Neuroimaging in Headache

Neuroimaging

Neuroimaging is divided into three types: *diagnostic, functional,* and *morphometric* or *structural* imaging. As the name implies, the first is used to rule out conditions such as a brain tumor (computer tomography and magnetic resonance imaging [MRI] scans), whereas *functional* imaging (e.g., positron emission tomography or functional MRI) is used to investigate how the brain works in headache. Finally, *morphometric* or *structural* imaging (e.g., voxel-based morphometry [VBM] or diffusion tensor imaging [DTI]) is used to investigate whether there are differences in brain morphology between headache patients and healthy volunteers.

The first neuroimaging method is used for clinical purposes and is routinely performed to rule out secondary causes in headache, whereas the other two—functional and morphometric imaging—are for scientific research purposes only.

Insights into the fundamental physiology of primary headache syndromes such as migraine or cluster headache have been limited by the lack of methods available to visualize the pathophysiological background of the trigeminovascular system and examine its source. Over the last few years, remarkable efforts have been made using functional imaging studies of the trigeminovascular system that demand renewed consideration of the neural influences at work in many primary headaches. However, this progress is only true of episodic headache types and not for chronic headache, such as tension-type headache or chronic migraine, where, due to methodological issues, no studies have been conducted so far.

Functional Imaging in Migraine

Pioneering work done in the early 1990s revealed that migraine patients who develop aura symptoms (neurological symptoms shortly before the headache phase) show a focal reduction of regional cerebral blood flow (rCBF), usually in the posterior parts of one hemisphere. However, these blood flow reductions have been shown only in the aura phase and not in the headache phase, and usually not in migraine without aura. Since this pioneering work, a number of studies have confirmed these findings, but the link between aura and headache remains controversial, and it must be remembered that only 15–30% of migraineurs experience aura.

Functional and structural brain imaging was instrumental in elucidating the role of the brainstem and midbrain in migraine. In 1995, a positron emission tomography (PET) study showed a highly specific activation of neurons in the brainstem in spontaneous untreated migraine attacks, which subsided during headache-free intervals. Several studies have replicated this finding, and it is now commonly accepted that the generator for migraine attacks is to be found in the brainstem and in midbrain structures. The exact mechanism is still not clear, but a very recent study has additionally shown that specific brainstem nuclei show a cyclical behavior over the migraine interval. The susceptibility of the brain to generate the next attack probably shows an oscillating behavior, which may well explain why migraine comes in attacks.

Functional Imaging in Cluster Headache

The trigeminal autonomic cephalalgias (TACs) are a group of primary headache disorders characterized by pain with a unilateral trigeminal distribution that occurs in association with ipsilateral cranial autonomic features (see the fact sheet on Trigemino-Autonomic Headaches). One of the most remarkable of the clinical features of cluster headache (CH) is the striking periodicity or cycling of the attacks and bouts. Neuroimaging has made substantial recent contributions to understanding this relatively rare but important syndrome.

Using PET in a larger patient sample, researchers observed significant activations ascribable to the acute cluster headache in the ipsilateral hypothalamic gray matter when compared to the headache-free state. This highly significant

activation was not seen in CH patients who were not experiencing an acute CH attack, and it is now commonly accepted that the hypothalamus is indeed some kind of "motor" for these excruciating headaches. These findings prompted the use of deep brain stimulation in the posterior hypothalamic gray matter in a patient with intractable CH headache, which led to complete relief of attacks. In contrast to migraine, no brainstem activation was found during the acute CH attack compared to the resting or control state. This finding is remarkable, as it clearly shows that despite often being discussed as related disorders, migraine and CH are different biological entities. Moreover, recent studies have shown that other trigemino-autonomic headache disorders also show some activation in the same region as CH. Just as the clinical similarity to these syndromes, such as strict one-sidedness and marked autonomic features, prompted the suggestion to unify them on clinical grounds as trigeminal-autonomic cephalgias, functional imaging emphasizes the importance of the hypothalamus as a key region in the pathophysiological process of this entity.
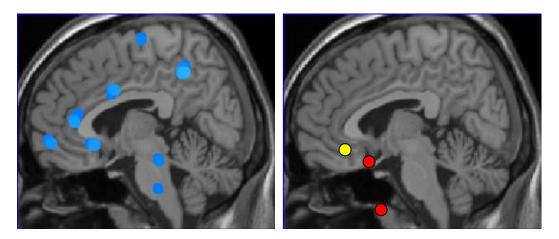

Fig. 1. A conceptual graph visualizing the brain areas commonly activated during pain in humans (at the left side of the figure in blue). The central network transmitting painful input is a very robust and evolutionarily old brain network (called the "pain matrix"). On the right side of the figure, the functional imaging findings in headache are shown, documenting specific activation in the midbrain and pons in migraine (red dots) and in the hypothalamic gray in cluster headache (yellow dot).

Conclusion

Neuroimaging of primary headache syndromes, such as CH and migraine, has begun to provide a better understanding of the neuroanatomical and physiological basis of these conditions. Although these headache types have been widely described as vascular, due to advanced imaging methods such as PET, functional MRI, and VBM, vascular changes are no longer seen as the primary cause for head pain. The shared anatomical and physiological substrate for migraine and CH is the neural innervation of the cranial circulation. Functional imaging with PET has shed light on the genesis of both syndromes, documenting activation in the midbrain and pons in migraine, and in the hypothalamic gray in CH. These areas are not simply a response to trigeminal nociceptive pain impulses but are inherent to each syndrome, probably in some permissive or dysfunctional role.

Taking these new data in acute CH together with what has been observed in experimental head pain and migraine, we can conclude that migraine and cluster headache, far from being primarily vascular disorders, are conditions whose genesis is to be found in the central nervous system in pacemaker or circadian regions specific to the syndrome. If further studies confirm these findings, better understanding will be gained of where and how acute and preventative therapy can be used.

References
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