Chapter 7
Imaging of Other Primary Headaches

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The use of structural and functional imaging of the human brain has led to significant advances in our understanding of pain processing and headache. The application of such techniques to primary headache conditions, especially migraine and the trigeminal autonomic cephalalgias, has provided major advances in the understanding of their underlying pathophysiology. This chapter will focus on trigeminal autonomic cephalalgias but will also briefly explore the findings of neuroimaging studies in tension-type and hypnic headache.

7.1 Tension-Type Headache

Tension-type headache (TTH) is a common condition with lifetime prevalence ranging from 30 to 80 %. The condition is characterized by episodes of bilateral, pressing or tight pain which is mild to moderate in intensity and which has no associated features [1]. It was previously thought to be psychogenic, but the current evidence base no longer supports this view [1].

7.2 Hypnic Headache

Hypnic headaches (HH) are frequent recurring headache attacks occurring only during sleep, generally without any cranial autonomic symptoms [1].

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7.3 Trigeminal Autonomic Cephalalgias

Trigeminal autonomic cephalalgias (TACs) are a group of primary headache disorders, which share distinctly similar phenotypes. The 3rd edition (beta version) of the International Classification of Headache Disorders (ICHD-IIIb) currently lists the TACs as cluster headache (CH), paroxysmal hemicrania (PH), short-lasting unilateral neuralgiform headache attacks (comprising both short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing [SUNCT] and short-lasting unilateral neuralgiform headaches with cranial autonomic features [SUNA]) and hemicrania continua (HC) [1]. The TACs are characterized by intense, unilateral trigeminal distribution pain with concomitant cranial autonomic features. The common clinical presentation of these disorders has raised the possibility of a shared pathophysiological mechanism.

7.4 Diagnostic Imaging of Primary Headaches

Diagnosis of all primary headaches is based on careful clinical phenotyping. The European Federation of Neurological Sciences guidelines state that neuroimaging should only be considered for those with atypical headache patterns or focal neurological signs [2]. Likewise, the National Institute for Health and Care Excellence (NICE) guidelines in the United Kingdom state that imaging should be reserved for those with atypical clinical features or other conditions making them high risk for secondary headaches (such as malignancy and immunodeficiency). The NICE guidelines specifically state that imaging should not be conducted purely for reassurance [3].

Recent reviews of the literature on symptomatic TACs have shown a number of secondary causes [4, 5]. The most striking finding to emerge from these reviews is the number of symptomatic TACs associated with pituitary lesions [4, 5]. A large observational study performed in a tertiary referral centre reported that 4 % of patients with pituitary tumours had CH; however, the objective of this study was to describe the phenotypes of the headaches that occur in patients with pituitary tumours and not the prevalence of the different headache types as the patient group was highly selected and therefore not representative of the general pituitary tumour cohort [6]. A causal link between pituitary tumours and trigeminal autonomic cephalalgias cannot be assumed on the basis of these observational findings, and there is no place for routine pituitary imaging in clinical practice until further data from population-based studies is available. Furthermore, there is considerable risk of incidental findings with 1 in 10 of the general population having a microadenoma and 1 in 500 a macroadenoma on routine MRI [5].

Recent evidence has suggested that a significant proportion of patient with SUNCT and SUNA have trigemino-vascular conflict and these patients respond well to trigeminal microvascular decompression [7]. It is therefore recommended that all patients with short-lasting neuralgiform headache attacks undergo dedicated trigeminal nerve imaging.

We suggest a routine MRI brain scan in CH, PH and HC and MRI brain scan with dedicated trigeminal nerve imaging in SUNCT and SUNA.

7.5 Functional Neuroimaging of Experimental Head and Facial Pain

Functional neuroimaging studies have helped to establish the brain structures involved in nociception. Two major studies on experimental facial and head pain, alongside a broad literature on experimentally induced pain, have shown a widespread brain network activated during nociceptive processing [8–11]. Positron emission tomography (PET) studies in experimental head and facial pain have demonstrated significant activations were recorded in the insulae, thalamus, anterior cingulate cortex (ACC), prefrontal cortex, periaqueductal grey and the cerebellum during the acute pain state when compared to the pain-free state [9, 10]. Findings are summarized in Table 7.1.

