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Hypothalamic regulation of headache and migraine

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Abstract

Background: The clinical picture, but also neuroimaging findings, suggested the brainstem and midbrain structures as possible driving or generating structures in migraine.

Findings: This has been intensely discussed in the last decades and the advent of modern imaging studies refined the involvement of rostral parts of the pons in acute migraine attacks, but more importantly suggested a predominant role of the hypothalamus and alterations in hypothalamic functional connectivity shortly before the beginning of migraine headaches. This was shown in the NO-triggered and also in the preictal stage of native human migraine attacks. Another headache type that is clinically even more suggestive of hypothalamic involvement is cluster headache, and indeed a structure in close proximity to the hypothalamus has been identified to play a crucial role in attack generation.

Conclusion: It is very likely that spontaneous oscillations of complex networks involving the hypothalamus, brainstem, and dopaminergic networks lead to changes in susceptibility thresholds that ultimately start but also terminate headache attacks. We will review clinical and neuroscience evidence that puts the hypothalamus in the center of scientific attention when attack generation is discussed.

Keywords

Migraine; attack; brainstem; hypothalamus; network

Introduction

Advances in neuroimaging have played a significant role in our current understanding of the pathophysiology of migraine and cluster headache (CH), as it has allowed us to get information how the brain and the vascular system that serves it function differently during the different phases of these two headache types (1). These processes, however, are still only

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partially understood, likely to be multifactorial, and involve multiple brain networks and structures. For several years, the hypothalamus has been thought to play an important role in the generation of some of the most common symptoms that appear after the onset of the headache phase of a migraine attack (2). Incorporating recent findings into the global understanding of the role played by the hypothalamus in maintaining the wellbeing of the organism, it appears that the hypothalamus plays a very specific and possibly critical role in attack initiation. Attempting to clarify some of the confusion regarding the involvement of peripheral and central neurons in migraine initiation, we wish to distinguish between initiation of a migraine attack and initiation of the headache phase. While it is likely that, in most cases, migraine and CH originate in the brain, it is likely that the perception of pain; that is, the headache/pain phase, depends on activation of nociceptors inside and/or outside the calvaria and that the maintenance (duration) of the ongoing headache involves both sensitization of all segments of the trigeminovascular pathway and defects in its modulation by brainstem, hypothalamic and possible cortical nuclei and regions. In this paper, we review clinical presentations and scientific evidence that support the view that the hypothalamus is involved in the initiation of migraine and CH, generation of migraine-associated symptoms, and potentially migraine termination. Before starting, we acknowledge that a critical gap in our ability to explain how the hypothalamus eventually leads to the very specific presentation of migraine or cluster headache is a lack of understanding of how altered hypothalamic functions eventually lead to activation of nociceptors in the meninges or orbito-maxillary area.

The clinical presentation of headache pointing to hypothalamic involvement

One could subdivide primary headache syndromes into those where the clinical picture points towards hypothalamic involvement (migraine, trigemino-autonomic headaches (TAC) and those where the clinical picture does not (tension type headache and most group 4 headaches (with the exception of hypnic headache) following the IHS classification (3)). The headache type where hypothalamic involvement is clinically rather obvious is cluster headache (4), which can be considered to exist on a continuum with the symptoms of other TACs including hemicrania continua, paroxysmal hemicrania, and the short-lasting unilateral neuralgiform headaches including short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA). Each of the TACs manifests with unilateral headaches associated with ipsilateral cranial autonomic features and can be differentiated by the duration and frequency of attacks and therapeutic response to indomethacin. The regularity and seasonal recurrence of these highly specific headache attacks, in conjunction with a relapsing-remitting presentation and ipsilateral cranial autonomic features, suggest that at least cluster headache (5,6) but more likely all TACs (7,8) may be related to a biological clock such as that found in the hypothalamus. Additionally, patients with CH often show accompanying neuro-endocrinological changes such as a blunted circadian rhythmicity of hypothalamically regulated hormones including testosterone, cortisol, growth hormone, thyroid-stimulating hormone, prolactin, melatonin, follicle-stimulating hormone, and luteinizing hormone (6,9).

Migraine is clinically characterized by various symptoms, which are defined by the IHS classification (3). What is not expressed by this classification is the fact that migraine is a multiphasic disorder and understanding of its pathophysiology starts with the acknowledgment that migraine is not simply a disease of headache attacks, but that it involves sensory processes that evolve over time. These processes can be best described as a step-wise increase of sensitivity and/or hyperexcitability of different brain regions (10), facilitating paroxysmal headache and aura (1). The accompanying symptoms of nausea, and photo- and phonophobia, are usually simultaneous to the headache but usually start before the headache. Though inconsistently, around 70–80% of migraine patients experience at least in some of these attacks migraine premonitory symptoms such as changes in appetite (food craving or nausea) and sleep-waking rhythms (yawning, fatigue, sleep disturbances), hypersensitivity to certain stimuli (photo-, osmo-, phonophobia), mood changes, and changes in liquid tolerance and others (11–17). And just as there are prodromal symptoms, a great percentage of patients experience a postdromal phase characterized as occurring after headache remission: Fatigue and tiredness but also euphoria or dysphoria are frequent, next to alterations in appetite or liquid tolerance (18–21).

Focusing only on the headache phase in migraine will miss the fact that migraine is a syndrome that evolves over time and in a timely order (10). If one follows this line of thought, migraine appears to be not an isolated event of headache but an oscillation of sensory and bodily functions where the headache appears to be just one of many symptoms (21–23).

Several clinical features point towards the limbic system and hypothalamus as prodrome/ attack-initiating brain structures. These include the well-described involvement of the hypothalamus in the regulation of yawning (24), tiredness and mood changes (17); the circadian rhythmicity of attacks (25); and the association of attacks with hormonal status and the menstrual cycle (26). Some of the typical premonitory symptoms (e.g. yawning and nausea) additionally point towards dopaminergic involvement (27). Recent evidence suggests that the above-mentioned clinical symptoms could possibly be explained by an involvement of the central nervous system; among these, the central dopaminergic system and the hypothalamus.

