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Large-Scale Brain Networks Alterations in Migraine

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Abstract

Background: An increasing number of researches on large-scale brain network alterations among migraine patients has prompted us to make a brief review of them.

Methods: We performed a literature search for original articles reporting data from resting-state functional connectivity secondary analyses for migraine patients only or compared with healthy controls. This review includes only large-scale brain network studies among migraine patients within the last five years.

Results: We founded 16 studies, including two during the ictal period and 14 during the migraine interictal period. The most significant alterations among migraine patients were founded across Default Mode Network, Salience Network, Sensori Motor Network, Executive Control Network, Visual Network, and Dorsal Attention Network.

Conclusion: Large-scale brain networks FC studies could help reveal hidden pathophysiological mechanisms of the migraine. Methodological guidelines will significantly improve the reproduction and possibility of comparing the FC studies, enhancing their scientific and clinical contributions.

Keywords: Migraine; Functional connectivity; FMRI

Abbreviations

RS-fMRI: Resting-state functional Magnetic Resonance Imaging; FC: Functional Connectivity; MO: Migraine without aura; MA: Migraine with aura; HC: Healthy Controls; CM: Chronic Migraine; ICA: Independent Component Analysis; ROI: Region Of Interests; DMN: Default Mode Network; SN : Salience Network; ECN/FPN: Executive Control or Fronto Parietal Network; SMN: Sensori Motor Network; VN: Visual Network; DAN: Dorsal Attention Network; VAN: Ventral Attention Network; AN: Auditory Network; FSL: FMRIB Software Library

Introduction

Migraine is one of the most important causes of disability worldwide, according to the Global Burden of Disease Study 2016 [1]. Despite this statement, the pathophysiological mechanisms of migraine are still in question. Resting-State functional Magnetic Resonance Imaging (RS-fMRI) studies allow finding alterations of large-scale brain networks associated with pathophysiologic issues of the disease.

It is often hard to compare fMRI studies due to different analysis methods and ways of presenting the results. Hence, we tried to summarize the primary outcome results only for large-scale brain networks fMRI researches.

Literature search

We performed a search on the ScienceDirect.com and PubMed.com websites to identify all original articles with large-scale brain networks FC data among migraine patients for the last five years (from 2016). Inclusion criteria: original articles restricted to adults' human studies, published in English within five last years, and the subject of study includes one of 8 main large-scale brain networks. We excluded reviews, pediatric studies, case reports, and letters and studies with improper methods or data descriptions.

Large-scale brain networks RS-fM

RS-fMRI method is based on Blood-Oxygen-Level Dependence (BOLD) recording when patients are closed eyes but do not fall asleep. BOLD-signal is recorded from each voxel of the brain. Then, comparing the degree of synchronization of signal frequency more (higher degree of synchronization) or less (lower degree of synchronization) functionally connected group of voxels being distinguished. Highly functionally connected areas of the brain during the same task or in resting-state are calling networks. There are eight main large-scale brain networks: Default Mode (DMN)–the main mind-wandering network which activates in resting-state; Salience (SN)–detecting and filtering salient stimuli; Fronto Parietal or Executive Control (FPN/ECN)–sustained attention and executive functions; Dorsal Attention (DAN)–engaged during externally directed attentional tasks; Ventral Attention (VAN)–reorient attention towards salient stimuli; Sensorimotor (SMN)–associated with pain and cognition; Visual (VN), and Auditory (AN).

Results

Our literature search was ended up with sixteen studies from 2016 to 2020, including fourteen during the interictal phase, and two studies during the ictal phase of migraine (Table 1).

