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REVIEW ARTICLE

# Cluster headache pathophysiology: What we have learned from advanced neuroimaging

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## Abstract

**Background:** Although remarkable progress has been achieved in understanding cluster headache (CH) pathophysiology, there are still several gaps about the mechanisms through which independent subcortical and cortical brain structures interact with each other. These gaps could be partially elucidated by structural and functional advanced neuroimaging investigations.

**Objective:** Although we are aware that substantial achievements have come from preclinical, neurophysiological, and biochemical experiments, the present narrative review aims to summarize the most significant findings from structural, microstructural, and functional neuroimaging investigations, as well as the consequent progresses in understanding CH pathophysiological mechanisms, to achieve a comprehensive and unifying model.

**Results:** Advanced neuroimaging techniques have contributed to overcoming the peripheral hypothesis that CH is of cavernous sinus pathology, in transitioning from the pure vascular hypothesis to a more comprehensive trigeminovascular model, and, above all, in clarifying the role of the hypothalamus and its connections in the genesis of CH.

**Conclusion:** Altogether, neuroimaging findings strongly suggest that, beyond the theoretical model of the "pain matrix," the model of the "neurolimbic pain network" that is accepted in migraine research could also be extended to CH. Indeed, although the hypothalamus' role is undeniable, the genesis of CH attacks is complex and seems to not be just the result of a single "generator." Cortical-hypothalamic-brainstem functional interconnections that can switch between out-of-bout and in-bout periods, igniting the trigeminovascular system (probably by means of top-down mechanisms) and the consensual trigeminal autonomic reflexes, may represent the "neuronal background" of CH.

KEYWORDS
advanced neuroimaging, cluster headache, functional connectivity, gray matter, hypothalamus, structural

**Abbreviations:** CBF, cerebral blood flow; CGRP, calcitonin gene-related peptide; CH, cluster headache; Cho, choline; Cr, creatine; DBS, deep brain stimulation; DLF, dorsal longitudinal fasciculus; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; GM, gray matter; HSA, human serum albumin; KOS, kinetic oscillation stimulation; MTF, mamillo-tegmental fasciculus; NAA, N-acetylaspartate; PET, positron emission tomography; ROI, region of interest; rs-fMRI, resting state-fMRI; RSN, resting-state networks; SP, substance P; SPECT, single photon emission computed tomography; SPG, sphenopalatine ganglion; SSN, superior salivatory nucleus; VBM, voxel-based morphometry; VIP, vasoactive intestinal peptide; WM, white matter.

## INTRODUCTION

Cluster headache (CH) is a primary headache disorder representing the most prominent and prevalent subtype of trigeminal autonomic cephalalgias, with a lifetime incidence ranging from 56 to 381 per 100,000 and affecting men about four times more than women.[1] CH is characterized by circadian and circannual episodes of excruciating and strictly unilateral pain localized in the orbital/periorbital or temporal regions; the episodes are concomitant with ipsilateral cranial autonomic symptoms (e.g., conjunctival injection, tearing, nasal congestion, rhinorrhea, eyelid edema, miosis, and ptosis) and psychological-behavioral manifestations (e.g., sense of restlessness or agitation).[2]

CH attacks are extremely disabling[3]; they can last between 15 and 180 min and can occur with a frequency from one every other day up to eight times daily (with such a severe pain that it can be described as worse than childbirth[4]). According to the International Classification of Headache Disorders, 3rd ed (ICHD-3) criteria,[5] CH is subclassified as either episodic or chronic. Episodic CH requires at least two cluster periods, each lasting from 7 days to 1 year (the so-called cluster bouts), that are separated by remission periods (the so-called out-of-bout periods), which last longer than 3 months and are missing in chronic CH.[5]

Although we are aware that important and conspicuous achievement in the comprehension of CH's underlying pathophysiological mechanisms came from preclinical, neurophysiological, and biochemical experiments, the present work aimed to achieve a comprehensive and unifying model by summarizing (1) the available findings from structural, microstructural, and functional neuroimaging investigations and (2) the consequent progress in the knowledge of episodic CH's subtending pathophysiological mechanisms.

## METHODS

Two of the authors (M.S. and I.O.) performed a search on the PubMed.com website to identify all the original articles by entering the keywords "cluster headache" combined with "neuroimaging" and/or "MRI," "SPECT," and/or "PET." The literature search was finalized on Pubmed.com May 5, 2021. The search was restricted to human studies published from 1970 up to May 5, 2021, that were written in the English language. Our search approach resulted in 244 papers. Among these, 206 papers were excluded, including reviews, letters, case reports, and studies that tested treatment effects, were on the pediatric population, or were not focused on CH, as well as other articles in which (1) methods were not properly described or (2) data on the comparison to a non-headache control group were not available. However, papers exploring patients with CH between in-bout and out-of-bout phases were included.

We also assessed a reference list of all the considered articles to further identify additional relevant studies. Finally, all the senior authors (A.R., A.T., and G.T.) checked the papers found in the preliminary phase to screen for inclusion and exclusion criteria. We ended with a total of 38 studies.

### The peripheral hypothesis

The peripheral origin of CH has been strongly supported based on the clinical features of the attacks. Because the cavernous sinus is the only peripheral anatomic site where both trigeminal C fibers and sympathetic fibers can be simultaneously affected by a single process, a CH model as a disease of the cavernous sinus has been previously proposed.[6] Starting from the seminal angiographic observations of focal narrowing of the internal carotid artery distal to the carotid canal in the course of CH attacks, different pathological abnormalities specifically involving the cavernous sinus have been hypothesized as primum movens of CH attacks.[7]

In particular, because neurogenic inflammation related to the plasma proteins' extravasation in the surrounding tissues has been hypothesized during CH attacks, a sterile inflammation of the cavernous sinus with irritation of autonomic fibers has been suggested.[8] Consistent with this hypothesis, an increased uptake of Gallium-67 in the region of the cavernous sinus during the in-bout periods was observed in a single photon emission computed tomography (SPECT) study, and its fading was noticed as the patients moved from in-bout periods.[9] Data were observed also in patients with chronic CH and in about half of patients with episodic CH.[10] However, because no differences were found in one-half of the patients with episodic CH between in-bout and out-of-bout periods and similar changes were observed in patients with migraine (in which there are no reasons to suggest parasellar inflammation), the hypothesis of inflammatory changes in the superior pericarotid plexus among the cavernous sinus appeared unlikely. Methodological and technical issues, such as qualitative evaluation of the isotope uptake and low spatial resolution power of the scan, made it difficult to clearly localize the observed abnormalities and to presume their nature.[10]

More recently, a study that used 99mTc human serum albumin and SPECT in six patients with episodic CH during and outside the attacks (triggered by intravenous nitroglycerin injection) did not support this causative mechanism.[11] Therefore, a constitutionally narrow cavernous sinus has been hypothesized as a predisposing factor in patients with CH.[12] However, a recent neuroimaging study conducted by means of high-resolution T2-weighted magnetic resonance imaging (MRI) failed in demonstrating differences in the dimensions of the cavernous sinus and surrounding structures in a cohort of 49 patients with CH (25 with episodic CH and 24 with chronic CH) compared with 22 healthy controls[13] (although patients with CH exhibit wider skulls when compared with healthy controls[14]; see Table 1 for further information). Taken together, the data emerging from neuroimaging studies allow us to refute the peripheral hypothesis for which anatomic or inflammatory changes of the cavernous sinus may represent the primum movens of CH attacks.

