R E V I E W

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A review of diagnostic and functional imaging in headache

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Abstract The neuroimaging of headache patients has revolutionised our understanding of the pathophysiology of primary headaches and provided unique insights into these syndromes. Modern imaging studies point, together with the clinical picture, towards a central triggering cause. The early functional imaging work using positron emission tomography shed light on the genesis of some syndromes, and has recently been refined, implying that the observed activation in migraine (brainstem) and in several trigeminal-autonomic headaches (hypothalamic grey) is involved in the pain process in either a permissive or triggering manner rather than simply as a response to first-division nociception *per se*. Using the advanced method of voxel-based morphometry, it has been suggested that there is a correlation between the brain area activated specifically in acute cluster headache – the posterior hypothalamic grey matter – and an increase in grey matter in the same region. No structural changes have been found for migraine and medication overuse headache, whereas patients with chronic tension-type headache demonstrated a significant grey matter decrease in regions known to be involved in pain processing. Modern neuroimaging thus clearly suggests that most primary headache syndromes are predominantly driven from the brain, activating the trigeminovascular reflex and needing therapeutics that act on both sides: centrally and peripherally.

Key words Migraine · Cluster headache · Pain · Functional imaging · PET · MRI · VBM

Introduction

The pathophysiological concept of vascular headaches is based on the reasoning that changes in vessel diameter or gross changes in cerebral blood flow trigger the pain and could, in part, explain the mechanism of action of vasoconstrictor drugs, such as ergotamine [1]. Previous regional cerebral blood flow (rCBF) studies have emphasised a dysfunction of the cerebrovascular regulation in headache, while, until about 10 years ago the central processing of headache was only marginally studied [2]. Insights into the fundamental physiology of these syndromes have been limited by the lack of methods to visualise the pathophysiological background of headache and to examine its source. Functional neuroimaging of patients has however revolutionised this area and provided unique insights into some of the commonest maladies in man.

Diagnostic imaging

The diagnosis of primary headaches is exclusively a clinical task. Population-based findings suggest that some patients with migraine – with and without aura – are at an increased risk for subclinical lesions in certain brain areas [3, 4], which was also suggested by a meta-analysis, demonstrating that subjects with migraine are at a higher risk of having white matter lesions on magnetic resonance images than those without migraine [5]. Whether or not this is clinically relevant, until today no single instrumental examination is able to define, ensure or differentiate idiopathic headache syndromes. However, in the clinical setting, the use of neuroimaging (CCT, MRI, MR angiography, etc.) in headache patients varies widely. Recently, an EFNS Task Force evaluated (amongst other instrumental examination tools) the usefulness of imaging procedures in non-acute headache patients on the basis of evidence from the literature [6]. Following these recommendations, in adult and paediatric patients with migraine with no recent change in attack pattern, no history of seizures and no other focal neurological signs or symptoms, the routine use of neuroimaging is not warranted. In patients with atypical headache patterns, a history of seizures and/or focal neurological signs or symptoms, magnetic resonance imaging (MRI) may be warranted. Regarding positron emission tomography (PET) and functional MRI, they are rated as of little or no value in the clinical setting, but have vast potential for exploring the pathophysiology of headaches and the effects of pharmacological treatment [6].

Functional neuroimaging in experimental headache

To understand the possible impact of functional studies in primary headache such as migraine and cluster headache, the neuroimaging pattern of activation in experimental headache needs to be established. In a PET study on experimental head pain [7], seven healthy male volunteers without a history of headache were studied during an acute pain state evoked by injecting a small amount of capsaicin subcutaneously into the forehead.

