EXPERT REVIEWS

Cluster headache and the hypothalamus: causal relationship or epiphenomenon?

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Typical clinical features of cluster headache (CH) include circadian/circannual rhythmicity and ipsilateral cranial autonomic features. This presentation has led to the assumption that the hypothalamus plays a pivotal role in this primary headache disorder. Several studies using neuroimaging techniques or measuring hormone levels supported the hypothesis of a hypothalamic involvement in the underlying pathophysiology of CH. Animal studies added further evidence to this hypothesis. Based on previous data, even invasive treatment methods, such as hypothalamic deep brain stimulation, are used for therapy. However, the principal question of whether these alterations are pathognomonic for CH or whether they might be detected in trigeminal pain disorders in general, in terms of an epiphenomenon, is still unsolved. This article summarizes studies on hypothalamic involvement in CH pathophysiology, demonstrates the involvement of the hypothalamus in other diseases and tries to illuminate the role of the hypothalamus based on this synopsis.

Keywords: deep brain stimulation • functional imaging • headache pain • hypothalamus • pain generator • tegmentum • voxel-based morphometry

Cluster headache (CH) is a rare primary headache disorder that is characterized by strictly unilateral headache attacks accompanied by ipsilateral trigeminal autonomic symptoms, such as lacrimation, rhinorrhea, conjunctival injection, tearing, facial sweating or ptosis [1]. In regard to its clinical presentation, CH is classified as a trigeminal autonomic cephalalgia (TAC). Up to eight headache attacks occur per day, often showing a strict time relationship, with a nocturnal predominance [1]. Most patients have an episodic course of disease with a circannual periodicity of symptoms that occur mainly in autumn and spring. These clinical features suggested a pivotal role of the hypothalamus in CH. It was even hypothesized that the hypothalamus could be the key 'pain generator' in this primary headache disorder [2].

The current opinion about the role of the hypothalamus in CH is based primarily on a strong *a priori* hypothesis mainly in regard to the clinical picture. This article analyzes the actual knowledge regarding the hypothalamus in the pathophysiology of CH and discusses whether these observations are specific for CH in terms of a '*primum movens*' or whether they might just be epiphenomena in pain/headache diseases in general.

As CH shares many clinical and pathophysiological similarities with other TACs in general (which are paroxymal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjuctival injection and tearing [SUNCT]), a particular comparison with these headache disorders will not be carried out in this article.

The hypothalamus

Although the hypothalamus is only a small brain structure and contributes to only 0.5% of total brain volume [3], it plays a pivotal role in the human organism; being involved in the regulation of different biological systems that are essential for human survival (i.e., hormones, the autonomic nervous system, temperature, emotional behavior, arousal, the cardiovascular system, appetite and body weight and sleep cycles) [4].

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Pain processing

The hypothalamus is currently not considered to be part of the classical central pain processing network. However, there is emerging evidence that it might also be involved in central pain processing, with predominantly antinociceptive effects contributing to descending pain modulation. The hypothalamus displays various ascending and descending connections to the nucleus tractus solitarius, rostroventromedial medulla, periaqueductal gray, raphe nuclei and corticolimbic structures, which have an important function in the central pain matrix [5]. In addition to this anatomical evidence, there are also functional data pointing towards the hypothalamus taking part in central pain processing. Stimulation of the hypothalamic medial preoptic nucleus (MPO) has antinociceptive effects on spinal cord neurons; after stimulation of the paraventricular nucleus, which is also localized within the hypothalamus, similar antinociceptive activations on hypothalamic subnuclei were detected [6]. Two hypothalamic neuropetides – orexine-A and orexine-B – also seem to play an important role in the central pain processing of the trigeminal systems as they display pronociceptive and antinociceptive effects [7].

Autonomic nervous system

The hypothalamus coordinates the interaction between autonomic function (facial nerve and parasympathetic outflow) and pain processing. The trigeminal autonomic reflex is thought be be involved in this connection, as TACs (including CH) show trigeminal autonomic symptoms, such as lacrimation and rhinorrhea [8].

