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MIGRAINE PATHOGENESIS

# Functional neuroimaging in migraine

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Several studies were performed in episodic migraine patients between attacks using functional MRI in response to noxious stimuli delivered over trigeminal or extra-trigeminal areas. Overall, they have shown an increased BOLD–response in brain areas involved in nociception/anti-nociception, affective and cognitive features related to pain processing, such as insula, middle cingulate and anterior cingulate [ACC] cortices, primary and secondary somatosensory cortices, amygdala, dorsolateral prefrontal cortex [DLPFC], perigenual part of the ACC, etc.), and reduced BOLD activation within the brainstem.

During the last decade, several fMRI studies in migraine assessed resting-state functional connectivity in different brain networks suggesting that this neurological condition is associated with brain functional network alterations. The intrinsic connectivity within brain areas anchored to the default-mode network, known to be the most pronounced network of the human brain, was found to be reduced by several independent groups of researchers during the interictal period of patients with migraine without aura compared to healthy subjects. Moreover, the DMN itself was observed to be more connected with the ECN as well as the insula, but less connected with the prefrontal and temporal regions as well as with the visuo-spatial system. On the contrary, in patients with migraine with aura, the DMN's intrinsic connectivity was increased between attacks. The intra-regional connectivity of several other networks (executive control network, salient network, limbic system, visuo-spatial network, dorsal attention systems, medial and lateral visual systems, sensorimotor, auditory, and cingulo-opercular networks) was abnormal in both patients with episodic migraine without aura and in chronic migraine patients with and without medication overuse than in healthy subjects.

To explore the influence of migraine clinical features to the changes in functional connectivity in migraine, several authors performed regression analyses within patient groups. Average pain intensity, duration of migraine disease, and mean monthly frequency of migraine attacks correlated with the functional connectivity between brain areas within the several networks.

Functional abnormalities within brain structures were also described during migraine attacks. An enhanced BOLD signal in response to noxious stimuli was observed within the temporal lobe structures and in the dorsal parts of the pons.

Recently, some researchers had the opportunity to scan a migraine patient every day for 30 days using olfactory stimuli as a functional task in the MRI during the ictal phase compared with pre-ictal and interictal phases. In this patient, the hypothalamus was significantly more active immediately before the headache phase when it also showed the greatest functional coupling with the spinal trigeminal nuclei. During the ictal state, the hypothalamus was functionally coupled with the dorsal rostral pons [1].

Few studies examined the brains of patients with migraines during the attacks using resting-state fMRI. During the initial 6 h of a spontaneous migraine attack, we found that the executive control network and the dorso-ventral attention system were significantly less interconnected, and that the higher the strength of the executive control network, the lower the number of monthly migraine days [2]. These patients showed also stronger functional connectivity between brain areas anchored to the DMN, and that the strength of middle prefrontal cortex (MPFC)-to-insula connectivity was negatively correlated with pain intensity [3]. During spontaneous migraine attacks, other authors also found evidence for abnormal network connectivity between the thalamus and several pain modulating and encoding cortical areas, such as superior parietal lobule, insular cortex, primary motor and premotor cortices, supplementary motor area and orbitofrontal cortex. Overall, these studies clearly suggest that single brain areas previously implicated in migraine pathophysiology should not be considered as isolated

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culprits for dysfunction, but as a network of functionally interconnected and mutually influencing cerebral areas.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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