Structure and function: The hypothalamus

The hypothalamus is a rather small brain area situated around the third ventricle of the brain, below the thalamus (hence its name) and above the adenohypophysis. The hypothalamus is in direct contact with the vasculature and serves as a brain-hormonal interface through which the brain controls peripheral body systems. Next to regulation of body temperature, sleep, food and water intake, it has specific control over the autonomic nervous system and cyclic phenomena such as circadian and circannual body rhythms. The hypothalamus also has various neuroanatomical connections to pain-modulating systems and also to the spinal trigeminal nuclei (see Figure 1) (28–30). The orexinergic system, which is known to regulate arousal and nociceptive processing as well as thermoregulation and autonomic functions, has only recently become a site of interest in migraine research (31,32). The orexinergic processing was suggested to be involved in migraine attack generation and/or sustainment of

migraine pain. Pharmacological blockade of orexin receptors inhibited cortical spreading depression in rats and attenuated meningeal artery dilation caused by nociceptive afferent trigeminal activation (33). However, orexin may have a more generalized cause-consequence relationship in trigeminal nociception rather than just migraine, as injection of orexins A and B (also known as hypocretins 1 and 2) into the posterior hypothalamus modulates neuronal activity in the TNC (34).

Another neurotransmitter system involving the hypothalamus is the central dopaminergic system. Typical premonitory symptoms such as yawning and fatigue, but also changes in appetite and nausea, involve the dopaminergic system (27,35). Dopaminergic agonists such as apomorphine increase yawning, dizziness, nausea and vomiting in migraine patients (27,36–39). It has been suggested that the midbrain dopaminergic system could play a role in cluster headache pathophysiology (40). Dopamine antagonists such as metoclopramide, which is usually given against nausea in migraine, has been proven to be also effective in the treatment of migraine headache itself (41–46). A specific cell group within the posterior hypothalamus has been shown to inhibit trigeminonociceptive firing of the trigeminocervical complex (47). Ascending projections from this cell group to thalamic regions possibly involved in photophobia and allodynia (posterior and latero-posterior thalamus) indicate another possible role of hypothalamic-thalamic interactions in migraine. This could also explain some accompanying symptoms such as craving or anorexia, given that the hypothalamus is involved in regulation of food intake (47).

Hypothalamic involvement in cluster headache attacks

The hypothalamus receives sensory input from areas innervated by the trigeminal nerve via the trigeminohypothalamic tract, and in return is able to modulate the neuronal activity of the trigeminal nucleus caudalis via the posterior part of the hypothalamus (48). Disturbances in the hypothalamic orexinergic system may be associated with CH pathophysiology (49) and patients with CH have decreased cerebrospinal fluid levels of orexin-1 (50). An increased risk for polymorphism in the hypocretin receptor 2 (orexin-2) gene has been shown in cluster headache patients (51), but this did not predict treatment responses with triptans, oxygen, verapamil and corticosteroids (52). Filorexant, an orexin receptor 1 and 2 antagonist, has failed a study on migraine prevention (53), valid data or RCTs for treatment of cluster headache with orexins are missing (54).

In a series of neuroimaging studies, marked increases in ipsilateral posterior hypothalamic activation in patients with CH during nitroglycerin-triggered (55,56) and spontaneous attacks (57,58) were observed compared to both the headache-free state and control subjects, suggesting that the hypothalamus plays a crucial role in initiation of CH. In contrast to migraine, no brainstem activation was found during the acute attack compared to the resting state. This is remarkable, as migraine and cluster headache are often discussed as related disorders and identical specific compounds, such as ergotamine and sumatriptan, are used in the acute treatment of both types of headache syndromes.

These findings prompted the use of deep brain stimulation in the posterior hypothalamic grey matter in a patient with intractable CH, and led to a complete relief of attacks (59). To

date, nearly 50 operated intractable CH patients, some with a follow-up of more than 4 years, have been reported and showed a significant effect of hypothalamic DBS in about 50–60% of CH patients (60–63). To understand how hypothalamic DBS may exert its effect, a PET study was applied in hypothalamic deep brain-stimulated patients. This study found that stimulation of the posterior hypothalamic area induced activation in the ipsilateral hypothalamic grey (the site of the stimulator tip) but also modulated a network of activated and deactivated brain regions belonging to neuronal circuits usually activated in pain transmission and notably in acute cluster headache attacks (64). These data argue against an unspecific antinociceptive effect or pure inhibition of hypothalamic activity and rather suggest a complex functional modulation of the pain processing network as the mode of action of hypothalamic deep brain stimulation (DBS) in cluster headache. Additional evidence from voxel-based morphometry (VBM) to investigate macrostructural brain abnormalities (55) and Proton magnetic resonance spectroscopy studies (65,66) suggest that there is persistent hypothalamic neuronal dysfunction in CH patients.

Hypothalamic involvement in migraine: How nociceptive signals produce endocrine, autonomic, and affective responses

As stated above, not all migraine patients report signs that warn them about incoming migraine attacks (i.e. premonitory signs or prodromes) and even among the 70–80% of those who report such signs, it is often the case that their warning signs are variable and inconsistent. In contrast, almost all patients report some hypothalamic-mediated symptoms during most, if not all of their migraine attacks. These observations have given rise to the view that many of the hypothalamic-mediated migraine-associated symptoms could be triggered by a stream of continuous pain signals that reach these limbic brain areas directly through neurons in the spinal trigeminal nucleus that process nociceptive information that arises in the meninges (67–71). Complex hypothalamic-mediated functions are commonly influenced by sensory (e.g. pain, vision, taste), and physiological (e.g. hunger, thirst, increased heart rate, overheating) signals arising from the head and body, but also cognitive signals arising from cortical and subcortical brain regions (28,72,73). The integration of sensory, physiological, and cognitive signals by hypothalamic neurons that regulate hormonal secretion and the activity of brain stem and spinal cord neurons that mediate autonomic responses could provide a partial answer to the question of how nociceptive signals produce endocrine, autonomic, and affective responses. In the past, it was thought that all sensory and nociceptive inputs that the hypothalamus receives (74–78) originate in brain stem nuclei such as the parabrachial nuclei (79–81), nucleus of the solitary tract (82,83), periaqueductal gray (84–87), and caudal ventrolateral medulla (88,89). It is now widely known that neurons in these hypothalamic areas and nuclei receive a large direct nociceptive input through the trigeminohypothalamic tract (THT) – a tract originating in spinal trigeminal nucleus neurons that process sensory signals from all organs and tissues in the head, including the meninges (67–69,71). Direct projections of axons of durasensitive THT neurons into hypothalamic nuclei that contain neurons that regulate body temperature, food and water intake, sleep and circadian rhythms and a wide range of affects (90–93), and rigorous scientific evidence for distinct responses to pain by hypothalamic neurons that mediate autonomic, neuroendocrine, physiological and behavioral responses (94–97) that

