Review Article

# Functional Neuroimaging in Trigeminal Autonomic Cephalalgias

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## Abstract

Functional neuroimaging was able to identify key structures for the pathophysiology of trigeminal autonomic cephalalgias (TACs) including cluster headache, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing or cranial autonomic features and hemicrania continua. The posterior hypothalamus was the structure most consistently depicted with functional imaging in different states of disease with and without pain. Network-oriented imaging techniques such as resting-state functional resonance imaging were able to show a broader involvement of human trigeminal pain processing in the underlying pathophysiological mechanisms of the different TACs, highlighting similarities between this distinct group of primary headache disorders, while also demonstrating the differences in brain activation across these disorders. The most important clinical assignment for neuroimaging research from the treating physician remains the objective and reliable distinction of each individual TAC syndrome from one another, to make the correct clinical diagnosis as the foundation for proper treatment. More research will be necessary to fulfill this unmet need.

**Keywords:** Cluster headache, functional imaging, magnetic resonance imaging, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, trigeminal autonomic cephalalgias

## Introduction

Neuroimaging studies on trigeminal autonomic cephalalgias (TACs) aim to identify unique pathophysiological correlates of each disorder with potential clinical implications for a specific treatment. TACs are summarized in group 3 in the current headache classification (ICHD3ß) and include cluster headache (CH), paroxysmal hemicrania, hemicrania continua, and the short-lasting unilateral neuralgiform headache attacks.[1] The latter is an umbrella diagnosis including short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and cranial autonomic features (SUNA). Except hemicrania continua, all TACs may present as chronic or episodic variant. Furthermore, TACs share many other clinical features but differ in others so that they entail a distinct and unique pathophysiology with a common pathway expressed in autonomic features, pain location, and circadian rhythmicity.[2] All of these are expressed to different extent in each of these disorders and in each individual patient, leading to a considerable overlap in clinical presentation and thus difficulty in distinguishing one from another in the unaccustomed eye. Therefore, modern functional imaging is not only interested in finding a potential pathophysiological origin of each disorder but also in developing a diagnostic tool to reliably and objectively differentiate the different TACs from one another as well as from other primary headache disorders such as migraine.[3] Several studies using different neuroimaging techniques supported the hypothesis of a hypothalamic involvement.[3,4] Neuroimaging found evidence to support but also to refute this hypothesis that has strong support from animal experiments.[5] Even though modern neuroimaging techniques have made a huge impact on the understanding of TACs, there is still much to learn about them.

## Cluster Headache

CH is the most common TAC and is characterized by recurring, strictly unilateral intense headaches accompanied by ipsilateral autonomic symptoms lasting 15–180 min. Most functional imaging studies on TACs focused on CH in an attempt to

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confirm the hypothalamus as the main pathophysiological origin of this disorder. This strong *a priori* hypothesis based on circadian rhythmicity leads to serious clinical implications extending as far as deep brain stimulation (DBS) therapy for strongly affected patients.[6-9]

### Positron emission tomography and functional magnetic resonance imaging

Functional imaging allows detection of alterations in the activity of the pain processing networks in the brain *in vivo* during ongoing pain. Several functional imaging studies with positron emission tomography (PET) have been performed in CH. Nitroglycerine triggered headache attacks in nine chronic CH patients during $H_2{}^{15}O$ PET resulted in a strong activation of the ipsilateral posterior hypothalamus.[10] A similar activation was present in spontaneous CH attacks in one patient receiving DBS.[11] In four patients with episodic CH, functional magnetic resonance imaging (fMRI) confirmed activation of the ipsilateral posterior hypothalamus.[12] However, some authors argued that the detected activation was located merely close to the hypothalamus, most likely the midbrain tegmentum, rather than the hypothalamus itself.[13] Other studies showed an activation of the hypothalamus together with other parts of human pain processing networks such as the cingulate cortex, the insula, temporal, and frontal cortex.[8] Table 1 summarizes the currently available studies and their findings [Table 1].