7.6 Structural Neuroimaging in Tension-Type Headache

A voxel-based morphometry (VBM) study investigated 20 patients with chronic TTH compared to subjects with medication-overuse headache (and migraine) and headache-free controls [12]. A significant decrease in grey matter density within the pain-processing networks was observed only in those with TTH thereby providing evidence that TTH is a different disorder from migraine. Areas involved in TTH included the dorsal rostral and ventral pons, ACC, bilateral insulae, orbitofrontal cortex, bilateral parahippocampal regions and cerebellum (Table 7.1).

7.7 Structural Neuroimaging in Hypnic Headache

VBM of 14 HH patients revealed decreased grey matter in areas known to be involved in cortical pain processing [13]. A reduction in grey matter was also seen in the left posterior hypothalamus, lateralized to the left independent of headache side (Table 7.1).

7.8 Structural and Functional Neuroimaging in Trigeminal Autonomic Cephalalgias

7.8.1 Cluster Headache

Typical features of cluster headache (CH) include a trigeminal distribution of pain, circadian and circannual rhythmicity and ipsilateral cranial autonomic features [1].

Table 7.1 Table showing patterns of activation or involvement in advanced neuroimaging studies of tension-type headache, hypnic headache and trigeminal autonomic cephalalgias and experimental head pain

			Specific structures activated in headache syndromes						Structures of general pain matrix										
Study	Imaging modality	Number imaged	Dorsal pons	Hy	RN	SN	PAG	PMJ	ACC	PCC	Ins	Th	BG	Frontal cortex	Parietal cortex	Temporal cortex	Occipital cortex	Cerebellum	Others
Tension-type headache																			
Schmidt-Wicke et al. (2005) [12]	VBM	20	✓						✓	✓	✓			✓		✓	✓	✓	
Hypnic headache																			
Holle et al. (2011) [13]	VBM	14		✓					✓		✓			✓		✓		✓	
Cluster headache																			
Di Piero et al. (1997) [22]	SPECT	7 ECH							✓			✓		✓	✓	✓			
Hsieh et al. (1996) [23]	PET	7 ECH							✓		✓			✓	✓	✓	✓		
May et al. (1998) [9, 27]	PET	9 CCH		✓					✓		✓	✓	✓	✓					

May et al. (2000) [28]	PET	18 ECH		✓														
Sprenger et al. (2004) [29]	PET	1 ECH		✓					✓			✓	✓	✓				
Sprenger et al. (2007) [25]	PET	11 ECH		✓					✓		✓	✓	✓	✓		✓		✓	
Morelli et al. (2009) [31]	BOLD-fMRI	4 ECH		✓					✓		✓	✓	✓	✓				✓	
May et al. (1999) [33]	VBM	25 ECH		✓															
Absinta et al. (2012) [34]	VBM	15 ECH								✓	✓	✓	✓	✓	✓	✓			
Yang et al. (2013) [26]	VBM	49 ECH							✓		✓			✓		✓	✓		

(continued)

Table 7.1 (continued)

Study	Imaging modality	Number imaged	Specific structures activated in headache syndromes						Structures of general pain matrix										
			Dorsal pons	Hy	RN	SN	PAG	PMJ	ACC	PCC	Ins	Th	BG	Frontal cortex	Parietal cortex	Temporal cortex	Occipital cortex	Cerebellum	Others
Teepker et al. (2011)	DTI	7 ECH										✓		✓		✓	✓	✓	Brainstem, internal capsule
Szabó et al. (2013) [39]	DTI	13 ECH												✓	✓	✓	✓		
Chou et al. (2014) [37]	DTI	17 ECH		✓							✓		✓	✓		✓		✓	
Rocca et al. (2010) [40]	RsfMRI	13 ECH		✓					✓		✓	✓		✓	✓	✓	✓		
Qiu et al. (2012) [42]	RsfMRI	12 ECH		✓					✓	✓	✓			✓	✓	✓	✓		
Yang et al. (2014) [41]	RsfMRI	18 ECH		✓										✓		✓	✓	✓	

