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The structural and functional importance of the thalamus in migraine processes with and without aura. A literature review

Juan José Valenzuela-Fuenzalida [b,c], Alejandra Suazo-Santibañez [d], Marjorie Gold Semmler [d], Carolina Cariseo-Avila [d], Edmundo Santana-Machuca [b], Mathias Orellana-Donoso [a,e,*]

[a] Escuela de Medicina, Universidad Finis Terrae, Santiago, Chile
[b] Department of Morphology and Function, Faculty of Health Sciences, Universidad de las Américas, Santiago, Chile
[c] Departamento de Ciencias Química y Biológicas Facultad de Ciencias de la Salud, Universidad Bernardo O'Higgins, Santiago, Chile
[d] Departamento de Morfología, Facultad de Medicina, Universidad Andrés Bello, Santiago, Chile
[e] Department of Morphological Sciences, Faculty of Medicine and Science, University San Sebastian, Santiago, Chile

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ABSTRACT

Introduction: The thalamus plays an important role in different brain functions which could include the following functions; memory, emotions, mediator in general cortical alert responses, sensorimotor control and one of the main ones which is to be a nucleus for processing sensitive information (including taste, somatosensory, visual and auditory) carrying all this towards the somatosensory cortex, which could explain the role of the thalamus in algesic processes. The exact mechanism for the generation of migraine is still a matter of research, although there is evidence that migraine pain originates in the trigeminovascular system, still it's not clear what are the morphofuncional connections of the thalamus that are implied on migraines. Therefore, the objective of this review is to know the morphofunctional alterations of the thalamus in the processes of migraine.

Methods: A systematic search was carried out in the following electronic databases: MEDLINE, SCIELO, WOS, CINHAL, SCOPUS and GOOGLE SCHOLAR, using as search terms Anatomy Thalamus, Function thalamus, Migraine, Pain head, Headache pain, for which the following Boolean connectors "AND" "OR" and "NOT" were used.

Results: After having applied the inclusion and exclusion criteria, 27 articles passed for the results analysis. 8 studies that reported the participation of nuclei of the thalamus in the process of migraine, 1 study that related the pulvinar of the thalamus with migraine; 2 articles that makes the relationship between the limbic system, thalamus and migraine; 3 articles that mention the trigeminovascular pathway and its relationship with the thalamus; 22 articles that relate the thalamocortical pathway with migraine.

Conclusion: We found in this review that the functional components and connection with other structures from the thalamus to the cortex or neighboring structures are altered or disrupted, expressed as the thalamocortical pathway. We believe that new studies must be made with a thorough analysis of the structural and functional role of the thalamus with larger samples could be crucial to integrate in theoretical frameworks in order to give a better conceptualization of migraine which could translate into a better management of it.

1. Introduction

1.1. Thalamus anatomy

The human thalamus is a nuclear complex located in the diencephalon and comprising of four parts (the hypothalamus, the epithalamus, the ventral thalamus, and the dorsal thalamus). It is conceived as the main relay center subserving sensory and motor mechanisms, such as arousal, cortical synchrony, emotion, cognition, and memory [1,2]. However, it has been shown that it also plays a role in controlling executive networks and in regulating complex behaviors, such as behavioral flexibility and reward-directed behavior [3]; Alstadhaug et al., 2009; [4].

The thalamus is divided into two symmetric hemispheres separated by the third ventricle but connected by an intermediate mass called the interthalamic adhesion [5]. The craniocaudal dimension of the human

* Corresponding author. Escuela de Medicina, Universidad Finis Terrae, Santiago, Chile.
E-mail addresses: miorellanadonoso@gmail.com, morellanadonoso@docente.uss.cl (M. Orellana-Donoso).

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thalamus is about 3 cm, its height about 2 cm, and its width about 2 cm. It has been estimated that there are approximately 10 million thalamic neurons in each hemisphere. From a structural point of view, it is classified by regions, dividing between 50 and 60 nuclei, which are named according to the location they present within the thalamus, and project to one or few well-defined cortical areas (Fig. 1). [5–7,164].

1.2. Anatomical classification of the thalamic nuclei

Anatomically, the thalamus can be subdivided in nuclear groups with respect to the internal medullary lamina, the anterior, medial, lateral, intralaminar, and posterior nuclei, and to the external medullary lamina, the reticular nucleus (RN). They can also be grouped into six functional classes: the RN, the specific sensory nuclei, the effector nuclei, the limbic nuclei, the intralaminar nuclei, and the associative nuclei [4,8].

The anterior thalamic nuclei group looks like an anterior extension of the intralaminar system that is encapsulated by myelinated fibers. Its afferent connections come mainly from the hippocampus and subiculum, projecting directly onto the anterior complex via the fornix and indirectly via the mammillary body and the mammillothalamic tract. But it also receives fibers from the dorsal raphe and pedunculopontine nuclei. Within this group, the anterior thalamic nucleus (ATN) is an important element of the hippocampal system for episodic memory and is formed of 3 subnuclei with distinct connectivity with the subicular cortex, retrosplenial cortex, and mammillary bodies. The ATN has connections with the anterior cingulate cortex and the orbitomedial prefrontal cortex, hence it contributes to reciprocal hippocampal-prefrontal dynamic interactions involved in emotional and executive functions [9,10].

The medial region of the human thalamus includes the mediodorsal nucleus (MD) and some midline structures, represented by reuniens, rhomboid, paraventricular, paratenial nuclei and subfascicular nuclei [11]. And in a more caudal sense, the medullary lamina splits and contains the parafascicular nucleus (Pf), and more laterally, the centré median (CeM). Which the visible boundary between them is undetectable in rodents and other smaller mammals; thus, the posterior intralaminar nuclei are referred to solely as the Pf in these species with the consideration that the lateral component of this nucleus is homologous to the CeM [11]. In a more anterior sense, there is within the lamina are the rostral intralaminar nuclei (rILN): the central lateral (CL), paracentral (PC), and central medial (CM) nuclei. The PC is usually defined by the more flattened appearance of cells compared to the adjacent medially-located CM and dorsally-positioned CL. This general structure of the rILN is discontinuous in the primate [11]. The nucleus reuniens has a bidirectional relationship with the prefrontal cortex and sends output to the entorhinal cortex. The thalamic intralaminar and midline nuclei, were first understood as a non-specific arousing system in the brain, now it is known that are involved in separate and specific brain functions, such as specific cognitive, sensory and motor functions, specifically involved in awareness [12]. The intralaminar and midline nuclei are considered as part of the ascending reticular activating system (ARAS), which is the rostral continuation of the reticular formation, due to their strong brainstem inputs [13]. Their activation provides the necessary arousal of cortical and subcortical regions supporting information processing that is correlated with awareness [14]. Also, it has been described a role in the awareness of tactile and nociceptive information, due to the anatomical connections that they received from the spinothalamic and reticulothalamic projections [15]. Lastly, the intralaminar thalamic nuclei also plays a role as a relay center for visual, somatosensory and auditory inputs toward the cortex [16].