During the acute pain state compared to the resting state, increases in rCBF were found bilaterally in the anterior insula, the contralateral thalamus, the ipsilateral anterior cingulate cortex and in the cerebellum bilaterally. Activation of the anterior cingulate cortex has been repeatedly reported in PET studies on the sensation of somatic or visceral pain and attributed to the emotional response to pain [8–11]. Activations in the insula have been demonstrated in previous studies following application of heat [9, 12, 13], subcutaneous injection of ethanol [14], somatosen-
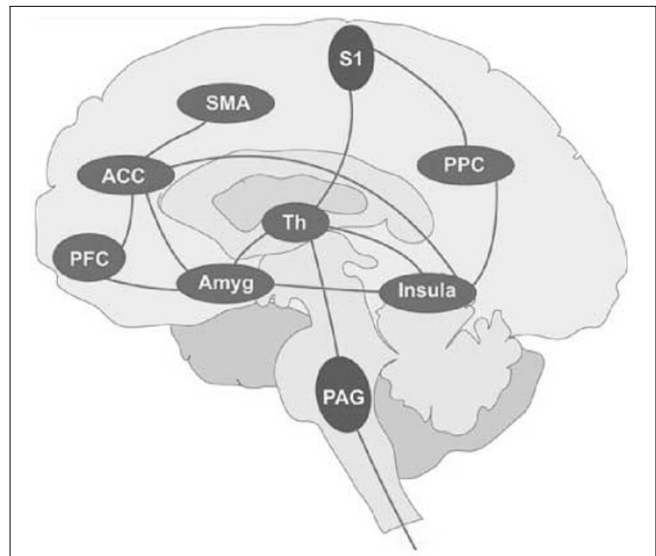

Fig. 1 The pain matrix mainly consists of the thalamus (Th), the amygdala (Amyg), the insula cortex (Insula), the supplementary motor area (SMA), the posterior parietal cortex (PPC), the prefrontal cortex (PFC), the cingulate cortex (ACC), the periaqueductal grey (PAG), the basal ganglia and cerebellar cortex (not shown) and the primary (S1) and secondary (S2, not shown) sensory cortex. For review see Refs. [19, 20]

sory stimulation [15], and during cluster headache [8] and atypical facial pain [16]. Given its anatomical connections, the insula has been suggested as a relay station for sensory information into the limbic system and is known to play an important role in the regulation of autonomic responses [17]. The thalamus is a site where activations would most be expected in the acute pain state. Activation of the contralateral thalamus due to pain is known from experimental animals [18] and functional imaging studies in humans [9, 11]. Figure 1 outlines the above-mentioned regions generally activated in functional imaging studies on pain, the so-called "pain-matrix".

More importantly, in comparison to the PET study on spontaneous migraine [21], no brainstem activity was found during the acute pain state compared to the resting state. Also, no hypothalamic activation was seen, as is seen in nitroglycerin-induced cluster headache [22]. This confirms that the activations seen in these primary headache syndromes are specific to the disease.

Neuroimaging in migraine

Migraine: the aura

In up to 15% of cases [23], the migraine headache is preceded by a visual phenomenon, typically jagged zig-zag

lines, that moves slowly across the visual field, known as an aura. Cortical spreading depression (CSD) of Leao [24] has been suggested to underlie migraine visual aura, based on the slow spread of clinical and electrophysiological events in animal experiments [25, 26]. However, it has been challenging to test this hypothesis in human cerebral cortex. The pioneering work of Olesen and colleagues [27–29] using single photon emission computed tomography (SPECT) revealed a focal reduction of rCBF for migraine attacks with aura, usually in the posterior parts of one hemisphere. These changes were produced by carotid angiography, but similar changes have been seen in spontaneous attacks with SPECT [30], PET [31] and perfusion-weighted MRI [32].

The early depolarising or activation phase of experimental spreading depression, however, is associated with a transient but pronounced cerebral blood flow increase that precedes spreading hypoperfusion. This typical hyperperfusion at the front of the wave has been described in animal experiments [25, 26], but was not detected in early work using SPECT. One explanation is the spatial and temporal resolution of SPECT-CBF measurements.

Using MRI-BOLD of visually triggered headache in patients with migraine, Cao et al. confirmed previous SPECT reports that CSD-like phenomena can be seen with neuroimaging techniques. They concluded that at least visually triggered headache in patients with migraine is accompanied by spreading suppression of initial neuronal activation and increased occipital cortex oxygenation [33].