Circadian rhythms

The hypothalamus is often referred to as a 'biological clock' as it is involved in several circadian patterns, such as the sleep–wake cycle, temperature and hormonal regulation [9]. The main anatomic structure for chronobiological regulation is the hypothalamic suprachiasmatic nucleus (SCN) [10]. Via direct neuronal connections, the SCN influences various parts of the brain and induces, in turn, endocrine and autonomic functions. For example, animal experiments have demonstrated that the application of light pulses can induce a rapid decrease in plasma corticosterone, confirming the strong functional connection of the SCN and endocrinological secretion pattern [11].

Clinical picture

The clinical presentation of CH has always been the foundation to allegedly prove the pathognomonic involvement of the hypothalamus in this disorder (Table 1). However, other diseases share common clinical features that also suggest hypothalamic involvement. Many migraneurs report premonitory symptoms that precede the virtual headache attack by up to 2 days and herald the pain ahead [12]. The underlying pathophysiology of these premonitory symptoms, which include irritability, craving for food, hunger or tiredness, are interpreted as clinical signs of hypothalamic dysregulation. Interestingly, most migraine attacks occur in the early morning, although this circadian rhythmicity is not as obvious as in CH patients [13]. In this context, a hypothalamic involvement has been suggested. Trigeminal autonomic features are a key clinical feature in CH, which also supports the hypothesis of a major role for the hypothalamus in the pathophysiology of CH. However, similar headaches accompanying cranial autonomic symptoms can also be detected in many migraneurs during the pain headache, questioning the uniqueness of this clinical feature [14]. Other primary headache disorders also share several important features of CH. Hemicrania continua (HC), a rare primary headache disorder, is characterized by strictly unilateral headache attacks accompanied by trigeminal autonomic symptoms. Hypnic headache (HH) patients share the characteristic time dependency and sleep association with CH. Some HH patients even report trigeminal autonomic symptoms [15,16].

Neuroendocrinal abnormalities

Neuroendocrinal abnormalities in CH

Many neuroendocrinological observations have suggested an involvement of the hypothalamus in CH in terms of a deranged hypothalamic function. During a cluster episode, reduced plasma testosterone concentration was measured in male CH patients [17]. Imbalances of other hormones, such as melatonin, cortisol, luteinizing hormone, follicle-stimulating hormone, prolactin, growth hormone and thyroid-stimulating hormone, the secretion of which is mainly controlled by the hypothalamus, have been detected [18]. These hormonal disturbances support the idea of a hypothalamic–pituitary–adrenal (HPA) axis malfunction in this primary headache disorder. Interestingly, changes of the cerebrospinal fluid (CSF) orexine level were not observed during active CH episodes, which are considered to play a pivotal role in the pain processing of CH patients. Cavoli *et al.* measured orexine-A in ten patients with CH by radioimmunoassay. CSF orexine levels were in normal range and no association between clinical presentation and orexine-A level could be observed [19].

Several possibilities were discussed regarding the observed alterations. First, these changes may be the result of the strong CH pain itself. Second, they may reflect a stress reaction (pain associated or independent) or, third, they may be induced by pain accompanying sleep disturbances. All of these possibilities would suggest that these alterations are rather unspecific phenomenons. Interestingly, some of the observed hypothalamic changes can also be detected in remission periods (i.e., CH outside bout), which would imply that these changes can be considered to be specific for CH itself, continuing independently of the pain, and therefore might be a kind of trait marker for the disease itself.

Neuroendocrinal abnormalities in other disorders

Even though endocrinal evidence suggests a strong involvement of the hypothalamus in CH, similar changes were also observed in very different disorders. Chronic migraneurs show an abnormal pattern of hypothalamic hormonal secretion, such as a decreased nocturnal prolactin peak, increased cortisol concentrations and delayed nocturnal melatonin peak. The 338 blood samples (13 per patient) from 17 patients with chronic migraine and nine age- and gender-matched controls were taken [20]. These observations question the exclusivity of the hypothalamic involvement in CH.

Table 1. Clinical features of cluster headache suggesting a hypothalamic involvement.