The lateral thalamic nuclei group are comprised by lateral posterior nucleus (LP, lateral dorsal group), ventral anterior nucleus or group (VA), ventral lateral nucleus or group (VL), ventral medial nucleus or group (VM), ventral posterior nucleus or group (VP), ventral posterolateral nucleus (VPL), ventral posteromedial nucleus (VPM), ventral posterior inferior nucleus (VPI). VPL and VPM nuclei are part of the somatosensory system, VPL relays medial lemniscal and spinothalamic input and relays the inferior portion of the postcentral gyrus. VL receives input mainly from the deep cerebellar dentate nucleus, and a smaller contribution from the basal nuclei to the rostral part of the VL. Projections from the VL, are the primary motor area, area 4, of the precentral gyrus and also has a smaller projection to premotor areas. Thus, involving the VL to motor feedback from the cerebellum and basal nuclei to the cerebral cortex [17]. The basal nuclei, especially the medial globus pallidus and the parts reticulata of the substantia nigra, send inputs to the VA, which in turn projects to premotor cortex including the supplementary motor area of the frontal lobes and is involved in

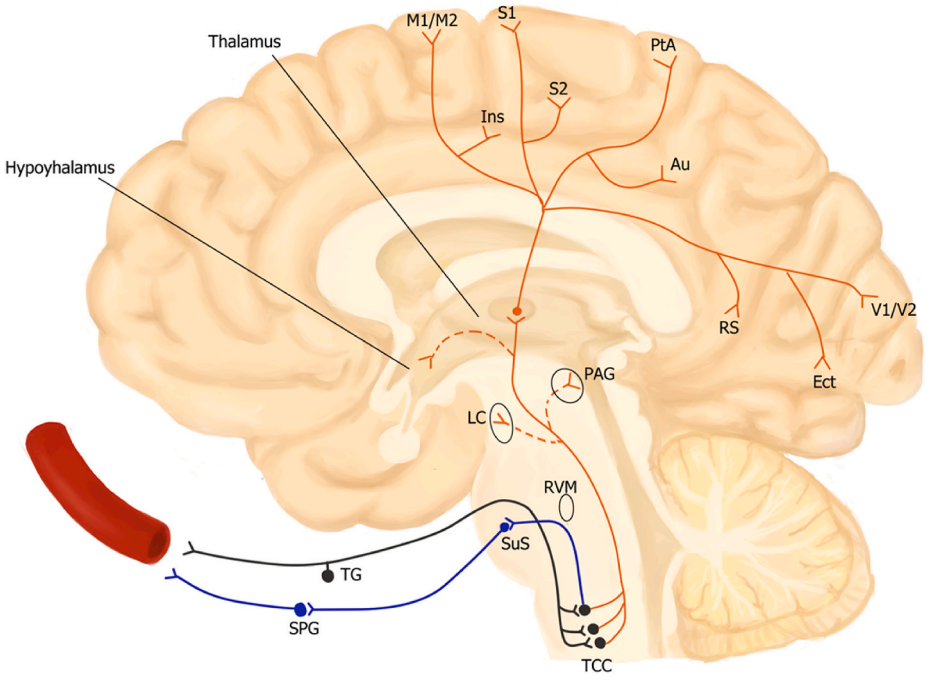

Fig. 1. Anatomy of the trigeminovascular system–ascending projections. The trigeminal ganglion (TG) gives rise to pseudo-unipolar trigeminal primary afferents which synapse on intra- and extracranial structures (blood vessels) as well as the spinal cord trigeminocervical complex (TCC). Second-order neurons from the TCC ascend in the quintothalamic (trigeminothalamic) tract synapsing on third-order thalamocortical neurons. Direct and indirect ascending projections also exist to the locus coeruleus (LC), periaqueductal gray (PAG), and hypothalamus. The third-order thalamocortical neurons in turn synapse on a diffuse network of cortical regions including the primary and secondary motor (M1/M2), somatosensory (S1/S2), and visual (V1/V2) cortices. A reflex connection from the TCC to the superior salivatory nucleus (SuS) exists, which projects via the sphenopalantine ganglion (SPG) providing parasympathetic innervation to the extra- and intracranial structures. Ins, insula; PtA, parietal association; RS, retrosplenial; Au, auditory; Ect, ectorhinal; RVM, rostral ventromedial medulla.

planning and initiating movements [17]. As for the LP, it has been demonstrated that plays an important integrative function for the limbic spatial learning systems, since it projects to the hippocampal formation directional information that it is not just a reflection of sensory inputs [18]. The VPI is the thalamic relay center in the vestibulo-cortical pathway, since its projections are mainly directed to the primary vestibular cortex [19].

The largest portion of the thalamic posterior nuclei is the pulvinar, and it's also the largest association nuclei found in the dorsal part of the thalamus. It receives inputs from the superior colliculus and from the association cortex. Its outputs are mainly directed to secondary visual areas and to association areas in the parietotemporal region, contributing to visual perception and eye movements, relating to attention to these stimuli and it conveys information only about the stimulus position, not involved in pattern recognition [17]. The posterior nucleus (Po) neurons receive reticular inputs from two different regions, one that is topographic near the reticulothalamic border and one that is diffuse and convergent from most of the thalamic reticular nucleus. The topographic reticular input is the basis of local inhibition and the latter one may represent neuronal network which the ventral posterior lateral and the posterior nuclei interact [20].

The metathalamus is the part of the diencephalon inferior to the caudal end of the dorsal thalamus, and it comprises the lateral and medial geniculate bodies. The medial geniculate nucleus receives ascending GABAergic afferents from the inferior colliculus, the lateral geniculate receives such afferents from the pretectum, there are GABAergic afferents from the zona incerta to higher order thalamic relays and the globus pallidus and substantia nigra and zona incerta send GABAergic axons to the ventral anterior and the center median nucleus [21]. The thalamic reticular nucleus (TRN) receives inputs from the brainstem reticular formation as well as from the cerebral cortex and thalamus, making a strong inhibitory inputs to the latter's nucleus, and is involved in the control of internal attentional searchlight, setting all the corresponding thalamocortical circuits in motion in perception, or when preparation and execution of any motor and/or cognitive task, and also plays a role in sleep awake cycles and maybe an important regulator of signals relaying through the thalamus [17,21].

1.3. Functional classification of the thalamic nuclei

As mentioned earlier, the nuclei of the thalamus can also be grouped from a functional point of view in six classes, and an important functional portion of it are the limbic nuclei, from which the mediodorsal (MD) and centromedian (CM) portions represent the autonomic component of emotional processing [4,9,22]. This has been further specified by Ref. [23] in the way that its activity is linked with dynamic emotional expression [23]. In monkeys it has been shown that the MD has strong cortical and subcortical connections. Within the cortical connections are described prefrontal cortex also in cats and humans, and to the anterior insula found in rodents, monkeys and in one study in humans [24–26,166]. Oher high resolution functional magnetic resonance imaging (hr-fMRI) studies have demonstrated reliable activation of the MD in mediating emotional intensity or valence and specific sexual arousal in distinction from the attentional process, which is associated with the centromedian/parafascicular complex (CM/PF) of the intralaminar thalamus [27,28]. The CM/PF complex forms the major part of the intralaminar nuclei, which in animals it has been shown that it has strong connections with the basal nuclei [29,30], motor, premotor and somatosensory cortices [31,32]. Moreover, in monkeys and rodents it has been described connections to the anterior insula [33–35], and that the parafascicular portion of CM/PF complex shows strong connections to BA24 as part of the dorsal anterior cingulate cortex (dACC) [12]. Additionally, it has been shown a coactivation of this CM/PF complex with the salience network, which comprises the anterior insula (aINS), the midcingulate cortex (MCC), temporoparietal junction (TPJ), and dorsolateral prefrontal cortex (dlPFC) bilaterally (Seeley et al., 2007 [36]; and its activity, particularly the regions of the right hemisphere are known to track the degree to which external stimuli intrinsically track attention [37–42]; while MD coactivated with more rostral parts of the anterior cingulate cortex as the pregenual anterior cingulate cortex (pgACC) which is a component of the default mode network (DMN) [43–45], which in turn, functions in a manner considered to be opposite to the salience network, it comprises posterior cingulate cortex (PCC)/precuneus, medial prefrontal cortex (mPFC), lateral parietal lobe, and areas within the medial temporal lobe, and its activated when the subjects are instructed to think about nothing in particular or when their attention is engaged with thoughts that are not related to the present sensory world [46].

1.4. Migraine

Migraine is identified by the Global Burden of Diseases, Injuries, and Risk Factors Study as a leading cause of disability worldwide [47,48], especially in subjects younger than 50 years old [49]. The International Classification of Headache Disorders (ICHD), in the most recent iteration of the ICHD (ICHD-3 beta) [50] specifies that patients must have 15 headache days per month, but migraine-associated features are required on only 8 of these 15 headache days, and that medication overuse can exist concurrently with a diagnosis of chronic migraine, causing confusion by the variability of attack features from person to person and from attack to attack in the same individual [51,52].

Another useful thing of the ICHD-3 is that has criteria to diagnosing vestibular symptoms, including vertigo and dizziness, which are common features of a migraine attack which were previously included as part of the diagnosis of basilar migraine, which in turn has been replaced by the diagnosis of migraine with brainstem aura [50]. And this is in part because of an acknowledgment of the understanding that these symptoms of migraine are unlikely to be due primarily to changes in blood flow through the basilar artery [53], but rather involve complex changes in neural activity in the brainstem and vestibular system [50].

