A review of diagnostic and functional imaging in headache

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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 migraine 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 migraine with 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-
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 hyperperfusion. 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 underlie 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 5HT1B/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 pathophysiologic 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 trigemino-vascular 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 prefrontal regions, 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 unrecognized 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-
Cal 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, typically between 5 and 250 s. The attacks are frequent, with a published mean of 30 attacks per day, and a range of 6–77 [86]. 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 trigeminal autonomic reflex has been suggested to account for many of its features [57]. 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 TACs [57].

Using functional MRI 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 [87]. These findings have recently been confirmed [88, 89]. The activation in the hypothalamus was seen solely in the pain state and was in the same area that was demonstrated to be activated in cluster headache patients [22] and patients suffering from paroxysmal hemicrania [90], suggesting considerable commonalities between SUNCT and cluster headache. Indeed the data may explain the episodic nature of the pain. Furthermore, a recent case report investigated, using f-MRI, a 68-year-old patient suffering from excruciating trigeminal autonomic headache attacks, in whom frequency, duration and therapeutic response allowed no clear-cut classification as one of the subtypes of TAC [91]. However, the cerebral activation pattern was similar although not identical to those previously observed in cluster headache [92] and SUNCT [87], with a prominent activation in the hypothalamic grey matter [91]. This case study underlines the conceptual value of the term “TAC” for the group of headaches focusing on the trigeminal autonomic reflex and moreover emphasises the importance of the hypothalamus as a key region in the pathophysiological process of this entity.

Another recent case report of 2 SUNCT patients investigated using f-MRI and BOLD reported a bilateral hypothalamic activation, which was even positively correlated to increasing pain levels [89]. This report certainly strengthens the role of the hypothalamus in the pathophysiology of TACs, but considering that only 2 patients are reported it does not justify questioning the basis for the laterality of the attacks.

Hemicrania continua is a strictly unilateral, continuous headache of moderate intensity, with superimposed exacerbations of severe intensity that are accompanied by trigeminal autonomic features and migrainous symptoms [93]. The syndrome is exquisitely responsive to
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 migraine 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 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 vasodilation 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.

References

1. Wolff HG (ed) (1963) Headache and other head pain, 2nd edn. Oxford University Press, New York
2. Russel D, Fanciullacci M (1993) Neurophysiology, hemodynamics, trigger factors, cerebrospinal fluid and psychological factors. Raven Press, New York
3. Kruit MC, van Buchem MA, Hofman PA et al (2004) Migraine as a risk factor for subclinical brain lesions. JAMA 291:427–434
4. Tietjen GE (2004) Stroke and migraine linked by silent lesions. Lancet Neurol 3:267
5. Swartz RH, Kern RZ (2004) Migraine is associated with magnetic resonance imaging white matter abnormalities: a meta-analysis. Arch Neurol 61:1366–1368
6. Sandrini G, Friberg L, Janig W et al (2004) Neurophysiological tests and neuroimaging procedures in non-acute headache: guidelines and recommendations. Eur J Neurol 11:217–224
7. May A, Kaube H, Büchel C et al (1998) Experimental cranial pain elicited by capsaicin: a PET-study. Pain 74:61–66
8. Hsieh JC, Hamnerz J, Ingvar M (1996) Right-lateralised central processing for pain of nitroglycerin-induced cluster headache. Pain 67:59–68
9. Casey KL, Minoshima S, Berger KL et al (1994) Positron emission tomographic analysis of cerebral structures activated specifically by repetitive noxious heat stimuli. J Neurophysiol 71:802–807
10. Jones AK, Friston K, Frackowiak RS (1992) Localization of responses to pain in human cerebral cortex. Science 255:215–216
11. Rosen SD, Paulus E, Frith CD et al (1994) Central nervous pathways mediating angina pectoris. Lancet 344:147–150
12. Coghill RC, Talbot JD, Evans AC et al (1994) Distributed processing of pain and vibration by the human brain. J Neurosci 14:4095–4108
13. Minoshima S, Morrow TJ, Koepp K, Casey KL (1995) Involvement of the insular cortex in central autonomic regulation during painful thermal stimulation. J Cereb Blood Flow Metan 15:859
14. Hsieh JC, Stable Backdahl M, Hagermark O et al (1996) Traumatic nociceptive pain activates the hypothalamus and the periaqueductal gray: a positron emission tomography study. Pain 64:303–314
15. Burton H, Viden TA, Raichle ME (1993) Tactile vibration activated foci in insular and parietal opercular cortex studied with positron emission tomography. Somatosens Mot Res 3:297–308
16. Derbyshire SW, Jones AK, Devani P et al (1994) Cerebral responses to pain in patients with atypical facial pain measured by positron emission tomography. J Neuro Neurosurg Psychiatry 57:1166–1172
17. Mesulam MM, Mufson EF (1985) The insula of Reil in man and monkey. Architectonics, connectivity and function. Plenum, New York
18. Goadsby PJ, Zagoni A, lambert GA (1991) Neural processing of craniovascular pain: a synthesis of the central structures involved in migraine. Headache 31:365–371
19. Peyron R, Laurent B, Garcia-Laurea L (2000) Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin 30:263–288
20. Forss N, Rait TT, Seppa M, Hari R (2005) Common cortical network for first and second pain. Neuroimage 24:132–142
21. Weiller C, May A, Limmroth V et al (1995) Brain stem activation in spontaneous human migraine attacks. Nat Med 1:658–660
22. May A, Bahr A, Büchel C, Frackowiak RSJ, Goadsby PJ (1998) Hypothalamic activation in cluster headache attacks. Lancet 352:275–278
23. Russell MB, Olesen J (1993) The genetics of migraine without aura and migraine with aura. Cephalalgia 13:245–248
24. Leao AAP (1944) Spreading depression of activity in the cerebral cortex. J Neurophysiol 7:391–396
25. Lauritzen M (1987) Regional cerebral blood flow during cortical spreading depression in rat brain: increased reactive hyperperfusion in low-flow states. Acta Neurol Scand 75:1–8
26. Mravočítek S, Calando Y, Goadsby PJ, Seyal J (1992) Subcortical cerebral blood flow and metabolic changes elicited by cortical spreading depression in rat. Cephalalgia 12:137–141