### Resting state functional magnetic resonance imaging

The analysis of low-frequency (<0.1 Hz) fluctuations seen on fMRI scans at rest allows detection of functionally connected brain regions, so-called resting state networks. Synchronous variations of the blood-oxygen level dependent (BOLD) signal can be measured as percentage signal change compared to the BOLD mean signal intensity over time.[27-30] Rocca *et al*. studied resting state activity in 13 patients with episodic CH in a pain-free state (= outside bout) compared with healthy controls. The authors observed altered functional connectivity (FC) within the network from the hypothalamus to the thalamus bilaterally and the sensorimotor cortex as well as the primary visual cortex.[16] More recent studies showed that a whole network including the hypothalamus but not restricted to it is active in resting state fMRI of episodic and chronic CH both on the headache and nonheadache side.[18] Episodic CH patients showed hypothalamic FC changes with the medial frontal gyrus, as well as the occipital cuneus in bout and out of bout. This hypothalamic FC was decreased in out-of-bout patients with the medial frontal gyrus, precuneus, and cerebellum (tonsil, declive, and culmen). The annual bout frequency correlated with the hypothalamic connections to the cerebellar culmen and declive. The authors concluded that CH pathophysiology extends beyond the traditional pain processing networks and suggests further research to unravel these additional aspects in CH.[19]

### 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 to healthy controls. These changes were even detectable when the patients were outside the bout, without current CH attacks.[6,9] This observation led to the suggestion that these alterations cannot simply reflect an epiphenomenon of the pain itself but has to be related to genuine CH pathophysiology.[9]

## Paroxysmal Hemicrania

It is estimated that paroxysmal hemicrania comprises about 3%–6% of all TACs.[31] The headache usually starts between the age of 20 and 40 although children with a clear indomethacin response have been described.[32,33] The clinical phenotype of paroxysmal hemicrania is highly characteristic – patients typically have unilateral, brief, severe attacks of pain associated with cranial autonomic features that recur several times per day. Headache lasts usually 2–30 min and has abrupt onset and termination.[34,35] The majority of attacks occur spontaneous, but approximately 10% of attacks may be precipitated mechanically, i.e., by bending or rotating the head.[36] Alcohol ingestion triggers headaches in only 7% of patients.[34] The importance of distinguishing paroxysmal hemicrania from other TACs lies in the dramatic and absolute response to indomethacin, which, according to ICHD3ß, is even a mandatory diagnostic criterion. Some authors suggest an indomethacin-trial for any patients with lateralized discrete attacks of head pain with associated cranial autonomic symptoms.[31,36,37] Indomethacin administration was able to turn off the previously detected activation in several pain processing structures using $H_2{}^{15}O$-PET imaging.[26] The authors documented an activation in the contralateral posterior hypothalamus, contralateral ventral midbrain, ipsilateral lentiform nucleus, anterior and posterior cingulate cortex, bilateral insulae, bilateral frontal and contralateral temporal cortex, contralateral postcentral gyrus, precuneus, and cerebellum contralaterally in seven patients with PH. Indomethacin administration was able to terminate this activation in patients that were previously taken off the indomethacin to provoke PH attacks.[26] This experiment nicely underlines the importance of indomethacin for the pathophysiology of PH [Table 1].

