosensory cortex. Significant differences in d-FC between migraine and PPTH were found in 10 region pairs and the major connections regions were the left secondary somatosensory cortex and left fusiform gyrus. There was overlap in the regions of difference in s- and d-FC between PPTH and migraine, but not in functional connectivity between region pairs. In the migraine group, s-FC between the left secondary somatosensory cortex and the right cuneiform cortex was significantly correlated with headache frequency, and d-FC between the right cingulate and right amygdala was significantly correlated with pain intensity. In the PPTH group, s-FC between the left middle cingulate and the right pulvinar, right posterior insula and hypothalamus was significantly correlated with headache frequency, and d-FC between the right middle cingulate and right supramarginal gyrus was significantly correlated with headache frequency. This study showed that s-FC and d-FC coupling of pain-processing and visual-processing regions was different in migraine and PPTH. Both static and dynamic functional analysis may be useful to study brain function in migraine and PPTH and perhaps to distinguish between PPTH and migraine.

3.3 Dynamic Functional Connectivity of the Migraine Brain During Interictal and Ictal/Peri-Ictal Phases

Migraine is a clinical syndrome characterized by headache with specific features and associated symptoms, such as nausea, vomiting, photophobia and phonophobia [1]. The period when the headache attacks is called the ictal phase. Some patients experience an aura, which is a prodromal phase occurring 24 hours before the headache and a postdromal phase following headache attacks. The aura, prodromal and postdromal phases together are called peri-ictal phase. The period outside ictal phase and peri-ictal phase is called interictal phase. Lee et al. examined the differences in dynamic functional connectivity between migraine patients and the controls [8]. 50 migraine patients and 50 age- and sex-matched control subjects were recruited. The migraine patients were

divided into interictal phase and ictal/peri-ictal phase. All subjects underwent resting-state functional magnetic resonance imaging.

First, ICs were calculated using GICA with the FSL MELODIC program [14-17, 41]. Second, the spatial map and temporal/spectral properties of each IC were taken into account [42, 43]. The signal ICs were employed for an investigation of functional connectivity while being regarded as brain networks. Only rs-fMRI data from interictal individuals were used for group ICA, and the ictal/peri-ictal subjects were then given access to the constructed brain networks. Based on graph theory, static and dynamic connectivity evaluations were carried out [24, 44]. The group ICA-defined brain networks were regarded as graph nodes. For static connectivity analysis, the Pearson correlation coefficient of the entire time series between various nodes was used to generate graph edges [24, 45, 46]. Dynamic connectivity analysis was carried out in addition to static connectivity analysis using sub-time series derived from sliding windows. Next, the subject-level regularized dynamic connectivity matrices were subjected to a k-means clustering technique to characterize brain states and decrease the dimensionality of the matrices [5, 22, 47]. The silhouette coefficient and elbow approach were used to calculate the ideal number of clusters [5, 22, 48]. The group-level brain states were defined using the most common number of clusters from the subject-level brain states. The average of the dynamic connectivity matrices in the identical brain states was used to determine the EC values for each individual. Finally, EC values were determined for each subject in various brain states. The calculated EC values were utilized to evaluate the differences between patients and controls within the interictal and ictal/peri-ictal groups.

This study defined significant networks from the interictal patients and matched controls in a data-driven manner and tested patients and controls in ictal or peri-ictal data sets. Static analysis revealed no significant networks in both the interictal and interictal/preictal/period data sets. While, dynamic analysis revealed significant group differences in 7 brain networks in the interictal data set (default mode network, frontoparietal network and cerebellum network; normal controls>patients, 3 brainstem networks and pain modulatory network; normal controls<patients) and in the ictal/peri-ictal data set (modulatory network; normal controls>patients, thalamus network, 2 brainstem networks and pain modulatory network; normal controls<patients) each. A frontoparietal network, 2 brainstem networks, and a cerebellar network remained significant in the ictal/peri-ictal data set. This study suggested that dynamic connectivity analysis can reveal more functional networks associated with migraine than conventional static analysis.