aim at preservation of homeostasis, mean one must take into consideration the possibility that migraine-associated symptoms such as food craving and loss of appetite, lethargy and fatigue, feeling hot and sweaty or cold and shivery, and submitting to being depressed, short tempered and easily angered may all be driven by nociceptive/pain signals that originate in the meninges through the long course of the headache phase of a migraine attack. Functionally, such hypothalamic-mediated responses are likely to involve input the hypothalamus receives from the amygdala, nucleus accumbens, septal nuclei, preoptic area, and different regions of the frontal cortex – all of which appear to receive direct nociceptive input from the meninges through the trigeminohypothalamic and/or reticulohypothalamic tracts.

Is hypothalamic involvement important in migraine attack generation?

Imaging findings

Several independent functional imaging studies have reinforced the crucial role for the brainstem in acute (98) and probably also chronic (99) migraine. The common finding of all these observations is a consistent increase in rCBF in the rostral brainstem (100) that persisted even after sumatriptan had induced complete relief from headache, nausea, phonophobia and photophobia (98,101,102). However, comparing the brain activity with different stages of the migraine cycle (102,103) has had tremendous impact on our understanding of migraine pathophysiology and draws a more complex picture of the evolution of a migraine attack. The first study investigated NO-induced migraine and the second study spontaneous attack generation. Administration of NO as a human model of the premonitory phase revealed an increased activity of the hypothalamus and the dorsal rostral pons even before the headache started (104). More recently, one migraine patient went into the scanner daily over a whole month, which included three spontaneous untreated headache attacks. This study found that distinct changes involving certain networks including the hypothalamus and the dorsal rostral pons with a rather specific connectivity pattern between them correlated with different stages of the migraine cycle (103). Whereas in the preictal phase the hypothalamus was functionally coupled with the spinal trigeminal nuclei, it showed increased functional coupling with the dorsal rostral pons (the so-called brainstem generator) during the ictal phase. These data strongly point towards alterations in functional connectivity between the hypothalamus and other brain regions as an independent oscillating system that lowers the susceptibility threshold for incoming sensory signals.

Hypothalamic involvement in migraine initiation and headache intensity – an alternative view

To generate the perception of migraine headache, nociceptive signals that originate in the meninges must reach the cortex. Because the thalamus plays a central role in the selection, amplification, and prioritization of information that is made available to the cortex at any given time (105,106), it is likely to play a key role in determining when nociceptive signals that originate in the meninges are “allowed” to reach the cortex. To help regulate the amount of sensory signals that reach the cortex, thalamic neurons are subjected to a variety of excitatory and inhibitory modulatory inputs (105,107–109) capable of producing sustained

neuronal firing or complete inhibition. Historically, most well-documented and heavily studied thalamic modulatory pathways include glutamatergic and GABAergic neurons (110,111). More recently, however, we demonstrated that hypothalamic neurons containing noradrenaline, histamine, dopamine, orexin and melanin-concentrating hormone (MCH) establish mono-synaptic connections with cell bodies and dendrites of trigeminovascular thalamic neurons that project to multiple cortical areas (47,112,113) and, based on these novel connections, proposed a new notion for hypothalamic involvement in migraine pathophysiology in general and in the initiation of a migraine attack in particular (47,112,113). In principle, this proposal is based on two sets of data. The first is the anatomical one described above, which confirms previous descriptions of projections of dopaminergic, noradrenergic, orexinergic, histaminergic and MCH-ergic neurons from the hypothalamus to the thalamus (113), and establishes a direct relevance to migraine pathophysiology. The second is functional. It is based on the widely accepted notion that relay thalamocortical neurons exhibit two distinct discharge modes (burst and tonic), one that is commonly associated with lower excitability, drowsiness and acute pain (the burst mode), and one that is commonly associated with higher excitability, wakefulness and chronic pain (the tonic mode) (105,108,114–117). Existing evidence for dopamine's ability to facilitate membrane depolarization (through D1 and D2 receptors) and increase excitability and firing of sensory thalamic neurons (118), noradrenaline's ability to prolong activation of sensory thalamic neurons (acting on α and β adrenoceptors) by altering their membrane resting potential and increasing their synaptic strength (119–122), histamine's ability to enhance the slow depolarization current (through H1), which switches discharge of thalamic neurons from burst to tonic mode (123), orexin's ability to depolarize thalamic neurons (by acting on the selective orexin receptor 1 and non-selective orexin receptor 2, also known as orexin A and orexin B receptors) to the extent that it can switch their firing from burst to tonic (124), and for hypothalamic MCH neurons' ability to release GABA upon their activation (125), which in turn tends to promote hyperpolarization and reduce neuronal excitability – all set the stage for our conceptual proposal that the hypothalamus is well positioned to regulate the strength of nociceptive signals the thalamus transmits (relays) to the cortex at a given time (during and in between migraine attacks). More precisely, we propose that because some of the hypothalamic pathways that modulate the activity of relay thalamocortical trigeminovascular neurons are inhibitory (capable of preventing pain signals from reaching the cortex) whereas others are excitatory (allowing and even facilitating the flow of meningeal pain signals to the cortex), it is reasonable to suggest that the hypothalamus helps the thalamus to “decide” when it is right and when it is not right to let the cortex know about the headache. The hypothalamus, it appears, determines which system (neuropeptide or neurotransmitter) will dominate the firing of a trigeminovascular thalamic neuron at any given time as it makes all necessary adjustments needed to keep homeostasis in response to the constantly changing physiological (sleep, wakefulness, food intake, body temperature, heart rate, blood pressure), behavioral (addiction, isolation), cognitive (attention, learning, memory use) and affective (stress, anxiety, depression, anger) conditions in the internal and external environment the patient lives in, moment to moment. Given the array of reciprocal connections between the hypothalamus, brainstem, spinal cord, subcortical limbic nuclei and the cortex, we propose here that the networks through which the hypothalamus fulfils this role in migraine are influenced by and sub-serve multiple

functions including setting brainstem oscillatory functions, sensory thresholds, and pain modulation at all levels of the neuraxis. In the context of this review, it seems reasonable to suggest that the large nociceptive input that the hypothalamus receives from second-order trigeminovascular neurons in the spinal trigeminal nucleus is capable of altering the firing of a variety of neurons in different hypothalamic nuclei that together define the proper brain/body response to the pain through neuroendocrine, neuroautonomic, and reciprocal connections with spinal cord, brainstem, thalamic, forebrain and cortical areas and nuclei.