**TABLE 1** The peripheral hypothesis

| Reference | *N* of patients | Technique | Main findings | Interpretation |
|---|---|---|---|---|
| Ekbom et al., 1970[7] | 18 patients with CH | Carotid angiography | • 4 subjects ectasia of all cerebral arteries<br>• 3 subjects questionable ectatic changes | Pathological involvement of the cavernous sinus as pathological "primum movens" of CH attacks |
| Gawel et al. 1990[9] | 6 patients with episodic CH | SPECT (using gallium) | • Increased uptake of Galllure-67 citrate in the cavernous sinus during the in-bout period, fading in the out of cluster bout period | Inflammation of the cavernous sinus as pathogenetic mechanism of CH attacks |
| Sianard-Gainko et al., 1994[10] | 30 patients with CH (22 episodic and 8 chronic); 6 patients with MwoA | SPECT (using gallium) | • Parasellar hyperactivity in patients with chronic CH, in over half of patients with episodic CH both during the in-bout and out-of-bout periods and patients with migraine | The increased activity did not reflect inflammatory changes in the superior pericarotid plexus |
| Schuh-Hofer et al., 2006[11] | 6 subjects (episodic CH at baseline and after NTG-induced CH attack) | SPECT (using 99m Tc-HSA)/MRI coregistration in cavernous sinus ipsilateral and contralateral to pain side | • No changes in 99mTc-HSA uptake in the ipsilateral cavernous sinus | This study neither supports the hypothesis of an ipsilateral extravasation of 99mTc-HSA in the cavernous sinus during an acute CH attack nor the idea of an inflammatory process during a CH episode that subsides in remission |
| Arkink et al., 2017[13] | 92 subjects (25 episodic CH in-bout; 24 chronic CH; 13 probable CH; 8 CPH; 22 healthy controls) | MRI (high-resolution T2w) | • No relevant structural abnormalities in the cavernous sinus, skull base or surrounding anatomic structures;<br>• The L-to-R transcranial diameter at the temporal fossa level was larger in patients with CH compared with healthy controls | This study did not support the hypothesis of a constitutionally narrow cavernous sinus as predisposing factor in patients with CH |

Abbreviations: CH, cluster headache; CPH, chronic paroxysmal hemicrania; HSA, human serum albumin; MRI, magnetic resonance imaging; MwoA, migraine without aura; NTG, nitroglycerin; SPECT, single photon emission computed tomography.

## The transition from the vascular hypothesis to the trigeminovascular model

Another disease model, although obsolete, looks at CH as a vascular headache like migraine.[15]

Based on the efficacy of vasoconstricting symptomatic drugs (e.g., sumatriptan and ergot alkaloid derivatives) and the possibility to trigger CH attacks by administering exogenous vasodilators (e.g., alcohol, nitroglycerin, and 5-hydroxytryptamine$_{2B}$ agonists) during cluster-bout periods, changes in intracranial and extracranial blood vessels were hypothesized as a CH model.[16,17]

However, initial SPECT studies aimed to explore putative changes in cerebral blood flow (CBF) during spontaneous or triggered CH attacks reported, owing to technical limitations, conflicting results in terms of increased, decreased, or unchanged CBF.[18–23]

In this frame, the CBF has been studied by 133-Xenon inhalation both during CH attacks triggered by alcohol and/or nitroglycerine and outside the attacks. Although no significant global CBF changes occurred from baseline to the CH attacks, the mean regional CBF significantly increased in the central and the basal region, and in a small part of the right parietotemporal region. The modest magnitude of regional CBF changes led the authors to interpret them as a mere pain epiphenomenon.[18]

However, the study conducted by May and colleagues[24] that used magnetic resonance (MR) angiography in patients with CH (during triggered or spontaneous attacks) as well as in healthy subjects during experimental pain (capsaicin injection into the forehead) surely represents an elegant experiment to overcome the concept of a vascular origin of the CH attacks. Indeed, a significant vasodilatation of the major basal arteries was observed during both triggered and spontaneous CH attacks like the findings observed in the healthy subjects after the capsaicin injection into the forehead. These data strongly suggest vasodilatation as a nonspecific pain-related epiphenomenon related to the cranial neurovascular activation mediated by the trigemino-parasympathetic reflex. In other words, vasodilation of cerebral arteries, although it probably represents a critical moment in the cascade of events toward pain generation, does not represent the primum movens of the CH attacks.

In the last decades, a more comprehensive model of CH invoking the involvement of the trigeminal-vascular system has been suggested.[25] More specifically, it has been hypothesized that the activation of the first branch of the trigeminal nerve may be able to: (1) induce the meningeal vessels vasodilation stimulating the meningeal nociceptors and the consequent ignition of pain; (2) stimulate the so-called trigeminal parasympathetic reflex through the superior salivatory nucleus (SSN) and the sphenopalatine ganglion, leading to autonomic symptoms, such as lacrimation, eyelid edema, and nasal congestion; (3) inhibit the cranial sympathetic system impelling a partial Bernard-Horner syndrome characterized by miosis and pseudoptosis, probably through a sustained neurapraxic injury due to the stretching of sympathetic fibers rising from the superior cervical ganglion and surrounding the carotid artery. Furthermore, increased plasma levels of markers of trigeminal (i.e., calcitonin gene-related peptide [CGRP]) and parasympathetic (i.e., vasoactive intestinal peptide [VIP]) activation found in the jugular vein ipsilateral to CH attacks and their normalization in the out-of-bout periods and after sumatriptan injection, as well as CGRP's ability to induce attacks in patients with CH, strongly support the trigeminal-vascular model by means of the paramount involvement of CGRP (which occurs during the active phase of episodic CH and chronic CH), substance P, and VIP (see Table 2 for further information).[26–29]

## The hypothalamic role

Although the previously mentioned data suggest the relevant role of the trigeminovascular system in the pathogenesis of CH, the core clinical features of CH attacks, such as circadian and circannual rhythmicity as well as behavioral features (e.g., agitation and restlessness), cannot be fully explained by this model.[30] On the other hand, the mechanism's ability to rhythmically ignite the trigeminal-vascular complex has represented, for a long time, a missing link between the CH pathophysiological cascade and the influence of central brain structures on it.

Specifically, the involvement of the hypothalamus, the principal biological clock of the brain, in CH pathophysiology has been suggested to explain the circadian rhythm and the circannual seasonal pattern of CH attacks. Furthermore, hormonal abnormalities in CH, such as abnormalities of melatonin or growth hormone, support the role of the hypothalamus.[31]

Although the hypothalamus has never been considered as a component of the classical central pain-processing network, emerging evidence has supported its involvement in pain control, exerting predominant antinociceptive effects on the descending pain modulation.[32,33]

In particular, it is now noteworthy that the hypothalamus is characterized by anatomic and functional connections with trigeminal brainstem nuclei.[32] Indeed, a trigeminal-hypothalamic tract is able to guarantee a continuous crosstalk by which the hypothalamus receives sensory input from the face and cranium structures within the trigeminal field of innervation (including nociceptive information); in turn, it modulates trigeminal caudal nucleus activity.[33]

The activation and the inhibition of the trigeminal caudal nucleus neurons, induced respectively by the injection of orexin A and orexin B into the posterior hypothalamus of rats, further support not only the mutual association between the hypothalamus and the trigeminal system but also highlight the role played by the hypothalamic–orexin system in CH pathophysiology.[34]

However, the proof of the critical role played by the hypothalamus in CH surely comes from advanced structural and functional neuroimaging investigations conducted in the last decades.

## Hypothalamic role during CH attacks

Evidence provided by May and colleagues[35] represents a landmark in the knowledge of CH mechanisms, clearly showing for the first