3.4 Aberrant Modulations of Static Functional Connectivity and Dynamic Functional Network Connectivity in Chronic Migraine

Default mode network (DMN), salience network (SN), and central executive network (CEN) are known as representative intrinsic functional brain networks. Previous studies have shown a significant decrease in DMN, SN and CEN connectivity for all CM participants, regardless of MOH status, when compared to controls [49, 50]. To confirm previous studies and evaluate d-FNC, Zuo et al. investigated the functional characteristics of brains with chronic migraine (CM) using s-FC, s-FNC, and d-FNC analyses [9].

13 ICs were identified from 17 CM patients and 20 gender- and age-matched HCs, which were classified into six static state networks.

The intrinsic connection networks were first identified using ICA by Group ICA Of fMRI Toolbox (GIFT) software [51]. The minimal description length criteria estimated 20 ICs and visual inspection identified 13 ICs as meaningful. The 13 ICs then categorized into 6 resting-state networks, such as DMN. SN, CEN, auditory network (AN), visual network (VN) and cerebellum network. The s-FNC was evaluated using MANCOVAN toolbox of GIFT software. The d-FNC was analyzed using the sliding window method with the temporal d-FNC toolbox in GIFT software [4, 52].

In s-FNC, there were no significant differences between CM and HCs. However, the d-FCN analysis between CM and HCs showed a significantly decreased connectivity between the DMN (IC11) and AN (IC 5) and 4 significant increased connectivity between ECN (IC2, IC4) and DMN (IC19), between the ECN (IC 4) and AN (IC 5), and between the ECN (IC 4) and VN (IC 13).

This study suggested that the functional connectivity of the CM brain was not static but may fluctuate over time. Significantly increased connectivity was found between the ECN and DMN, the ECN and AN, and the ECN and VN. The DMN and ECN appeared to be related with cognitive functions. AN and VN probably regulated the sensory system. This study provided further evidence that the chronicity of migraine may be related to abnormalities in connectivity between sensory and cognitive brain networks.

3.5 Disrupted Dynamic Functional Connectivity of the Visual Network in Episodic Patients with Migraine Without Aura

Migraine can be classified into migraine with aura (MwA) and MwoA, depending on the presence or absence of aura [1]. The visual aura is the most common type of aura and occurs among more than 90 % of patients with MwA [53]. Photophobia, like visual aura, is a common visual symptom of migraine. Photosensitivity is one of the most bothersome symptoms of MwoA as well as MwA. Photophobia is not only present during the ictal phase, but also during the interictal phase. Several recent studies have addressed the altered s-FC of the visual cortex in MwoA [32, 54, 55]. Wei et al. investigated the relationship between d-FC of the visual cortex and clinical features in patients with MwoA in interictal phase [10].

Fifty-five MwoA patients and 50 sex- and age-matched HCs were included in the study. Data preprocessing was as follows. First, commonly affected brain regions were chosen as seeds, and 5 mm peak MNI coordinates were used to build them. The Dynamic Brain Connectome Toolbox (V2.1 http://restfmri.net/forum/DynamicBC) was used to conduct the d-FC analysis [22, 56]. A sliding window strategy was used to convolve the rectangles with a Gaussian kernel to create temporal dynamic patterns. 64 windows per person were created with a window size of 30 TRs and a window overlap of 90%. In each sliding window, the temporal correlation coefficient (r) between each seed and the remaining brain voxels over time were measured. Multiple sliding window correlation maps were obtained for each subject. To quantify temporal variation in functional connectivity, the coefficient of variation over time for each voxel in each window were computed and the Fisher Z transform was used to obtain variables that were close to a normal distribution.