Migraines are classified as with or without aura, migraines with aura have completely reversible sensory, visual or other symptoms related to the central nervous system. The aura usually begins before the onset of the migraine but can occur with the onset of the headache or after the headache has stopped. The most common type of aura in migraine patients is the visual aura, followed by sensory disturbances and, less frequently, speech disturbances. Sensory disorders can include a tingling sensation that travels slowly from one point of origin and affects one side of the tongue, body, and/or face. It can also be accompanied by numbness; however, numbness can also occur independently as the sole symptom [2,54,55]. There are several risk factors associated with the onset of migraine. Non-modifiable factors include genetics, gender, and age. In a person with one of her parents who suffers from migraines, the probability that they will also generate migraines is 40%, which can be as high as 75% if both parents experience migraines. On the other hand, adult women are 3 times more likely to have migraines than men [56–58].

The exact mechanism for the generation of migraine is still a matter of research, but there are several theories that have been proposed. The vascular theory proposed that there was vasoconstriction of the intracerebral arteries, followed by extracranial vasodilation would be responsible for the pain associated with migraine. This hypothesis was refuted and the findings of Amin et al. [53] stated that it was unlikely that dilation of the extracranial artery played a role in migraines. The now accepted mechanism for migraines is the neurovascular hypothesis, which postulates that migraine pain originates in the trigeminovascular system, which is the system that allows nociceptive signals from the meningeal blood vessels to be transmitted to the higher centers of the central nervous system [53,59,60].

1.5. Trigeminovascular system

The pain associated with the head in a migraine attack, including the frontal, temporal, parietal, occipital and high cervical region, is thought to be the consequence of activation of the trigeminovascular system (Fig. 1). Its anatomy consists of rich plexus of nociceptive nerve fibers that originate in the trigeminal ganglion (TG) that innervates the pial, arachnoid, and dural blood vessels, including the superior sagittal sinus and middle meningeal artery, as well as large cerebral arteries. Mechanical, chemical, or electrical activation of these structures, especially the dura mater, results in a similar headache pain that the one seen in migraine, as well as other symptoms associated with migraine including nausea and photophobia, which fades away if the stimulation sites are moved away [61–63]. The afferent nociceptive fibers that are found innervating the intracranial vasculature includes nonmyelinated (C-fibers) and thinly myelinated (Aδ-fibers) axonal projections, mainly through the ophthalmic (V1) division of the trigeminal nerve, but also to a lesser extent, through the maxillary (V2) and mandibular divisions (V3). And the dura mater also receives innervation from the cervical spinal ganglia. The axon terminals of nociceptive nerve fibers that innervate the dura mater contain vasoactive neuropeptides CGRP, substance P, neurokinin A, and pituitary adenylate cyclase-activating peptide (PACAP) [64–66], which are thought to be released upon stimulation causing vasodilation of dural and pial vessels [67–69]. There is also a central afferent projection from the trigeminal ganglion via the trigeminal tract that enters the caudal medulla of the brain stem which terminates in the spinal trigeminal nucleus caudalis (Sp5C; TNC), as well as the upper cervical spinal cord (C1–C2). Nociceptive Aδ- and C-fibers predominantly terminate in the superficial laminae, I and IIo, as well as deeper laminae V–VI [70–74] of the TNC and cervical extension. It has been shown in animal models that stimulation of the dural vasculature including the superior sagittal and transverse sinuses, and middle meningeal artery, results in activation of neurons in the TNC, C1 and C2 regions of the cervical spinal cord, together known as the trigeminocervical complex (TCC) [70,75–77]. In addition to this, it has been shown that stimulation of the greater occipital nerve also causes neuronal activation in the same regions and enhances convergent inputs from the dural vasculature [78,79], suggesting that the trigeminal nucleus extends beyond its caudalis boundary to the dorsal horn of the higher cervical region in a functional continuum that includes the cervical extension. Furthermore, this convergence of neuronal inputs to the TTC and the convergence of inputs from intracranial and extracranial structures probably accounts for the frontal and temporal regions, as well as parietal, occipital, and higher cervical regions [80].

Apart from the central projections described above, there're other projections between the TCC and thalamic nuclei, as well as pain processing and modulation nuclei such as rostral ventromedial medulla (RVM), nucleus raphe magnus (NRM), parabrachial nucleus and locus coeruleus [81,82], and midbrain nuclei, the ventrolateral periaqueductal gray (vlPAG) and cuneiform nucleus [81].), with demonstrated functional nociceptive inputs from the dura mater [70,83–87]. These functional dural inputs are relayed through the caudal medullary TCC, via the trigeminothalamic tract, to the thalamus [88–91]; [81]. Specifically, dural nociceptive inputs are processed in the VPM nucleus and its ventral periphery, the medial nucleus of the posterior complex, including posterior thalamic nucleus and the intralaminar thalamus [70, 92–94]. Therefore, they have been identified and are believed to be the principal thalamic relay conveying nociceptive information to higher cortical pain processing regions [95]. Other thalamic nuclei, which may also be involved in processing nociceptive craniovascular inputs includes the posterior Po and LP/LD thalamic nuclei [94,96,97]. The processing of craniovascular sensory and discriminatory information, particularly in the ophthalmic (V1) trigeminal division, is somatotopically organized to cortical regions, which may account for the ability of migraineurs to localize their intracranial pain to specific head regions, as well as the intensity and quality of their pain. This is supported by two studies made in rats [98] and cats [99], where they observed that dural nociceptive VPM neurons projected to mainly primary (S1) and secondary (S2) somatosensory cortices, as well as the insula. Moreover, dural nociceptive Po, LP, and LD thalamic neurons project to many functionally distinct and anatomically remote cortical regions, including S1 and S2, but also to motor, parietal association, retrosplenial, auditory, visual and olfactory cortices which could suggest a role in cognitive and motor deficits during migraine, as well as allodynia, photophobia, phonophobia, and osmophobia [98].

The objective of this review is to know the morphofunctional alterations of the thalamus in the processes of migraine.

2. Methods

This systematic review of the literature considered specific scientific articles and books of human anatomy, written in Spanish or English, published between 2000 and 2020.

A systematic search was carried out in electronic databases, in order to compile the available literature on the subject to be treated. The search process was carried out in the following databases: MEDLINE, SCIELO, WOS, CINHAL, SCOPUS and GOOGLE SCHOLAR, using as search terms **Anatomy Thalamus, Function thalamus, Migraine, Pain head, Headache pain,** for which the following Boolean connectors "AND" "OR" and "NOT" were used, the search algorithm is shown in Fig. 2. The inclusion criteria where full text articles that has established a clinical correlation between migraine and thalamus. The exclusion criteria were letters to the editor, bibliographic reviews and articles of gray literature, and studies made on animals. Table 1 shows the levels of evidence of the articles included in the review based on the description of Sackett et al. [100].

3. Results

In this article we seek to see the clinical importance of the thalamus and its pathways in migraine processes. After having applied the inclusion and exclusion criteria, we were left with 26 articles for the analysis of the results. Of the 26 studies in humans, while 1 article did not state whether it was in humans or in animals since it made a descriptive analysis without incorporating a sample which is equivalent to 3,7% of the studies (Table 2). In the studies sample size was 1234 (23 articles reported, 1 didn't report). Next, the pathways or structures of the thalamus associated with migraine processes will be described (Table 3).

3.1. Thalamic nuclei and migraine

In this review we found 8 studies that reported the participation of nuclei of the thalamus in the process of migraine [101,109]; [94, 102–106]. Of which 1 study was associated with migraine with aura, 3 studies were associated with migraine without aura and lastly 3 studies did not report the type of migraine and 1 study reported a vestibular migraine. Of these 8 studies, the nucleus of the thalamus that most confused between the studies was the posterior thalamic nucleus reported by 3 studies, while later the posterior and ventral posteromedial thalamic nucleus was found in 2 studies that associated these nuclei with migraine. The studies that mention the participation of the thalamus nuclei associated with migraine attribute it to some mechanisms of perception of allodynia in which thalamic nuclei would be involved, it is also associated with the effect of pain modulation, which also includes the reticular thalamic nucleus and the thalamic nuclei of the posterior region that are in charge of transmitting information transthalamically between the visual, somatosensory and motor cortical areas, which also explains the participation of the thalamocortical pathway. Finally, the thalamic nuclei with abnormal volumes are densely connected to the limbic system.