Paroxysmal hemicrania																			
Matharu et al. (2005) [51]	PET	7		✓	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓		✓	
Schlake et al. (1990) [44]	SPECT	1												✓	✓				
SUNCT/SUNA																			
May et al. (1999) [33]	BOLD-fMRI	1		✓							✓	✓							
Sprenger et al. (2005) [47]	BOLD-fMRI	1		✓				✓	✓		✓	✓		✓				✓	
Cohen et al. (2006) [45]	BOLD-fMRI	2		✓														✓	
Auer et al. (2009) [49]	BOLD-fMRI	1												✓					Brainstem
Hemicrania continua																			
Matharu et al. (2005) [51]	PET	7	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	

(continued)

Table 7.1 (continued)

Study	Imaging modality	Number imaged	Specific structures activated in headache syndromes						Structures of general pain matrix										
			Dorsal pons	Hy	RN	SN	PAG	PMJ	ACC	PCC	Ins	Th	BG	Frontal cortex	Parietal cortex	Temporal cortex	Occipital cortex	Cerebellum	Others
Experimental head pain																			
May et al. (1998) [9, 27]	PET	7							✓		✓	✓						✓	
Kupers et al. (2004) [10]	PET	10					✓		✓		✓		✓	✓	✓			✓	

ACC anterior cingulate gyrus, *BG* basal ganglia, *BOLD-fMRI* blood-oxygenation-level-dependent functional magnetic resonance imaging, *CCH* chronic cluster headache, *DTI* diffusion tensor imaging, *ECH* episodic cluster headache, *Hy* posterior hypothalamus, *Ins* insula, *PAG* periaqueductal grey, *PCC* posterior cingulate gyrus, *PET* positron emission tomography, *PMJ* pontomedullary junction, *RsfMRI* resting state functional magnetic resonance imaging, *RN* red nucleus, *SN* substantia nigra, *SPECT* single-photon emission computed tomography, *SUNCT* short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, *SUNA* short-lasting unilateral neuralgiform headache attacks with autonomic features, *Th* thalamus, *VBM* voxel-based morphometry

Neuroimaging has made a substantial contribution to the understanding of this condition (Table 7.1).

Recent experimental work into the pathophysiology of CH has led to the understanding that the severe unilateral pain is likely mediated by activation of the first division of the trigeminal nerve, whilst autonomic symptoms are due to the activation of the cranial parasympathetic outflow via the seventh cranial nerve [14]. The circannual and circadian periodicity of CH led to the concept of a central origin of the headache condition and implicated the hypothalamus, in particular, as this is the structure where the body clock is located in the brain [15, 16]. Functional neuroimaging involving blood flow studies, magnetic resonance spectroscopy (MRS) and more recently connectivity studies have all been studied in CH and have led to advances in pathophysiology constructs and clinical treatments.

The current findings of studies into TACs can be summarized by three major abnormalities:

1. Involvement of the pain matrix
2. Posterior hypothalamic dysfunction
3. Involvement of the central opioid system

7.8.1.1 Pain Neuromatrix

Early studies on cerebral blood flow in CH were few in number and used single-photon emission computed tomography (SPECT) techniques. This semiquantitative technique taken together with the methodological differences led to heterogeneous results, with some studies reporting increases, some decreases and some no detectable difference in cortical blood flow in CH [17–21]. A more recent study investigating the cerebral blood flow changes using Xenon-133 SPECT in CH patients outside of a bout and healthy controls [22] demonstrated differences in cerebral blood flow in the contralateral primary sensorimotor and thalamic regions of CH sufferers compared to controls. The presence of alterations in pain processing outside of an active cluster bout suggested a possible involvement of central tonic pain mechanisms in the pathogenesis of cluster headache.