Regional changes in visual cortex were assessed using ReHo and ALFF. ReHo is one of the indicators of regional synchronization of spontaneous brain activities, and ALFF is one of the markers of the regional intensity of spontaneous brain activities. Seed-based analysis was performed to evaluate d-FC between the visual cortex and the whole brain using the Dynamic Brain Connectome Toolbox (V2.1 http://restfmri.net/forum/DynamicBC).

The results showed that patients with MwoA had reduced ReHo values in the right lingual gyrus and reduced ALFF levels in the the right lingual gyrus and angular gyrus, and increased ALFF levels in the left superior frontal gyrus, right inferior frontal gyrus, and right middle frontal gyrus compared with HCs. To evaluate the d-FC between the visual cortex and the whole brain, the right lingual gyrus was selected as the seed region because of reduced ReHo values and ALFF levels. And the d-FC analysis showed asignificant decrease in the lingual gyrus in relation to the right calcarine sulcus, bilateral cuneus, right fusiform gyrus and bilateral postcentral gyrus, and a significant increase relation to the left thalamus, right insula, right parahippocampus, right hippocampus, right angular gyrus, bilateral middle cingulate cortex, bilateral posterior cingulate cortex and bilateral precuneus. Abnormalities in the d-FC of the right lingual gyrus and bilateral cuneus were positively correlated with anxiety scores evaluated using General Anxiety Disorder scores [10]. Previous study showed Alzheimer's disease patients with depression have decreased FC between the right lingual gyrus and dorsal anterior cingulate cortex [57]. Anxiety, like depression, is a risk factor for migraine chronicity [53]. A recent study reported that anxiety was more robustly associated with increased risk of migraine than depression [58]. This study suggested that d-FC abnormalities in the visual cortex were involved in multinetwork pain integration in episodic MwoA patients and may be associated with anxiety disorders.

3.6 Functional Connectivity in Migraineurs with Photophobia, Phonophobia, or Osmophobia

Finally, differences in s-FC and d-FC between patients with and without photophobia, phonophobia, or osmophobia were explored [11]. Sixty-two migraine patients with/without photophobia, phonophobia, or osmophobia underwent fMRI during the interictal phase. ROI-to-ROI analysis in the whole brain was performed to compare s-FC and d-FC.

This study started with the d-FC analysis using the CONN toolbox [59-62] with dynamic ICA. The dynamic properties (temporal modulation) of the ROI-to-ROI connection matrix were investigated by dynamic connectivity analysis, which also identified some connectivity circuits with similar modulations. Next, various modulating circuits were depicted through the dynamic ICA matrix and the rate of change connectivity between each pair of ROIs was measured. The rate of connectivity change was determined by the strength and sign of connectivity change conjugated to a particular component/circuit time series. The simple generalized form of the context-dependent psychophysiological interaction (gPPI) model was used to estimate the group-level modulation component gamma _l(i,j). The fast ICA with hyperbolic tangent contrast functions was then used to rotate the group-level modulation components gamma _l(i,j), and the ICA mixing matrix W was inverted to compute the dynamic iIC/circuit time series. Finally, the estimated dynamic IC/circuit time series h(t) was back-projected to a set of group-level modulation components of subject-level components gamma _nk(i,j) using a variety of conventional first-level gPPI models with gPPI psychological variables. The ROI-to-ROI connectivity matrix was used to determine the correlations between the conditions for each participant.

Analysis of s-FC showed that 18 significant different connectivity pairs patients in photophobic patients, 15 significant different connectivity pairs in phonophobic patients, while connectivity between the right cerebellar lobe and the brainstem was significantly higher in patients with osmophobia (Figure 1 A, Figure 1B, Figure 1C, static).