**TABLE 2** The transition from the vascular hypothesis to the trigeminovascular model

| Reference | *N* of patients | Technique | Main findings | Interpretation |
|---|---|---|---|---|
| Krabbe et al. 1984[18] | 18 patients (9 chronic CH; 9 episodic CH during the attacks) | CBF/rCBF evaluation by SPECT ($^{133}$Xe inhalation) | • No significant CBF changes during CH attacks;<br>• Increased rCBF in the central, basal region, and parieto-temporal region | CBF changes as the result of pain activation not playing a pathophysiological role in the CH attacks ignition |
| Norris et al., 1976[19] | 1 patient (chronic CH before and during attack) | rCBF evaluated by SPECT (injection of $^{133}$Xe into internal carotid artery):<br>1. during attack<br>2. hyperventilation<br>3. after ergotamine | • No significant rCBF changes during CH attack;<br>• Normal response to hyperventilation;<br>• After ergotamine increased CBF without any significant rCBF differences | Severe pain alone is responsible for the increased rCBF values |
| Henry et al., 1978[20] | 3 episodic CH patients during attacks | CBF evaluation by SPECT ($^{135}$Xe intra-arterial injection) during CH attack and under anesthesia | No modifications of CBF in any of 3 cases of CH who were studied during attacks | No changes in mean CBF |
| Sakai et al. 1978[22] | 103 subjects (43 migraine; 9 CH during and out attacks; 19 tension-type headache; 32 healthy controls) | rCBF evaluation by SPECT ($^{133}$Xe inhalation) | CBF increase by 44.5% during the CH attacks compared to the headache-free interval | During CH, mean CBF values were significantly increased and the extracerebral flow indices showed marked increases with highest values recorded ipsilaterally to the CH attack |
| Steinberg et al. 2012[23] | 19 subjects (14 episodic CH in-bout and out-of-bout; 5 healthy controls) | WBC-SPECT | No significant difference in 99mTc-labeled WBC uptake between patients with CH in-bout and both patients with CH out-of-bout and healthy controls | No significant differences between patients with CH during and outside bouts |
| May et al. 2000[24] | 17 patients (8 out-of-bout CH; 9 in-bout CH) | $H_2{}^{15}O$ PET scans/MRA | • Increased CBF in the internal carotid artery ipsilateral to the headache side, both in CH patients and in healthy controls during experimentally induced pain with capsaicin<br>• Increased activity in ACC, ipsilateral posterior thalamus, basal ganglia, inferior posterior hypothalamus (not seen in patients out-of-bout), frontal lobes, insula. and contralateral inferior frontal cortex during CH attacks | Dilatation of cranial vessels is a generic phenomenon of cranial neurovascular activation, probably mediated by the trigemino-parasympathetic reflex |

Abbreviations: ACC, anterior cingulate cortex; CBF, cerebral blood flow; CH, cluster headache; $H_2{}^{15}O$ PET, $H_2{}^{15}O$ positron emission tomography; MRA, magnetic resonance angiography; rCBF, regional cerebral blood flow; SPECT, single photon emission computed tomography; WBC, white blood cells; Xe, xenon.

time the hypothalamic involvement in these patients, which was previously only suspected based on clinical and biochemical findings. Indeed, by using a positron emission tomography (PET) technique, increased regional CBF within the hypothalamus was observed in patients with chronic CH (ipsilateral to the attacks) when compared with a control group of patients with episodic out-of-bout CH during nitroglycerine-induced attacks. Subsequently, this finding has been replicated in a single patient experiencing a spontaneous CH attack and strengthened the idea of using a functional MRI (fMRI) approach.[36] Specifically, a higher activation of the hypothalamus ipsilateral to the side of the pain was observed in patients with episodic CH in comparison with the same subjects outside the attacks during in-bout periods, and this activation also seemed to follow pain resolution after subcutaneous sumatriptan was administered as a rescue treatment of the attack.[37] Similarly, an increased functional connectivity (FC) has been detected in patients with CH during spontaneous CH attacks compared with the same subjects outside the attacks during the in-bout period, between the right hypothalamus and ipsilateral cortical brain regions (i.e., in the angular gyrus, supramarginal gyrus, insula, superior temporal gyrus, and precuneus; see Figure 1).[38]

Based on the previously mentioned evidence, the hypothalamic connections with the trigeminovascular system as well as its role in CH attack pathophysiology are undeniable. However, the mechanism by which hypothalamic activation can trigger the trigeminal-autonomic reflex during the CH attacks remains an only partially solved conundrum in the pathophysiology of this condition.

To date, the anterior hypothalamus seems to mediate the rising of autonomic symptoms more than the thalamus and the brainstem nuclei. However, that could happen only when the trigeminal system is activated. This hypothesis has been supported recently by an fMRI study in which a trigeminal stimulation by kinetic oscillation stimulation was applied in the left nostril of 26 healthy controls to provoke autonomic symptoms (e.g., lacrimation) to explore the neuronal substrates of the trigeminal-autonomic reflex.[39] Whereas nonpainful stimuli induced the activation of specific brainstem (i.e., 2 different pontine nuclei located within the ventral portion of the pons) and cerebellar regions (i.e., lobule VIII) known to be involved in the trigeminal autonomic reflex (but not the hypothalamus), painful stimuli were able to induce the activation of anterior hypothalamus other than locus coeruleus, thalamus, and insula.

## Hypothalamic role outside CH attacks—Spectroscopic and structural findings

Observations from proton MR spectroscopy demonstrated a decreased *N*-acetylaspartate-to-creatine (NAA/Cr) ratio (which is a neuronal marker of mitochondrial functioning that is known to be reduced when neuronal dysfunction or loss occurs) in the hypothalamus of patients with CH compared with healthy controls.[40,41] Interestingly, NAA reduction persisted also when the sample of patients was divided into episodic (both in-bout and out-of-bout) and chronic CH, suggesting that a hypothalamic neuronal dysfunction could subtend and may represent a permanent CH fingerprint, even during the interictal period.[40] Some years later, the reduced hypothalamic NAA/Cr ratio was confirmed in 47 patients with episodic CH when compared with 21 healthy controls and 16 patients with chronic migraine, along with a decrease of choline-to-Cr ratios, allowing the authors to hypothesize that both hypothalamus neuronal

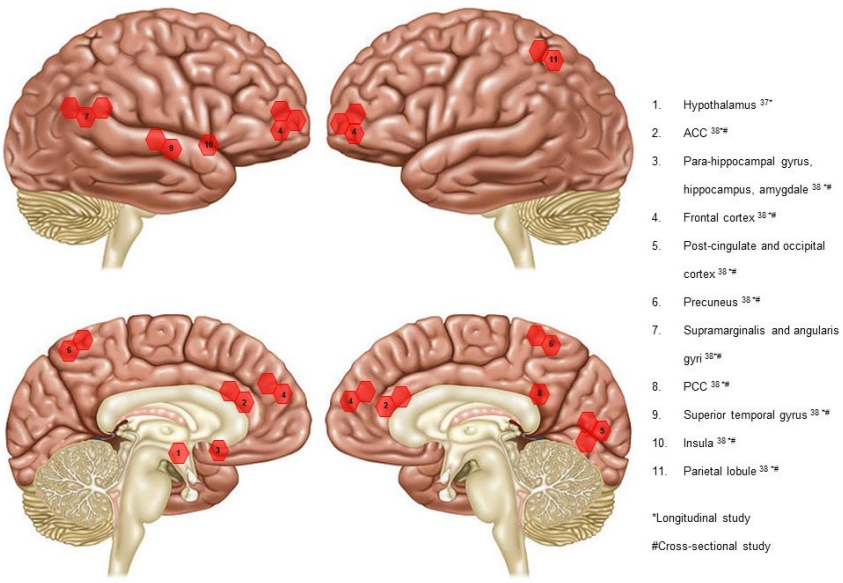


**FIGURE 1** Representation of FC changes demonstrated in patients with episodic CH during versus outside of attacks. ACC, anterior cingulate cortex; CH, cluster headache; FC, functional connectivity; PCC, posterior cingulate cortex [Color figure can be viewed at wileyonlinelibrary.com]

dysfunction and changes in the membrane lipids may be a hallmark of patients with CH.[41]

Furthermore, hypothalamic abnormalities are not exclusively functional but also structural in nature. Specifically, an isolated increase in the volume of gray matter (GM) has been demonstrated in the inferior-posterior hypothalamus in patients with CH in comparison with healthy controls by a voxel-based morphometry (VBM) study.[42] Subsequently, thanks to the evolution of region-of-interest (ROI) and manual segmentation approaches, increased GM volume has also been observed in the anterior hypothalamus (mirrored to the headache side) in patients with either episodic or chronic CH compared with healthy controls as well as patients with migraine.[43] Interestingly, the structural abnormalities observed in the anterior hypothalamus were centered in the supraoptic nucleus (strictly related to the biological rhythms), giving support to the comprehension of the characteristic circadian and circannual periodicity in CH (see Figure 2).