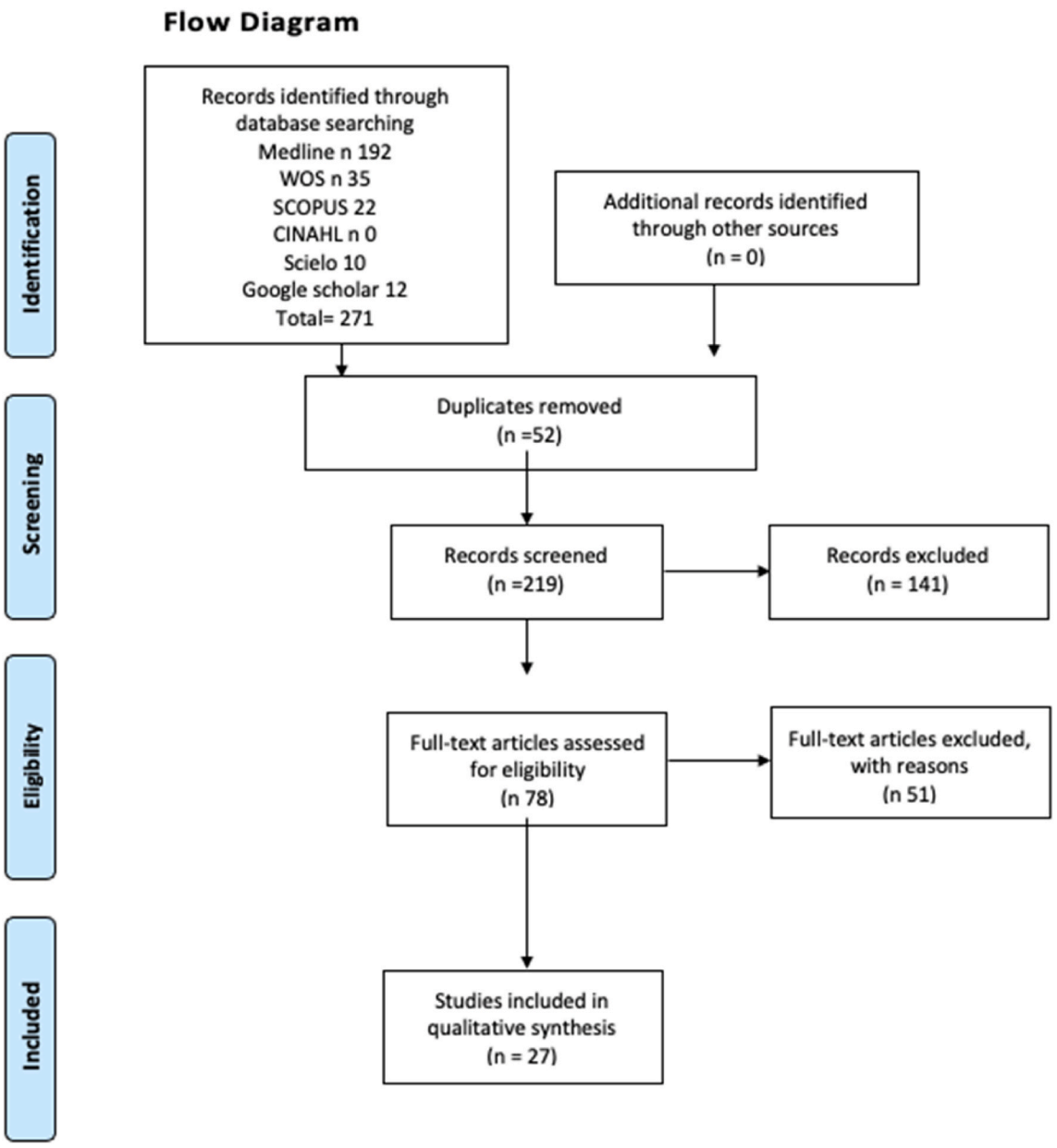

Fig. 2. Flow diagram.

3.2. *Pulvinar of the thalamus and migraine*

In this review we found 1 study that reported the participation of pulvinar of the thalamus in the process of migraine [107] The pulvinar of the thalamus is the largest thalamic nucleus within the diencephalon and is also the largest within the brain, but regardless of its size, its functions remain unclear and are still a challenge for different scientific groups. Pulvinar one of the attributed functions is its connection with the visual system and how they can interact with each other [108]. In this review we only found 1 study that related the pulvinar of the thalamus with migraine [107], although it does not declare the type of migraine, it describes that the migraine patients curiously the posterior thalamus presented abnormal connectivity networks (pulvinar nucleus) as well as in the visual cortex and the precuneus nucleus, altering the dynamic and functional networks, which was significantly correlated with the frequency of headache associated with migraine.

3.3. *Trigeminovascular pathway*

In this review we found 3 studies that reported the participation of the trigeminovascular pathway in the process of migraine [94,109,110]. Migraine is recognized by a series of events that trigger a trigeminal nervous response, based on a previously studied genetic predisposition. The trigeminovascular pathway is one of the most studied and most important pathways in migraine studies, where the thalamus acts as a relay nucleus for this pathway, but a direct function is not completely attributed to the thalamus [111]. This review found 3 articles that mention the trigeminal vascular pathway and its relationship with the thalamus [109], of which no study specified the type of migraine attributed to the trigeminovascular pathway. It should be noted that in the literature there is much evidence that the trigeminovascular pathway participates directly in migraine processes, but within our search we only found these studies that associated the thalamus with this pathway, the activation of the trigeminovascular pathway contributes to the phase of headache that triggers a migraine attack, which

Table 1
Type of study and level of evidence according to Ref. [100].

Author/year	Type studies	Evidence Level
[101]	Clinical trial	1b
[109].	Descriptive	5
[113]	Clinical Trial	2b
[112].	Randomized clinical trial	1b
[114]	Case study	3b
[102].	Randomized clinical trial	1b
[115].	Randomized clinical trial	1b
[116].	Randomized clinical trial	1b
[103].	Cohort study	2b
[117].	Randomized clinical trial	1b
[118].	Retrospective study	4
[119].	Randomized clinical trial	1b
[104].	Randomized clinical trial	1b
[107].	Randomized clinical trial	1b
[120].	Randomized clinical trial	1b
[105].	Randomized clinical trial	1b
[122].	Descriptive	5
[110]	Review	3a
[126]	Descriptive	5
[121]	Randomized clinical trial	2b
[166]	Clinical trial	2b
[106]	Randomized clinical trial	1b
[94]	Randomized clinical trial	1b
[123]	Randomized clinical trial	1b
[124]	Randomized clinical trial	1b
[125]	Systematic review	3a

contributes to the development of pulsations in the initial phase of migraine, this process is mediated by GABAA and GABAB receptors in thalamic neurons can modulate nociceptive transmission of the trigeminovascular pathway in the ventroposteromedial nucleus (VPM) producing migraine.

3.4. Thalamocortical pathway

The thalamocortical pathway is defined as any pathway that is joining the thalamus with some region of the cortex, such as the thalamus and frontal cortex, thalamus and somatosensory cortex, in this review we found 20 articles that relate the thalamocortical pathway with migraine [101,102,104,105,107,112–125,166]. Within these studies, 1 study declared migraine with aura, 8 studies declared migraine without aura, 7 studies did not report type of migraine and 4 study declared migraine with and without aura. The main functions or characteristics that are attributed to the thalamocortical pathways in migraine, is that there are altered patterns of connectivity, which converges in most of the studies that propose an alteration of the thalamocortical pathway, which is associated with migraine, in addition to the fact that there may be multisensory conditions or alterations in the modulation or increase in pain discharge. It is also proposed that there is a temporary sensitization of third-order thalamic neurons, which receive convergent information from the dura, the periorbital skin and the more distal skin regions, which play a critical role in the clinical manifestation of central sensitization. of allodynia and referred pain. This abnormal activity is attributed to the lateral geniculate complex, the thalamic networks of the visual system, which are associated with the processes responsible for the symptoms associated with migraine such as photophobia.