In a recent study, using high-field functional MRI during visual aura in three subjects, blood oxygenation level-dependent (BOLD) signal changes were demonstrated to be time-locked to onset of the aura [34]. Initially, a focal increase in BOLD signal developed within extrastriate cortex. This BOLD change progressed contiguously and slowly over the occipital cortex, congruent with the retinotopy of the visual percept. Following the same retinotopic progression, the BOLD signal then diminished, as did the BOLD response to visual activation. Changes in occipital blood flow have also been reported using PET [35]. Together, these imaging data strongly suggest that migraine aura is not evoked by ischaemia, but is more likely due to an electrophysiological event such as CSD [34]. Given that the global and regional values for cerebral blood flow decreased significantly after triptan administration, the aura data also underline that potentially vasoconstrictive agents, such as triptans or ergots, should not be used during the aura phase of migraine [36].

Migraine: the headache

In contrast to migraine with aura, using SPECT in migraine without aura, no blood flow changes have been noticed [37, 38]. These data have been reproduced and are stable. In 1994 Friberg and colleagues [39] again demonstrated with SPECT that interictally almost 50% of migraine sufferers had abnormal interhemispherical asymmetries in rCBF. These asymmetries were discrete compared to those seen during the aura phase of a migraine attack. The authors concluded that, at least interictally, a cerebrovascular dysregulation existed. In a very elegant study, the same group [40] combined the measurement of rCBF and blood flow velocity in the middle cerebral arteries using transcranial Doppler sonography. Middle cerebral artery (MCA) velocity on the headache side was significantly lower than on the non-headache side, returning to normal values after treatment with sumatriptan. Using SPECT, no change was seen in the rCBF in the MCA supply territory. The authors concluded that in the headache phase there might be a dilatation in the MCA on the headache side which was reversed by the vasoconstrictor action of the $5HT_{1B/1D}$ receptor agonist sumatriptan [41, 42]. However, as the cerebral blood flow was unaffected, its role as such in the pathogenesis of migraine remains unproven. In contrast, it should be noted that a transcranial Doppler study has shown that the vasoconstrictor effect of sumatriptan is not coupled in time with headache relief [43].

Woods et al. [31] published the first report of PET measurements in a patient from the start of a spontaneous migraine attack without aura, while lying in the PET-scanner for another purpose. Previous studies have been few and in these studies the headache attacks had already commenced [44]. The patient was studied while she was participating in a visual activation paradigm and was scanned with 12 successive measurements of rCBF. After the sixth scan she developed unilateral headache, nausea and photo- and phonophobia. The first decrease in rCBF, noted during the seventh scan, was found bilaterally in the visual association cortex. In each subsequent scan, every 12 min, the decrease in rCBF spread contiguously across the cortical surface at a relatively constant rate, sparing the cerebellum, basal ganglia and the thalamus. The hypoperfusion involved the middle as well as the posterior cerebral artery territories. The authors estimated the maximal decrease of rCBF to be about 40%, potentially approaching an ischaemic level. However, most of these changes were relatively short lasting, with substantial recovery by the time of the next measurement 12–15 min later. This case report is remarkable for two reasons. First, it illustrates for the first time a bilateral spreading hypoperfusion in a spontaneous migraine attack measured with PET. Even more remarkable is the fact that this patient suffered from visual blurring only and thus from migraine without aura [45]. These findings are not in line with the SPECT studies [28, 37, 46] in which no changes in rCBF in migraine attacks without aura have been observed.

In the first PET study in patients with migraine without aura [21], significantly higher rCBF values were found during the acute attack compared to the headache-free interval in brainstem structures over several planes. These structures were towards the midline but contralateral to the headache side and their localisation has been refined to the dorsal pons [47, 48]. It has been speculated that the contralateral changes may represent rostral rather than caudal control systems [49]. Increased activation was also found in the inferior anterocaudal cingulate cortex as well as in the visual and auditory association cortices during the attack, but was not detectable in these areas in the interval scan or after relief from headache- and migraine-related symptoms through treatment [21].