Clinical feature	Explanation
Circadian periodicity	Headache attacks mainly occur at fixed times during the day and night. The times of day vary interindividually, but are stable intraindividually
Sleep association	In most patients, many of the headache attacks occur during sleep and wake the patients
Circannual periodicity	Most of the patients report that most of the cluster headache episodes start during spring or autumn
Ipsilateral cranial autonomic features	Cluster headache attacks are characterized by ipsilateral trigeminal autonomic symptoms, such as lacrimation, rhinorrhea, nasal congestion, conjunctival injection, ptosis and facial sweating

A hyporeactive HPA axis similar to the changes observed in CH can also be detected in patients suffering from fibromyalgia. Changes included disturbance of the cortisol secretions (flattening of the circadian level and increased daytime levels in plasma and saliva) and increased nocturnal melatonin levels [21]. HPA axis alterations were also observed in chronic widespread pain [21], chronic fatigue syndrome [22] and irritable bowel syndrome [23] (for a meta-analysis of HPA axis activity in functional somatic disorders, see [24]).

Genetic studies in CH

Children rarely suffer from CH. In these rare cases, a genetic background is presumable as 2–7% have a positive family medical history for this disorder [25]. First-degree relatives develop CH 5–18-times more often and second-degree relatives one- to three-times more often than the general population [26]. Genetic alterations within the orexinergic system of the hypothalamus were suggested to be responsible for this observation, although measurements of CSF orexine levels have failed to support this hypothesis [19]. Despite this observation, one genetic study identified a G1246A polymorphism of the OX_2R gene (*HCRTR2*) as a risk factor for developing CH [27]. These data were not replicated in larger CH patient populations [28]. In migraineurs, this gene polymorphism was not observed [29]. Based on these conflicting data, the role of orexines in the pathophysiology of CH cannot be determined.

Cerebral imaging: voxel-based morphometry, MRI, PET & SPECT

An increasing number of imaging studies were performed over the last years in CH. Although initial data were quite promising in detecting specific morphological changes in CH and distinct activation patterns, previous data were often not able to replicate these findings or have questioned the specificity of these observations for CH.

Structural imaging

Structural imaging of the hypothalamus in CH

One of the pioneer studies showing hypothalamic involvement in CH was performed by May *et al.* in the late 1990s. He used the method of voxel-based morphometry (VBM), which is an automated, unbiased, whole brain technique that allows the comparison of structural brain images, especially with regard to the volume or density of gray and white matter. May *et al.* investigated 25 CH patients, as well as 29 healthy controls, and detected isolated increased gray matter in the inferior posterior hypothalamus [30]. Owing to the low prevalence of this headache disorder, it took several years to repeat a CH VBM study in a larger patient population. To date, three studies have been performed or are still ongoing, which did not confirm the initial finding. Matharu *et al.* investigated 66 patients suffering from CH, and 96 age- and gender-matched healthy subjects. This study did not detect any hypothalamic changes at all [31]. Similar findings were reported by two later studies [32,33]. Our own working group investigated 91 CH patients and failed to detect any hypothalamic changes. However, we were able to demonstrate several changes within the central pain processing network [32]. The observed differences of the study results when comparing the initial imaging data with the newer VBM studies are presumably based on two main factors. First, the initial study was performed with an older MRI scanner. In addition, it is well known, that VBM studies are often hardly comparable when performed with different MRI scanners. Second, the analysis algorithms for VBM have since been further developed and influenced the study outcome (Statistical Parametric Mapping initial version vs advanced version 8).

Structural imaging of the hypothalamus in other pain & headache disorders

An alteration of hypothalamic gray matter in a similar area to that described in CH was detected in HH [34]. HH is a different rare primary headache entity that mainly affects elderly patients. Patients report strictly nocturnal headache attacks, mostly at the same time during the night. That is why this headache disorder is also called alarm clock headache [1]. Interestingly, hypothalamic structural changes are even observed in irritable bowel syndrome [35], a pain disease that does not share the sleep relationship of CH and HH.

Structural imaging of the hypothalamus in other diseases

In addition to pain and headache disorders, structural hypothalamic alterations can also be observed in other diseases with or without prominent pain symptoms. Boghi *et al.* investigated 21 anorexic patients and 27 healthy control subjects using VBM. In the patient group they observed focal atrophy in the hypothalamus, as well as other changes. These changes correlated with the BMI. The authors suggested that these hypothalamic changes point to hormonal dysfunction and central dysregulation of homeostasis [36]. Hypothalamic gray matter loss was also observed in 52 children and adolescents with autism. The authors contemplated that

this alteration underlies the theory of dysfunction of the hormonal system in autism, mainly an alteration of oxytocin and arginine vasopressin [37]. Reduced hypothalamic gray matter was also found in boys suffering from fragile X syndrome [38].