## Short-Lasting Unilateral Neuralgiform Headache Attacks with Conjunctival Injection and Tearing/Short-Lasting Unilateral Neuralgiform Headache Attacks With Conjunctival Injection And Tearing Or Cranial Autonomic Features (Severe Unilateral Neuralgiform Headache Attacks with Conjunctival Injection and Tearing/with Cranial Autonomic Features)

The name of this syndrome (SUNCT) describes its clinical features. Attacks are usually very short and happen at least

**Table 1: Summary of functional imaging studies on trigeminal autonomic cephalalgias (functional magnetic resonance imaging and positron emission tomography)**

| Number of patients and disease entity | Imaging technique | Result | Reference |
|---|---|---|---|
| | | **CH** | |
| 7 episodic CH (CH; 4 during bout, 3 out of bout) | PET during nitroglycerine-induced attacks | Increased rCBF right caudal and rostrocaudal ACC, temporopolar, supplemental motor area, bilateral primary motor cortex, premotor area, opercular region, insula, putamen, lateral inferior frontal cortex<br>rCBR decreases bilateral posterior parietal cortex, occipitotemporal region, and prefrontal cortex | Hsieh *et al*., 1996[14] |
| 9 chronic CH during a bout | PET nitroglycerine-induced attacks | Increased rCBF inferior hypothalamic gray matter ipsilateral to headache, contralertal ventroposterior thalamus, ACC, insula bilaterally | May *et al*., 1998[10] |
| 1 chronic CH during bout | PET spontaneous attack | Increased rCBF inferior hypothalamus, medial thalamus, contralateral inferior frontal cortex | Sprenger *et al*., 2004[11] |
| 17 episodic CH (9 during bout, 8 outside of bout) | PET nitroglycerine-induced attacks, 1 spontaneous attack | Increased rCBF ACC bilaterally, ipsilateral posterior thalamus, ipsilateral basal ganglia, ipsilateral inferior posterior hypothalamus, frontal lobes, insula bilaterally, contralateral inferior frontal cortex | May *et al*., 2000[15] |
| 4 episodic CH inside the bout | fMRI, acute attack | Activation of hypothalamus, prefrontal cortex, ACC, contralateral thalamus, ipsilateral basal ganglia, insula, cerebellar hemispheres bilaterally | Morelli *et al*., 2009[12] |
| 13 episodic CH out of bout | Resting state fMRI (seed-based analysis, independent component analysis) | Increased FC in hypothalamus and thalamus bilaterally, decreased FC sensorimotor cortex and primary visual cortex | Rocca *et al*., 2010[16] |
| 12 episodic CH | Resting state fMRI (seed-based analysis), acute attacks, and interictal | Altered FC in hypothalamus and precentral gyrus, superior, middle temporal gyrus, parahippocampus, occipital, precuneus, cuneus | Qiu *et al*., 2013[17] |
| 21 episodic CH out of bout | Resting state fMRI (independent component analysis) | Decreased FC between hypothalamus and the salience network | Qiu *et al*., 2015[18] |
| 18 episodic CH in and out of bout | resting state fMRI (seed-based analysis) | Hypothalamic FC changes in frontal, occipital cortex, and cerebellum | Yang *et al*., 2015[19] |
| 17 episodic CH in and out of bout | resting state fMRI (independent component analysis) | Abnormal FC within temporal, frontal, salience, default mode, somatosensory, dorsal attention, and visual networks | Chou *et al*., 2016[20] |
| 17 episodic CH out of bout | resting state fMRI (independent component and wavelet decomposition analysis) | Increased frequency specific activity in attention ipsilateral to headache and contralateral cerebellar network | Faragó *et al*., 2017[21] |
| | | **PH** | |
| 7 PH | PET | Increased rCBF contralateral posterior hypothalamus, ventral midbrain, lentiform nucleus, anterior and posterior cingulate cortices, bilateral insulae, bilateral frontal cortex, contralateral temporal cortex, contralateral postcentral gyrus, precuneus, contralateral cerebellum | Matharu *et al*., 2006[22] |
| | | **SUNCT** | |
| 1 SUNCT | fMRI during 6 consecutive attacks | Ipsilateral inferior posterior hypothalamus | May *et al*., 1999[23] |
| 2 SUNCT | fMRI during attacks | Inferior posterior hypothalamus bilateral | Cohen *et al*., 2004[24] |
| 1 probable SUNCT | fMRI during attack | Ipsilateral hypothalamus, cingulate cortex, insula, temporal, and frontal cortex | Sprenger *et al*., 2004[8] |
| 1 SUNCT | fMRI during 3 consecutive attacks | Brainstem, right precentral, superior frontal, inferior frontal cortex, supplementary motor area bilaterally | Auer *et al*., 2009[25] |

