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脑科学与神经物理

基于磁共振成像技术的偏头痛脑部异常模式

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【摘 要】偏头痛是一种普遍、慢性、多因素的神经血管机能紊乱病症。为了揭示偏头痛的病理机制和临床特征,近年来学者应用磁共振成像技术(MRI)对偏头痛进行了脑功能和脑结构两个方面的研究,但是结果并不完全一致。本文对偏头痛的发病机制、脑部结构变化和静息态脑功能连接异常3个方面的研究进展进行了综述,并讨论功能异常和结构异常的依赖关系。最后总结了基于MRI的偏头痛研究成果并提出展望。

【关键词】偏头痛;磁共振成像;脑部结构改变;静息态功能连接
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Migraine abnormal brain pattern based on magnetic resonance imaging

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Abstract: Migraine is a common, chronic and multi-factor disorder of nerve vascular dysfunction. In recent years, researchers have done many brain function and structure studies on migraine by using magnetic resonance imaging (MRI) to reveal the pathological mechanism and clinical characteristics of migraine. However, these results were not consistent completely. In this paper, the pathogenesis of migraine, the brain microstructure change and altered resting-state function connection were analyzed. And the dependencies between the structure and function were discussed on. The research results of migraine based on MRI were finally summarized and the prospect of migraine study was putted forward.

Key words: migraine; magnetic resonance imaging; brain structural abnormality; resting-state function connection

前 言

2001年发布的世界卫生报告以正常生活工作的减少年限和相对缩短的寿命为标准,将偏头痛列为严重致残性疾病,类同于痴呆、四肢瘫痪和严重精神疾病[1]。目前,偏头痛的病理机制还不清楚。神经影像学试图通过偏头痛的发展、演化及其特定的症状来阐明其病理机制,并应用于偏头痛的临床诊断和治疗。

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1 偏头痛的分类与病理机制

根据2013年国际头痛协会(International Headache Society, IHS)颁布的IHS国际头痛疾病分类标准,偏头痛被归类为原发性头痛。根据有无先兆症状可将偏头痛分为无先兆型偏头痛(Migraine without Aura, MwoA)和有先兆型偏头痛(Migraine with Aura, MA),超过1/3的病人有神经学上的先兆症状。先兆症状作为两种主要偏头痛的诊断标准,一般表现为一个或多个视觉、感觉、声音、运动和脑干先兆,其中前两种先兆特征较常发生[2]。

偏头痛的发病机制尚不完全清楚,主要有以下几种猜想:血管学说、皮层扩散性抑制学说、三叉神经血管学说、5-羟色胺学说、脑干中枢异常、基因异常、脑膜异常等[3]。最初偏头痛被定义为血管类疾病,但是随着影像学的发展,偏头痛逐渐被视为中枢

神经系统疾病[3-5]。目前三叉神经血管学说综合了血管源性学说和神经源性学说，在偏头痛病理生理机制中占主导地位[5]。

2 MRI在偏头痛病理异常分析中的应用

MRI可以显示脑的结构和功能信息，本文对偏头痛相关结构异常和功能异常的研究进展进行了综述。

2.1 结构异常

偏头痛脑部结构变化主要包括灰质异常、白质异常和缺血性损伤，研究的重点为由神经元组成的灰质[6]。在对灰质的研究中，基于体素的形态学分析（Voxel Based Morphometry, VBM）的应用最为广泛，与基于感兴趣区域形态学分析不同的是，VBM可以全面显示脑组织形态学变化。在灰质密度计算方面，基于表面的形态学分析是一种新兴的方法。近年来基于MRI的偏头痛脑部结构异常研究结果见表1。

表1 基于MRI的偏头痛脑结构异常研究

Tab.1 Abnormal brain structure study for migraine based on magnetic resonance imaging (MRI)