The first PET study on CH was performed examining seven patients (four in and three out of a cluster bout) during nitroglycerine evoked pain [23]. The authors reported a significant increase in regional cerebral blood flow (rCBF) in the right caudal and rostrocaudal ACC, temporopolar region, supplementary motor area, bilateral primary motor and premotor areas, bilateral opercula region, bilateral insula and bilateral inferior frontal cortex. A reduction in rCBF bilaterally in the posterior parietal cortex, occipitotemporal region and prefrontal cortex was observed in the pain state. The authors concluded that this work supported their earlier findings suggesting a preference of the nondominant hemisphere, especially the ACC, in affective processing of chronic ongoing pain [24]. Sprenger and colleagues conducted fluoro-D-glucose PET (FDG-PET) in 11 episodic CH subjects both during and out of a cluster

bout [25]. In a bout compared to out of a bout scans showed increased metabolism in the ACC, posterior cingulate gyrus, insula, thalamus and temporal cortex. Decreased metabolism was observed in the cerebellopontine area. The authors surmised that the structures activated are involved in descending pain control and hypothesized a deficient top-down modulation of the antinociceptive circuits in CH patients.

Using VBM analysis, Yang and co-workers studied CH patients in and out of a bout [26]. They reported that in bout, CH patients had significantly reduced grey matter volume in the middle frontal and in the superior and medial frontal gyri when compared to controls. A significant increase in grey matter volume outside a bout compared to in a bout was reported in the anterior cingulate, insula and fusiform gyrus. The affected regions were all frontal pain modulation areas and may reflect an insufficient pain modulation capacity in CH patients.

7.8.1.2 Hypothalamic Dysfunction

May and colleagues conducted PET imaging in nine chronic CH subjects using $H_2{}^{15}O$ PET during nitroglycerine-induced attacks and were the first to demonstrate ipsilateral hypothalamic grey matter activation during cluster attacks [27]. Increased rCBF was also observed in the areas known to be involved with pain processing such as the contralateral ventroposterior thalamus, the ACC, bilateral insulae, basal ganglia and anterior frontal cortex and extracerebral areas consistent with large intracranial blood vessels. The significant activation of the ipsilateral hypothalamus was not seen when patients were out of a bout [28]. Findings were reproduced during $H_2{}^{15}O$ PET studies of patients during a spontaneous attack [28, 29]. Given that hypothalamic activation had not been observed in migraine or in experimental facial pain, it was concluded that the hypothalamus is involved in the underlying pathogenesis of CH rather than activation being due to a secondary response to first division trigeminal pain [30]. In contrast to migraine, none of these studies reported brainstem activation during an acute attack compared to resting state [28, 30].

Morelli and colleagues were the first to use functional magnetic resonance imaging (fMRI) employing the blood-oxygenation-level-dependent effect (BOLD-fMRI) techniques to study cerebral activation in CH patients during a bout, both in and out of attacks [31]. In the pain state compared to pain-free states, significant activation was reported in the ipsilateral hypothalamus. Trends towards activation were also reported in areas involved in pain processing.

Further evidence for hypothalamic involvement in CH has also emerged from other neuroimaging techniques. A study of magnetic resonance spectroscopy ($^{1H\text{-}MRS}$) on 26 patients (18 ECH, 10 in a bout and eight out of a bout; eight CCH) showed that N-acetyl aspartate levels (a marker of neuronal density) were reduced in the hypothalamus of CH patients compared to healthy controls [32]. The reduction of this neuronal marker was surmised to be consistent with persistent hypothalamic dysfunction in CH patients.

VBM analysis of CH patients compared to healthy subjects has provided some data to suggest that posterior hypothalamic grey matter is increased in volume, both

in patients examined during and outside a bout [33]. This study was highly flawed with poor age and sex matching of subjects and controls as well as errors in the software used to analyse the data. More recent VBM studies have failed to show any grey matter changes in the hypothalamus but did show grey matter volume changes within the pain matrix previously described in a number of other chronic pain syndromes [26, 34].