Figure 1A

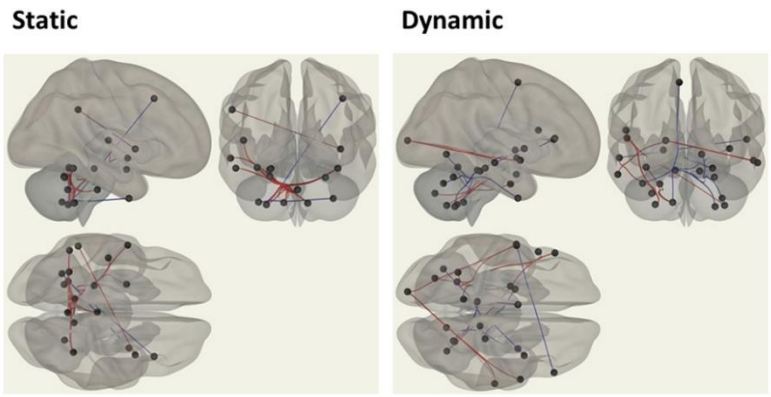

Figure 1B

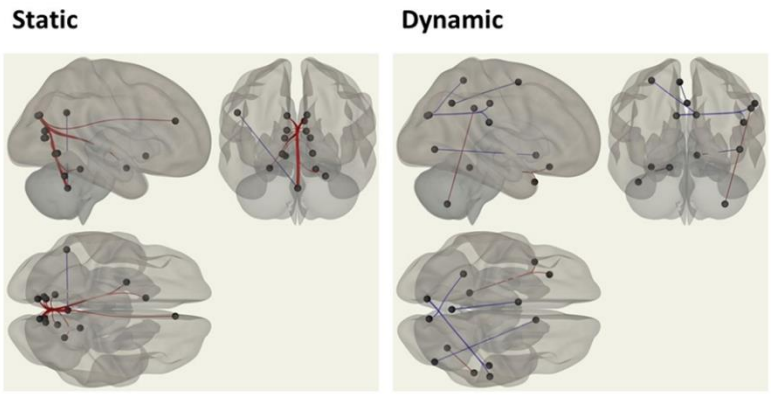

Figure 1C

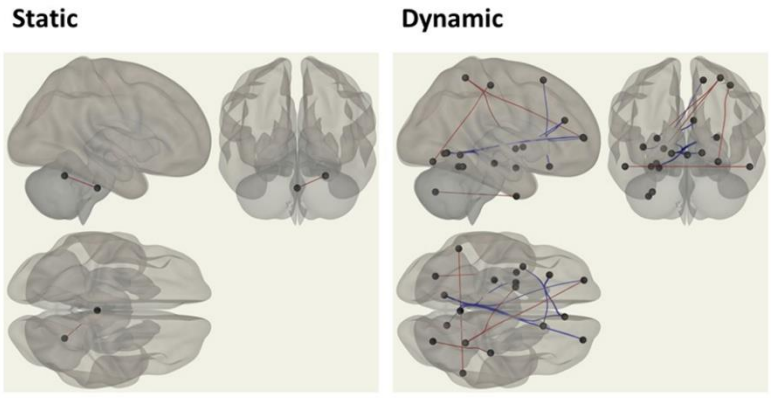

Figure 1 Results of s-FC and d-FC using ROI-to-ROI analysis. The Figure in (A), (B), and (C) demonstrated significantly different s-FC and d-FC between migraineurs with or without photophobia, phonophobia, and osmophobia. Patients with photophobia, phonophobia, or osmophobia have much higher connections on the red line than those who do not. Patients with photophobia, phonophobia, or osmophobia have much lower connectivity on the blue line than those without these phobias.

According to the analysis d-FC, patients with photophobia had 16, patients with phonophobia had 8, and patients with osmophobia had 14 distinct significant connectivity pairs (Figure 1A, Figure 1B, Figure 1C, dynamic). There were no appreciable overlapping linkages between the s-FC and d-FC in phonophobic and osmophobic patients.

Our study revealed that patients with photophobia, phonophobia, or osmophobia had different s-FC and d-FC values. We hypothesized that these variations in s-FC and d-FC might be due to distinct brain dynamics and that s-FC and d-FC analyses could be useful for determining the pathophysiological mechanisms behind migraine.