The consistent increases in rCBF in the brainstem persisted, even after sumatriptan had induced complete relief from headache, nausea, phonophobia and photophobia. This increase was not seen outside the attack. It can be concluded that the observed activation was unlikely to be just the result of pain perception or increased activity of the endogenous anti-nociceptive systems. Very recently, these findings have been replicated and significantly extended. It seems clear now that the brainstem activation is indeed highly specific to migraine, but ipsilateral to the pain and at a slightly different location [48, 50]. Interestingly, the same area was found to be activated in chronic migraine which was treated using a suboccipital stimulation [51]. It is certainly beyond the resolution of the PET scanner to attribute foci of rCBF increases to distinct brainstem nuclei. However, dysfunction of the regulation of brainstem nuclei involved in anti-nociception and extra- and intracerebral vascular control provides an encompassing explanation for many of the facets in migraine [18, 52]. The importance of the brainstem for the genesis of migraine is further underlined by the presence of binding sites for specific anti-migraine compounds within these structures [53]. The only direct clinical evidence for the brainstem as primum movens in migraine was reported by Raskin et al. [54] on non-headache patients who developed migraine-like episodes after stereotactic intervention with lesioning of the PAG and more specifically the DRN. Interestingly, these headaches responded to specific serotonergic agonists.

Migraine and medication overuse headache

Recently, 16 migraine patients suffering from medication overuse headache were investigated using 18-FDG PET (measuring glucose metabolism) before and 3 weeks after medication withdrawal and compared to a control population. Before withdrawal, the bilateral thalamus, orbitofrontal cortex, anterior cingulate gyrus, insula/ventral striatum and right inferior parietal lobule were hypometabolic, while the cerebellar vermis was hypermetabolic [55]. Following withdrawal of analgesics, all areas but the orbitofrontal cortex showed an almost normal glucose uptake. The authors suggested that medication overuse headache may be associated with reversible metabolic changes in pain processing structures like other chronic pain disorders, but also with persistent orbitofrontal hypofunction. Interestingly, the latter is known to occur in drug dependence, which may predispose subgroups of migraineurs to recurrent analgesic overuse.

Neuroimaging in trigeminal autonomic cephalalgias

Primary short-lasting headaches broadly divide themselves into those associated with prominent cranial autonomic symptoms, so-called trigeminal autonomic cephalalgias (TACs), and those where autonomic symptoms are minimal or absent. The group of TACs comprises cluster headache, paroxysmal hemicranias and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT syndrome) [56]. The concept of TACs signifies a possibly shared pathophysiological basis for these syndromes that is not shared with other primary headaches, such as migraine or tension-type headache [57]. As thus far findings in functional imaging of primary headache syndromes have been specific to the disease [58, 59], these techniques may be helpful in unravelling the degrees of relationship between clinically analogous headache syndromes.

TACs are relatively rare when compared to migraine or tension-type headache, which is likely to be why they are poorly recognised in primary care. The most remarkable of the clinical features of cluster headache is the striking rhythmicity or cycling of the attacks and bouts. Cluster headache is probably the most severe pain syndrome known to humans, with female patients describing each attack as being worse than childbirth. The syndrome is well defined from a clinical point of view [56] and despite the fact that it has been recognised in the literature for more than two centuries [60], its pathophysiology has been hitherto poorly understood. Neuroimaging has made substantial contributions in recent times to understanding this relatively rare but important syndrome [61, 62].

Despite the fact that the clinical picture of cluster headache is characteristic, patients are often misdiagnosed and undertreated [61, 63]. One possible explanation is that the pathophysiological background of this disease is still vague and the treatment empirical. In recent years some pieces of the pathophysiological puzzle have been reassembled in that the excruciatingly severe unilateral

pain is likely to be mediated by activation of the first (ophthalmic) division of the trigeminal nerve, while the autonomic symptoms are due to activation of the cranial parasympathetic outflow from the VIIth cranial nerve [64]. The noteworthy circadian rhythmicity of cluster headache has led to the concept of a central origin for its initiation [65–67].

Previous studies of cerebral blood flow in cluster headache are few in number. Most have been done with SPECT and the results of this semi-quantitative method have been quite heterogeneous, some reporting an increase, some a decrease and some no differences in cortical blood flow, probably due to methodological differences [68–72]. The more recent study by Di Piero and co-workers (1997) [73] studied cluster headache patients out of the active period and normal volunteers using the cold water pressor test. They demonstrated changes in pain transmission systems, which bear more detailed examination. The fact that the alterations are also present out of the active period of the disease suggested a possible involvement of central tonic pain mechanisms in the pathogenesis of cluster headache.