However, hypothalamic structural abnormalities have never been replicated by subsequent studies, even those conducted with the same VBM approach, probably because of the use of different scanners or the development of more stringent algorithms of analysis.[44,45] Nevertheless, the inclusion of different CH phenotypes in individual studies, investigations performed in different phases of the CH cycle (in-bout vs. out-of-bout periods; see Figure 3), in order to make the samples inhomogeneous (e.g., group of patients with either chronic or episodic CH vs. group of patients with only episodic CH), may partially explain the presence of nonconverging conclusive results to date. Further studies are needed to overcome such a scarcity of findings to achieve convincing results able to shed light on this issue. Therefore, hypothalamic volume abnormalities in patients with CH cannot be considered a solved question. On the other hand, it could be argued that the hypothalamus is not structurally compromised per se in CH, because it is indirectly affected via a loop of defective pain transmission signaling instead.[46] The latter hypothesis has been sustained in an elegant VBM study showing a decreased GM volume in several brain structures involved in pain processing (e.g., posterior cingulate cortex, caudate nucleus, thalamus, inferior parietal lobe, middle temporal gyrus, insula, precentral gyrus, and frontal gyrus) in patients with chronic CH.[47] The reduced GM volume in the frontal areas has also been confirmed in a study conducted on a larger cohort of patients with CH, along with an increased GM volume of anterior cingulate cortex, insula, and fusiform gyrus. The authors interpreted the volumetric abnormalities observed in these areas as the correlates of dysfunctional, descending, pain-modulatory systems in these patients.[48] Interestingly, VBM changes in brain areas—known to be involved in pain processing—have been subsequently upheld in the largest cohort of patients with CH and strengthened by a positive correlation between the severity of structural abnormalities and the burden of disease experienced by the patients.[45] Moreover, exclusive alteration of anterior cingulate cortex, amygdala, and secondary somatosensory cortex in patients with chronic CH further underlined the role of these structures in chronification of CH (see Table 3 for further information).

## Hypothalamic role outside CH attacks—FC findings

In the last decade, driven by the ascendancy of the novel methodological approach represented by fMRI, a plethora of studies have been conducted in patients with CH. The fMRI investigations typically include two main categories: event-related studies that investigate the brain activity in response to specific tasks or events, and resting-state investigations that explore the connectivity between functionally linked but anatomically separated brain regions during the brain's resting state. In turn, resting state-fMRI (RS-fMRI) investigations may be conducted according to a whole-brain approach or by using an ROI analysis (the so-called seed-based approach). The whole-brain RS-fMRI studies identify neuro-anatomic, biologically meaningful, spatial brain maps consisting of independent components, showing both spontaneous and simultaneous fluctuations that are organized in distributed and reproducible functional networks, called resting-state networks, such as the default mode network, central executive network, salience networks, and so on. On the other hand, the seed-based approach is usually used when a strong a priori hypothesis on the involvement of a specific brain area is present, allowing the investigation of the reciprocal FC between that area and other brain regions. Indeed, several studies have consistently explored the intrinsic and extrinsic FC of the hypothalamus in patients with CH.[49,50]

Among RS-fMRI studies using an ROI-based approach, Ferraro and colleagues[51] demonstrated increased FC between the posterior hypothalamus (ipsilateral to the side of pain) and diencephalic-mesencephalic structures (such as the ventral tegmental area, dorsal nuclei of raphe, bilateral substantia nigra, and bilateral subthalamic and red nuclei) outside the attacks during in-bout periods in patients with chronic CH when compared with healthy controls. Because the diencephalic-mesencephalic regions were part of (i.e., ventral tegmental area or substantia nigra) or modulate (e.g., dorsal nuclei of raphe or subthalamic nucleus) the midbrain dopaminergic system, the authors suggested that the latter could take part in CH pathophysiology and, speculatively, in the chronification processes.

However, the discovery that abnormal FC is extended far beyond the connections between the hypothalamus and diencephalic structures in patients with CH surely represents a turning point.

Indeed, a significant higher FC between the right hypothalamus and several cortical areas (such as anterior and posterior cingulate cortices; superior frontal, middle frontal, inferior frontal, and superior temporal gyri; inferior parietal lobule; parahippocampal gyrus; and amygdala) known to be involved not only in pain-perception but also in more complex aspects of pain experience, has been observed in patients with episodic CH outside the attacks during in-bout period and healthy controls (see Figure 4).[38]

In the attempt to clarify whether such FC abnormalities vary between the in-bout and out-of-bout periods, a longitudinal resting-state

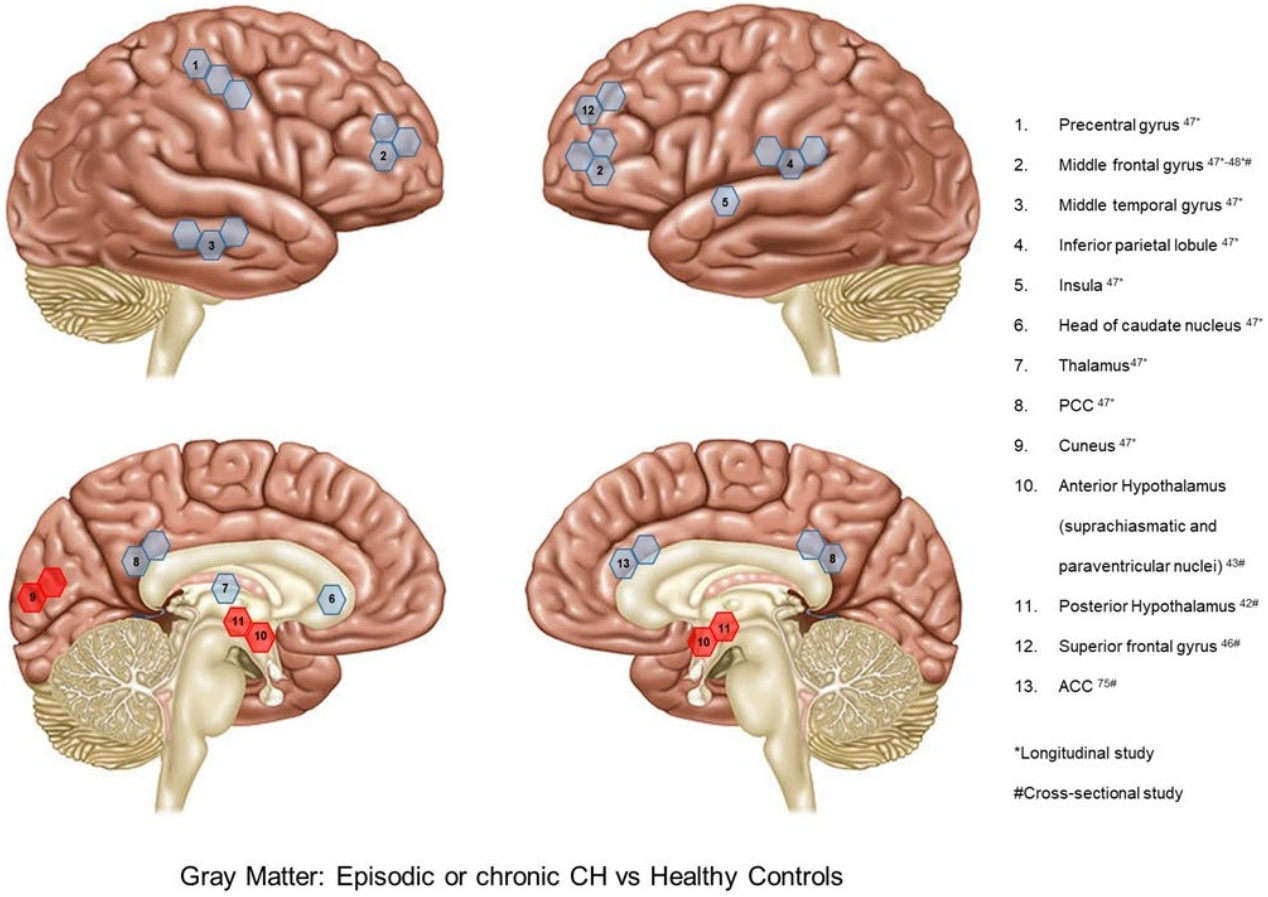


**FIGURE 2** Representation of GM changes demonstrated in patients with episodic or chronic CH compared with healthy controls. ACC, anterior cingulate cortex; CH, cluster headache; GM, gray matter; PCC, posterior cingulate cortex [Color figure can be viewed at wileyonlinelibrary.com]

study that used the seed-based approach on the hypothalamus has been conducted in patients with episodic CH outside the attacks during both in-bout and out-of-bout periods compared with healthy controls.[52] These data showed a decreased hypothalamic FC with medial frontal gyrus, precuneus, and cerebellar areas during in-bout periods when compared with those performed during the out-of-bout periods (see Figure 5). Interestingly, the annual frequency of bouts correlated negatively with FC between hypothalamus and cerebellar culmen and declive. Interestingly, the same group showed regional changes in anatomic connections between the cerebellar areas and the hypothalamus in patients with CH during the in-bout periods compared with the out-of-bout periods. Based on these findings, the authors argued that cerebellohypothalamic circuits might play a role in CH pathophysiology.

