Headache: lessons learned from functional imaging

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Most idiopathic headache syndromes are still recognized as vascular headaches although the clinical picture points towards a central triggering cause. The early functional imaging work using PET shed light on the genesis of some syndromes, implying that the observed activation in migraine (brainstem) and in cluster headache (hypothalamic grey) is involved in the pain process in 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 (VBM), it has been suggested that there is a correlation between the brain area activated particularly in acute cluster headache, the posterior hypothalamic grey matter, and some change in grey matter in the same region. Moreover, also in a PET study in cluster headache and experimental headache, a vasodilation of major basal vessels has been observed which is non-specific to the cause and most likely the effect of a trigemino-parasympathetic reflex. Taken together, functional neuroimaging in headache patients has revolutionised this area of study and provided unique insights into some of the commonest maladies in man, suggesting that migraine and cluster headache are primarily driven from the brain.

The issue of vascular versus neurogenic mechanisms in primary headaches such as migraine and cluster headache is still unresolved. The pathophysiological concept of vascular headaches is based on the idea that changes in vessel diameter or gross changes in cerebral blood flow would trigger the pain and could, in part, explain the mechanism of action of vasoconstrictor drugs such as ergotamine. Previous regional cerebral blood flow (rCBF) studies have emphasised a dysfunction of the cerebrovascular regulation in headache while few studies have been conducted to evaluate the central processing of headache. Insights into the fundamental physiology of these systems has been limited by the lack of methods to visualize the pathophysiological background of headache and examine its source. Functional neuroimaging in patients has, however, revolutionised this area and provided unique insights into some of the commonest maladies in man.
Neuroimaging in migraine

Migraine: the aura

In up to 15% of cases\(^3\), the migraine headache is preceded by visual phenomena, typically jagged zig-zag lines, that move slowly across the visual fields known as an ‘aura’. Cortical spreading depression (CSD) of Leao\(^4\) has been suggested to underlie migraine visual aura, based on the slow spread of clinical and electrophysiological events in animal experiments\(^5,6\). However, it has been challenging to test this hypothesis in human cerebral cortex. The pioneering work of Olesen and colleagues\(^7-9\), using single photon emission computed tomography (SPECT), revealed a focal reduction of regional cerebral blood flow 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\(^10\), positron emission tomography (PET)\(^11\), and perfusion-weighted magnetic resonance imaging (MRI)\(^12\).

The early depolarizing 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 that has been described in animal experiments\(^5,6\) was not detected in the 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\(^13\).

In a recent study, using high-field functional MRI during visual aura in three subjects, blood oxygenation level-dependent (BOLD) signal changes were demonstrated time-locked to precept/onset of the aura\(^14\). 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. These imaging data strongly suggest that migraine aura is not evoked by ischaemia, but more likely due to an electrophysiological event such as CSD\(^14\).

Migraine: the headache

In contrast to migraine with aura, using SPECT in migraine without aura, no blood flow changes were noticed\(^15,16\). These data have been
reproduced and are stable. In 1994, Friberg and colleagues\textsuperscript{17} demonstrated, again 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\textsuperscript{18} 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 that 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 5HT1B/1D receptor agonist sumatriptan\textsuperscript{19,20}. 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\textsuperscript{21}.

Woods \textit{et al}\textsuperscript{11} 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 had been few and attacks had already commenced\textsuperscript{22}. 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\textsuperscript{23}. These findings are not in line with the SPECT studies\textsuperscript{8,15,24} in which no changes in rCBF in migraine attacks without aura has been observed.

In the first PET study in patients with migraine without aura\textsuperscript{25}, 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 have most recently been refined in their localisation to the dorsal pons\textsuperscript{26}. It has been speculated that the contralateral changes may represent rostral, rather than caudal, control systems\textsuperscript{27}. 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\textsuperscript{25}. 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 to pain perception or increased activity of the endogenous anti-nociceptive systems. It is 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 a far reaching explanation for many of the facets in migraine\textsuperscript{28,29}. The importance of the brainstem for the genesis of migraine is further underlined by the presence of binding sites for specific antimigraine compounds on these structures\textsuperscript{30}. The only direct clinical evidence for the brainstem as \textit{primum movens} in migraine was reported by Raskin on non-headache patients who developed migraine-like episodes after stereotactic intervention with lesioning of the PAG and more specifically the DRN\textsuperscript{31}. Interestingly, these headaches responded to specific serotonergic agonists.

**Neuroimaging in cluster headache**

\textit{Functional imaging studies: pointing towards a change of state}

Despite the fact that the clinical picture of cluster headache is characteristic, making it probably the easiest idiopathic headache syndrome to diagnose, patients are often misdiagnosed and undertreated. 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 re-assembled 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 out-flow from the VIIth cranial nerve\textsuperscript{32}. 
The noteworthy circadian rhythmicity of cluster headache has led to the concept of a central origin for its initiation. 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. The more recent study by Di Piero and co-workers investigated 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. Although the authors investigated only 4 patients, their findings supported their earlier work suggesting a preference of the non-dominant hemisphere, especially for the anterior cingulate cortex (ACC), in affective processing of chronic on-going pain syndromes. These interesting results contribute to understanding central pain transmission systems, but given the small numbers require confirmation.

Using PET in a larger patient series, significant activations ascribable to the acute cluster headache were observed in the ipsilateral hypothalamic grey matter when compared to the headache-free state. 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. In contrast to migraine, 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. 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 presentation and responses to preventative agents.

