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Views and Perspectives

Functional Neuroimaging in Migraine: Chances and Challenges

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Functional neuroimaging studies are an indispensable tool in headache research and have greatly contributed to our understanding of migraine pathophysiology. The past two decades have identified the brainstem as the target region of interest in migraine pathophysiology: Recent evidence suggests that certain areas of the central nervous system and especially the brainstem periodically change activity during different stages of the migraine cycle. Additionally, the number of resting-state functional MRI studies in migraine has increased greatly in recent years. Three future trends in migraine neuroimaging can be identified: brainstem optimized functional imaging, longitudinal approaches tracking biological changes through the migraine cycle, and optimized resting-state fMRI. Consequently, we face a lot of difficulties regarding image noise and artifacts, organizational details, and data interpretation. Optimized neuroimaging studies and new approaches will continue to greatly contribute to our pathophysiological understanding of migraine.

Key words: fMRI, pathophysiology, brainstem, resting state, BOLD, networks

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INTRODUCTION

In the last two decades, neuroimaging studies have become an indispensable tool in headache research and have greatly contributed to our understanding of primary headache pathophysiology.[1,2] Especially in migraine research the past two decades have identified various, partly even disease or attack-specific alterations in brain activity,[2–5] stimulus processing,[4,6–8] and functional connectivity[9,10] within the migraine brain. Judging by this important research, two future loci of interest can be identified: first, the brainstem has been shown to play a crucial role in migraine in general and in attack generation in specific and is thus an important objective of future investigation. Second, as migraine is a cyclic disorder, simple cohort studies are no longer sufficient, ie, to solely compare migraineurs to healthy controls. Rather, imaging findings should be compared to electrophysiological, genetic, or other independent methods to better judge the functionality of imaging results. Given that migraine is a cyclic disorder, future studies should investigate migraineurs repeatedly during different stages of the migraine cycle including, but not limited to, the acute pain phase. These longitudinal approaches will be of growing influence in future migraine research. Regarding current trends in migraine neuroimaging, the past decade has seen an increasing amount of resting-state studies,

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showing – despite various default network alterations – altered functional connectivity of the periaqueductal grey (PAG) and the insula in migraine.[9,10] Thus, resting-state functional magnetic resonance imaging (MRI) is of increasing influence also in migraine research. Here we discuss chances and challenges of current trends and future research directions in the neuroimaging of migraine to which the partly amazing imaging studies of the past years may lead us.

IMAGING OF BRAINSTEM FUNCTION IN MIGRAINE

Neuroimaging techniques have helped tremendously to unravel the central pain processes as a response to experimental trigeminal pain and even acute headache attacks. Brain regions most commonly reported to be involved in pain processing are the thalamus, primary somatosensory cortex (S1), secondary somatosensory cortex (S2), insular (IC), and anterior cingulate cortex (ACC).[11] In the past two decades the most important functional imaging studies in migraine have repeatedly identified the brainstem as the one area in the central nervous system (CNS) to differentiate migraineurs from healthy controls and the ictal from the interictal state: a small area located at the dorsal pontomesencephalic junction seems to be specifically activated during migraine attacks, ie, both constitutively and as a response to standardized external nociceptive and olfactory stimulation during migraine attacks,[2–4,7] and also within the headache-free interval between initial headache and onset of migraine like headache in nitric oxide (NO)-triggered attacks,[12] although recent studies might suggest also a physiological role of the dorsal pons in trigeminal pain processing.[13,14] Moreover, connectivity analyses have revealed altered functional connectivity of certain brainstem centers in migraine.[10,15] Especially the trigeminal nuclei have been shown to differentiate interictal migraine patients from healthy controls and also to change activity levels in response to noxious stimuli during different stages of the migraine cycle.[4] They also seem to be the primary site of action of the antimigraine drug sumatriptan within the human CNS, by decreasing functional coupling between the spinal trigeminal nuclei and higher cortical and subcortical pain transmitting areas.[16] The brainstem thus is the main region of interest when investigating migraine pathophysiology. However, functional neuroimaging of this area is challenging as the poor spatial resolution of common approaches (positron emission tomography [PET], whole-brain-fMRI) renders a clear attribution of found activations to specific brainstem nuclei nearly impossible. To adequately detect brainstem activations in functional imaging studies, multiple challenges have to be addressed: the brainstem is a very small area and single functional nuclei lie in a close spatial relationship to each other. To satisfactorily attribute found activations to single brainstem nuclei, a high spatial resolution in primary image acquisition is necessary, which in turn decreases temporal resolution – an unwanted effect especially in task-related designs – and decreases the signal to noise ratio (SNR). Lower temporal resolution can be compensated for by decreasing the imaged volume that, in turn, will cause artifacts, making special correction techniques necessary. A reasonable SNR despite a high in-plane resolution can be achieved by increasing the slice thickness that might still properly reflect the elongated structure of most brainstem nuclei. Artifacts due to a smaller field of view might be eliminated by adding saturation pulses or shimming procedures to the scanning protocol.[17] Due to its anatomical location – surrounded by large blood vessels and cerebrospinal fluid – the brainstem is also very susceptible to periodic signal changes correlated with the arterial pulse curve and breathing rate.[18,19] This is especially problematic if heart rate and breathing changes correlate with the experimental paradigm or different imaging conditions, as it is often the case in pain experiments or in comparisons between the pain and the non-pain state of migraineurs. A special correction technique for physiological noise is thus indispensable and can be done in different ways.[20] Regarding noise distribution, the brainstem is more similar to the spinal cord than to the cerebrum. Physiological noise correction techniques established for functional imaging of the spinal cord are thus also