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Study	Population and Methods	Main findings
During ictal period		
Amin, 2016 Neurol [2]	16 MO patients scanned before and during drug provoked attack Seed-based FC analysis of SN, SMN, and DMN components.	During attack versus before attack SN: increased FC with bilateral opercular part of inferior frontal gyrus. SMN: increased FC with right premotor cortex and decreased with left visual cortex. DMN: increased FC with left primary auditory, secondary somatosensory, premotor, and visual cortices.
Coppola, 2017 Cephalalgia [3]	13 MO and 19 HC Seed-based analysis of DMN regions and bilateral insula during acute migraine attack.	MO versus HC DMN: increased FC between medial prefrontal cortex and posterior cingulate cortex; between medial prefrontal cortex and bilateral insula; The strength of DMN-to-insula connectivity was negatively correlated with pain intensity.
During interictal period		
Li, 2016 Cephalalgia [4]	100 MO and 46 HC Seed-based FC analysis of right FPN, which was produced by ICA.	MO versus HC Right FPN: decreased FC between right FPN and right precuneus, and its association with headache intensity.
Yu, 2017 MPX [5]	31 MO and 31 HC ICA-based approach using FSL to identify alterations in DMN, ECN, and SN; ROI-to-ROI analysis of founded altered networks.	MO versus HC Right hemisphere: decreased FC between SN and DMN (anterior cingulate cortex and posterior cingulate cortex), and ECN (anterior cingulate cortex and prefrontal cortex); Left hemisphere: decreased FC between SN and ECN (insula and prefrontal cortex), and DMN (insula and posterior cingulate cortex).
Zhang, 2017 J Neurol [6]	30 MO and 31 HC Seed-based FC analysis of SMN.	MO versus HC SMN: decreased FC between S1 and brain areas within the pain intensity and spatial discrimination pathways and trigemino-thalamo-cortical nociceptive pathway.
Androulakis, 2017 Neurology [7]	29 CM and 29 HC ROI-to-ROI analysis of intranetwork FC within DMN, SN, ECN.	CM versus HC Decreased FC within each observed network; These alterations were associated with frequency of moderate to severe headache and cutaneous allodynia.
Androulakis, 2018 J Neurol Disord [8]	13 CM, 17 CM with medication-overuse headache, 19 HC. ROI-to-ROI analysis within ECN and within DMN.	CM and CM with medication-overuse headache versus HC ECN: decreased FC between left dorsal prefrontal cortex and dorsomedial prefrontal cortex; between right ventrolateral prefrontal cortex and left anterior thalamus. CM with medication-overuse headache versus HC DMN: decreased FC between left lateral parietal and posterior cingulate cortex.
Han, 2018 J Clin Nerosci [9]	32 MO and 32 HC Response time of ECN, DAN, and VAN during attention network test.	MO versus HC ECN: longer response time during the interictal period.
Lisicki, 2018 Cephalalgia Rep [10]	19 MO and 19 HC Seed-based analysis of Ventral Attention Network component (right angular gyrus).	MO versus HC VAN: increased FC within between right angular gyrus and bilateral temporal poles; decreased FC between VAN and VN.

Soheili-Nezhad, 2019 Front in Neurol [11]	36 MO and 33 HC ICA-based approach using FSL to identify alterations in main large-scale networks.	MO versus HC Decreased FC within DMN, VN, FPN, and SN.
Coppola, 2019 J Neurol [12]	20 CM compared to 20 HC. Seed-to-voxel analysis between hypothalamus and cortical networks.	CM versus HC DMN: increased FC between medial prefrontal cortex and hypothalamus; between bilateral parietal lobule and hypothalamus; VN: increased FC between hypothalamus and left dorsal visual network.
Coppola, 2019 J Neurol [13]	20 CM compared to 20 HC. ICA-based approach using MATLAB to examine DMN, ECN, and DAN.	CM versus HC Decreased FC between DMN and ECN; DAN: increased FC with DMN, decreased FC with ECN. The higher the severity of headache, the increased the strength of DAN connectivity, and the lower the strength of ECN connectivity.
Veréb, 2020 Pain [14]	57 migraineurs (37 MO and 20 MA) compared to 32 HC. ICA-based approach using MATLAB to examine SN; Causal interactions between DMN, SN, and DAN.	MA versus MO and HC More fluctuating interregional connections within the salience network; Reduced effective connectivity between SN and DAN.
Russo, 2020 Headache [15]	20 MO with cutaneous allodynia, 17 MO without cutaneous allodynia, 19 HC. ICA-based approach to investigate correlation between FC differences within DMN, ECN, SN and cutaneous allodynia.	MO with cutaneous allodynia versus MO without cutaneous allodynia and HC Reduced intranetwork FC within DMN and ECN.
Wei, 2020 J. Headache Pain [16]	40 MO compared to 34 HC. ICA-based approach to examine SMN.	MO versus HC Higher activity in bilateral postcentral gyri, lower activity in the left midcingulate cortex; Decreased effective FC from the SMN to left middle temporal gyrus, right putamen, left insula and bilateral precuneus; Increased effective FC to the right paracentral lobule
Tu, 2020 Neurology [17]	70 MO compared to 46 HC. ROI-to-ROI analysis of 6 networks and 160 regions.	MO versus HC Abnormal FC in VN, DMN, SMN, and FPN as a neural marker of the disease.
Abbreviation: MO: Migraine without Aura; MA: Migraine with Aura; HC: Healthy Controls; CM: Chronic Migraine; FC: Functional Connectivity; ICA: Independent Component Analysis; ROI: Region of Interests; DMN: Default Mode Network; SN: Salience Network; ECN/FPN: Executive Control or Fronto Parietal Network; SMN: Sensori Motor Network; VN: Visual Network; DAN: Dorsal Attention Network; VAN: Ventral Attention Network; FSL: FMRIB Software Library		