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. This is important because injection of the forehead would activate first (ophthalmic) division afferents which are the trigeminal division predominantly responsible for pain activation in cluster headache. Thus two other types of first division of trigeminal nerve pain, while sharing neuro-anatomical 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, these data establish an involvement of this hypothalamic area as a *primum movens* in the acute cluster attack.

**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. Given the consistency of the PET findings with the clinical presentation in cluster headache, the subsequent question is whether the brain of such patients is structurally normal. Voxel-based morphometry, an objective and automated method of analysing changes in brain structure, was used to study the structure of the brains of patients with cluster headache. 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, co-incident with the inferior posterior hypothalamus. In terms of the stereotaxic co-ordinates, it is virtually the identical area in which activation during an acute cluster headache attack is demonstrated in the PET study. No other areas of change were noted.

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. 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. Furthermore, given that this area is involved in circadian rhythm and sleep-wake cycling, these data suggest an
involvement of this hypothalamic area as a *primum movens* in the acute cluster attack.

*Trigemino-autonomic headaches: shared pathophysiological background?*

Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) is among the rarest idiopathic headache syndromes. Several clinical features differentiate it from other primary headaches, such as cluster headache and chronic paroxysmal hemicrania (CPH) with the most prominent one being that the paroxysms of the unilateral pain are very short lasting, between 5–250 s. The attacks are frequent with a published mean of 30 attacks per day, and a range of 6–77 per day. The pain is accompanied by autonomic features like conjunctival injection and tearing, but also sweating of the forehead and rhinorrhoea.

Little is known about its pathophysiology, although the trigeminal pathways seem to be involved in the entire range of the idiopathic headaches, and the trigemino-autonomic reflex has been suggested to account for many of its features. Even though there are marked differences in the clinical pictures, such as the frequency and duration of attacks and the different approach to treatment, many of the basic features of SUNCT, such as episodicity, autonomic symptoms and unilaterality, are shared by other headache types, such as cluster headache and CPH. This suggests a pathophysiological similarity to these syndromes and prompted the suggestion to unify them on clinical grounds as trigeminal-autonomic cephalgias (TACs).

Using functional magnetic resonance imaging in 6 consecutive spontaneous pain attacks in a patient with SUNCT, activation was seen in the ipsilateral inferior posterior hypothalamic grey when comparing the pain attacks with the resting state. The activation in the hypothalamus was seen solely in the pain state and was in the same area which was demonstrated to be activated in cluster headache patients, suggesting considerable commonalities between SUNCT and cluster headache. Indeed, the data may explain the episodic nature of the pain. There is a strong need to investigate other related idiopathic headache syndromes such as chronic paroxysmal hemicrania and hemicrania continua with functional imaging to seek for the anatomical or functional basis for the variation in trigeminal autonomic cephalgias.

**Experimental headache and PET**

In a PET study on experimental head pain, 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\cite{42,60–62}. Activations in the insula have been demonstrated in previous studies following application of heat\cite{60,63,64}, subcutaneous injection of ethanol\cite{65}, somatosensory stimulation\cite{66}, and during cluster headache\cite{42} and atypical facial pain\cite{67}. Given its anatomical connections, the insula has been suggested as a relay of sensory information into the limbic system and is known to play an important role in the regulation of autonomic responses\cite{68}. 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\cite{29} and functional imaging studies in humans\cite{60,62}.

More importantly, in comparison to the PET study in spontaneous migraine\cite{25}, no brainstem activity was found during the acute pain state compared to the resting state. Also, no hypothalamic activation was seen, as in nitroglycerine-induced cluster headache\cite{44}. This confirms that the activations seen in these primary headache syndromes are specific to the disease.

**Vascular headache: are blood vessels involved?**

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\cite{47} 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\cite{69}. 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\cite{45}, 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 base-line\cite{70}. 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 neurovascular activation in the trigeminal system is a function of its afferent role in any 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.

### Conclusions

Neuroimaging of primary headache syndromes, such as cluster headache and migraine, has begun to provide a better understanding of the neuro-anatomical and physiological basis of the conditions. Although these headache types have been widely described as vascular, due to advanced methods like PET, fMRI and VBM, vascular changes are no longer seen as the primary cause for head pain. The shared anatomical and physiological substrate for migraine and cluster headache is the neural innervation of the cranial circulation. Functional imaging with positron emission tomography (PET) has shed light on the genesis of both syndromes, documenting activation in the midbrain and pons in migraine, and in the hypothalamic grey in cluster headache. Furthermore, using the voxel-based morphometric analysis of the structural T1-weighted MRI scans, a significant structural difference in grey matter density of the hypothalamus was found in patients with cluster headache when compared to healthy volunteers. These areas are involved not simply as a response to first division nociceptive pain impulses, but are inherent to each syndrome, probably in some permissive or dysfunctional role.

In addition to activation within the brain, there was a highly significant activation observed in the region of major vessels. This phenomenon was seen in cluster headache as well as experimental trigeminal transmitted pain using capsaicin injections into the forehead. Magnetic resonance angiography (MRA) demonstrated dilatation in both the basilar and intracranial carotid arteries, clarifying the nature of the changes observed in headache, being most likely inherent to the trigeminovascular system itself.
Taking these observations on acute cluster headache together with what has been observed in experimental head-pain and migraine, the data establish 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, a better understanding will be gained of where and how acute and preventative therapy can be targeted.

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