27. Olesen J, Larsen B, Lauritzen M (1981) Focal hyperemia followed by spreading oligemia and impaired activation of CBF in classic migraine. Ann Neurol 9:344–352

28. Olesen J, Friberg L (1991) Xenon-133 SPECT studies in migraine without aura. In: Olesen J (ed) Migraine and other headaches: the vascular mechanisms. Raven Press, London, pp 237–243

29. Friberg L, Olesen J, Lassen NA, Olsen TS, Karle A (1994) Cerebral oxygen extraction, oxygen consumption, and regional cerebral blood flow during the aura phase of migraine. Stroke 25:974–979

30. Lauritzen M (1994) Pathophysiology of the migraine aura. The spreading depression theory. Brain 117:199–210

31. Woods RP, Iacoboni M, Mazzotta JC (1994) Brief report: bilateral spreading cerebral hyperperfusion during spontaneous migraine headache. N Engl J Med 331:1689–1692

32. Cutrer FM, Sorensen AG, Weisskoff RM et al (1998) Perfusion-weighted imaging defects during spontaneous migraine aura. Ann Neurol 43:25–31

33. Cao Y, Welch KM, Aurora S, Vikingstad EM (1999) Functional MRI-BOLD of visually triggered headache in patients with migraine. Arch Neurol 56:548–554

34. Hadjikhani N, Sanchez Del Rio M, Wu O et al (2001) Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci USA 98:4687–4692

35. Afridi S, Kaube H, Goadsby PJ (2005) Occipital activation in glyceryl trinitrate induced migraine with visual aura. J Neurol Neurosurg Psychiatry 76:1158–1160

36. Okazawa H, Tsuchida T, Pagani M et al (2006) Effects of 5-HT1B/1D receptor agonist rizatriptan on cerebral blood flow and blood volume in normal circulation. J Cereb Blood Flow Metab 26:92–98

37. Olesen J, Lauritzen M, Tfelt Hansen P, Henriksen L, Larsen B (1982) Spreading cerebral oligemia in classical- and normal cerebral blood flow in common migraine. Headache 22:242–248

38. Olien J, Friberg L, Olsen TS et al (1990) Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. Ann Neurol 28:781–798

39. Friberg L, Olesen J, Iversen H et al (1994) Interictal “patchy” regional cerebral blood flow patterns in migraine patients. A single photon emission computed tomographic study. Eur J Neuro 1:35–43

40. Friberg L, Olesen J, Iversen HK, Sperling B (1991) Migraine pain associated with middle cerebral artery dilatation: reversal by sumatriptan. Lancet 338:13–17

41. Humphrey PP, Goadsby PJ (1994) The mode of action of sumatriptan is vascular? A debate. Cephalalgia 14:401–410

42. Henkes H, May A, Kuhne D, Berg Dammer E, Diener HC (1996) Sumatriptan: vasoactive effect on human dural vessels, demonstrated by subselective angiography. Cephalalgia 16:224–230

43. Limroth V, May A, Auerbach P et al (1996) Changes in cerebral blood flow velocity after treatment with sumatriptan or placebo and implications for the pathophysiology of migraine. J Neurol Sci 138:60–65