beneficiary in brainstem imaging. There are currently two well accepted methods for physiological noise correction in task-dependent designs of the spinal cord: the selective averaging method according to Deckers et al[21] and retrospective image correction (RETROICOR).[22] Both rely on a simultaneous recording of pulse and breathing curve on the one hand and scanner pulses on the other hand, which later makes an attribution of individual volumes to certain phases of the pulse and breathing curve possible. Thus heart rate and breathing regressors can be created to later be included in the first level general linear model analysis. In addition, application of techniques to reduce general image noise in functional volumes with a high spatial resolution such as pre-whitening or denoising filters might be beneficiary.[23] Brainstem optimized imaging protocols of trigeminal nociception might offer further insight into migraine pathophysiology in the future.[14]

IMAGING MIGRAINE ATTACKS

Some of the most important findings in neuroimaging of headaches in the last two decades have arisen from imaging the acute pain stage of either spontaneous migraine attacks, triggered attacks, or pharmacologically induced migraine like headaches.[2–5,7,12,24] The investigation and neuroimaging of spontaneous migraine attacks is particularly challenging as it requires a lot of flexibility regarding patient motivation and dedication, scanner schedules, availability of trained personnel, and other organizational aspects that are usually not given in most clinical and neuroscientific settings when planning of schedules has to be done weeks ahead of scanning. It is therefore understandable that some studies resolve to investigating pharmacologically provoked migraine like headache or try to trigger attacks using natural stimuli.[5,12,24–28] Both approaches are problematic: at the moment we do not know whether the migraine like headache experienced by migraine patients following NO[29,30]- or pituitary adenylate cyclase activating peptide (PACAP)[31]-administration is pathophysiologically identical to spontaneous migraine attacks.[32–37] A crucial point in imaging studies using pharmacological induction of headaches is to separate the headache-specific signal changes, ie, the condition of interest, from general drug effects. It is thus necessary during piloting to exclude any such changes or, if they exist, to control them via an apt control group. During piloting, a placebo-controlled design in healthy participants can be an appropriate tool to discover drug-related signal changes. If these changes still exist, there is the question whether in any following study these effects can be reasonably controlled. One way imaginable to accomplish this in attack-induction studies would be to investigate responders (patients, who develop migraine like headaches after administration) and non-responders (patients not developing migraine-like headaches after administration) using the same protocol. Nonetheless, the question whether the drug might primarily act differently in responders and non-responders including possible signal changes cannot be answered with this method. Using natural migraine trigger factors for attack induction such as flickering lights or exercise on the other hand is particularly challenging as empirical evidence that these triggers can reliably provoke migraine headache is rare[27,38] and, more to the point, it is currently not clear whether so-called "triggers" as such exist or whether they are just the result of misinterpreted migraine premonitory symptoms.[39] Using natural trigger factors for "planning" migraine attacks might thus be far too unreliable to be successfully applied in neuroimaging studies. Pharmacologically evoked migraine like pain on the other hand might not adequately reflect the pathophysiological mechanisms of spontaneous migraine attacks regarding both the premonitory and the acute pain phase. Furthermore, as there is currently a lot of evidence that specific neuronal changes leading to an attack of migraine pain take place hours and even days before an attack,[4,40] it might not be sufficient to only investigate the acute pain phase and the pain-free interval. Consequently, to adequately assess different stages of the migraine cycle longitudinal approaches are necessary investigating migraine patients frequently in time intervals shorter than the average duration of the migraine pain phase. Only by this means will we ever be able to understand the

pathophysiological mechanisms leading to an acute migraine attack.