What migraine-type photophobia teaches us about hypothalamic involvement

Many patients report that their need to avoid light is driven mainly by how aversive (i.e. unpleasant) it makes them feel. While the hypothalamus appears to play a very limited role in the intensification of headache by light, it seems to be ideally positioned to mediate most, if not all of the “reasons” migraine patients find the light aversive. In this regard, it was reported recently that during a migraine attack, exposure to light can give rise to a variety of autonomic and affective responses or perceptions of symptoms such as chest and throat tightness, shortness of breath, fast breathing, faster than usual heart rate, light-headedness, dizziness, nausea, vomiting, dry mouth, salivation, rhinorrhea, stuffy sinuses and lacrimation, thirst and food craving, drowsiness, sleepiness and fatigue or actual yawning, irritability, anger, nervousness, sadness, depression, anxiety, panic fear and crying (126). Reading through this long list of responses, one cannot ignore the notion that the hypothalamus must be heavily involved in the production of this complex array of symptoms that lead patients to perceive light as aversive. Mechanistically, we now know that axons of retinal ganglion cells carry photic signals directly to hypothalamic neurons that (i) project to preganglionic parasympathetic neurons in the superior salivatory nucleus, (ii) preganglionic sympathetic neurons in the thoracic spinal cord, and (iii) dopaminergic, noradrenergic, histaminergic, orexinergic, MCH-ergic, oxytocinergic and vasopressinergic neurons located in many areas and nuclei of the hypothalamus (126). A synthesis of current understanding of the role played by each of these chemical and functional pathways in the production of the different responses to light, and the discovery of novel retinohypothalamic, retinohypothalamic-sympathetic and retinohypothalamic-parasympathetic pathways suggest that the hypothalamic role in migraine is more complex and much greater than previously thought, that there is no one truth to its involvement in migraine, and that any attempt to simplify it is bound to lead us wrong. Furthermore, the many reciprocal connections between the hypothalamus and limbic system dictate that the hypothalamus’ role in migraine cannot be achieved in isolation from the rest of the brain as its function is determined largely by inputs it receives from areas involved cognition, memory, previous experience, fear, anger, happiness, reward, learning, and sensory processing. Rather than viewing the hypothalamus as the new “migraine generator”, it may be more accurate to view the hypothalamus as a central component of a multifaceted network of brain areas that in concert shift the brain from a non-migraine to a migraine state and vice versa.

In summary, we are proposing at least two very different scenarios for hypothalamic involvement in migraine. One scenario, the one supported by the findings that the

hypothalamus exhibits enhanced activity the day before a migraine attack commences and which suggests that when homeostasis is shifted (hunger, sleep deprivation, being too cold or too hot, etc) the hypothalamus can lower the threshold for the onset of the next migraine attack, outlines a mechanistic explanation for how the hypothalamus may be involved in the generation of a migraine attack (which by definition must take place before the onset of headache and the activation of the meningeal nociceptors). The other scenario, the one supported by the very large nociceptive projections of trigeminovascular neurons in the spinal trigeminal nucleus to hypothalamic nuclei and neurons that regulate many of the most common migraine symptoms, and the wide projections of these (chemically identified) hypothalamic neurons to the cortex, brainstem, and preganglionic sympathetic and parasympathetic neurons, outlines a mechanistic proposal for how pain signals that originate in the meninges and are transmitted to the hypothalamus during the headache phase of a migraine attack may contribute to the classical affective, autonomic, endocrine and general physiological responses patients identify as migraine-associated symptoms.

Taken together, recent data suggest that the pathophysiology and genesis of headache attacks, namely migraine and cluster headache, are probably not just the result of peripheral vasculature changes or one single “generator”. A more complex picture of attack generation is likely: Spontaneous oscillations of complex networks involving the hypothalamus, brainstem, and dopaminergic networks lead to changes in activity in certain subcortical and brainstem areas, thus changing susceptibility thresholds and starting but also terminating headache attacks.

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References

1. May A and Goadsby PJ. The trigeminovascular system in humans: Pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. *J Cereb Blood Flow Metab* 1999; 19: 115–127. [PubMed: 10027765]
2. Lance JW. Headache. *Ann Neurol* 1981; 10: 1–10. [PubMed: 7023351]
3. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition *Cephalalgia* 2018; 38: 1–211.
4. Snoer A, Lund N, Beske R, et al. Pre-attack signs and symptoms in cluster headache: Characteristics and time profile. *Cephalalgia* 2017; 38: 1128–1137. [PubMed: 28816505]
5. Pringsheim T Cluster headache: Evidence for a disorder of circadian rhythm and hypothalamic function. *Can J Neurol Sci* 2002; 29: 33–40. [PubMed: 11858532]
6. Strittmatter M, Hamann GF, Grauer M, et al. Altered activity of the sympathetic nervous system and changes in the balance of hypophyseal, pituitary and adrenal hormones in patients with cluster headache. *Neuroreport* 1996; 7: 1229–1234. [PubMed: 8817538]
7. May A. Pearls and pitfalls: Neuroimaging in headache. *Cephalalgia* 2013; 33: 554–565. [PubMed: 23671252]
8. Matharu M and May A. Functional and structural neuroimaging in trigeminal autonomic cephalalgias. *Curr Pain Headache Rep* 2008; 12: 132–137. [PubMed: 18474194]
9. Leone M and Bussone G. A review of hormonal findings in cluster headache. Evidence for hypothalamic involvement. *Cephalalgia* 1993; 13: 309–317. [PubMed: 8242722]