It should be emphasized that although the cerebellum is widely known for its involvement in motor processing, its role in cognition and nociceptive modulation has been demonstrated in other types of primary headaches also.[53] Furthermore, bidirectional functional connections between the cerebellum and hypothalamus have later been found to be involved in modulation of autonomic responses and pain modulation, as demonstrated in experimental and clinical studies that have shown the participation of the cerebellum in the regulation not only in motor activities but even in visceral responses.[54–56]

In line with these observations and supporting the involvement of hypothalamic-diencephalic-cortical circuitry in the pathophysiology of CH, functional connections among the hypothalamus, thalamus, and cortical areas have been specifically investigated when evaluating the FC among these regions (identified by a seed-based approach) and the resting-state networks (identified by means of independent component analysis) in patients with episodic CH in the out-of-bout periods. Starting from hypothalamic and thalamic "seeds," an increased FC with the sensorimotor and primary visual networks has been observed in patients with CH in comparison with healthy controls.[57]

With the same methodological paradigm, another study demonstrated a decreased FC between the hypothalamus (both ipsilaterally and contralaterally to the side of pain) and the salience network in patients with episodic CH outside the attacks during in-bout periods when compared with healthy controls.[58] Moreover, an increased frequency-specific activity (a different FC parameter/measurement) between the hypothalamus and attention network ipsilateral to the headache side as well as the cerebellar network contralateral to the headache side were found in patients with episodic CH outside the attacks during in-bout periods when compared with healthy controls.[59]

Because hypothalamic changes are not exclusive to CH and are detected in other primary headache disorders (primarily in

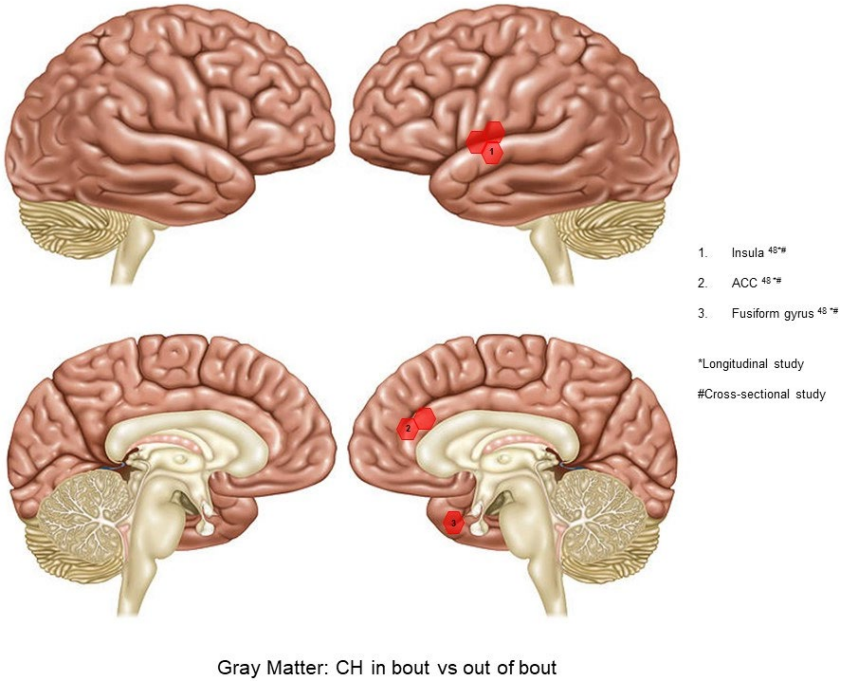


**FIGURE 3** Representation of GM changes in patients with CH during in-bout period compared with out-of-bout period. ACC, anterior cingulate cortex; CH, cluster headache; GM, gray matter [Color figure can be viewed at wileyonlinelibrary.com]

migraine) as well as in very different pain conditions (such as angina pectoris and irritable bowel syndrome), it cannot be excluded that abnormal hypothalamic activity in CH is a nonspecific pain-related epiphenomenon rather than the "CH generator."[60–62] On the other hand, the observed hypothalamic functional and structural/microstructural abnormalities failed in defining an exact and reproducible anatomic localization, probably owing to not only the known limitations related to the spatial resolution of the advanced neuroimaging methods (PET vs. fMRI) but also to the poor homogeneity among the patients' samples (e.g., episodic vs. chronic CH and patients in in-bout vs. out-of-bout periods) and the low samples sizes, as confirmed by data from deep brain stimulation (DBS) coordinates in patients with refractory CH.[63] Indeed, the spatial resolution of PET is limited to 2 to 7 mm owing to the distance that positron travels through the tissue prior to the annihilation event; whereas fMRI, although characterized by better spatial resolution, is constrained to the order of 4 to 5 mm. Starting from these limitations, a re-examination of statistical parametric maps and coordinates of the diencephalic and mesencephalic activations in PET studies in patients with CH revealed that the diencephalic/mesencephalic activations are centered over the midbrain tegmentum, extending anteriorly to about the posterior hypothalamus.[63] These quandaries are further fueled by investigations conducted in patients with drug-resistant CH undergoing DBS interventions. Indeed, although pioneering interventions were believed to stimulate the posterior hypothalamus, some authors have suggested that the stimulated volume spreads to the periaqueductal GM or that active contacts are located in a bridging zone between the hypothalamus and the mesencephalic GM.[64–66] Fontaine and colleagues,[67] using the Schaltenbrand atlas and a stereotactic 3-dimensional MRI atlas, accurately explored the exact anatomic location of the effective contacts in a cohort of 11 patients with chronic CH who underwent therapeutic DBS. Interestingly, the electrodes were observed in the posterior and ventral wall of the third ventricle, posterior to the mamillary body and the mammillothalamic tract, which mark the caudal border of the hypothalamus.[68–70] These observations led the way to several tractography investigations showing that, more than stimulating the posterior hypothalamus, the DBS acts on the dorsal longitudinal fasciculus (DLF) and the mammillotegmental fasciculus (MTF),[71] two fascicles directly involved in autonomic response modulation.[72] Indeed, the DLF, after receiving afferent inputs from the posterior and lateral hypothalamic nuclei and the dorsal tegmental nucleus, ends at the parasympathetic centers of the brainstem, whereas the MTF is the main component responsible for autonomic information transfer between the posterior hypothalamus and nuclei of the cranial nerves. In other words, the therapeutic activity of DBS seems to be caused by orthodromic and antidromic neuromodulation over both the MTF and the DLF. Once they are orthodromically modulated, the MTF and the DLF attenuate the parasympathetic activity of the SSN and thus the efferent branch of the trigeminal autonomic reflex.[73] On the other side, the lateral and posterior hypothalamic nuclei, where the MTF originates, are modulated antidromically by DBS, reinforcing the therapeutic effect. All in all, these findings suggest that, along with the hypothalamus, the hypothalamic-brainstem-cerebellar interconnections play a paramount role in CH attacks' ignition and characterization.