*Contd...*

**Table 1: Contd...**

| Number of patients and disease entity | Imaging technique | Result | Reference |
|---|---|---|---|
| | | **HC** | |
| 7 HC | PET during pain and after indomethacin | Posterior hypothalamus, dorsal rostral pons, ipsilateral ventrolateral midbrain | Matharu *et al*., 2004[26] |

fMRI = Functional magnetic resonance imaging, PET = Positron emission tomography, CH = Cluster headache, rCBF = Regional cerebral blood flow, FC = Functional connectivity, ACC = Anterior cingulate cortex, PH = Paroxysmal hemicranias, SUNCT = Syndrome of unilateral neuralgiform headache attacks with conjunctival injection and tearing, HC = Hemicrania continua

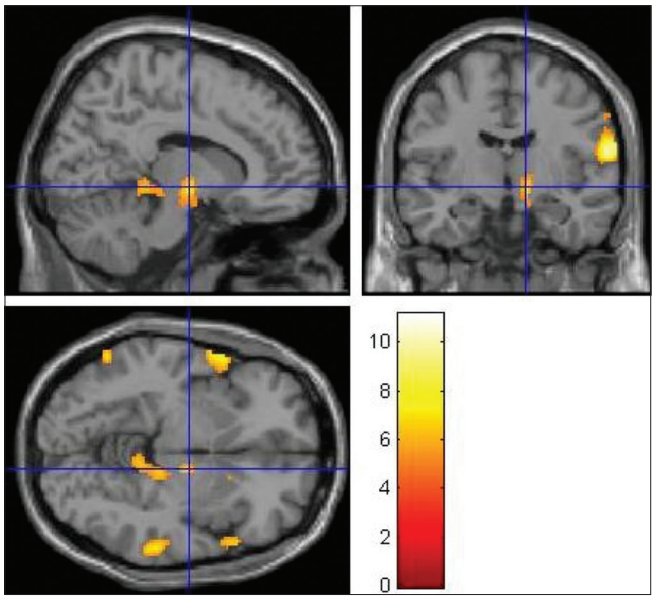


**Figure 1:** Functional magnetic resonance imaging activation in typical regions of the trigeminal pain processing system including primary and secondary somatosensory cortex, anterior cingulate cortex, thalamus and insular cortex as well as the hypothalamus in spontaneous attacks of one SUNCT patient (FWE = Family wise error correction; $P < 0.05$)