10. Blau JN. Migraine: Theories of pathogenesis. *Lancet* 1992; 339: 1202–1207. [PubMed: 1349944]
11. Laurell K, Artto V, Bendtsen L, et al. Premonitory symptoms in migraine: A cross-sectional study in 2714 persons. *Cephalalgia* 2016; 36: 951–959. [PubMed: 26643378]
12. Giffin NJ, Ruggiero L, Lipton RB, et al. Premonitory symptoms in migraine: An electronic diary study. *Neurology* 2003; 60: 935–940. [PubMed: 12654956]
13. Kelman L The premonitory symptoms (prodrome): A tertiary care study of 893 migraineurs. *Headache* 2004; 44: 865–872. [PubMed: 15447695]
14. Quintela E, Castillo J, Muñoz P, et al. Premonitory and resolution symptoms in migraine: A prospective study in 100 unselected patients. *Cephalalgia* 2006; 26: 1051–1060. [PubMed: 16919055]
15. Schoonman GG, Evers DJ, Terwindt GM, et al. The prevalence of premonitory symptoms in migraine: A questionnaire study in 461 patients. *Cephalalgia* 2006; 26: 1209–1213. [PubMed: 16961788]
16. Cuvellier J-C, Mars A and Vallée L. The prevalence of premonitory symptoms in paediatric migraine: A questionnaire study in 103 children and adolescents. *Cephalalgia* 2009; 29: 1197–1201. [PubMed: 19811504]
17. Schulte LH, Jürgens TP and May A. Photo-, osmo- and phonophobia in the premonitory phase of migraine: Mistaking symptoms for triggers? *J Headache Pain* 2015; 16: 14. [PubMed: 25904144]
18. Giffin NJ, Lipton RB, Silberstein SD, et al. The migraine postdrome: An electronic diary study. *Neurology* 2016; 87: 309–313. [PubMed: 27335112]
19. Bose P and Goadsby PJ. The migraine postdrome. *Curr Opin Neurol* 2016; 29: 299–301. [PubMed: 26886356]
20. Kelman L The postdrome of the acute migraine attack. *Cephalalgia* 2006; 26: 214–220. [PubMed: 16426278]
21. May A Understanding migraine as a cycling brain syndrome: Reviewing the evidence from functional imaging. *Neurol Sci* 2017; 38: 125–130. [PubMed: 28527054]
22. Dahlem MA, Kurths J, Ferrari MD, et al. Understanding migraine using dynamic network biomarkers. *Cephalalgia* 2014; 35: 627–630. [PubMed: 25228683]
23. Stankewitz A and May A. Cortical excitability and migraine. *Cephalalgia* 2007; 27: 1454–1456. [PubMed: 18034689]
24. Güven B, Güven H and Çomo lu SS. Migraine and yawning. *Headache* 2018; 58: 210–216. [PubMed: 28960327]
25. Alstadhaug K, Salvesen R and Bekkelund S. Insomnia and circadian variation of attacks in episodic migraine. *Headache* 2007; 47: 1184–1188. [PubMed: 17883523]
26. Silberstein S and Merriam G. Sex hormones and headache 1999 (menstrual migraine). *Neurology* 1999; 53: S3–S13.
27. Charbit AR, Akerman S and Goadsby PJ. Dopamine: What's new in migraine? *Curr Opin Neurol* 2010; 23: 275–281. [PubMed: 20164768]
28. Mayanagi Y, Hori T and San K. The posteromedial hypothalamus and pain, behavior, with special reference to endocrinological findings. *Appl Neurophysiol* 1978; 41: 223–231. [PubMed: 365099]
29. Buller KM. Neuroimmune stress responses: Reciprocal connections between the hypothalamus and the brainstem. *Stress* 2003; 6: 11–17. [PubMed: 12637203]
30. Bartsch T, Levy MJ, Knight YE, et al. Inhibition of nociceptive dural input in the trigeminal nucleus caudalis by somatostatin receptor blockade in the posterior hypothalamus. *Pain* 2005; 117: 30–39. [PubMed: 16043293]
31. Holland P and Goadsby PJ. The hypothalamic orexinergic system: Pain and primary headaches. *Headache* 2007; 47: 951–962. [PubMed: 17578557]
32. Tso AR and Goadsby PJ. New targets for migraine therapy. *Curr Treat Options Neurol* 2014; 16: 318. [PubMed: 25238732]
33. Hoffmann J, Suprinsinchai W, Akerman S, et al. Evidence for orexinergic mechanisms in migraine. *Neurobiol Dis* 2015; 74: 137–143. [PubMed: 25447225]