TABLE 3 The role of the hypothalamus

| Reference | *N* of patients | Technique | Main findings | Interpretation |
|---|---|---|---|---|
| May et al., 1998[35] | 17 subjects (9 chronic CH during NTG-induced attacks; 8 CH out-of-bout) | $H_2{}^{15}O$ PET scans | Higher activations during acute CH attack compared with the headache-free in the ipsilateral hypothalamic grey area, ACC, posterior thalamus, basal ganglia, insula, and cerebellum | Hypothalamic dysfunction as the primum movens in CH pathophysiology |
| Sprenger et al. 2004[36] | 1 subject (chronic CH) | $H_2{}^{15}O$ PET scans | Higher activation of ipsilateral hypothalamus, medial thalamus, and contralateral perigenual ACC in patients with CH | Key role of posterior hypothalamus in the CH pathogenesis |
| Möller et al. 2020[39] | 26 subjects (healthy controls) | fMRI during KOS | KOS was applied in the L nostril to provoke autonomic symptoms through the trigeminal-autonomic reflex:<br>• nonpainful stimuli induced the activation of specific brainstem, cerebellar regions, and bilateral insular regions;<br>• painful stimuli were able to induce the activation of anterior hypothalamus other than locus coeruleus, thalamus, and insula | Anterior hypothalamus plays a significant role in autonomic response (e.g., lacrimation) following trigeminal inputs, only if the trigeminal system is activated by painful stimuli |
| Lodi et al. 2006[40] | 38 subjects (26 CH of which 18 episodic CH in-bout and out-of-bout, 8 chronic CH; 12 healthy controls) | $^1$H-MRS | • Reduced hypothalamic NAA/Cr and NAA/Cho in patients with CH compared to healthy controls;<br>• Similar Cho/Cr in patients with CH and healthy controls;<br>• Reduced hypothalamic NAA/Cr in patients with episodic CH out-of-bout and in-bout periods and chronic CH | The reduction of NAA is consistent with hypothalamic neuronal dysfunction in patients with CH |
| Wang et al. 2006[41] | 84 subjects (35 episodic CH in-bout; 12 episodic CH out-of-bout; 16 chronic migraine; 21 healthy controls) | $^1$H-MRS | • Hypothalamic NAA/Cr and Cho/Cr levels were lower in patients with CH in comparison with both healthy controls and chronic migraine groups;<br>• NAA/Cr and Cho/Cr levels did not differ between in-bout and out-of-bout | Hypothalamic neuronal dysfunction and changes in the membrane lipids characterize patients with CH independently from CH phase |
| May et al. 1999[42] | 54 subjects (25 episodic or chronic CH; 29 healthy controls) | VBM | • Increased in posterior hypothalamic GM density between CH and healthy controls;<br>• No difference between in-bout (14) and out-of-bout periods (11) | Observed hypothalamic structural changes support abnormalities affecting the hypothalamus seem to be not exclusively functional in nature |
| Arkink et al. 2017[43] | 151 subjects (24 episodic CH; 23 chronic CH; 14 probable CH; 9 CPH; 14 migraine with aura; 19 migraine without aura; 48 healthy controls) | VBM | The anterior part of the hypothalamus (encompassing suprachiasmatic and paraventricular nuclei) is bilaterally enlarged in typical episodic and chronic CH, possibly also in probable CH and CPH | Suprachiasmatic nucleus (the so-called "endogenous biological clock") abnormalities may cause the striking circadian and circannual CH rhythms. Paraventricular nucleus abnormalities could modulate or trigger CH attacks by mediating nociceptive and autonomic input |
| Matharu et al. 2006[44] | 66 subjects (episodic CH) | VBM | No alterations in GM or WM in inferior-posterior hypothalamus | Previous VBM results were false positive due to methodological limitations |

TABLE 3 (Continued)

| Reference | *N* of patients | Technique | Main findings | Interpretation |
|---|---|---|---|---|
| Naegel et al. 2014[45] | 169 subjects (46 episodic CH out-of-bout; 22 episodic CH in bout; 23 chronic CH; 78 healthy controls) | VBM | • WM, CSF, or total intracranial volume did not differ between groups;<br>• GM changes in temporal lobe, hippocampus, insular cortex, cerebellum;<br>• The extent, location and direction of observed GM alterations depended on the state of disease and appeared dynamic in relation to pain state;<br>• No hypothalamic changes were detected in CH compared to healthy controls | GM changes are highly dynamic reflecting the cortical plasticity of the brain in response to pain. CH is more likely to be caused by a network dysfunction rather than a single malfunctioning structure |
| Chong et al. 2020[46] | 59 subjects (18 episodic CH out-of-bout; 19 migraine; 22 healthy controls) | VBM | • No significant between-group differences in total brain volume or hypothalamic region volume;<br>• Weaker structural connectivity in CH between hypothalamus and frontal (rostral middle frontal, superior frontal) and the temporal-parietal (superior temporal, fusiform, posterior cingulate) pain control system | The reduced structural covariance in CH might suggest abnormal functioning of the pain control circuitry and contribute to mechanisms underlying central sensitization and chronification of pain |
| Absinta et al. 2011[47] | 34 subjects (15 episodic CH out-of-bout; 19 healthy controls) | VBM | • Compared to healthy controls, patients with CH showed GM atrophy in thalamus, head of caudate nucleus, PCC, middle frontal gyrus, precuneus, middle temporal gyrus, and precentral gyrus;<br>• Middle frontal gyrus atrophy significantly correlated with disease duration;<br>• No volume abnormalities in the hypothalamus;<br>• No abnormalities of the brain WM | Patients with CH have structural abnormalities in GM regions involved in the antinociceptive system |
| Yang et al. 2013[48] | 98 subjects (49 episodic CH in-bout of which 12 rescanned out-of-bout; 49 healthy controls) | VBM | • Lower total GM volume in CH<br>• CH in bout vs. healthy controls: significant GM volume reduction in middle frontal gyri, superior and medial frontal gyri;<br>• In-bout vs. out-of-bout CH: significant GM volume increases in L ACC, insula, and fusiform gyrus;<br>• CH out-of-bout vs. healthy controls: trend of GM volume reduction in L middle frontal gyrus | GM volume changes may reflect insufficient pain-modulating capacity in the frontal areas of patients with CH |

Abbreviations: 1H-MRS, proton magnetic resonance spectroscopy; ACC, anterior cingulate cortex; CH, cluster headache; Cho, choline; CSF, cerebrospinal fluid; Cr, creatine; fMRI, functional magnetic resonance imaging; GM, gray matter; $H_2{}^{15}O$ PET, $H_2{}^{15}O$ positron emission tomography; KOS, kinetic oscillation stimulation; L, left; MRA, MR inflow angiogram; NAA, *N*-acetylaspartate; NTG, nitroglycerin; PCC, posterior cingulate cortex; R, right; SC, subcutaneous; SPECT, single photon emission computed tomography; VBM,voxel-based morphometry; WM, white matter.