7.8.1.3 Opioidergic System

Opioid receptor binding in CH patients has been studied during a cluster bout but out of an attack [35]. Decreased opioid receptor binding was observed in the pineal gland. The pineal gland is known to have functional connections to the trigeminal system – mainly ophthalmic division projections from the trigeminal ganglion [36]. The authors suggest that the findings are due to receptor downregulation or an increased release of endogenous opioids. Opioids are known to act on melatonin release, and these alterations of opioidergic function may relate to the therapeutic effect of melatonin in CH. The same study also reported decreased opioid activity in the ipsilateral hypothalamus and ACC, which were inversely related to the duration of disease.

7.8.1.4 Connectivity Studies in CH

A number of recent studies have reported on white matter microstructure abnormalities or functional connectivity changes in CH subjects. Diffusion tensor imaging (DTI) techniques have been applied by Teepker and colleagues, Szabó and colleagues and Chou and colleagues [37–39]. All groups reported significant differences in white matter microstructure in areas of the pain matrix (frontal, parietal and temporal lobes). In addition all described involvement of areas of the traditional pain matrix, Chou et al. in the limbic system, Szabo and colleagues in the occipital lobes and Teepker and colleagues in the occipital lobe and cerebellum [37–39]. Chou and colleagues also used probabilistic tractography to identify highly consistent and direct anatomical connections between the altered areas of diffusivity on DTI and the hypothalamus and thalamus [37].

Resting state functional MRI (RsfMRI) has also shown significant differences in the functional connectivity of white matter networks in CH patients compared to controls. Both Rocca and colleagues and Yang and colleagues reported increased functional connectivity within networks related to the ipsilateral hypothalamus and to areas of the pain matrix [40, 41]. Another RsfMRI study compared CH patients in and out of attacks compared to controls [42]. In an attack, there was significant increase of functional connection to the ipsilateral hypothalamus when compared to out of an attack. Further alterations in connectivity were seen in areas involved with pain processing and the emotional modulation of pain.

7.8.2 Paroxysmal Hemicrania

Paroxysmal hemicrania (PH) is a rare syndrome characterized by severe unilateral paroxysms of pain localized to the ophthalmic division of the trigeminal distribution accompanied by autonomic features. A diagnostic feature of the headache is an absolute response to indometacin [1].

Matharu and colleagues are the only group to have performed PET imaging in PH. $H_2{}^{15}O$ PET scanning during acute attacks and pain-free states revealed that during the headache phase compared to pain-free state, significant activation occurred in the contralateral posterior hypothalamus [43]. Other areas of the general pain matrix also showed activation in the headache state (Table 7.1). Indometacin administration was found to reverse this activation.

The only other functional imaging work in PH is of an HMPAO SPECT scan conducted on a single patient in 1990 by Schlake and colleagues [44]. Bilateral hypoperfusion in the frontoparietal region was noted between attacks with normalization of the perfusion pattern during a headache.

7.8.3 Short-Lasting Unilateral Neuralgiform Headache Attacks (SUNCT and SUNA)

SUNCT is a rare disorder with distinctive clinical similarities to CH and PH thus suggesting a shared pathophysiology [1]. SUNCT and SUNA are characterized by very brief, unilateral, severe, neuralgic attacks involving the ophthalmic distribution of the trigeminal nerve associated with conjunctival injection and lacrimation [45].

As with CH, May and colleagues observed activation of the ipsilateral inferior posterior hypothalamus on fMRI scanning during spontaneous SUNCT attacks when compared to the pain-free state [46]. However, although other groups have also identified activation of the hypothalamus in SUNCT and SUNA attacks using fMRI techniques, both bilateral and also contralateral activations are described [47, 48]. Auer and colleagues used fMRI imaging to study three attacks in a single patient and reported strong activation in the brainstem region, which were suggested to represent activation of the trigeminal autonomic reflex [49]. These studies are summarized in Table 7.1.