Several studies have shown changes to the hypothalamus in patients with narcolepsy and cataplexy [39,40]. Narcolepsy is a sleep disorder, characterized by reduced hypocretin concentration in the CSF. As hypocretin neurons are exclusively localized in the hypothalamus, hypothalamic dysfunction was suggested. Another VBM study demonstrated gray matter atrophy in the area of the hypothalamus in patients with Huntington's disease [41].

Functional imaging

Functional imaging in CH

Functional imaging allows characterization of ongoing pain in the suffering brain *in vivo*. Thus, this technique offers the possibility to investigate acute pain processing and to figure out which anatomic structures might be involved. Nitroglycerine-triggered headache attacks in nine chronic CH patients resulted in a strong activation of the ipsilateral posterior hypothalamus detected by $H_2{}^{15}O$ PET [2]. This activation pattern was also observed in spontaneous CH attacks in one patient who had underwent deep brain stimulation (DBS) [42]. In four patients with episodic CH, functional MRI (fMRI) confirmed the activation pattern within the ipsilateral posterior hypothalamus [43].

However, some authors have suggested that the detected activation pattern in the functional imaging only shows activation of an area close to the hypothalamus, most likely the midbrain tegmentum [44].

Sprenger *et al.* investigated cerebral glucose metabolism using (18F)-2-fluoro-2-deoxy-D-glucose (FDG)-PET in CH. A total of 11 patients were measured inside and outside bout, as well as 11 healthy controls. The authors described several changes within brain metabolism, such as hypometabolism of the anterior cingulate cortex, prefrontal and orbitofrontal cortex, in the patient group compared with the healthy controls. Alteration of the hypothalamic area was not reported in this study [45]. By contrast, Magis *et al.* detected persistent hypermetabolism of the hypothalamus in patients treated with occipital nerve stimulation also using FDG-PET [46].

Functional imaging in other pain & headache conditions showing hypothalamic involvement

Hypothalamic involvement sometimes appears to be almost a pathognomic feature in CH or TACs in general, but carefully cross-checking the literature does not confirm this first impression.

In several other pain disorders and even in experimental pain conditions, distinct hypothalamic activation during the acute pain state has been demonstrated, suggesting that hypothalamic involvement might be a more general feature of pain itself.

In seven migraneurs without aura, cerebral activations were recorded (by $H_2{}^{15}O$ PET) during spontaneous migraine attacks without aura [47]. The observed activation pattern included several brainstem areas (bilateral ventral midbrain, dorsal contralateral midbrain in regards to the headache side and the dorsomedial pons), cerebellum, frontal cortex and cingulate cortex, which had been shown in prior studies. In addition, activation of the bilateral hypothalamus was detected during the acute migraine attack. This activation pattern had never been described before. By contrast, further functional imaging studies studying migraneurs did not detect any hypothalamic activation [48–50].

In HC, an activation of the contralateral posterior hypothalamus was observed during acute pain exacerbation using PET [51].

A total of 12 patients with angina pectoris were treated with intravenous dobutamine to elicit an acute sensation. Owing to this pain experience, the blood flow in the pain matrix and the hypothalamus increased [52].

One patient who was implanted with a stimulation electrode within the left ventroposterior medial thalamic nucleus because of a chronic facial pain was also investigated using functional imaging methods. The patient was measured when the stimulation electrode was working (without pain) and without stimulation (with ongoing pain). During the experience of pain, a significant increase of blood flow was observed in common areas of the central pain matrix and also in the hypothalamus [53].

Hypothalamic activation is not only shown during pain disorders, but can also be observed during experimental pain. A total of 12 healthy volunteers were stimulated with pain and warm sensations, which were applied to the left leg. Pain-related skin conductance reactivity was measured and the association with fMRI activation pattern determined. Pain sensation activated several areas of the central pain processing systems, such as the anterior cingulate cortex, amygdala and thalamus, and also the contralateral hypothalamus [54]. In another PET study, ethanol was injected intracutaneously in the right upper arm of four healthy volunteers to elicit acute traumatic nociceptive pain. Pain lead to a strong activation of the contralateral (left) hypothalamus [55]. Another study used the cold pressor test, which applies prolonged tonic, painful, cold stimulation to investigate pain-associated activation patterns in healthy subjects. In addition, cold nonpainful stimulation was applied. Painful and nonpainful sensations lead to an activity increase in the brainstem and hypothalamic areas. Simultanously, the galvanic skin response decreased. In line with the expectations, the painful conditions induced a significantly stronger activation compared with the cold sensation [56].