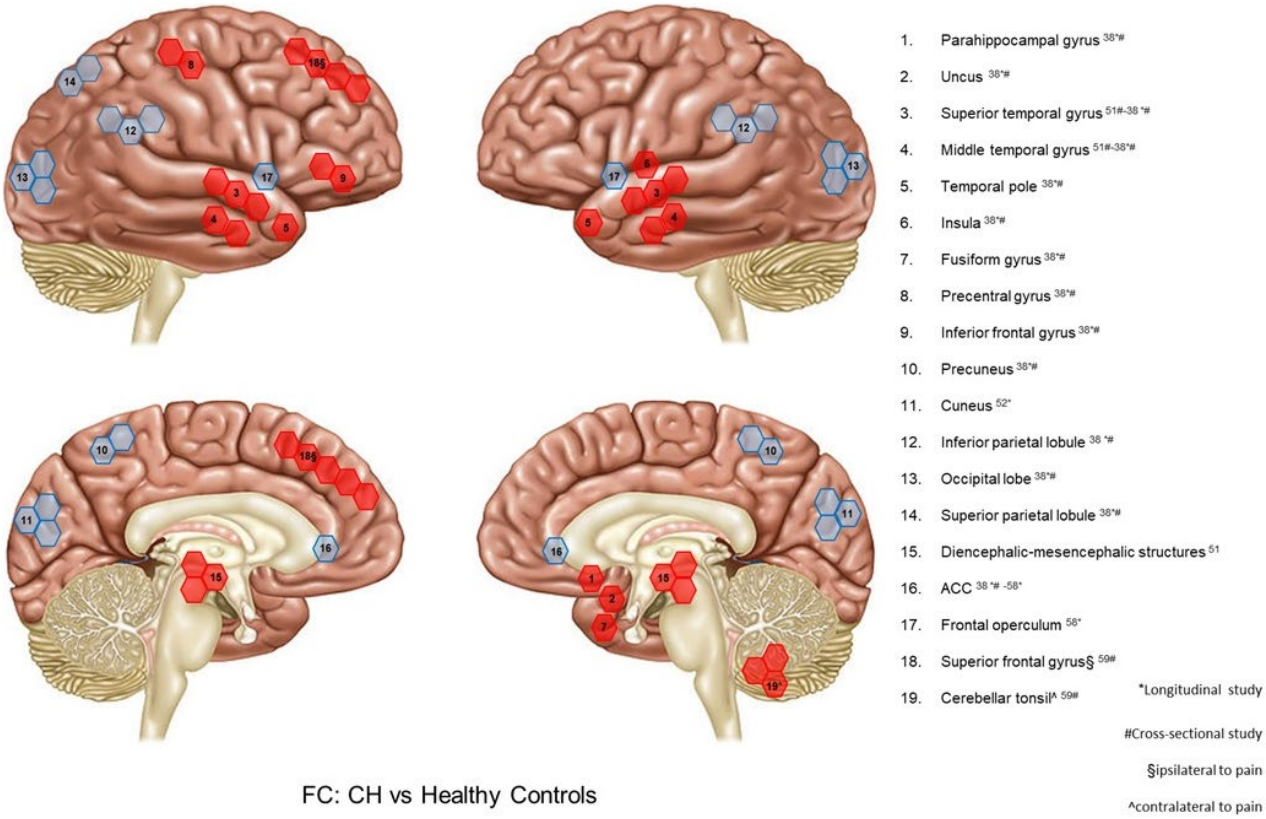


**FIGURE 4** Representation of FC changes demonstrated in patients with CH compared with healthy controls. ACC, anterior cingulate cortex; CH, cluster headache; FC, functional connectivity [Color figure can be viewed at wileyonlinelibrary.com]

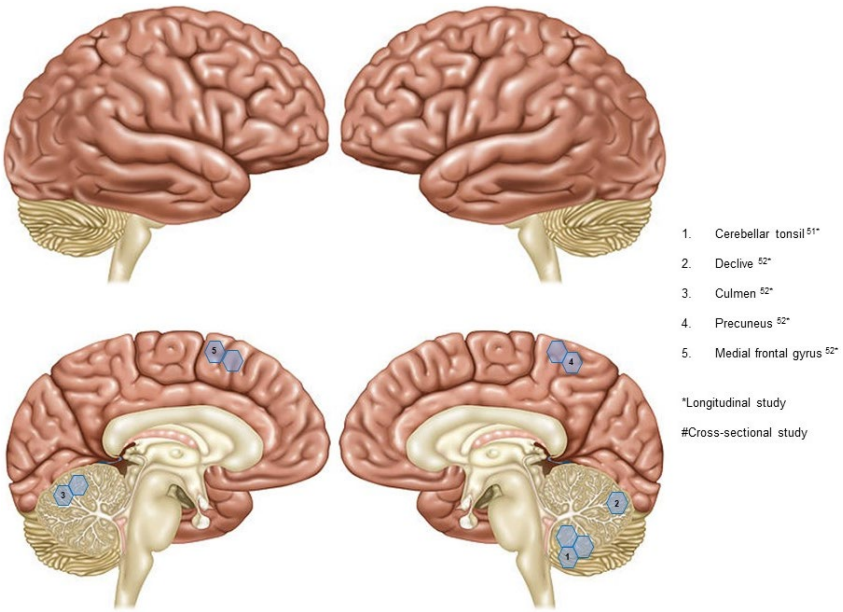


**FIGURE 5** Representation of FC changes demonstrated in patients with episodic CH during the in-bout compared with out-of-bout periods. FC, functional connectivity; CH, cluster headache [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 4** Microstructural and FC investigations

| Reference | *N* of patients | Technique | Main findings | Interpretation |
|---|---|---|---|---|
| Morelli et al., 2009[37] | 4 subjects (episodic CH before, during attacks and after s.c. administration of sumatriptan) | fMRI | Significant cerebral activation in the ipsilateral hypothalamus during CH attacks | This study has demonstrated the anatomical location of CNS activation with the first fMRI study during CH attacks |
| Qiu et al., 2013[38] | 24 subjects (12 episodic CH in-bout in and out of attacks; 12 healthy controls) | RS-fMRI | CH in attack vs. out of attack:<br>• increased RS-FC between hypothalamus and ACC, PCC, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, superior temporal gyrus, inferior parietal lobule, para-hippocampal gyrus, and amygdala during spontaneous CH attacks<br>CH (out of attack) vs. healthy controls:<br>• increased RS-FC between hypothalamus and parts of the frontal, parietal and temporal cortex in CH during headache-free intervals, but not with ACC and PCC;<br>• decreased RS-FC between hypothalamus and occipital cortex in patients with CH | Diffuse RS-FC abnormalities between hypothalamus and brain regions related to pain processing and emotional modulation during spontaneous CH attack, and between hypothalamus and pain processing brain regions along with visual system during CH attack intervals |
| Ferraro et al., 2018[51] | 33 subjects (17 chronic CH; 16 healthy controls) | RS-fMRI | Patients with CH vs. healthy controls:<br>• increased RS-FC between the ipsilateral posterior hypothalamus and diencephalic-mesencephalic structures (ventral tegmental area, dorsal nuclei of raphe, and bilateral substantia nigra, subthalamic nucleus, and red nucleus);<br>• No difference compared to the contralateral hypothalamus | The midbrain dopaminergic systems could play a role in CH pathophysiology and might be involved in both pain chronification of CH and in the addictive behavior observed in patients with CH |
| Yang et al., 2015[52] | 37 subjects (18 episodic in-bout and out-of-bout CH; 19 healthy controls) | RS-fMRI | • Patients with CH vs. healthy controls: hypothalamic RS-FC changes with the medial frontal gyrus and occipital cuneus in CH;<br>• In-bout vs. out-of-bout: decreased RS-FC between hypothalamus and medial frontal gyrus, precuneus, and cerebellar areas (tonsil, declive, and culmen) in in-bout patients;<br>• The annual bout frequency correlated significantly with RS-FC between hypothalamus and cerebellar culmen and declive | RS-FC changes between hypothalamus and its regional distribution extends beyond traditional pain processing areas (primarily to the cerebellar, frontal, and occipital areas) in CH |
| Chou et al., 2017[57] | 35 subjects (17 episodic CH in-bout and out-of-bout; 18 healthy controls) | RS-fMRI | • Patients with CH vs. healthy controls: patients with CH had RS-FC changes in the temporal, frontal, salience, default mode, somatosensory, dorsal attention, and visual networks, independent from bout period;<br>• Out-of-bout vs. in-bout: altered RS-FC in the frontal and dorsal attention networks during in-boutLower frontal network RS-FC correlated with longer duration of CH disease | Episodic CH with dynamic bout period shifts may involve bout-associated FC changes in multiple discrete cortical areas within networks outside traditional pain processing areas |
| Qiu et al., 2015[58] | 42 subjects (21 episodic CH in bout; 21 healthy controls) | RS-fMRI/ICA-ROI | Decreased RS-FC between R and L hypothalamus with salience network in patients with CH | Decreased hypothalamus-salience network RS-FC may have a role in CH attacks by the defective central pathway of pain control and autonomic nervous system dysregulation |