44. Diener HC, May A (1996) New aspects of migraine pathophysiology: lessons learned from positron emission tomography. Curr Opin Neurol 9:199–201

45. Headache Classification Committee of the International Headache Society (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 8:1–96

46. Lauritzen M, Olesen J (1984) Regional cerebral blood flow during migraine attacks by Xenon-133 inhalation and emission tomography. Brain 107:447–461

47. Bahra A, Matharu MS, Buchel C, Frackowiak RS, Goadsby PJ (2001) Brainstem activation specific to migraine headache. Lancet 357:1016–1017

48. Afridi SK, Matharu MS, Lee L et al (2005) A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate. Brain 128:932–939

49. Goadsby PJ, Fields HL (1998) On the functional anatomy of migraine. Ann Neurol 43:272

50. Afridi SK, Giffin NJ, Kaube H et al (2005) A positron emission tomographic study in spontaneous migraine. Arch Neurol 62:1270–1275

51. Matharu MS, Bartsch T, Ward N et al (2004) Central neuromodulation in chronic migraine patients with subocipital stimulators: A PET study. Brain 127:220–230

52. Lance JW, Lambert GA, Goadsby PJ, Duckworth JW (1983) Brainstem influences on the cephalic circulation: experimental data from cat and monkey of relevance to the mechanism of migraine. Headache 23:258–265

53. Goadsby PJ, Gundlach AL (1991) Localization of [3H]-dihydroergotamine-binding sites in the cat central nervous system: relevance to migraine. Ann Neurol 29:91–94

54. Raskin NH, Hosobuchi Y, Lamb S (1987) Is the brain pain-insensitive? Cephalalgia 7[Suppl 6]:23–25

55. Fumal A, Laureys S, Di Clemente L et al (2006) Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. Brain 129:543–550

56. Headache Classification Committee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edition. Cephalalgia 24[Suppl 1]:1–160

57. Goadsby PJ, Lipton RB (1997) A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic feature, including new cases. Brain 120:193–209

58. May A, Buchel C, Turner R, Goadsby PJ (2001) Magnetic resonance angiography in facial and other pain: neurovascular mechanisms of trigeminal sensation. J Cereb Blood Flow Metab 21:1171–1176
93. Matharu MS, Boes CJ, Goadsby PJ (2003) Management of trigeminal autonomic cephalalgias and hemicrania continua. Drugs 63:1637–1677

94. Matharu MS, Cohen AS, McGonigle DJ et al (2004) Posterior hypothalamic and brainstem activation in hemicrania continua. Headache 44:747–761

95. May A, Ashburner J, Buchel C et al (1999) Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nat Med 5:836–838

96. Sprenger T, Boecker H, Tolle TR et al (2004) Specific hypothalamic activation during a spontaneous cluster headache attack. Neurology 62:516–517

97. Matharu MS, Goadsby PJ (2005) Functional brain imaging in hemicrania continua: implications for nosology and pathophysiology. Curr Pain Headache Rep 9:281–288

98. Ashburner J, Friston KJ (2000) Voxel-based morphometry – the methods. Neuroimage 11:805–821

99. Ashburner J, Friston KJ (2001) Why voxel-based morphometry should be used. Neuroimage 14:1238–1243

100. Good CD, Ashburner J, Frackowiak RS (2001) Computational neuroanatomy: new perspectives for neuroradiology. Rev Neurol (Paris) 157:797–806

101. May A (1999) Functional imaging of cluster headache: insights into an idiopathic headache syndrome. In: Olesen J, Goadsby PJ (eds) Frontiers in headache research. Oxford University Press, Oxford, pp 163–170

102. Evans AC, Kamber M, Collins DL, Macdonald D (1994) An MRI-based probabilistic atlas of neuroanatomy. In: Shorvon S, Fish D, Andermann F, Bydder GM, Stefan H (eds) Magnetic resonance scanning and epilepsy. Plenum Press, New York, pp 263–274

103. Lance JW, Goadsby PJ (1998) Mechanism and management of headache, 6th Edn. Butterworth-Heinemann Ltd, Oxford

104. Matharu MS, Good CD, May A, Bahra A, Goadsby PJ (2003) No change in the structure of the brain in migraine: a voxel-based morphometric study. Eur J Neurol 10:53–57

105. Schmidt-Wilecke T, Leinisch E, Straube A et al (2005) Gray matter decrease in patients with chronic tension type headache. Neurology 65:1483–1486

106. May A, Büchel C, Bahra A, Goadsby PJ, Frackowiak RSJ (1999) Intra-cranial vessels in trigeminal transmitted pain: a PET study. Neuroimage 9:453–460