7.8.4 Hemicrania Continua

Hemicrania continua is a primary headache condition that has clinical similarities to both migraine and TACs. HC is characterized by a strictly unilateral headache of moderate intensity with superimposed exacerbations of severe intensity accompanied by autonomic features and migrainous symptoms [50]. Similar to PH, it has an absolute response to indometacin [1].

Only one functional imaging study has been conducted in HC, and that is from Matharu and colleagues [51]. PET scans of seven patients in the pain state showed significant activations of the contralateral posterior hypothalamus and ipsilateral dorsal rostral pons (Table 7.1).

7.9 Conclusion

Neuroimaging has made substantial contributions to the understanding of these rare but important primary headache syndromes.

For chronic TTH and HH, the single publications on each subject report a decrease in grey matter in areas involved in pain processing. It is postulated that these findings may be a sign of neural plasticity in response to prolonged nociceptive input and generation of central sensitization. However, little conclusion can be drawn on the basis of a single publication, so more studies are needed into these disorders.

The hypothesis of a common pathophysiological background for all TACs has been strengthened by the use of functional neuroimaging. Hypothalamic involvement has been shown in CH, SUNCT, PH and HC (Table 7.1). The pathophysiological importance of the hypothalamus would appear to be robust on the basis of the neuroimaging studies reviewed here. However, it is important to consider any contradictory evidence before concluding a causal link between hypothalamic dysfunction and TACs. Many positive studies have focused on the hypothalamus, and other data has been considered insignificant. Hypothalamic activation and structural changes have now been reported in other primary headache conditions such as migraine and HH [10, 13, 52]. In fact, hypothalamic changes have been observed in a wide range of pain conditions such as angina and irritable bowel syndrome but also non-pain-related conditions such as narcolepsy and autism [52–55]. Although the majority of neuroimaging studies on non-CH pain do not report hypothalamic dysfunction, most of these would not be using the hypothalamic area as a target region thus making them less likely to detect any subtle changes below the set threshold for significance.

The limited spatial resolution of VBM, PET and fMRI techniques has led some groups to suggest that the observed areas of activation are not in the hypothalamus but actually within the midbrain tegmentum [56]. This observation again challenges the conclusions made from neuroimaging studies that the hypothalamus is the key region of importance in TACs.

Consistent findings of involvement of various areas belonging to the pain matrix (e.g. prefrontal cortex, ACC, thalamus, insula and cerebellum) are seen across imaging techniques (Table 7.1). These areas are not specific to TACs but are seen across a very broad range of acute and chronic pain conditions including migraine [8] and TTH [12] and are believed to be involved in descending pain modulation. Therefore, in TACs, activation of these areas is likely due to a response to acute pain and not indicating areas of attack generation. This view is supported by the observations that

abnormal activation patterns return to normal in CCH when treated with neuromodulation or when indometacin is used in PH or HC [43, 51, 57].

Opioidergic system involvement in TACs is suggested by the observations of decreased activity in the ACC in ECH compared to controls [25]. This area is thought to play a major role in the central descending opioidergic pain control mechanisms, and dysfunction in this area may therefore predispose to CH and or its recurrence. Further evidence of the importance of this system is the decreased receptor binding seen in the rostral ACC and hypothalamus related to CH disease duration [35]. The observation that those who respond to ONS for CCH have increased metabolism in their ACC compared to nonresponders also supports the concept and suggests that restoration of a normal opioidergic system is important in treatment mechanisms [57].

To conclude, the rapid advancements in functional and structural imaging techniques will continue to advance our understanding of the complex nature of brain dysfunction in primary headaches. On balanced reflection, neuroimaging studies of primary headaches, especially the TACs, appear to suggest a complex neural pain network dysfunction. Although the hypothalamus is of definite importance in the pathophysiology of TACs, neuroimaging studies cannot be used to indicate that it acts on a region of pain generation. Challenges for the future include defining the importance of the hypothalamus and its associated pain pathways in TACs and the possible mechanisms of treatment effects.

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