RESTING-STATE FUNCTIONAL CONNECTIVITY

Over the past decade the number of studies on resting-state functional connectivity has increased exponentially,[41] a trend which also greatly affects headache research. The past five years have found various alterations regarding resting-state functional connectivity in migraineurs, especially pain-related regions and networks showing altered functional connectivity in migraine,[42–46] including the periaqueductal gray area[9] as well as the insular cortex, which is stronger functionally coupled to the dorsal caudal pons and the PAG[10] in interictal migraineurs as compared to healthy controls. Other recent studies have found altered functional connectivity in various networks[47] such as the executive control network,[48,49] the default mode network,[50,51] the visual network,[52] between salience and visual networks,[53] and changes in functional connectivity dependent on disease duration, sex, and migraine chronification.[54–57] Although these studies are heterogeneous and as yet have not been able to show robust and reproducible results, resting-state studies constitute a growing percentage of functional imaging studies on headache and may in the future contribute to our knowledge and understanding of the pathophysiology of migraine.

However, as resting state is – as the word indicates – a study of the brain "at rest," it relies on the identification of intrinsic brain activity and connectivity and does so by scanning the brain "task-free." As there is no task-specific activity that can be adequately modeled and identified, this method is specifically susceptible to multiple confounders of which only a few can be controlled, including cognition, alertness, fatigue, eye-opening or closing, and mood[58–63] to name but a few. Consequently, the first big challenge is primary data acquisition: participants have to be carefully instructed and experimental procedures have to be kept as constant as possible. As participants do not undergo any demanding tasks during resting-state measurements, they are more likely to fall asleep or to let their mind wander than during task-related functional imaging studies. One recent study could show that during ~10 minutes of resting-state fMRI recording only 50% of participants had been continuously awake during this interval.[64] Any findings between cohorts could in theory entirely be explained by such changes in alertness. Consequently, resting-state studies are difficult to interpret as intrinsic connectivity and brain activity are hard to separate from general cognition and other confounders.[41,65] We will never be able to tell at which point precisely which thought exactly might have crossed a participant's mind during the measurement and even general cognition is hard to control for, but simultaneous electroencephalography (EEG) recordings can be used to control at least for sleep,[64] eye opening or closing, and basic brain activity. Unfortunately, the possibility to simultaneously record an EEG during scanning is not established in most clinical neuroimaging centers. Furthermore, as most resting-state analyzing methods are mostly data driven, this method is very susceptible to recurring signal changes due to structured noise as it is usually caused by arterial pulsation, breathing, cerebrospinal fluid (CSF)-fluctuations, or white matter signal.[41,66,67] Cardiac and respiratory noise in particular can account for up to 15% of the variance of the blood oxygenation dependent signal in the resting-state MRI.[65,68–70] This challenge can be addressed in multiple ways. For example, pulse and breathing curves can be recorded during scanning. The recorded signals can later be used to create regressors of no interest and the corresponding signal changes can be regressed out. Similarly, main CSF and white matter signal can be erased from the analysis. There are also commonly used model-based approaches to eliminate physiological noise from resting-state data such as the independent component analysis (ICA), a method that allows a reliable post hoc correction for cardiac and respiratory signal changes even if heart rate and breathing have not been recorded during scanning.[41,66,71–73] Additionally, seed-based connectivity results depend tremendously on seed region definition – a task that is especially challenging in brain areas for which anatomical masks might not be available. These various challenges and

confounders might also explain why resting-state functional connectivity analyses in migraine yield varying and sometimes even contradictory results.[9,10,42,74] Future resting-state studies in migraine will have to specifically address these challenges. Nonetheless, although resting-state fMRI faces a lot of difficulties, it is of gaining influence in the field of headache and migraine research. Thus it can offer further and more detailed insight into neuronal connectivity in headache and pain and might help to identify migraine-specific network alterations.

CONCLUSIONS

Neuroimaging studies have become an indispensable tool in headache and especially migraine research. Future studies will have to focus on brainstem mechanisms of migraine attack generation and should aim at investigating migraine patients repeatedly in short intervals during different stages of the migraine cycle to understand the pathophysiological mechanisms leading to an acute attack of migraine pain. Resting-state studies face a lot of challenges but are of growing influence in migraine research.

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