34. Bartsch T, Levy MJ, Knight YE, et al. Differential modulation of nociceptive dural input to [hypocretin] orexin A and B receptor activation in the posterior hypothalamic area. *Pain* 2004; 109: 367–378. [PubMed: 15157698]
35. Akerman S and Goadsby PJ. Dopamine and migraine: Biology and clinical implications. *Cephalalgia* 2007; 27: 1308–1314. [PubMed: 17970991]
36. Cerbo R, Barbanti P, Buzzi MG, et al. Dopamine hypersensitivity in migraine: Role of the apomorphine test. *Clin Neuropharmacol* 1997; 20: 36–41. [PubMed: 9037571]
37. Del Zompo M, Lai M, Loi V, et al. Dopamine hypersensitivity in migraine: Role in apomorphine syncope. *Headache* 1995; 35: 222–224. [PubMed: 7775179]
38. Blin O, Azulay JP, Masson G, et al. Apomorphine-induced yawning in migraine patients: Enhanced responsiveness. *Clin Neuropharmacol* 1991; 14: 91–95. [PubMed: 2029696]
39. Del Bene E, Poggioni M and De Tommasi F. Video assessment of yawning induced by sublingual apomorphine in migraine. *Headache* 1994; 34: 536–538. [PubMed: 8002329]
40. Ferraro S, Nigri A, Bruzzone MG, et al. Defective functional connectivity between posterior hypothalamus and regions of the diencephalic-mesencephalic junction in chronic cluster headache. *Cephalalgia* 2018; 38: 1910–1918. [PubMed: 29517304]
41. Eken C Critical reappraisal of intravenous metoclopramide in migraine attack: A systematic review and meta-analysis. *Am J Emerg Med* 2015; 33: 331–337. [PubMed: 25579820]
42. Ellis GL, Delaney J, DeHart DA, et al. The efficacy of metoclopramide in the treatment of migraine headache. *Ann Emerg Med* 1993; 22: 191–195. [PubMed: 8427430]
43. Factor SA, Jankovic J, Friedman BW, et al. Randomized trial of IV valproate vs metoclopramide vs ketorolac for acute migraine. *Neurology* 2014; 83: 1388–1389.
44. Gaffigan ME, Bruner DI, Wason C, et al. A randomized controlled trial of intravenous haloperidol vs. intravenous metoclopramide for acute migraine therapy in the emergency department. *J Emerg Med* 2015; 49: 326–334. [PubMed: 26048068]
45. Talabi S, Masoumi B, Azizkhani R, et al. Metoclopramide versus sumatriptan for treatment of migraine headache: A randomized clinical trial. *J Res Med Sci* 2013; 18: 695–698. [PubMed: 24379846]
46. Tek DS, McClellan DS, Olshaker JS, et al. A prospective, double-blind study of metoclopramide hydrochloride for the control of migraine in the emergency department. *Ann Emerg Med* 1990; 19: 1083–1087. [PubMed: 2221512]
47. Kagan R, Kainz V, Burstein R, et al. Hypothalamic and basal ganglia projections to the posterior thalamus: Possible role in modulation of migraine headache and photophobia. *Neuroscience* 2013; 248C: 359–368.
48. Malick A, Strassman RM, Burstein R, et al. Trigeminohypothalamic and reticulohypothalamic tract neurons in the upper cervical spinal cord and caudal medulla of the rat. *J Neurophysiol* 2000; 84: 2078–2112. [PubMed: 11024099]
49. Holland P and Goadsby PJ. The hypothalamic orexinergic system: Pain and primary headaches. *Headache* 2007; 47: 951–962. [PubMed: 17578557]
50. Barloese M, Jennum P, Lund N, et al. Reduced CSF hypocretin-1 levels are associated with cluster headache. *Cephalalgia* 2015; 35: 869–876. [PubMed: 25492975]
51. Schürks M, Kurth T, Geissler I, et al. Cluster headache is associated with the G1246A polymorphism in the hypocretin receptor 2 gene. *Neurology* 2006; 66: 1917–1919. [PubMed: 16554494]
52. Schürks M, Kurth T, Geissler I, et al. The G1246A polymorphism in the hypocretin receptor 2 gene is not associated with treatment response in cluster headache. *Cephalalgia* 2007; 27: 363–367. [PubMed: 17376114]
53. Chabi A, Zhang Y, Jackson S, et al. Randomized controlled trial of the orexin receptor antagonist filorexant for migraine prophylaxis. *Cephalalgia* 2015; 35: 379–388. [PubMed: 25106663]
54. Wei DY and Jensen RH. Therapeutic approaches for the management of trigeminal autonomic cephalalgias. *Neurotherapeutics* 2018; 15: 346–360. [PubMed: 29516437]
55. May A, Ashburner J, Büchel C, et al. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. *Nat Med* 1999; 5: 836–838. [PubMed: 10395332]

56. May A, Bahra A, Büchel C, et al. Hypothalamic activation in cluster headache attacks. *Lancet* 1998; 352: 275–278. [PubMed: 9690407]
57. Sprenger T, Boecker H, Tolle TR, et al. Specific hypothalamic activation during a spontaneous cluster headache attack. *Neurology* 2004; 62: 516–517. [PubMed: 14872051]
58. May A, Bahra A, Büchel C, et al. PET and MRA findings in cluster headache and MRA in experimental pain. *Neurology* 2000; 55: 1328–1335. [PubMed: 11087776]
59. Leone M, Franzini A and Bussone G. Stereotactic stimulation of posterior hypothalamic gray matter in a patient with intractable cluster headache. *N Engl J Med* 2001; 345: 1428–1429. [PubMed: 11794190]
60. Leone M Deep brain stimulation in headache. *Lancet Neurol* 2006; 5: 873–877. [PubMed: 16987734]
61. Akram H, Miller S, Lagrata S, et al. Ventral tegmental area deep brain stimulation for refractory chronic cluster headache. *Neurology* 2016; 86: 1676–1682. [PubMed: 27029635]
62. Nowacki A, Moir L, Owen SLF, et al. Deep brain stimulation of chronic cluster headaches: Posterior hypothalamus, ventral tegmentum and beyond. *Cephalalgia* 2019; 39: 1111–1120. [PubMed: 30897941]
63. Seijo-Fernandez F, Saiz A, Santamarta E, et al. Long-term results of deep brain stimulation of the mamillotegmental fasciculus in chronic cluster headache. *Stereotact Funct Neurosurg* 2018; 96: 215–222. [PubMed: 30064130]
64. May A, Leone M, Boecker H, et al. Hypothalamic deep brain stimulation in positron emission tomography. *J Neurosci* 2006; 26: 3589–3593. [PubMed: 16571767]
65. Lodi R, Pierangeli G, Tonon C, et al. Study of hypothalamic metabolism in cluster headache by proton MR spectroscopy. *Neurology* 2006; 66: 1264–1266. [PubMed: 16636250]
66. Wang S-J, Lirng J-F, Fuh J-L, et al. Reduction in hypothalamic H-MRS metabolite ratios in patients with cluster headache. *J Neurol Neurosurg Psychiatry* 2006; 77: 622–625. [PubMed: 16614022]
67. Burstein R, Yamamura H, Malick A, et al. Chemical stimulation of the intracranial dura induces enhanced responses to facial stimulation in brain stem trigeminal neurons. *J Neurophysiol* 1998; 79: 964–982. [PubMed: 9463456]
68. Malick A, Strassman RM and Burstein R. Trigeminohypothalamic and reticulohypothalamic tract neurons in the upper cervical spinal cord and caudal medulla of the rat. *J Neurophysiol* 2000; 84: 2078–2112. [PubMed: 11024099]
69. Malick A and Burstein R. Cells of origin of the trigeminohypothalamic tract in the rat. *J Comp Neurol* 1998; 400: 125–144. [PubMed: 9762871]
70. Burstein R, Cliffer KD and Giesler GJ. Cells of origin of the spinohypothalamic tract in the rat. *J Comp Neurol* 1990; 291: 329–344. [PubMed: 2298937]
71. Cliffer KD, Burstein R and Giesler GJ. Distributions of spinothalamic, spinohypothalamic, and spinotelencephalic fibers revealed by anterograde transport of PHA-L in rats. *J Neurosci* 1991; 11: 852–868. [PubMed: 1705972]
72. Vandewalle G, Maquet P and Dijk D-J. Light as a modulator of cognitive brain function. *Trends Cogn Sci* 2009; 13: 429–438. [PubMed: 19748817]
73. Herrera CG, Cadavieco MC, Jago S, et al. Hypothalamic feedforward inhibition of thalamocortical network controls arousal and consciousness. *Nat Neurosci* 2016; 19: 290–298. [PubMed: 26691833]
74. Bernard JF, Peschanski M and Besson JM. A possible spino (trigemino)-ponto-amygdaloid pathway for pain. *Neurosci Lett* 1989; 100: 83–88. [PubMed: 2474780]
75. Kannan H, Osaka T, Kasai M, et al. Electrophysiological properties of neurons in the caudal ventrolateral medulla projecting to the paraventricular nucleus of the hypothalamus in rats. *Brain Res* 1986; 376: 342–350. [PubMed: 3015338]
76. Pan B, Castro-Lopes JM and Coimbra A. Central afferent pathways conveying nociceptive input to the hypothalamic paraventricular nucleus as revealed by a combination of retrograde labeling and c-fos activation. *J Comp Neurol* 1999; 413: 129–145. [PubMed: 10464375]
77. Person RJ. Somatic and vagal afferent convergence on solitary tract neurons in cat: Electrophysiological characteristics. *Neuroscience* 1989; 30: 283–295. [PubMed: 2747918]