3.5. Limbic system and thalamus

In our review we found 2 article that makes the relationship between the limbic system, thalamus and migraine [103,126]. This study does not declare the type of migraine, from the functional point of view it indicates that thalamic anomalies can affect the connections to the amygdala, which is why this theory supports that the integration systems between different higher-order structures are altered in the migraine processes. However, this theory has not been fully studied and it is not known whether this alteration of the migraine is the cause of the migraine or is a consequence of it.

3.6. Ascending and descending pathways of pain

The perception of pain is the result of multiple and dynamic mechanisms belonging to the central and peripheral nervous system that inhibit or facilitate the stimulus and nociceptive response [127]. The importance of these mechanisms lies in the painful experience, which depends on the dynamic modulation of the internal circuits of the nervous system. The pain pathways can be ascending towards structures of the cortex or subcortical, plus some descending pathways of pain modulation [128,129]. In our review we found 2 studies that saw the participation of the ascending and descending pain pathways and associated with thalamus and migraine [105,120]. These studies showed that the presentation of migraine was without aura. The ascending/-descending pain pathways are involved between the regions of the posterior thalamus and the cortical regions, such as the prefrontal cortex and the pre-wedge, in the processes of migraine they show a dysfunction in the modulation of pain in the sensory and affective domains, which suggest an imbalance of pain facilitation inhibition in migraine without aura.

4. Discussion

Migraine is a very disabling pathological condition in people that becomes chronic, one of the main mechanisms proposed to explain the appearance of these painful episodes is the trigeminal vascular pathway or also, on some occasions, alterations of components of the nervous system associated with the visual system such as scintillations, scotoma or paresthesia, numbness in the extremities which are recognized as aura symptoms [98,109,117,121,130]. This initially were thought to be caused by underlying cortical spreading depression (CSD) waves, which is a neuronal and glial depolarization wave that slowly propagates within the cerebral cortex that is followed by an electrical shift and regional blood flow increase along the cortex, left long-lasting decreased neuronal excitability and reduced regional blood flow behind, causing transient electrical and functional silence of the involved area [130, 131].

In this review we focus on describing how the thalamus participates either structurally or functionally in the processes of migraine. The nuclei of the thalamus are numerous relay centers and some alteration of these same, especially the VPM nucleus of the thalamus, can alter the cortical connections and it has been seen that in migraine patients this nucleus is altered [109,120].

In addition to this, a functional magnetic resonance imaging (fMRI) study that investigated the thalamic functional connectivity in the interictal state of migraine without aura patients compared to healthy controls, reported increased activity only in the right thalamus and increased connectivity between the right thalamus and bilateral caudate nuclei in patients compared to controls, which could be associated with functional impairments of pain processing, but they found no correlation between activation of the right thalamus at rest and disease duration or attack frequency. It should be noted that usual pain side location during attacks was not reported and therefore it was not possible for them to determine whether the interictally increased right thalamic connectivity to the caudate nuclei was independent of the pain side, as previously reported during spontaneous attacks [132]. Although the study conducted by Amin et al. [133], found an increased functional connectivity between the right thalamus and several contralateral brain regions (superior parietal lobule, insular cortex, primary motor cortex, supplementary motor area and orbitofrontal cortex), and that there was decreased functional connectivity between the right thalamus and three ipsilateral brain areas (primary somatosensory cortex and premotor cortex), showing an altered network connectivity between thalamus and

Table 2
Summary of the articles included in this review.

Author/ year	Structure and/or thalamic pathway involved	Physiological or pathophysiological presentation	Type of migraine	Characteristics and number of patients
[101]	Posterior ventral nucleus Thalamocortical pathway	Some altered patterns of thalamocortical connectivity may contribute to multisensory integration abnormalities, in addition to mentioning that other deficits such as pain management, cognitive assessment, and pain modulation may occur.	Without aura	96 humans
[109].	Posterior thalamic nucleus (Po), associated with the trigeminovascular pathway	The activation of the trigeminovascular pathway contributes to the headache phase that could trigger migraine attacks, this process is mediated by the sensitization of the peripheral trigeminovascular neurons that innervate the meninges, this causes the development of cephalic allodynia that is driven by sensitization of second order trigeminovascular neurons.	Not declared.	Humans.
[113]	Thalamocortical pathway	The results provide evidence that abnormal connectivity between the thalamus and attentional brain networks at rest during migraine attacks, which may be a cause of migraine or the culprit.	Without aura	32 humans
[112].	Thalamocortical pathway	It is described that the highest values of thalamic fractional anisotropy that normalized during a migraine attack, these are probably related to plastic modifications and permanent to be considered as the anatomical counterpart of the cyclical functional fluctuations observed in the neurophysiology of migraine.	Without aura	39 humans.
[114]	Thalamocortical pathway	The results support the hypothesis that an abnormal rest generates a negative effect in terms of network connectivity that are associated with significant differences in the thalamic microstructure, this could contribute to migraine pathophysiology.	Without aura	37 humans.
[102].	Higher order thalamic nuclei, medial dorsal thalamic nucleus is associated with the thalamocortical pathway.	Spontaneous low-frequency oscillations in the thalamus were selectively associated with headache attack frequency, meaning that variable amplitude could be present in migraineurs.	Not declared.	80 humans.
[115].	Thalamocortical pathway	Migraine patients with aura exhibit extensive changes in the nuclei of the thalamus compared to patients without aura and healthy patients who do not have significant changes in the thalamus or modulation of the thalamocortical pathways.	With and without aura.	57 humans.
[116].	Thalamocortical pathway	In the thalamus and other areas of pain processing. Furthermore, topiramate increased the functional coupling between the thalamus and various brain regions such as the bilateral precuneus, the posterior cingulate cortex, and the somatosensory cortex. These data suggest that topiramate exhibits modulatory effects on nociceptive processing in the thalamocortical networks during migraine pain.	Not declared.	23 humans.
[103].	Limbic system. ATN, central nuclear complex (CN), and LP	This study indicates structural thalamic abnormalities in migraine patients. Thalamic nuclei with abnormal volumes are densely connected to the limbic system. Therefore, the data support the view that higher-order integration systems are disrupted in migraine.	Not declared.	246 humans
[117].	Thalamocortical pathway.	There is a temporary sensitization of the third order thalamic neurons, which produces an abnormal modulating activity of the lateral geniculate complex, the thalamic networks of the visual system, it may be involved in the process responsible for the symptoms associated with migraine, such as that of photophobia.	Without aura	40 humans.
[118].	Thalamocortical pathway	It is in common agreement that sensitization in third-order thalamic neurons and at the cortical level promote functional and clinical changes accompanying the chronification of migraine, which influences the detection of	Not declared.	40 humans.

(*continued on next page*)

Table 2 (*continued*)