Table 1: FC alterations in large-scale brain networks in migraine patients compared to healthy controls

DMN: During the ictal period increased FC within DMN, and also between DMN and SN [3], DMN and SMN, VN, AN [2]; during the interictal period decreased FC within DMN [7, 8, 11, 15], and also between DMN and SN [5], ECN [13], whereas increased FC between DMN and DAN [13], VAN [10] and with hypothalamus [12].

SN: During the ictal period increased FC within SN [2] and between SN and DMN [3]; during the interictal period decreased intranetwork FC [7, 11], and decreased FC between SN and DMN [5], DAN [14].

ECN: No significant FC alterations during the ictal period; during the interictal period decreased intranetwork FC [7, 8, 15], and decreased FC between ECN and SN [5], DAN, DMN [13].

SMN: During the ictal period increased FC within SMN [2], between SMN and DMN, and decreased FC between SMN and VN [2]; during the interictal period increased FC within SMN [16], and decreased FC between SMN and pain pathway regions [6, 16], between SMN and SN [16].

DAN: No significant FC alterations during the ictal period; during the interictal period decreased FC between DAN and ECN [13], SN [14], whereas increased FC between DAN and DMN [13].

VN: No significant FC alterations during the ictal period; during the interictal period decreased intranetwork FC and decreased FC between VN and VAN [10], also increased FC between VN and hypothalamus.

Discussion

This mini-review sums up the results of FC alterations of large-scale brain networks among migraine patients. Despite the great variety of migraine symptoms and possible comorbidities, the main cause of patients' disability is pain. We supposed that the cumulative effect of reviewed articles also reflects the reaction of the brain to pain.

We founded only decreased FC within large-scale brain networks in the interictal period of a migraine attack. FC between networks was also predominantly decreased, except intranetwork SMN, DMN-VAN in migraine without aura, DMN-DAN, hypothalamus-VN hypothalamus-DMN connections observable among chronic migraine patients only. SMN, DAN, VAN, and VN are task-positive networks involved in the attention process, whereas DMN is a task-negative network involved in self-directed mind-wandering during the resting state. The hypothalamus plays a crucial role in the initiation and termination of migraine attacks [18]. We supposed that increased FC within SMN represents the sensibilization of cortical pain regions in the migraine brain. Whereas increased FC between VAN and DMN can reflect the heightened attention to pain stimulus, which could be salient even in resting-state. Moreover, it was also confirmed by decreased attention to sustained external attention [9]. Chronic migraine characterized by involving the hypothalamus and larger increased FC between attention networks and DMN, what can be assumed as progressive impairment.

There are only two researches made during the ictal period, but both reported an increase in FC both within and between large-scale brain networks.

Our research [19] in appliance with this review confirm that frequently repeating headache disturb pain pathway that leads to central sensitization and increased saliency of pain stimuli. Hence, highly intrinsic attention to pain accompanied by decreased externally directed cognition finally results in a constant state of expectation of a pain stimulus during the interictal period.

Conclusion

According to the review results and results of our research, we supposed that altered FC in large-scale brain networks could clarify the pathophysiological mechanisms of migraine and distinguish the type of disease. However, moreover, their results could be used for objective control of treatment effectiveness. Furthermore, we also plan to examine repetitive transcranial magnetic stimulation's effectiveness among migraine patients through the prism of altered FC.

It should be noted that we consolidate the unique results from each research, and the reproducible of them in other studies was low. In our opinion, it also was pretty hard to summarize all results of the studies due to the lack of methodological guidelines or standards for functional connectivity studies.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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