4. Discussion

Univariate and multivariate approaches commonly applied to resting-state data assume that the strength of interactions between regions is not changing over time [2-5]. However, recent theories have demonstrated that the brain is a highly interconnected and dynamic system [4, 5]. Therefore, conventional functional coupling analysis has limited ability to reflect the dynamic processes of neural signals and may ignore potential changes. Resting-state d-FC and d-FNC analysis may be a useful neuroimaging method to overcome this static limitation and explore temporally changing patterns. As mentioned in Section 2.4, four of six studies compared d-FC with s-FC, suggesting that dynamic connectivity analysis can detect more significant networks and different connectivity pairs compared to static connectivity analysis [7-9, 11]. For example, the study by Dumkrieger et al. showed significantly different ROI pairs between migraine and PPTH, migraine and controls, and PPTH and controls differed between s-FC and d-FC [7]. In our previous study, comparing migraineurs with and without photophobia, 18 significantly different functional connectivity were found in s-FC and 16 in d-FC [11]. These significantly different functional connectivities were found mainly between the cerebellum and temporal lobe regions. And significantly different functional connectivities were found in the cerebellum and temporal lobe, but not in the occipital lobe and the visual cortex, suggesting that photophobia may be associated not only with the occipital lobe but also with a wide range of regions, including the cerebellum and temporal lobe. Meanwhile, we found 15 significantly different functional connectivity in s-FC and 8 in d-FC comparing migraineurs with and without phonophobia, one significantly different functional connectivity in s-FC and 14 in d-FC comparing migraineurs with and without osmophobia [11]. These results suggested that different hypersensitivity symptoms such as photophobia, phonophobia and osmophobia have different time windows in which significantly different functional connectivity may be detected. The results of two other studies that may have demonstrated the advantages of d-FC are as follows [6, 10]: Previous studies have suggested that thalamocortical dysrhythmia and abnormal low-frequency oscillations in thalamocortical networks are associated with clinical symptoms of migraine and strongly influence important pain processes with combining multisensory [18-20]. The study by Tu et al. specified taht the posterior–pulvinar thalamic complex was an abnormal functional component of migraine [6]. Anxiety, like depression, is a risk factor for migraine chronicity [53]. Wei et al. suggested that abnormalities in d-FC of the visual cortex may be associated with anxiety disorders [10]. In summary, dynamic connectivity analysis can detect more significant networks and different connectivity pairs than static connectivity analysis.

Schwedt et al. mentioned several limitations of conventional fMRI studies [2]. First, some fMRI studies of migraine involved small numbers of patients, which limited statistical power and was

often suboptimal methods for determining significance, limiting the generalizability of the results. In addition, there were few replicated studies confirming fMRI results. For example, several studies have suggested that MwA undergo s-FC changes compared to MwoA and HCs, not only in the visual cortex but also in a wide range of regions involved in visual processing. However, the study by Hougaard et al. reported that among 40 MwA patients with 40 age- and sex-matched HCs, there was no difference between MwA patients and HCs in these networks, or even a trend towards no difference [63]. Therefore, the absence of s-FC difference in a large sample of MwA and HCs questioned the findings of previous studies and emphasized the general requirement for rs-fMRI results to be replicated before making solid conclusions [63, 64]. These limitations also apply to the d-FC and d-FNC analysis in the presented studies. The results of these studies have not been followed up, and have not been evaluated for reproducibility. The study by Zuo et al. was based on17 CM and 20 HCs [9], which was a relatively small number of patients. For heterogeneity, different methods were used to analyze d-FC, such as model-dependent methods and the model-free methods.

5. Conclusions

Dynamic connectivity analysis can detect more significant networks and different connectivity pairs compared to static connectivity analysis. Dynamic connectivity analysis might be a potential method to reveal unknown migraine pathologies.

Author Contributions

The author did all the research work of this study.

Competing Interests

The authors have declared that no competing interests exist.

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