In 1996, the first PET study in cluster headache was reported [8]. Although the Authors investigated only 4 patients, their findings supported their earlier work [74] suggesting a preference of the non-dominant hemisphere, especially for the anterior cingulate cortex, in affective processing of chronic ongoing pain syndromes. These interesting results have contributed to an understanding of central pain transmission systems, but given the small numbers, require confirmation.

Using PET in a larger patient sample, significant activations ascribable to acute cluster headache were observed in the ipsilateral hypothalamic grey matter when compared to the headache-free state [22]. This highly significant activation was not seen in cluster headache patients out of the bout when compared to the patients experiencing an acute cluster headache attack [75]. In contrast to migraine [21], no brainstem activation was found during the acute attack compared to the resting state. This is remarkable, as migraine and cluster headache are often discussed as related disorders and identical specific compounds, such as ergotamine and sumatriptan, are currently used in the acute treatment of both types of headache agents [76]. These data suggest that while primary headaches such as migraine and cluster headache may share a common pain pathway, the trigeminovascular innervation, the underlying pathogenesis, differs significantly, as might be inferred from the different patterns of clinical presentation and responses to preventative agents [76].

Just as it is striking that no brainstem activation occurs in contrast to acute migraine, no hypothalamic activation was seen in experimental pain induced by capsaicin injection into the forehead [7]. This is important because injection of the forehead would activate first (ophthalmic) division afferents, which belong to the trigeminal division predominantly responsible for pain activation in cluster headache. Thus, two other types of first division of trigeminal nerve pain, while sharing neuroanatomical pathways with cluster headache, do not give rise to hypothalamic activation. This finding clearly implies that the activation specific to cluster headache is involved in the pain process in a permissive or triggering manner rather than simply representing a response to first division nociception *per se*. From the clinical point of view, it is tempting to consider a trait change in the hypothalamus that is converted to a state change when the patient is in the acute bout. Furthermore, given that this area is involved in circadian rhythm and sleep-wake cycling [77, 78], these data establish an involvement of this hypothalamic area as a primum movens in the acute cluster attack.

These findings prompted the use of deep brain stimulation in the posterior hypothalamic grey matter in a patient with intractable cluster headache, and led to a complete relief of attacks [79]. To date, 20 operated intractable cluster headache patients have been reported [80, 81], some with a follow up of more than four years [82, 83]. In order to unravel the brain circuitry mediating stimulation-induced effects, a very recent study applied PET in hypothalamic deep brain stimulated patients and found that stimulation induced activation in the ipsilateral hypothalamic grey (the site of the stimulator tip), the ipsilateral thalamus, somatosensory cortex and praecuneus, the anterior cingulate cortex and the ipsilateral trigeminal nucleus and ganglion [84]. The authors additionally observed deactivations in the middle temporal gyrus, posterior cingulate cortex and contralateral anterior insula. Both activations and deactivations are situated in cerebral structures belonging to neuronal circuits usually activated in pain transmission and notably in acute cluster headache attacks. These data argue against an unspecific anti-nociceptive effect or pure inhibition of hypothalamic activity. Instead, the data suggest a hitherto unrecognised functional modulation of the pain processing network as the mode of action of hypothalamic deep brain stimulation in cluster headache [84].

Shared pathophysiological background?

If it is correct that TACs share a common pathophysiological background, it should be possible to delineate similar structures using functional imaging. SUNCT is among the rarest idiopathic headache syndromes [85]. Several clini-

indomethacin. In seven patients with hemicrania continua a significant activation of the contralateral posterior hypothalamus and ipsilateral dorsal rostral pons in association with the headache was described. In addition, there was activation of the ipsilateral ventrolateral midbrain, which extended over the red nucleus and the substantia nigra, and bilateral pontomedullary junction. This study demonstrated nicely that the neuroimaging markers of trigeminal autonomic headaches and migrainous syndromes are also apparent in hemicrania continua, mirroring the clinical phenotype, which exhibits a certain overlap with trigeminal autonomic headaches and migraine [94]. Taken together, just as in the case of an atypical trigeminal autonomic headache [91], the functional imaging data in hemicrania continua [94] impressively emphasises that primary headache syndromes can be distinguished on a functional neuroanatomic basis by areas of activation specific to the clinical presentation (Fig. 2).