78. Zhang X, Fogel R and Renehan WE. Physiology and morphology of neurons in the dorsal motor nucleus of the vagus and the nucleus of the solitary tract that are sensitive to distension of the small intestine. *J Comp Neurol* 1992; 323: 432–448. [PubMed: 1281172]
79. Cechetto DF, Standaert DG and Saper CB. Spinal and trigeminal dorsal horn projections to the parabrachial nucleus in the rat. *J Comp Neurol* 1985; 240: 153–160. [PubMed: 3840498]
80. Saper CB and Loewy AD. Efferent connections of the parabrachial nucleus in the rat. *Brain Res* 1980; 197: 291–317. [PubMed: 7407557]
81. Slugg RM and Light AR. Spinal cord and trigeminal projections to the pontine parabrachial region in the rat as demonstrated with Phaseolus vulgaris leucoagglutinin. *J Comp Neurol* 1994; 339: 49–61. [PubMed: 8106661]
82. Menétrey D and Basbaum AI. Spinal and trigeminal projections to the nucleus of the solitary tract: A possible substrate for somatovisceral and viscerovisceral reflex activation. *J Comp Neurol* 1987; 255: 439–450. [PubMed: 3819024]
83. Ricardo JA and Koh ET. Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat. *Brain Res* 1978; 153: 1–26. [PubMed: 679038]
84. Beitz AJ. The organization of afferent projections to the midbrain periaqueductal gray of the rat. *Neuroscience* 1982; 7: 133–159. [PubMed: 7078723]
85. Eberhart JA, Morrell JI, Krieger MS, et al. An autoradiographic study of projections ascending from the midbrain central gray, and from the region lateral to it, in the rat. *J Comp Neurol* 1985; 241: 285–310. [PubMed: 4086658]
86. Lima D and Coimbra A. Morphological types of spino-mesencephalic neurons in the marginal zone (lamina I) of the rat spinal cord, as shown after retrograde labelling with cholera toxin subunit B. *J Comp Neurol* 1989; 279: 327–339. [PubMed: 2913071]
87. Liu RP. Laminar origins of spinal projection neurons to the periaqueductal gray of the rat. *Brain Res* 1983; 264: 118–122. [PubMed: 6189550]
88. Lima D, Mendes-Ribeiro JA and Coimbra A. The spinolatero-reticular system of the rat: Projections from the superficial dorsal horn and structural characterization of marginal neurons involved. *Neuroscience* 1991; 45: 137–152. [PubMed: 1721691]
89. Sawchenko PE and Swanson LW. Central noradrenergic pathways for the integration of hypothalamic neuroendocrine and autonomic responses. *Science* 1981; 214: 685–687. [PubMed: 7292008]
90. Bernardis LL and Bellinger LL. The dorsomedial hypothalamic nucleus revisited: 1998 update. *Proc Soc Exp Biol Med* 1998; 218: 284–306. [PubMed: 9714072]
91. Norgren R. Gustatory responses in the hypothalamus. *Brain Res* 1970; 21: 63–77. [PubMed: 5433117]
92. Peyron C, Tighe DK, van den Pol AN, et al. Neurons containing hypocretin (orexin) project to multiple neuronal systems. *J Neurosci* 1998; 18: 9996–10015. [PubMed: 9822755]
93. Sherin JE, Shiromani PJ, McCarley RW, et al. Activation of ventrolateral preoptic neurons during sleep. *Science* 1996; 271: 216–219. [PubMed: 8539624]
94. Kai Y, Oomura Y and Shimizu N. Responses of rat lateral hypothalamic neurons to periaqueductal gray stimulation and nociceptive stimuli. *Brain Res* 1988; 461: 107–117. [PubMed: 3224271]
95. Hamba M. Effects of lesion and stimulation of rat hypothalamic arcuate nucleus on the pain system. *Brain Res Bull* 1988; 21: 757–763. [PubMed: 3219607]
96. Hamamura M, Shibuki K and Yagi K. Noxious inputs to supraoptic neurosecretory cells in the rat. *Neurosci Res* 1984; 2: 49–61. [PubMed: 6536907]
97. Hilton SM. Hypothalamic control of the cardiovascular responses in fear and rage. *Sci Basis Med Annu Rev* 1965; 217–238. [PubMed: 5321377]
98. Weiller C, May A, Limmroth V, et al. Brain stem activation in spontaneous human migraine attacks. *Nat Med* 1995; 1: 658–660. [PubMed: 7585147]
99. Matharu MS, Bartsch T, Ward N, et al. Central neuromodulation in chronic migraine patients with suboccipital stimulators: A PET study. *Brain* 2004; 127: 220–230. [PubMed: 14607792]