Resting state fMRI

The analysis of low-frequency (<0.1 Hz) fluctuations seen on fMRI scans at rest allows the detection of functionally connected brain regions, so-called resting state networks (RSNs). Synchronous variations of the blood oxygenation level dependent (BOLD) signal can be measured as percentage signal change compared with the BOLD mean signal intensity over time [57–59]. The fluctuations observed by resting state analysis are thought to reflect the intrinsic property of the brain to handle the past and prepare for the future [60]. RS alterations were observed in chronic pain [61]. Rocca *et al.* studied RS in 13 patients with episodic CH compared with healthy controls. Patients were studied in a pain-free state. Apart from the other changes the authors observed altered functional connectivity within the network using a hypothalamic seed region of interest in patients with CH compared with healthy controls [62].

Magnetic resonance spectroscopy

An additional exciting imaging technique to study brain biochemistry *in vivo* is magnetic resonance spectroscopy. In episodic CH patients, hypothalamic *N*-acetylaspartate:creatine and choline:creatine levels are significantly reduced compared with healthy controls. Interestingly, changes were even detectable when the patients were outside bout, which means that they were no longer experiencing actual CH attacks anymore [63,64]. This observation led to the assumption that these alterations cannot simply reflect an epiphenomenon of pain itself [64].

Deep brain stimulation: evidence of hypothalamic involvement in CH?

The clinical picture of CH and the results from imaging studies provided the rationale for hypothalamic DBS in the treatment of CH. It was thought that this technique might offer a possibility to 'turn off the CH generator' as high-frequency hypothalamic stimulation would inhibit hypothalamic hyperactivity [65]. The stimulation area was mainly chosen by adoption of the results from the initial VBM study [30]. To assess to what extent DBS stimulation is able to abort acute CH attacks, Leone *et al.* investigated 136 CH attacks in 16 chronic CH patients [66]. Only 23% of patients reported a reduction of pain intensity greater than 50%, and only 16% of headache attacks were completely terminated. These data indicated that DBS is not sufficient in the treatment of active CH attacks [66]. Further studies demonstrated that only continuous stimulation over several weeks markedly reduced or terminated CH attacks (for a review, see [67,68]). A total of 58 patients with chronic drug-resistant CH and posterior hypothalamic DBS have been documented in the literature so far. Leone *et al.* investigated 16 drug-resistant chronic CH patients who received hypothalamic implants over a mean period of 4 years. After the first 2 years 83.3% of patients had experienced pain termination or at least major pain reduction. After 4 years, 62% of patients were still pain free [69]. These results were confirmed by several other studies.

Interestingly, there were no changes in regard to long-term stimulation in electrolyte balance, sleep–wake cycle or hormone levels of cortisol, prolactin, thyroid hormone or thyroid-stimulating hormone, which were previously thought to be involved in the occurrence of CH attacks [65,69–76].

Brittain *et al.* performed an interesting study on local field potentials (LFP) that were recorded during a CH attack within the hypothalamus while the patient was undergoing DBS for chronic CH [77]. The authors observed pathological rhythms in LFPs, with an approximately 20-Hz peak within the anatomic area that has been shown to be most sufficient in treatment of CH attacks. It has been reported previously that implantation of DBS stimulating electrodes sometimes can induce CH attacks within itself, which additionally supports the important role of the hypothalamus in the context of triggering CH attacks [77,78]. Brittain *et al.* suggested that DBS high-frequency stimulation of the hypothalamic area disrupts the pathological LFPs and, in turn, the trigeminoautonomic reflex [77], which might be the pathophysiological correlate of DBS efficacy in CH.