Author/ year	Structure and/or thalamic pathway involved	Physiological or pathophysiological presentation	Type of migraine	Characteristics and number of patients
		alterations in the dynamics of different cortical networks in patients with chronic migraine.		
[119].	Thalamocortical pathway	Left thalamic activation was uniquely correlated with frequency of migraine attacks in patients with vestibular migraine, in addition to being associated with alterations in the thalamocortical pathway to the somatosensory cortex.	Not declared.	12 humans.
[104].	Thalamocortical pathway. Anteroventral geniculate nucleus.	Various regions of the diencephalon including the thalamus, as well as the cingulate cortex, cerebellum, periaqueductal gray matter, hypothalamus, pons, spinal trigeminal nucleus, visual cortex, middle frontal cortex, somatosensory cortex, and temporo-occipital cortex it may be related to the different phases of migraine, which does not clarify the mechanisms of migraine.	Without aura.	75 humans
[107].	Thalamocortical pathway. Pulvinar of the thalamus.	It was detected that in migraine patients, curiously, it was found that the posterior thalamus presented abnormal connectivity networks (pulvinar nucleus), abnormal dynamic functional network connectivity, as well as in the visual cortex and the precuneus were significantly correlated with the frequency of migraine.	Not declared.	159 humans.
[120].	Thalamocortical pathway. Ascending/descending pathway of pain associated with the thalamus	Most migraineurs develop cutaneous allodynia (CA) during migraine and the underlying mechanism of cutaneous allodynia in migraine is believed to be sensitization of third order trigeminovascular neurons in the posterior region of the thalamic nuclei.	Without aura.	59 humans.
[105].	Thalamocortical pathway. Ascending/descending pathway of pain associated with the thalamus. Ventromedial nucleus.	Ascending/descending pain pathways are involved between the posterior thalamus (PTH) regions and the cortical regions, such as the prefrontal cortex and the pre-wedge, show a dysfunction in the modulation of pain in the sensory and affective domains, suggesting an imbalance of inhibition and facilitation of pain in migraine without aura (MWoA.) understanding the pathophysiology of migraine.	Without aura	45 humans.
[122].	Thalamocortical pathway.	A fundamental role of the thalamus in migraine-related allodynia and photophobia is well established. Furthermore, the thalamus is most likely involved in dysfunctional pain modulation and processing in migraine.	Not declared	Not declared
[106]	Compared to controls, vestibular migraine (VM) patients had increased volume of the left thalamus. Compared to migraine wothout aura (MWoA), VM patients had increased volume of the left thalamus. Compared to migraine with aura (MWA), VM patients had increased volume of the left thalamus.	A dismodulation of thalamocortical regions processing vestibular and nociceptive information has been revealed in VM patients	Vestibular migraine	57 right-handed patients with episodic migraine (19 VM, of which 3 had a past history of migraine with visual aura, 19 MWA and 19 MWoA patients) in headache-free state for at least one month prior to MRI acquisition
[94]	Sensitized trigeminovascular neurons in the rat mediodorsal region of the thalamus (posterior group (Po), lateral dorsal (LD), lateral posterior (LP)). Sensitized trigeminovascular neurons in the human VPL, rostral part of the human pulvinar, and the centrolateral (CL) and centromedian-paarafascicular (CM-PF) complex.	The spreading of multimodal allodynia and hyperalgesia beyond the locus of migraine headache is mediated by sensitized thalamic neurons that process nociceptive information from the cranial meninges together with sensory information from the skin of the scalp, face, body and limbs	Migraine with and without aura	Extracephalic allodynia was assessed using single unit recording of thalamic trigeminovascular neurons in rats and contrast analysis of BOLD signals registered in fMRI scans of patients exhibiting extracephalic allodynia. 18-55-year-old patients whose clinical history met the criteria for migraine with or without aura. They had 1-6 migraine attacks per month in the preceding 3 years, experienced migraine with cephalic and extracephalic allodynia
[123]	In both MWA and MWoA there was increased connectivity between the left and the right amygdala and the anterior insula, as well as with secondary somatosensory cortex (SII) and thalamus, but more marked in MWA	They strongly support the hypothesis that CSD-induced amygdala activation during repetitive episodes of migraine with and without aura consolidates connectivity within the visceroceptive cortex, and that amygdala interactions with areas involved in interoception could play a role in the development of migraine symptoms.	Migraine with (MWA) and without aura (MWoA)	Twenty-two subjects with migraine (20 females, age (mean $\pm$ SD) = 31.2 $\pm$ 7.6 years; disease duration = 14.8 $\pm$ 8.8 years, range 1–30 years), 11 with migraine with aura (MWA), and 11 with migraine without aura (MWoA).
[124]	1) identification of interictal atypical rs-fc supports the notion that CM has persistent manifestations between migraine attacks; 2)	Studies comparing episodic migraine and CM and longitudinal studies are needed to determine if atypical rs-fc is a result of having	Chronic migraine (CM)	Twelve minutes of resting blood oxygenation level dependent data were collected from 20 interictal adult chronic migraneurs CM and 20

(*continued on next page*)

Table 2 (*continued*)

Author/ year	Structure and/or thalamic pathway involved	Physiological or pathophysiological presentation	Type of migraine	Characteristics and number of patients
	atypical functional connections with affective pain regions involve regions that participate in multiple domains of the pain experience, including sensory-discriminative, cognitive, modulating and integrative domains; 3) atypical rs-fc between affective pain processing regions with middle temporal cortex and with the pulvinar may relate to intolerance to sound and light, two key characteristics of migraine.	CM or if atypical rs-fc predisposes the individual to developing CM.		healthy controls. Resting state functional connectivity (Rs-fc) between 5 affective regions (anterior cingulate cortex, right/left anterior insula, and right/left amygdala) with the rest of the brain was determined.
[125]	More than 20 functional connectivity (FC) networks (including amygdala, caudate nucleus, central executive, cerebellum, cuneus, dorsal attention network, default mode, executive control, fronto-parietal, hypothalamus, insula, neostriatum, nucleus accumbens, occipital lobe, periaqueductal gray, prefrontal cortex, salience, somatosensory cortex I, thalamus and visual) were reported.	It seems very difficult to extract knowledge of migraine pathophysiology or to identify a biomarker of migraine.	Interictial migraine	Literature review
[110]	Cerebral cortex and trigeminovascular pathway in migraine processes	The peripheral as well as the central part of the trigeminal system are involved in the pathophysiology of migraine pain, since they are involved in the peripheral and central sensitization processes, together with various subcortical and cortical brain structures.	Not defined	Literature Review
[126]	Role of the limbic system in migraine	Chronic headache struggles with emotional problems, drug response, and other behavioral situations and conditions that confuse the headache scientist.	Not defined	Descriptive study with no subjects
[121]	Impaired intrinsic functional connectivity between the thalamus and the visual cortex in migraine without aura	Functional magnetic resonance imaging (fMRI) in the resting state has confirmed the alteration of the connectivity of the visual network in migraine without aura (MwoA). The thalamus plays a critical role in a number of pain conditions, including migraine. However, the importance of altered thalamic-visual functional connectivity (FC) in migraine remains unknown. The aim of this study was to explore the integrity of the thalamic-visual HR in patients with MwoA and to investigate its clinical importance.	Without Aura	They obtained resting-state functional MRI data from 33 MwoA patients and 22 well-matched healthy controls. After identifying the visual network by independent component analysis, they compared neuronal activation in the visual network and thalamic-visual HR and assessed whether these changes were related to clinical characteristics. They used voxel-based morphometry to determine whether functional differences depended on structural differences.
[166]	Altered cortical and subcortical connections in migraine with and without aura	The results suggest that abnormalities in the resting state of these regions may be associated with functional deficits in pain processing in migraine. Specifically, the results for brain regions may reflect both similarities and differences in pathophysiological mechanisms in relation to the main migraine subtypes.	With and without aura.	23 MwoA eligible patients, 12 MA patients who were treated at the neurology clinics at Hebei Medical University Second Hospital from March to October 2014, and 25 healthy volunteers matched for gender, age and education participated in this study. Demographic and clinical characteristics, a 3.0 T magnetic resonance imaging system was used to obtain rfMRI and the ReHo method was applied to analyze the synchronization of the BOLD signal in the same time series between neighboring voxels of the brain.

pain modulating as well as pain encoding cortical areas [133] suggesting that pain modulation is disrupted [105]. Taking this together we can say that rather than having a specific alteration of the structure of the thalamus, the functional components and connection with other structures from the thalamus to the cortex or neighboring structures are altered or disrupted [101,104,107,112–119,121,122].

We know that the thalamus has several cortical connections but the most studied and with the greatest evidence are those that join the parietal lobe and the frontal lobe, mainly associated with the conceptualization of central sensitization or allodynia [109,120,122,134].

4.1. *Proposed mechanisms of migraine and the thalamic NUCLEI'S role*

There has been proposed several mechanisms that could explain the thalamic role in migraine, the trigeminovascular system, the thalamocortial pathway as well as a dysfunctional neurolimbic pain network and the cortical body matrix theory [135].