Reference	Participant	Key results
Hougaard (2015)[7]	MA (20); HC (20); Headache (13)	No differences were found in GM structure between MA patients and HC. And differences were found in the cortical thickness of inferior frontal gyrus between the typical migraine headache side of patients and the contralateral side.
Granziera (2014)[8]	MwoA (22); MA (15); HC (20)	Compared with the other two groups, the structure change of thalamus was more significant in MA group.
Kim (2014)[9]	Female MwoA (56); Female HC (34)	Compared with HC, migraine patients showed cortical thickening in left rostral middle frontal gyrus and bilateral post-central gyri.
Obermann (2014)[10]	Migraine (17); HC (17)	In migraine group, GM volume reduced in superior, inferior and middle temporal gyrus, mid cingulate, dorsolateral prefontal, parietal and occipital cortex, and insula.
Rocca (2014)[11]	Pediatric MwoA (5); Pediatric MA (7); HC (15)	In pediatric migraine group, frontal and temporal lobes showed a significant GM atrophy; GM volume increased in right putamen. Compared with the other two groups, left fusiform gyrus of pediatric MA had an increased volume, whereas left fusiform gyrus of pediatric MwoA significantly atrophied. No abnormalities of WM volume were detected.
Yuan (2013)[12]	MWoA (40); HC (40)	GM volume of left caudate and right nucleus accumbens reduced in MWoA group.
Jin (2013)[13]	MwoA (21); HC (21)	MwoA patients showed significantly decreased GM volume in five brain regions, including left medial prefrontal cortex, dorsal anterior cingulate cortex, right occipital lobe, cerebellum and brainstem.
Maleki (2013)[14]	MHF (10); MLF (10)	The volume of hippocampal increased in MHF group.
Russo (2012)[15]	MwoA (14); HC (14)	No differences were found in global GM, WM, and cerebrospinal fluid volume between the two groups.
Maleki (2012)[16]	HC (22); Female migraine (11); Male migraine (11)	Compared with male migraineurs and HC, female migraineurs had thicker posterior insula and precuneus cortices.
Riederer (2012)[17]	Medication-overuse headache (29); HC	GM volume of medication-overuse headache patients increased in thalamus and ventral striatum, but decreased in frontal regions, including orbitofrontal cortex, anterior cingulate cortex, left and right insula, and precuneus.
Maleki (2012)[18]	MHF (10); MLF (10); HC (20)	HF patients showed thicker post-central gyrus. Both HF and LF attacks induced change in insula, but the degree of HF was more than that of LF.
Liu (2012)[19]	Female MwoA (43); Female HC (43)	GM volume reduced in anterior cingulate cortex.
Kurth (2011)[20]	Headache (780)	WM high signal of headache patients increased.

GM: Grey matter; WM: White matter; MA: Migraine with aura; MwoA: Migraine without aura; HC: Healthy control; MHF: Migraineur with high frequency; MLF: Migraineur with low frequency

在复杂的脑部结构中，偏头痛患者最易受损脑区包括丘脑、基底神经节、下丘脑等亚皮层区域，以及额叶、扣带回、颞叶皮质、枕叶皮质、脑岛、杏仁核等大脑皮层区域。多年来研究者对偏头痛脑部结构的研究结果未达成一致，偏头痛和脑部结构的关系至今还不完全清楚，但是多数研究者认为偏头痛可能是某些脑部结构改变的风险因素[6, 20-21]，长期的疼痛会改变大脑区域组织损失模式，这些大脑区域会参与疼痛过程[18, 21-22]。研究发现患有偏头痛、慢性每日头痛、丛集性头痛、慢性疼痛等多种疼痛的病人的额中回会出现萎缩[23]。这表明长期的疼痛不仅对灰质有损害，而且其灰质异常化的模式也可能相同[24]。相关性分析发现性别、先兆、病程、发作频率等因素都可能成为偏头痛患者病变的危险因素，而病程与发作频率是最具指导意义的变量。偏头痛脑部结构的改变与病程、发作频率呈负相关[22-24]，并且其异常化程度超越了组织正常的老化[25]。这种相关性似乎为偏头痛是一种伴有器质性损害的进展性疾病的理论提供了新证据，即多数学者认为这种反复的头痛发作造成了脑部损害[20, 24-25]。

2.2 功能异常

在探索脑功能方面，静息态下血氧水平依赖功能MRI（BOLD fMRI）技术成为最常用的成像方法。它基于氧合血红蛋白（抗磁性）和脱氧血红蛋白（顺磁性）之间磁特性的差异，具有相对较高的空间分辨率[26]。静息状态下BOLD信号的波动反映了大脑神经元活动的基线水平，代表了神经元在缺乏目标导向和外部输入下的自然状态[27-28]。对脑功能的研究角度包括功能分化和功能整合：功能分化体现的是脑区的局部功能信息，通常要先根据先验知识选择感兴趣区域（Region of Interest, ROI）；功能整合反应的是全脑功能的组织模式，空间分离的脑区根据BOLD信号波动的一致性形成功能连接或组成静息态网络，这些网络不仅功能相关且具有高度可复制性[28-29]。通过验证这些功能连接的存在与否以及功能连接的强弱可以揭示偏头痛的病理特征，近几年基于静息态fMRI的偏头痛功能研究见表2。