Morphometric studies: pointing towards a lesion

Fundamental to the concept of idiopathic or primary headache, including migraine, tension-type headache and cluster headache, is the currently accepted view that these conditions are due to abnormal brain function with completely normal brain structure [45]. Given the consistency of the PET findings with the clinical presentation in cluster headache, the subsequent question is whether the brains of such patients are structurally normal. Voxel-based morphometry, an objective and automated method of analysing changes in brain structure [98–100], was used to study the structure of the brains of patients with cluster headache [101].

Using the voxel-based morphometric analysis of the structural T1-weighted MRI scans, a significant structural difference in grey matter density was found in patients with cluster headache when compared to healthy volunteers. This difference consists of an increase in volume and was present for the entire cohort. The difference was also present when patients in- and outside a bout were compared with the control group. This structural difference is bilaterally situated in the diencephalon, adjacent to the third ventricle and rostral to the aqueduct, coinciding with the inferior posterior hypothalamus. In terms of the stereotaxic coordinates [102] it is virtually identical to the area in which activation during an acute cluster headache attack was demonstrated in the PET study. No other areas of change were noted [95].

Co-localisation of morphometric and functional changes means that two different imaging techniques separately identify a highly specific brain area previously considered on clinical and biological grounds to be involved in the genesis of the cluster headache syndrome [103]. The structural data relate to a morphometric change of the neuronal density in this region, whilst the functional imaging data are related to the neuronal activity in this area. Together they demonstrate for the first time the precise anatomical location for the central nervous system lesion of cluster headache.

Regarding migraine, no global or regional structural differences between patients with migraine [104] and controls, or between patients suffering from medication overuse headache (MOH) and controls [105] were found. The authors suggested that migraine and MOH, in contrast to cluster headache, may primarily be a biochemical/biophysical disorder. It may well be, however, that structural studies of a condition that is potentially genetically heterogenous, such as migraine, miss subtle changes that might segregate with a more homogenous genotype. A very recent finding suggests that the brains from CTTH patients are different on a structural level from the brains of migraine patients and the brains of healthy controls [105]. This change in grey matter in CTTH patients is restricted to structures involved in pain processing and could reflect either the cause or the consequence of chronic head pain. At the moment these data suggest that while CTTH and MOH may share a common signature feature, namely the frequent head pain, the underlying pathogenesis differs significantly, as inferred from the different clinical patterns of pain characterisation and responses to treatment.

Dilatation of cerebral blood vessels in headache is an epiphenomenon

In addition to the activations in non-specific structures associated with pain transmission, such as the cingulate, insula cortex, frontal lobe and thalamus, in the study of experimental head pain described above [7] there was a bilateral pattern of activation in midline structures over several planes, slightly lateralised to the left, anterior to the brainstem and posterior to the chiasmatic region [106]. Superimposed on an MRI template, the location of the activation covers intracranial arteries as well as the region of the cavernous sinus bilaterally. Similarly, in the cluster headache study there was a strong activation observed in the same region, the cavernous sinus [75] suggesting a vasodilatation mediated by the ophthalmic division of the trigeminovascular system.

Using magnetic resonance angiographic techniques, injection of capsaicin into the skin innervated by the ophthalmic (first) division of the trigeminal nerve elicited an

increase in vascular diameter of the internal carotid artery when compared to the mean baseline [58]. Injection of capsaicin into the skin of the chin to stimulate the mandibular (third) division of the trigeminal nerve, and into the leg, led to a similar pain perception but failed to produce any significant change in vessel calibre. The data suggest that there is a highly functionally organised, somatotopically congruent trigeminal innervation of the cranial vessels, with a potent vasodilator effect of the ophthalmic division on the large intracranial vessels.

Taken together the data suggest that neurovascular activation in the trigeminal system is a function of its afferent role in any form of pain, and is highly potent and somatotopically organised. Pain signals in the ophthalmic division can generate vascular change *de novo* without a superimposed primary headache. The data are consistent with the notion that pain triggers changes in vessel calibre in migraine and cluster headache, not vice versa. These conditions should therefore be regarded as primary neurovascular headaches and not as vascular headaches.

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