Some authors raised the question of the precise anatomical localization of the DBS. Sanchez del Rio and Linera questioned whether the displayed diencephalic/midbrain activity pattern corresponds to the midbrain tegmentum rather than to the genuine hypothalamus [44,79]. Although the anatomical boundaries of the hypothalamus are quite clear (anterior: lamina terminalis; posterior: posterior margin of the maxillary bodies; superior: hypothalamic sulcus; medial: third ventricle; lateral: subthalamus and internal capsule; and inferior: optic chiasm, median eminence, tuber cinereum, mammillary bodies and posterior pituitary), the functional boundaries are more vaguely determined [80]. Matharu *et al.* re-examined the statistical parametric maps and coordinates of the activation pattern of PET studies in CH [79]. The observed activation in the diencephalon and the mesencephalon in CH is centered over the midbrain tegmentum and is close to the hypothalamus, but located more anteriorially [2]. By contrast, functional imaging studies in CH using BOLD-fMRI detected activation of the posterior and middle hypothalamus rather than the mesencephalon. The authors suggest that these differences are most likely based on methodological issues, mainly the problem of insufficient spatial resolution (fMRI: 4–5 mm; PET: 5–10 mm). They conclude that these data can only be interpreted in the context of other knowledge, but might be, therefore, also influenced by *a priori* hypotheses. Moreover, stimulation of the trigeminal pain processing network by greater occipital nerve (GON) stimulation in CH patients presented similar results with regards to pain reduction efficacy, suggesting a rather unspecific role of DBS stimulation in CH.

Positive DBS results were also observed in other pain disorders, questioning the pathophysiological concept of specific hypothalamic alteration in CH, and raising some serious concerns regarding their validity and specificity. Interestingly, hypothalamic DBS was also effective in the treatment of symptomatic trigeminal neuralgia in five multiple sclerosis patients [81]. These patients had to be therapy refractory prior to electrode implantation. Beneficial effects in regard to pain reduction were observed in three of the patients, even within the first 24 h following implantation. Symptomatic trigeminal neuralgia seems to be, according to the opinion of the study authors, a possible area of application for DBS. As long as controlled studies are missing in this regard the results of such studies should be interpreted with caution and careless utilization should be avoided. However, one can conclude, based on the reported study results, that DBS of the posterior hypothalamus is not exclusively effective in CH and also shows beneficial effects in other pain conditions.

By contrast, there are also chronic pain conditions where hypothalamic DBS seems to not be effective. Franzini *et al.* reported on four patients with secondary neuropathic trigeminal pain (pain after resection of a posterior mandibular carcinoma; unspecified facial pain; pain after radiotherapy of a nasopharyngeal carcinoma; and no description) who did not experienced any relevant pain reduction after electrode implantation [81]. However, the reported patient population was inhomogenous with not comparable clinical features, which makes interpretation of the study results difficult.

Hypothalamus: *primum movens* in CH or only part of the central pain processing network?

Looking at the clinical features of CH with circadian/circannual rhythmicity and ipsilateral cranial autonomic symptoms in combination with the results from the many imaging studies, the pathophysiological importance of the hypothalamus in CH seemed to be unquestionable [30,42,43]; however, newer data dispute the hypothalamic impact in this disorder. The exact anatomic localizations of the observed activations or structural alterations in CH has been discussed quite controversially in the past [44,79] in regard to the limitations of the spatial resolution of the imaging methods. Based on these methodological limitations, it was suggested that the observed activations might be localized in the midbrain tegmentum, rather than in the hypothalamus itself. Taking the limitation of spatial resolution into consideration, PET and MRI do not seem to be the proper methods to anatomically distinguish between these two regions. This might challenge the validity of many of the neuroimaging results that have been presented in regard to anatomic precision.

Deep brain stimulation has been shown to be an effective treatment method in CH. It was suggested that the high-frequency stimulation induces a disruption of pathological LFPs within the hypothalamic area [77], pointing towards a pivotal role of the hypothalamus in the pathophysiology of CH. A causal relationship in provoking CH attacks can be suggested based on the observation that the implantation of stimulating electrodes can sometimes induce CH attacks itself [77,78].

However, other contrary findings should also be taken into account before prematurely adopting the hypothalamic hypothesis. One major criticism about most of the interpretations from previous studies is that the focus was directed almost exclusively at results that support the importance of the hypothalamus in CH, while other data were often neglected or rendered unimportant. It might be useful to take a step back and have a look at the whole picture, as this strong hypothesis-driven research might have led us in a one-sided direction.