表2 基于静息态功能MRI的偏头痛脑功能异常研究

Tab.2 Brain function research for migraine based on resting state fMRI

Reference	Participant	Method	Key results
Li (2015)[30]	MWoA (12); HC (12)	Comparing treatment effect of acupuncture for migraine on the right frontoparietal network	Functional connectivity (FC) of MWoA patients decreased in the right frontoparietal network, but the FC could be changed after acupuncture treatment.
Hougaard (2015)[31]	MA with visual aura (40); HC (40)	ROI: cortical visual areas, amygdale, PAG	No differences were found in FC between patients and HC.
Ren (2014)[32]	Migraine (16); HC (16)	Calculating the FC of ROI which was determined by ALFF value	Compared with HC, ALFF values of migraine patient decreased in the left triangle and orbital section of inferior frontal gyms, the left insula, but significantly increased in the right occipital, calcarine and cuneus.
Zhang (2014)[33]	MwoA(10); HC (10)	ROI: PCC Calculating the FC between PCC and the region within DMN	FC degree among the frontal lobe, temporal lobe, anterior cingulate, precuneus, inferior parietal lobule and cingulate cortex reduced in MwoA group.
Schwedt (2014)[34]	Migraine with allodynia (8); Migraine without allodynia (8); HC(20)	ROI: pain modulating region (PAG and cuneate nucleus)	Migraine with allodynia had stronger PAG and nucleus cuneiformis FC to brainstem, thalamic, insula and cerebellar regions, as well as to frontal and temporal regions. The FC differences between migraine with severely allodynia and migraine without allosynia didn't overlap with the FC differences between all migraine patients and HC.
Hadjikhani (2013)[35]	MA (11); MwoA (11); HC (20); Carpal tunnel syndrome (11); Trigeminal neuralgia (9)	ROI: amygdala	Compared with the HC, migraine patients showed stronger FC of amygdala to insular cortex.

续表2（Continued Tab.2）

Reference	Participant	Method	Key results
Xue (2013)[36]	Migraine (18); HC (18)	Calculating the FC of ROI which was determined by ALFF value	ALFF: For migraine patients, the ALFF value of prefrontal cortex and rostral anterior cingulate cortex decreased, while the ALFF value of thalamus increased. FC: Compared with HC, migraine patients showed stronger FC between the left rostral anterior cingulate cortex and bilateral frontal lobe and left parietal lobe; right thalamus and bilateral caudate, left temporal lobe and right putamen; left prefrontal cortex and right precuneus and bilateral parietal lobe; right prefrontal cortex and bilateral parietal lobe and left temporal lobe; and right insula and left temporal pole, right frontal lobe and left parietal lobe.
Jin (2013)[13]	MwoA (21); HC (21)	Calculating the FC of ROI which was determined by VBM result	Compared with HC, MwoA patients showed stronger FC of anterior cingulate cortex to middle temporal, orbitofrontal cortex, and dorsolateral prefrontal cortex.
Tessitore (2013)[37]	MwoA (20); HC(20)	DMN	Compared with HC, MwoA patients showed weaker FC of superior frontal gyrus and temporal pole to other regions of default mode network.
Maleki (2013)[14]	MHF (10); MLF (10)	ROI: hippocampus	Compared with MLF group, MHF group showed weaker FC of hippocampus to supramarginal gyrus, temporal pole, fronto-orbital, nucleus accumbens, anterior insular cortex, middle frontal, and paracingulate gyrus.
Schwedt (2013)[38]	Chronic migraine (20); HC (20)	ROI: anterior cingulate cortex, insula, amygdala	Migraine patients showed atypical FC of ROI to pulvinar, mediodorsal thalamus, middle temporal and PAG.
Yuan (2013)[39]	MwoA (40); HC (40)	Basal ganglia network; bilateral caudate nucleus network; right nucleus accumbens	Compared with HC, MwoA patients showed stronger FC between the bilateral caudate and left insula, as well as the right NAc and bilateral anterior cingulate cortex.
Zhao (2013)[40]	MwoA (40); HC (20)	ReHo	MwoA group showed abnormal ReHo in thalamus, brainstem and temporal pole. And the abnormal ReHo of long duration (>10 years) was more significant than that of short duration (<5 years).
Yu (2012)[41]	MwoA (26); HC (26)	ReHo	ReHo of MwoA patients decreased in anterior cingulate cortex, prefrontal cortex, orbitofrontal cortex and supplementary motor area.
Xue (2012)[42]	MwoA (23); HC(23)	ICA: DMN, CEN, SN	Compared with HCs, MwoA patients showed aberrant intrinsic connectivity within the bilateral CEN and SN, and greater connectivity among DMN and CEN and insula cortex within SN.
Russo (2012)[15]	MwoA (14); HC (14)	Frontoparietal network	FC in right frontoparietal network was weaker in MwoA group than that in HC.
Liu (2012)[19]	Female MwoA (43); Female HC (43)	Graph theory	Compared with HCs, MwoA patients showed higher mean clustering coefficients without significant changes in the shortest absolute path length. Abnormal nodal centrality was found in brain hubs, including precentral gyrus, inferior frontal gyrus, parahippocampal gyrus, anterior cingulate gyrus, thalamus, temporal pole of the middle temporal gyrus and the inferior parietal gyrus.
Mainero (2011)[43]	Migraine (17); HC (17);	PAG network	Compared with HC, migraine patients showed stronger FC of PAG to ventrolateral prefrontal cortex, supramarginal gyrus, anterior insula, precentral gyrys, postcentral gyrus, and thalamus. Compared with migraine without allodynia, migraine with allodynia showed weaker FC of PAG to prefrontal, anterior cingulate cortex, and anterior insula.
Maleki (2011)[44]	MHF (10) MLF (10)	ROI: basal ganglia	MHF showed weaker FC of caudate nucleus to middle frontal, insular cortex, temporal pole, and parahippocampus.

