

Pain cognition in migraine

The evolving concept of pain has led to the reformulation of its biological meaning by placing it in a much broader frame. Currently, we look at pain as a multidimensional sensation, aimed not only to the localization and the recognition of the threat, but also to induce most appropriate emotional and cognitive processing of the stimulus that might lead, in turn, to the selection of the best context-specific behavioural defensive response. In this key, pain should be viewed as the starting point of a complex response aimed to the preservation of the biological homeostasis from the continuous perturbations arising by the interactions with the variable environment conditions. This process requires the interplay of brain areas involved (at least) in somatic sensation, in emotion modulation, in cognitive processing, in vegetative control and motor behaviour and must include inhibitory/facilitatory mechanism for the ascending painful signals control. The so-called pain matrix, a major component of the limbic system, seems well appropriated for the goal, linking with reciprocal connections many cortical and subcortical brain structures involved in the central processing of the pain.

Being associated with a complex behavioral pattern leading to a substantial disengagement from the external environment, migraine may be viewed as a complex adaptive response. The pivotal role of the trigeminovascular activation in the migraine attack is fully recognized and has promoted the development of triptans, as well of the newly proposed anti-CGRP monoclonal antibodies. Trigemino-vascular involvement makes migraine a *visceral pain*, mostly driven by unmyelinated trigeminal C fibers. However, the univocal dependence of the trigeminovascular-dependent neurogenic inflammation by cortical spreading depression (CSD) has been deeply reconsidered in the last years, and the research has been re-oriented towards the understanding of the central mechanisms responsible for an alternative *top-down* activation of the trigeminovascular system. Despite no true "migraine generator" could ever been found, neurophysiological and, more recently, functional neuroimaging studies have confirmed that the "migraine brain" is characterized by subtle changes ranging from the lack of cortical habituation phenomenon for both non-painful and painful repetitive stimuli to connectivity abnormalities involving the periaqueductal grey, the prefrontal cortex, and the anterior cingulate cortex, all brain structures encompassed into the pain-processing network. In chronic forms of migraine there is strong evidence that allodynia plays a significant role. Interestingly, the main risk factors for the progression of migraine, such as analgesic overuse, female sex, obesity, psychiatric and, more recently, idiopathic intracranial hypertension without papilledema comorbidity, all appear to converge on the sensitization of central pain pathways, a mechanism considered the neurophysiologic correlate of allodynia. In addition, according to recent findings, subtle cognitive disturbances are detectable in migraine patients such as difficulties in attention focusing, memory retrieval, and decision-making impairment possibly relying on a malfunctioning of thalamo-cortical circuits.

Despite the continuous research advancement accumulated in the last decades, the fundamental question that remains unanswered is if the neurophysiological, cognitive and connectivity changes characterizing the "migraine brain" should be considered the markers of a functional derangement

of the pain processing structures interplay or if they are to be considered just the physiological correlates of the ongoing pain.

On one hand, the behaviour associated with migraine has a stereotyped pattern leading to disengagement from the environment through passive coping strategies including motor quiescence, hyporeactivity, decreased vigilance, reduced responsiveness to tactile or visual stimuli, sympathoinhibition, and vasodepression. On the other hand, migraine have probably provided evolutionary advantages. Actually, not only migraine has not been eliminated by natural selection but, according to epidemiological evidences, its high prevalence is furtherly expanding in general population. Following these considerations, we would mention a fascinating perspective put forward by Montagna et al. in 2010. In a very interesting reconceptualization of primary headaches, the inextricable puzzle represented by the multifaceted clinical characteristics of migraine pain attack can be solved considering its striking similarity with the innate, pan-mammalian, adaptive behavioral response to visceral "inescapable" pain represented by what Hart termed "sickness behaviour". This includes the avoidance of food intake, of food or sexual searching behaviours, and the inescapable need for a quiet place where to lay or to sleep, a pattern of events fully matching the migraine-associated behaviours, emotions, and symptoms. In this light, the clinical complexity of the migraine attack presentation could reflect the physiologic response to internal or external stimuli perceived (more or less inappropriately in migraineurs) as a body homeostasis threat. The homeostatic imbalance restoration is promoted through a temporary retire of the individual from any environmental interaction, including that arising from ordinary daily life activities. In this light, migraine (and probably other primary headaches) could be seen as a necessary, but evolutionistically affordable, biological cost.

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