20 times a day. In recognition of the possibility that all patients with this condition might not have both, conjunctival injection and tearing, the IHS classification committee introduced the umbrella term severe unilateral neuralgiform headache attacks (ICHDß 3.3) which consist of SUNCT (3.3.1) and SUNA (3.3.2, short-lasting unilateral neuralgiform headache attacks with cranial autonomic features).[1] In both, there may be cranial autonomic symptoms other than conjunctival injection and lacrimation. In SUNA, indeed only one (or even neither) of conjunctival injection and tearing may be present. SUNCT was first described in 1989[38] and is characterized by very short (5–240 s) attacks with neuralgiform pain quality and severe intensity, resembling trigeminal neuralgia attacks. Attacks are often triggered by touching, speaking, or chewing but without refractory period after the trigger. Imaging studies tried to find a common denominator between trigeminal neuralgia on the one hand and the other TACs as well as migraine on the other hand to better classify SUNCT/SUNA in regard to its underlying pathophysiology. An interesting finding in these patients is their comorbidity with migraine. Approximately 37% of patients had a personal history of migraine and 50% had migrainous symptoms.[39] This is in contrast to the 11%–15% migraine prevalence in the general population.[40] Migraine is also more common in patients with CH[41] and may coexist with paroxysmal hemicrania.[42] This may reflect a predisposition for primary headache syndromes or may be expression of a pathophysiological connection between these disorders. On the ground of gathered pathophysiological evidence, we suggested a common final pathway of TACs and migraine in the past.[43] It could be possible that unilateral headaches might share a common pathway in the development of autonomic symptoms and head pain that might include functional alterations in hypothalamic or brainstem circuits.[44] As one contributing factor, it has been postulated that pain intensity may correlate positively with the development of autonomic symptoms,[45] i.e., the stronger the pain, the more likely the development of unilateral autonomic symptoms (UAs). The trigeminovascular reflex is most strongly expressed in patients with trigeminal autonomic cephalalgias but also exists in normal persons[46] and may be active in patients with migraine.[47] Pain might work as a trigger for the occurrence of UAs. There could be a particular threshold for pain, after which the trigeminal system causes parasympathetic overflow leading to activation of the trigeminovascular reflex and consequently to UAs. This may also explain a connection or potential clinical overlap with trigeminal neuralgia.

Several fMRI studies have been performed in SUNCT during attacks and showed a consistent activation of the posterior hypothalamus in all studies [Table 1 and Figure 1]. One study was able to demonstrate additional activation in the cingulate cortex, the insula, temporal, and frontal cortex in a single patient that was classified probable SUNCT.[8] A different study on a 60-year-old patient was able to detect brainstem activation during three typical SUNCT attacks. Activations were also found in the right precentral, superior frontal, inferior frontal (opercular part) cortex, as well as the superior frontal (medial part), middle frontal cortex, and bilateral supplementary motor area.[25] Authors suggested a broader concept of network connections within pain processing structures that become activated during spontaneous SUNCT attacks but may also be active in a similar but not identical way during other headache entities such as migraine or CH.

## Hemicrania Continua

Hemicrania continua is another indomethacin-responsive primary headache disorder characterized by a continuous,

unilateral headache that varies in intensity, waxing, and waning without disappearing completely. The continuous baseline headache is frequently associated with autonomic features such as ptosis, miosis, tearing, and sweating.[48] Exacerbations of headache are common features of hemicrania continua, occurring in 74% of patients.[49] Most pathophysiological studies aim to identify hemicrania continua as one specific TAC rather than a variant or chronic form of other primary headaches such as migraine or CH. There is one functional imaging study with PET that investigated seven right-handed patients with HC in their painful state, as well as after indomethacin administration compared to seven age- and gender-matched healthy controls. Two of these patients had concomitant infrequent migraine as relevant comorbidity. During the pain condition, PET activity was shown in the posterior hypothalamus, the dorsal rostral pons, and the ipsilateral ventrolateral midbrain. This activation was completely blocked with intramuscular indomethacin linking their origin clearly to the HC associated pain. The authors concluded that the activation is different from migraine but related to SUNCT and CH so that HC can be distinguished from migraine and shares pathophysiological features of other TACs.[26]

## Conclusion

Functional neuroimaging on TACs point toward a complex neural network performance deficit rather than a single locus of abnormality even though it remains undisputed that the hypothalamus plays an important role in the pathophysiology of this group of disorders. Imaging has given some important insights into the pathophysiology but may not be able to resolve this puzzle alone, as the exact mechanisms of neuronal modulation between hypothalamus and other pain-processing brain regions remain unknown. More sophisticated studies (especially longitudinal designs) are needed to address every aspect of these disorders properly. The similarities that most TACs share on functional neuroimaging justify their status as unique disease entities in a common subgroup of primary headache disorders. The distinction of each individual TAC syndrome from one another will be the future challenge with most useful results in everyday clinical practice.

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### Conflicts of interest

There are no conflicts of interest.

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