FC: Functional connectivity; ROI: Region of interest; ALFF: Amplitude of low frequency fluctuation; ReHo: Regional homogeneity; ICA: Independent component analysis; PAG: Periaqueductal grey; DMN: Default mode network; PCC: Posterior cingulate cortex; CEN: Central executive network; SN: Salience network; fMRI: Functional MRI; VBM: Voxel based morphometry

偏头痛脑功能研究的ROI主要涉及:疼痛进程调节相关脑区(导水管周围灰质、楔状核),疼痛识别相关脑区(躯体感觉皮质、后脑岛),认知加工相关脑区(海马、海马回、眶额皮质,情感处理进程相关脑区(前脑岛、前扣带回、杏仁核)。偏头痛脑功能研究的静息态网络主要包括默认网络、中央执行网络(额顶网络)、凸显网络3大核心认知网络。这些ROI和网络的选取主要依据偏头痛伴随的认知、执行能力下降以及偏头痛的疼痛特征[15, 34, 45-46]。尽管这些结果并不完全一致,但都近似这样一个结论:偏头痛患者疼痛进程相关的功能连接增加,而与调节疼痛回路有关的功能连接会减弱,这可能是由于长期的疼痛输入降低了疼痛抑制[14, 47-49]。相关分析研究表明:功能连接程度的改变与疼痛发作频率与病程呈正相关,并且这种改变也会使得患者头痛的频率更频繁[13,19, 36, 50]。

3 讨论和展望

脑部解剖结构的改变、功能的减弱或者增强以及偏头痛症状三者之间的关系目前尚不完全清楚。一些研究倾向于支持频繁的疼痛输入改变皮层结构和功能模式,并且这些变化可以解释偏头痛患者的功能障碍[12-14, 18]。相反,另一些研究没有发现结构异常与功能异常的任何依赖关系[15, 31, 51]。

为什么对于偏头痛的研究会出现不一致的结果?首先,偏头痛的病理机制比较复杂,在对偏头痛的分类研究中,除了要把有无先兆症状作为一个主要标准外,还应对伴随其它症状的偏头痛亚型进行具体分析;其次,对偏头痛的研究大多数是在发作间期进行采集的,但是偏头痛先兆期、发作期以及发作间期的脑区活动存在差异[52],因此采集时间不同也导致研究结果的不同;再次,在方法论方面,不同的软件、不同版本以及不同参数设置都会产生不同的结果;最后,从统计学的角度,样本数量也会对统计结果有所影响,在之前的研究中,样本量大多是十几个,在以后的研究中应增加样本量以获取统计学上更准确的结果。因此,对偏头痛的研究还需要做进一步的标准化,形成具有可比性的多中心研究。

尽管成像技术已经改变了人们对偏头痛的理解,但偏头痛的研究仍然处于不成熟期,影像学的不断发展和技术的广泛应用都会为偏头痛的研究提供越来越真实客观的数据资料。在未来,大脑结构和功能的变化可能成为偏头痛患者潜在的生物标记,为偏头痛子类型预测、识别和诊断提供依据。总之,偏头痛作为一种精神类疾病,它的病理生理学机制和临床意义尚不完全清楚。随着越来越多的研究人员参与到偏头痛研究中,希望能有更深化理解这种疾病的研究成果,从影像学角度为偏头痛的诊断、治疗以及神经病理学提供一些新见解。

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