TABLE 4 (Continued)

| Reference | *N* of patients | Technique | Main findings | Interpretation |
|---|---|---|---|---|
| Faragò et al., 2017[59] | 43 subjects (17 episodic CH out-of-bout; 26 healthy controls) | RS-fMRI/ICA-ROI | Increased frequency specific activity in patients with CH in the attention network ipsilateral to the headache side and in the contralateral cerebellar network | Increased RS-FC ipsilateral to headache might be a signature of increased cortical excitability in CH |
| Chou et al., 2014[70] | 34 subjects (17 episodic CH during in-bout and out-of-bout periods; 17 healthy controls) | Whole brain DTI scans using TBSS | • Compared to healthy controls, in-bout patients with CH showed regionally higher absolute (radial and mean) diffusivities in frontal regions and lower absolute (axial, radial, and mean) diffusivities in the limbic lobe<br>• Microstructural changes during the in-bout period generally persisted in the out-of-bout period, except for the left cerebellar tonsil<br>• Increased connections between altered areas and hypothalamus in patients with CH | Connections between the pain-modulation areas and hypothalamus may be involved in CH pathophysiology |
| Giorgio et al., 2019[74] | 38 subjects (12 patients with CH during out-of-bout period; 13 MwoA; 13 healthy controls) | RS-fMRI | RS-FC of CH was higher than MwoA and healthy controls within working memory and executive control networks | Increased RS-FC of cognitive networks is likely due to maladaptation toward more severe pain experience in patients with CH |
| Ha et al., 2019[75] | 30 subjects (10 episodic CH and 20 healthy controls) | MRI/Graph Theory | • Volumes of the caudal ACC and postcentral gyrus in patients with CH significantly decreased compared with healthy controls<br>• Increased strength and closeness centrality of the cingulate gyrus in patients with CH | Structural volumes and connectivity in patients with CH are significantly different from healthy controls, especially revealing hub re-organization (alterations probably implicated in the pathogenesis of CH suggesting CH as a network disease) |
| Teepker et al., 2012[77] | 14 subjects (6 episodic CH during out-of-bout, 1 episodic CH during in bout periods; 7 healthy controls) | Whole brain DTI scans using TBSS | Microstructural changes in patients with CH in the white matter within the brainstem, basal frontal lobe (olfactory system) and brainstem (medial lemniscus and central sympathetic pathways) | Widespread microstructural changes of the olfactory system and of trigeminal and sympathetic systems in CH |
| Szabò et al., 2013[78] | 29 subjects (13 patients with CH during interictal period; 16 healthy controls) | Whole brain DTI scans using TBSS | • Increment of the mean, axial and perpendicular diffusivity in widespread white matter regions in the frontal, parietal, temporal, and occipital lobes;<br>• Reduced fractional anisotropy in the corpus callosum and some frontal and parietal (contralateral to pain side) | Microstructural alterations in CH provides important features of the disease |
| Kiràly et al. 2018[79] | 116 subjects (22 patients with CH during out-of-bout period; 94 healthy controls) | High-resolution T1-weighted and DTI scans | In patients with CH, the mean fractional anisotropy of the right amygdala, the mean axial and mean diffusivity of the right caudate nucleus and the radial diffusivity of the right pallidum were higher | Subcortical structures involvement extends beyond hypothalamus in patients with episodic CH |

Abbreviations: ACC, anterior cingulate cortex; CH, cluster headache; CNS, central nervous system; DTI, diffusion tensor imaging; FC, functional connectivity; fMRI, functional magnetic resonance imaging; L, left; MwoA, migraine without aura; PCC, posterior cingulate cortex; R, right; RS-FC, resting state functional connectivity; ROI, region of interest; RS-fMRI, resting state-functional magnetic resonance imaging; TBSS, track-based spatial statistics.

## FC and structural abnormalities beyond the hypothalamus

Using a whole-brain approach, FC abnormalities in the default mode, temporal, frontal, salience, somatosensory, dorsal attention, and visual networks have been demonstrated in patients with episodic CH during in-bout periods.[57] A higher short-range FC has recently been shown in patients with CH compared with healthy controls and patients with migraine within both the working memory network (inferior and middle frontal gyrus) and the executive control network (superior frontal gyrus and frontal pole). Interestingly, all resting state (RS)-FC changes were mapped ipsilaterally to the side of experienced pain in almost all the patients with CH (e.g., the right hemisphere).[74]

Furthermore, the comparison between in-bout and out-of-bout scans showed an altered FC in the frontal and dorsal attention networks, suggesting that episodic CH with dynamic bout period shifts (e.g., periodic recurrence of in-bout and out-of-bout intervals) may involve bout-associated FC changes in multiple discrete cortical areas within cerebral networks involved not only in the pain experience but also in the cognitive and affective correlates. The structural substrates enabling the functional communications among the brain network or connectome, characterized by high stability and reproducibility, have been investigated in CH to overcome the variability and susceptibility of signal fluctuations across the course of RS-FC investigations. A significant hub reorganization, characterized by increased strength and closeness centrality of the cingulate gyrus, has been demonstrated in patients with CH.[75]

Altogether, RS-FC findings strongly suggest that beyond the involvement of the so-called "pain matrix" in the mechanism underlying CH, the hypothesis of CH as a "neurolimbic pain network" disorder, as recently considered for migraine, could be invoked also in CH pathophysiology[76] (see Table 4 for further information).

Diffusion tensor imaging investigations showed microstructural abnormalities in white matter (WM) of patients with CH.[77–79] Specifically, a significant increase of mean, axial, and radial diffusivity have been demonstrated in widespread WM in the frontal, parietal, temporal, and occipital lobes. Interestingly, axial diffusivity abnormalities showed positive correlation with the frequency of the CH attacks. Furthermore, reduced fractional anisotropy was found in the corpus callosum and several frontal and parietal WM tracts, mainly in the contralateral side of the pain, in these patients. However, the meaning of the observed WM microstructural changes and its role in CH pathophysiology remain to be further elucidated.

## CONCLUSIONS

Although the role of the hypothalamus in the pathophysiological mechanisms subtending CH is undeniable, we believe that the genesis of the attacks is remarkably complex and seems to not be just the result of a single CH "generator." Indeed, changes in the activity of the hypothalamus and the brainstem nuclei seem to play a critical role in the previously mentioned CH genesis, via a continuous mutual cross-talk along with abnormal connectivity between different higher cortical brain regions encompassing the so-called neurolimbic pain network.

In particular, it could be argued that higher cortical areas may play a permissive role on the abnormal activity of subcortical structures, suggesting a dysfunctional top-down mechanism that is able to switch between out-of-bout and in-bout periods. Particularly, hypothalamic-cerebellar changes and differences in hypothalamic FC (especially in the cerebellar areas with the loss of cerebellar inhibition and modulation of the hypothalamus) between in-bout and out-of-bout periods may underlie the mechanism of bout period transitions.[80] In this scenario, the hypothalamus and the hypothalamic-brainstem-cerebellar interconnections might be involved in igniting the trigeminovascular system (on which cortical structures act) during CH attacks. The afferences from posterior and lateral hypothalamus, transported to parasympathetic centers by DLF and MTF, justify the consensual trigeminal autonomic reflexes during CH attacks.

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### CONFLICT OF INTEREST

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.S. has received speaker honoraria from Novartis, Lilly, and Teva. A.T. has received speaker honoraria from Novartis, Schwarz Pharma/UCB, Lundbeck, Abbvie, and Glaxo. G.T. has received speaker honoraria from Sanofi-Aventis, Merck Serono, Bayer Schering Pharma, Novartis, Biogen-Dompe´ AG, Teva, and Lilly; has received funding for travel from Bayer Schering Pharma, Biogen-Dompe´ AG, Merck Serono, Novartis, and Sanofi Aventis; and serves as an associate editor of *Neurological Sciences*. A.R. has received speaker honoraria from Allergan, Lilly, Novartis, and Teva and serves as an associate editor of *Frontiers in Neurology* (Headache Medicine and Facial Pain section). The other authors have nothing to declare.

### AUTHOR CONTRIBUTIONS

*Study concept and design*: Marcello Silvestro, Antonio Russo. *Acquisition of data*: Marcello Silvestro, Ilaria Orologio, Antonio Russo, Mattia Siciliano. *Analysis and interpretation of data*: Marcello Silvestro, Mattia Siciliano. *Drafting of the manuscript*: Marcello Silvestro, Antonio Russo, Giorgia Battista. *Revising it for intellectual content*: Antonio Russo, Gioacchino Tedeschi, Alessandro Tessitore, Mattia Siciliano. *Final approval of the completed manuscript*: Antonio Russo, Gioacchino Tedeschi.

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