100. IL A Pharmacological neuroimaging in headache and pain. *Curr Opin Neurol* 2013; 26: 254–261. [PubMed: 23511443]
101. Bahra A, Matharu MS, Buchel C, et al. Brainstem activation specific to migraine headache. *Lancet* 2001; 357: 1016–1017. [PubMed: 11293599]
102. Stankewitz A, Aderjan D, Eippert F, et al. Trigeminal nociceptive transmission in migraineurs predicts migraine attacks. *J Neurosci* 2011; 31: 1937–1943. [PubMed: 21307231]
103. Schulte LH and May A. The migraine generator revisited: Continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain J Neurol* 2016; 139: 1987–1993.
104. Maniyar FH, Sprenger T, Monteith T, et al. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain J Neurol* 2014; 137: 232–241.
105. Sherman SM. Thalamic relays and cortical functioning. *Prog Brain Res* 2005; 149: 107–126. [PubMed: 16226580]
106. Sherman SM and Guillery RW. On the actions that one nerve cell can have on another: Distinguishing “drivers” from “modulators”. *Proc Natl Acad Sci USA* 1998; 95: 7121–7126. [PubMed: 9618549]
107. McCormick DA. Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. *Prog Neurobiol* 1992; 9: 337–388.
108. Steriade M, McCormick DA and Sejnowski TJ. Thalamocortical oscillations in the sleeping and aroused brain. *Science* 1993; 262: 679–685. [PubMed: 8235588]
109. Guillery RW and Sherman SM. Thalamic relay functions and their role in corticocortical communication: Generalizations from the visual system. *Neuron* 2002; 33: 163–175. [PubMed: 11804565]
110. Kaneko T and Mizuno N. Immunohistochemical study of glutaminase-containing neurons in the cerebral cortex and thalamus of the rat. *J Comp Neurol* 1988; 267: 590–602. [PubMed: 2450108]
111. McCormick DA and von Krosigk M. Corticothalamic activation modulates thalamic firing through glutamate “metabotropic” receptors. *Proc Natl Acad Sci USA* 1992; 89: 2774–2778. [PubMed: 1313567]
112. Nosedá R, Jakubowski M, Kainz V, et al. Cortical projections of functionally identified thalamic trigeminovascular neurons: Implications for migraine headache and its associated symptoms. *J Neurosci* 2011; 31: 14204–14217. [PubMed: 21976505]
113. Nosedá R, Kainz V, Borsook D, et al. Neurochemical pathways that converge on thalamic trigeminovascular neurons: Potential substrate for modulation of migraine by sleep, food intake, stress and anxiety. *PloS One* 2014; 9: e103929. [PubMed: 25090640]
114. McCarley RW, Benoit O and Barrionuevo G. Lateral geniculate nucleus unitary discharge in sleep and waking: State- and rate-specific aspects. *J Neurophysiol* 1983; 50: 798–818. [PubMed: 6631464]
115. Steriade M and Deschenes M. The thalamus as a neuronal oscillator. *Brain Res* 1984; 320: 1–63. [PubMed: 6440659]
116. Steriade M, Domich L and Oakson G. Reticularis thalami neurons revisited: Activity changes during shifts in states of vigilance. *J Neurosci* 1986; 6: 68–81. [PubMed: 3944624]
117. McCormick DA and Bal T. Sleep and arousal: Thalamocortical mechanisms. *Annu Rev Neurosci* 1997; 20: 185–215. [PubMed: 9056712]
118. Govindaiah G, Wang Y and Cox CL. Dopamine enhances the excitability of somatosensory thalamocortical neurons. *Neuroscience* 2010; 170: 981–991. [PubMed: 20801197]
119. Pape HC and McCormick DA. Noradrenaline and serotonin selectively modulate thalamic burst firing by enhancing a hyperpolarization-activated cation current. *Nature* 1989; 340: 715–718. [PubMed: 2475782]
120. Lüthi A and McCormick DA. Periodicity of thalamic synchronized oscillations: The role of Ca²⁺-mediated upregulation of I_h. *Neuron* 1998; 20: 553–563. [PubMed: 9539128]
121. Lüthi A and McCormick DA. H-current: Properties of a neuronal and network pacemaker. *Neuron* 1998; 21: 9–12. [PubMed: 9697847]
122. Robinson RB and Siegelbaum SA. Hyperpolarization-activated cation currents: From molecules to physiological function. *Annu Rev Physiol* 2003; 65: 453–480. [PubMed: 12471170]

123. McCormick DA and Williamson A. Modulation of neuronal firing mode in cat and guinea pig LGNd by histamine: Possible cellular mechanisms of histaminergic control of arousal. *J Neurosci* 1991; 11: 3188–3199. [PubMed: 1658246]
124. Govindaiah G and Cox CL. Modulation of thalamic neuron excitability by orexins. *Neuropharmacology* 2006; 51: 414–425. [PubMed: 16713607]
125. Elias CF, Lee CE, Kelly JF, et al. Characterization of CART neurons in the rat and human hypothalamus. *J Comp Neurol* 2001; 432: 1–19. [PubMed: 11241374]
126. Nosedá R, Lee AJ, Nir R-R, et al. Neural mechanism for hypothalamic-mediated autonomic responses to light during migraine. *Proc Natl Acad Sci USA* 2017; 114: E5683–E5692. [PubMed: 28652355]

Article highlights

- The hypothalamus plays a far-reaching role in primary headaches.
- The posterior hypothalamic area is crucial in cluster headache pathophysiology.
- Alterations in hypothalamic functional connectivity shortly before the beginning of migraine headaches play a predominant role in migraine attack generation.
- Hypothalamic nuclei receive direct nociceptive input through the trigeminohypothalamic tract (THT).
- Migraine-associated symptoms involving mood changes, fatigue, food cravings and so on are processed by hypothalamic areas, possibly driven by (dural) nociceptive input.

Figure 1.

Prominent anatomical connections of the hypothalamus (here in orange) with other brain areas. While an important function of the hypothalamus is to link the central nervous system to the endocrine system via the pituitary gland, it also has pivotal modulatory functions on the sympathetic and parasympathetic system (not pictured) and modulates most hormonal and other rhythms of the body.

Th: thalamus; Cingulate: cingulate cortex; Insula: insular cortex; PAG: periaquadal gray; TCC: trigeminocervical complex.