Hypothalamic activation and structural changes can also be detected in other primary headache disorders, such as migraine [47], HC [51], chronic facial pain [53] and HH [34], and is not an exclusive feature in CH. Interestingly, hypothalamic changes can even be observed in totally different pain conditions, such as angina pectoris [52], irritable bowel syndrome [35] or even conditions that do not involve pain at all, such as anorexia nervosa [36], autism [37], fragile X syndrome [38], narcolepsy [39,40] and Huntington's disease [41]. However, most of the neuroimaging studies that investigated pain disorders other than CH did not observe any hypothalamic alterations. In contrast to other studies, most of the CH studies take the involvement of the hypothalamus *a priori* as a basis for their analysis, which allows reduction of the significance level. By contrast, most of the other studies that investigated pain disorders, did not predefine the hypothalamus as target anatomic region, which impedes the detection of more subtle activation or structural change below the threshold of statistical significance.

Some data suggest that the observed hypothalamic involvement in CH is an epiphenomenon rather than the 'headache generator' in CH. Neuroendocrine changes [18] can be detected not only in CH, but also in fibromyalgia [21], chronic fatigue syndrome [22], irritable bowel syndrome [23] and migraine [20]. DBS might also be effective in other pain disorders.

Another more general problem is that many observed hypothalamic changes are not reproducible in other CH patient cohorts, leading to conflicting results (e.g., VBM [30–33], FDG-PET [45,46] and genetic mutations [27]).

In summary, the precise nature of hypothalamic involvement in CH remains unclear based on our current knowledge. It seems to be obvious that the hypothalamus plays some role in the pathophysiology of this disease. Whether its involvement can just be considered as epiphenomen or whether the hypothalamus generates the CH attacks itself in terms of a true 'headache generator' remains enigmatic. Presumably, an additional temporal dynamic (e.g., during a CH attack, inside bout and outside bout) has to be taken into account when evaluating hypothalamic involvement as its role might change during the course of disease.

Expert commentary

The clinical picture of CH with its circadian/circannual rhythmicity and ipsilateral cranial autonomic features led to the hypothesis of hypothalamic changes as pathopyhsiological correlates in CH. Although an increasing number of studies are conducted in CH, the distinct role of the hypothalamus in this disease is still enigmatic. It seems to be unquestionable that CH attacks are associated with increased neuronal hypothalamic activation, shown by functional imaging studies, as well as electrophysiological conduction studies, although the precise anatomic localization has been doubted. The nature of the hypothalamic influence, whether it is only an epiphenomenon as one part of the cerebral pain network or whether it is some kind of 'CH headache generator', has been widely discussed. Based on the current data, which are often conflicting and not reproducible, no final conclusion can be made in this regard. In addition, it is likely that the hypothalamic role is more diverse and depends on the time of investigation (e.g., inside bout, outside bout, during attacks) and might even change within the course of the disease.

However, it seems to be an important lesson to learn from CH that despite clear pathophysiological concepts, reality may sometimes look different. Strong *a priori* hypotheses might lead to overinterpretation and bias of the study result in the context of this hypothesis. From our point of view it seems mandatory to question even strong plausible hypotheses more often, because they might not explain the whole truth and may point future science in a one-sided direction.

Five-year view

In the future, presumably a broader pathophysiological concept of CH will be established. As well as the hypothalamus, other parts within the cerebral pain matrix will be demonstrated to be involved. It is possible that the hypothalamus might only be considered as part of the general pain matrix. Furthermore, time-dependent pathophysiological changes in CH, such as endocrinological and imaging alterations, will be detected in this headache disorder.

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Key issues

- Circadian and circannual rhythmicity, as well as trigeminal autonomic features, suggest a hypothalamic involvement in cluster headache.
- Functional imaging has shown a strong activation pattern within the posterior hypothalamus during acute cluster headache attacks.
- Structual imaging data have provided conflicting results concerning the affect of the hypothalamus.
- Some data suggest that hypothalamic involvement might be an epiphenomenon, but not the *primum movens*, in cluster headache, as similar hypothalamic changes and alteration can also be observed in other pain and headache diseases.
- The ultimate role of the hypothalamus in the pathophysiology of cluster headache remains enigmatic.
- Potentially, the nature of the hypothalamic influence changes during the course of disease and depends on the time point of investigation.

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