4.1.1. *Trigeminovascular system*

In this review we found studies that proposed an implication of the trigeminovascular system [94,109,110], previously described, and that it's activation results in a similar headache pain that the one seen in migraine, as well as other symptoms associated with migraine including nausea and photophobia, which fades away if the stimulation sites are moved away [61–63]. However, there are also many endogenous mechanisms that modulate trigeminovascular nociceptive traffic, which can further determine the perception of this information, since evidence of activation in areas of the brain stem and diencephalic nuclei before, during, and after the cessation of migraine with treatment [136–140] that cannot be explained as solely a consequence of the pain response. TCC is subject to direct and indirect descending pain modulatory pathways arising in the cortex. Direct projections arise from the primary

Table 3
Structures involved in migraine.

Structure involved	Authors	Additional considerations
Thalamic nuclei	[101]	1 study declared migraine with aura
	[109]	3 studies reported migraine without aura
	[102]	
	[103]	3 studies did not report type of migraine
	[104]	
	[105]	1 study reported a vestibular migraine.
	[106]	
	[94]	
Pulvinar of the thalamus	[107]	Does not report the type of migraine
Limbic system	[126]	1 descriptive study
	[103]	Does not report the type of migraine
Trigeminovascular pathway	[94]	The type of migraine was not reported in any of the studies.
	[109]	
	[110]	1 literature review
Thalamocortical pathway	[101]	1 study declared migraine with aura
	[112]	9 studies reported migraine without aura
	[113]	
	[114]	7 studies did not report type of migraine
	[102]	
	[115]	4 study declares migraine with and without aura
	[116]	
	[117]	
	[118]	
	[119]	
	[104]	
	[107]	
	[120]	
	[105]	
	[122]	
	[123]	
	[124]	
	[125]	
	[121]	
	[166]	
Ascending and descending pathways of pain	[120]	Both report migraine without aura
	[105]	

somatosensory (S1) and insular (Ins) cortices while indirect projections arising in S1 that project via the hypothalamus. A local corticothalamic circuit also exists which can modulate trigeminothalamic processing. Hypothalamic projections again form direct TCC modulatory projections as well as indirect projections via the locus coeruleus (LC) and periaqueductal gray (PAG) which can further pass via the rostral ventromedial medulla (RVM). This complex network of direct and indirect pathways provides potent anti and pro nociceptive modulation of incoming trigeminal nociceptive signaling, the dysfunction of which is thought to contribute to triggering migraine attacks [141–144,165]. Here there have been implicated the VPM, Po, LP thalamic nuclei, which have all been demonstrated to receive functional nociceptive inputs from the dura mater [94,96,97], and this can modulate how this painful experience is perceived.

4.1.2. Thalamocortical pathway

Others studies described the implication of the thalamocortical pathway [101,102,104,105,107,112–125,166], which comprises the axons that communicate the thalamic nuclei and the cerebral cortex. For instance, neurons of posterolateral thalamus, who's been implicated in allodynia in both rat and human models [94,120,145], send particularly broad projections to several cortical areas, including V1, V2, auditory, and parietal association cortices; this pattern of direct projection to multiple cortices might be a distinct feature of the trigeminovascular pathway, given the limited cortical projections of nociceptive thalamic neurons that respond to somatic skin stimulation [98]. In addition, posterolateral nuclei and other higher-order (Fig. 3) thalamic nuclei participate in cortico-thalamo-cortical (transthalamic) circuits and are involved in cortico-cortical communication [146]. The transthalamic circuits and the specific broad direct projection pattern to multiple cortices of dura-sensitive Po/LP neurons may provide an anatomical substrate for the global dysfunction in multisensory information processing and integration that characterizes migraineurs in the interictal period [124].

4.1.3. Limbic system and thalamic nuclei

On the other hand, we found two studies [103,126] that found implications of limbic thalamic nuclei on migraine. Magon et al. [103], found a statistically significant volume reduction in the ATN, central nuclear complex (CN), and LP nucleus with no statistical differences between migraineurs patients with aura (MwA) vs without aura (MwoA).

In 1878, Broca's original designation of the "limbic lobe", Papez and Maclean are credited with first designating the "limbic system" as the functional organization of emotions [147] The limbic system today is generally thought of as including the amygdala, the anterior cingulate cortex (ACC), the orbital and medial prefrontal cortex (PFC), the insula, and hypothalamus [147–149].

Furthermore, Maizels et al. [150] proposed a dysfunctional neurolimbic pain network model for migraine, which involves the PAG, the rostral pons near the locus ceruleus (LC) as well as the ACC (Fig. 4) [140,148,149,151]. It has been shown an increased resting-state connectivity between the PAG and several cortical regions primarily involved in nociceptive and somatosensory processing (thalamus, posterior parietal cortex, anterior insula, somatosensory cortex) in migraineurs, and they also higher frequency of attacks showed greater connectivity between the PAG and specifically anterior insula, nucleus cuneiformis, and hypothalamus. Conversely, high frequency migraineurs displayed prominent reduced functional connectivity between the PAG and PFC, and to a lesser degree with ACC, amygdala, and medial thalamus. On the other hand, migraineurs with allodynia showed decreased connectivity between the PAG, PFC, ACC, and anterior insula [126,152–154].

4.1.4. Connectome, migraine and thalamic nuclei

Finally, we'd like to discuss the role of thalamic nuclei within the neural substrate of migraine or connectome. The connectome is the full description of anatomical connections in the brain, and it is now known that neural communication across the whole brain wide network, including pain- and attention-related circuits, is intrinsically dynamic and spontaneously fluctuates on multiple timescales [155–158]. Understanding attentional states as a constant fluctuation regardless of ongoing task demands and contents of sensory input [159–161]. Furthermore, since pain is considered as an intrinsically dynamic experience and process encoded by a 'pain connectome,' the spatiotemporal signature of brain network communication that represents the integration of all cognitive, affective, and sensorimotor aspects of pain.

Kucyi et al. [162], found that three key brain systems, and their dynamic interactions, are involved in spontaneous attentional fluctuations toward and away from pain. These networks are crucial components of the pain connectome and are key contributors to the ongoing dynamics of pain. The first system is the salience network (aINS, MCC, TPJ, and dlPFC bilaterally), which has a sustained activation during attention to pain. The second system is the default mode network (DMN: PCC/precuneus, mPFC, lateral parietal lobe, and areas within the medial temporal lobe), which on the contrary, is suppressed when attending to pain but increased when mind wandering away. And the third system is the descending pain modulatory (or antinociceptive) system, which was previously described, is increased functional connectivity during mind wandering away from pain [162].

In the study performed by Shin et al. [104]; they found that the right anteroventral and right and left medial geniculate nuclei volumes were significantly increased, whereas the right and left parafascicular nuclei volumes were decreased in the patients with migraine compared with healthy controls, even after multiple corrections, despite the fact that thalamic volumes as a whole were not changed [104], which are part of the salience network [5,36,163]. However, the intrinsic thalamic network was not different between them [104]. In another study

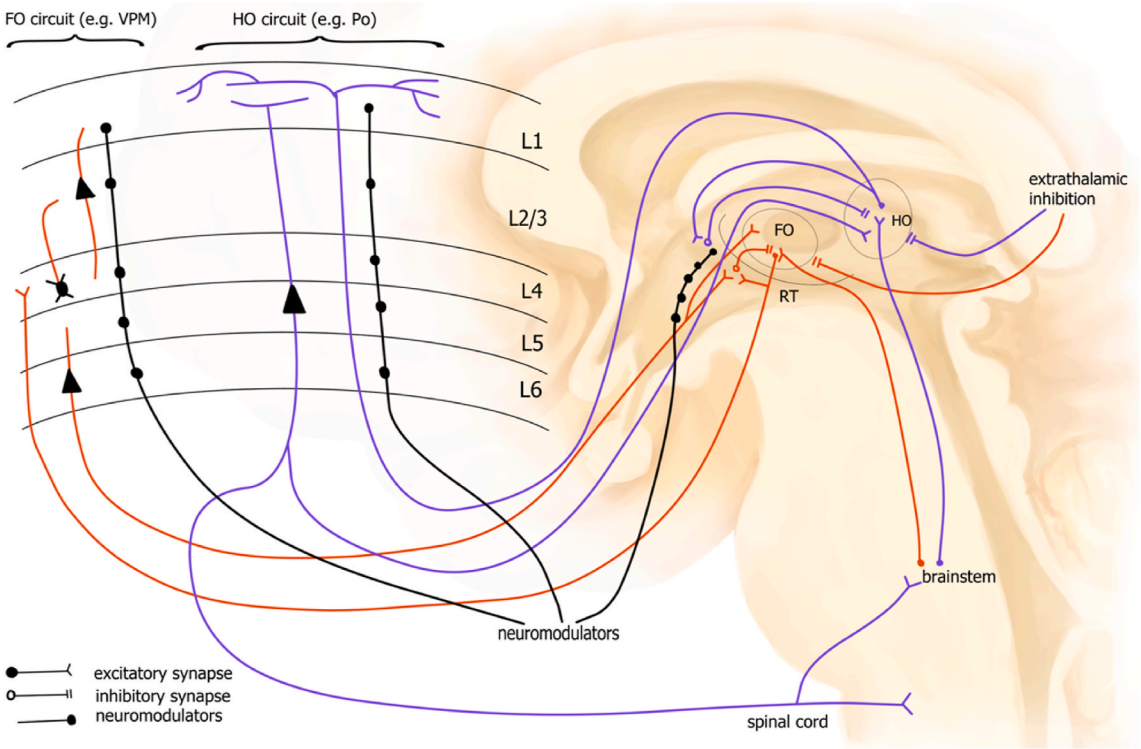

Fig. 3. Thalamocortical pathway. Thalamic relay nuclei whose primary (driver) input is from brainstem and spinal cord afferents, and higher order (HO; blue traces) are classified as first order (FO; red traces), where a significant proportion of driver input is from layer 5 of the cortex. FO nuclei serve as sensory relays from the periphery, projecting primarily to cortical layer 4. HO nuclei may play a more integrative role, projecting more diffusely throughout the cortex, especially within layer 1. Thalamic activity is constrained by two sources of inhibition: local inhibition from the reticular nucleus (RT) and extrathalamic inhibition (ETI) from zona incerta, basal ganglia, pretectal nucleus, and pontine reticular formation. ETI is suppressed in neuropathic pain models, leading to significantly increased activity in the posterior (Po) thalamus, an HO relay. Both FO and HO circuits are susceptible to neuromodulation (black traces) at the thalamic and cortical levels. VPM, Po, ventroposteriomedial and posterior nuclei of the thalamus; L1–L6, cortical layers 1–6.

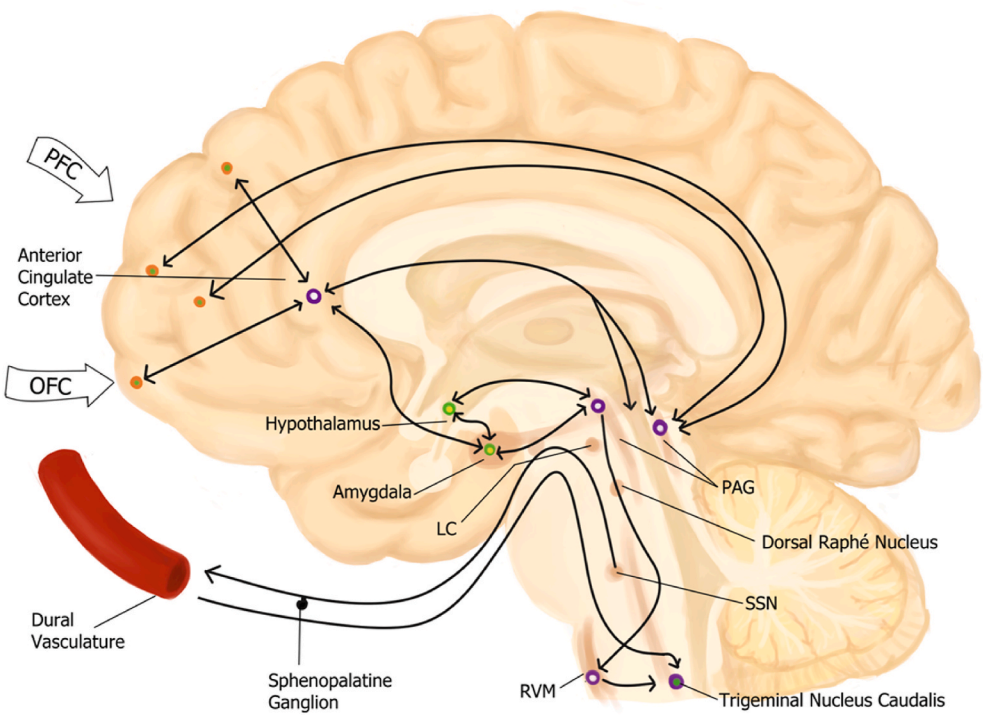

Fig. 4. Pathways of the neurolimbic model of migraine proposed by Maziel et al. [150]. The concept of periaqueductal gray (PAG) as "migraine generator" is expanded to a neurolimbic pain network. Brainstem pain-modulating circuits have bidirectional connections with the limbic system (anterior cingulate cortex, amygdala, insula, orbito-frontal cortex [OFC] and prefrontal cortex [PFC], hypothalamus), and tonically influence migraine expression. Cortical hyperexcitability (shown in occipital cortex) is also influenced by brainstem circuits. See text for detailed description of interrelationships. ACC = anterior cingulate cortex; RVM = rostral ventral medulla; SSN = superior salivatory nucleus.

performed by Coppola et al. [113,114], in their results from the correlation analysis fit strikingly with evidence coming from neuroimaging studies showing a distinct functional connectivity between the thalamus and several areas within the visuo-spatial system and medial visual areas (e.g. posterior cingulate cortex, visual cortex, precuneus) with no significant difference in the lag in intrinsic activity, an indirect estimation of the direction of the connection, between the pair of less interconnected networks (ie DMN and a network composed of the visuo-spatial system and medial visual cortical areas), it is possible that the thalamic relay contributes the most to the cortical networks activity via the thalamocortical loops. Suggesting that a deficient thalamic activity in migraine between attacks, as highlighted by an increased fractional anisotropy, activates less the visuo-spatial system and medial visual cortical areas, which in turn leads to less activation of the DMN [113, 114]. In addition, Hodkinson et al. [102] found alterations in the MD nucleus associated with the thalamocortical network which is a thalamic nucleus that is within the DMN [46,102,125].

We believe that it's important to identify the thalamic nuclei that are involved in the dynamic migraine connectome, and to understand their importance on migraineurs patients, and we present the morphological features of the thalamic nuclei involved in migraine, its morphological alterations, and discuss their role in the underlying neural networks of migraine, which are important in order to have a better therapeutic and research guidelines [102,113,114,125].

Finally, we did not find any review that made the same comparison proposed in this study and, we already know that the thalamus is affected in the migraine processes, so leaving it out of the clinical analyzes could give us a bias in the treatment, the same in this way, we propose to continue studying migraine and giving the importance of the structures that is affected in the thalamus.

5. Conclusion

The studies analized in this literature review shows that the main thalamic nuclei that are involved and altered in the migraine are the posterior (Po), the pulvinar and it's posterior ventral nucleus (PV), the mediodorsal nucleus (MD) anterior thalamic nucleus (ATN), centra nuclear complex (CN), lateral posterior nucleus (LP), ventral medial nucleus (VM), ventral posterolateral nucleus (VPL), centrolateral nucleus (CL), and centromedian/parapascifular complex (CM/PF); which are closely related to the limbic system, the trigeminovascular system, the antinociceptive or descending pain modulation of the trigeminovascular system, as well as the extrinsic connectivity in the salience, and default mode network. Understanding the anatomical structures that participate in the pathological processes of migraine can help the clinician to make the best therapeutic decision for its treatment, it is also necessary to elucidate which are the specific structures that participate in the production of migraine and which are the structures are affected by migraine, the studies should focus their greatest effort on knowing which anatomical structures play a greater role in neurophysiological processes and how they appear in the clinical picture of the patient. We found that rather than having a specific alteration of the structure of the thalamus, the functional components and connection with other structures from the thalamus to the cortex or neighboring structures are altered or disrupted, expressed as the thalamocortical pathway.

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Ethical statement

The present study has no implications in human treatments or interventions, therefore it doesn't have any ethical issues.

Declaration of competing interest

The authors of this study do not report a conflict of interest for this research.

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