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EPISODIC MIGRAINE (S PARIKH, SECTION EDITOR)

Neurovascular Compression-Induced Intracranial Allodynia May Be the True Nature of Migraine Headache: an Interpretative Review

Valdas Macionis[1]

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Abstract

Purpose of Review Surgical deactivation of migraine trigger sites by extracranial neurovascular decompression has produced encouraging results and challenged previous understanding of primary headaches. However, there is a lack of in-depth discussions on the pathophysiological basis of migraine surgery. This narrative review provides interpretation of relevant literature from the perspective of compressive neuropathic etiology, pathogenesis, and pathophysiology of migraine.

Recent Findings Vasodilation, which can be asymptomatic in healthy subjects, may produce compression of cranial nerves in migraineurs at both extracranial and intracranial entrapment-prone sites. This may be predetermined by inherited and acquired anatomical factors and may include double crush-type lesions. Neurovascular compression can lead to sensitization of the trigeminal pathways and resultant cephalic hypersensitivity. While descending (central) trigeminal activation is possible, symptomatic intracranial sensitization can probably only occur in subjects who develop neurovascular entrapment of cranial nerves, which can explain why migraine does not invariably afflict everyone. Nerve compression–induced focal neuroinflammation and sensitization of any cranial nerve may neurogenically spread to other cranial nerves, which can explain the clinical complexity of migraine. Trigger dose-dependent alternating intensity of sensitization and its synchrony with cyclic central neural activities, including asymmetric nasal vasomotor oscillations, may explain the laterality and phasic nature of migraine pain. Intracranial allodynia, i.e., pain sensation upon non-painful stimulation, may better explain migraine pain than merely nociceptive mechanisms, because migraine cannot be associated with considerable intracranial structural changes and consequent painful stimuli.

Summary Understanding migraine as an intracranial allodynia could stimulate research aimed at elucidating the possible neuropathic compressive etiology of migraine and other primary headaches.

Keywords Migraine · Review · Pain · Pathophysiology · Sensitization · Trigeminal nerve compression

Introduction

Why does migraine headache exist? Many theories have been proposed to explain this enigmatic and disabling condition that affects over a billion people worldwide [1]. Success of migraine treatment by trigger site deactivation [2, 3•, 4], commonly understood as decompression of the occipital nerves and extracranial branches of the trigeminal nerve, suggests neuropathic etiology of migraine. The surgical, entrapment concept of migraine is in line with its numerous neuropathic features [5•]. On the other hand, there are many questions unanswered by any theory of migraine. We have no clear understanding of the nature of migraine headache, its cyclicity, and side shift. It still needs to be explained why after surgical trigger site deactivation, not all migraine patients improve [2, 3•, 4, 6, 7] and new trigger sites emerge [2, 4, 6]. While the number of publications on migraine surgery is growing, in-depth analyses of the pathophysiological basis of this treatment are limited [8]. In an attempt to address these issues, the below sections provide an interpretative literature review from the perspective of the entrapment concept of migraine.

✉ Valdas Macionis
valdas.macionis.md@gmail.com

[1] Independent researcher, Vilnius, Lithuania

Vasodilation and Neurovascular Entrapment in Migraine

The time-honored vasodilation theory of migraine [9] has been a subject of dispute between advocates [10] and critics [11] of this concept. The intensely debated extracranial vasodilation as a cause of migraine [12, 13] can be supported by the fact that migraine surgery reveals signs of extracranial neurovascular entrapment. Dilation and pulsation of the occipital and superficial temporal artery have been suggested to cause irritation of the adjacent greater occipital [14] and auriculotemporal nerve [15], respectively, and thus trigger migraine attacks. Histological changes of the arteries at these sites have been observed in migraineurs [16]. In tight compartments, even slight vasodilation may produce pressures of 30 mm Hg that are sufficient to disturb nerve function [17]. Unfortunately, no studies could be found to attempt induction of neurovascular compression by vasodilation in animals.

Calcitonin gene–related peptide (CGRP), a potent vasodilator, plays an important function in migraine pathophysiology [18–20]. Peripheral nerve injury can stimulate expression of calcitonin gene–related peptide in the dorsal root ganglia [21] and in the nerve trunk [22], which may lead to paraneural and intraneural vasodilation. Sympathetic fiber damage may also contribute to intraneural hyperemia following nerve lesion [23]. Percutaneous trigeminal nerve stimulation produces increased concentrations of cerebral CGRP and cerebral vasodilation [24]. Even antidromic stimulation of sensory nerves may result in CGRP perivascular release and vasodilation [20, 25]. Thus, compression of the trigeminal nerve can lead to its hyperactivity and consequent *secondary* vasodilatory compression because of CGRP release at the perivascular neural terminals. In migraineurs, trigeminal nerve hyperactivity may also be induced by environmental irritants, which have been shown to stimulate CGRP release [26].

Cerebral vasodilation may be caused by activation of neural pathways other than the trigeminal system, e.g., via olfactory stimulation [27] or other mechanisms of neurovascular coupling [28, 29]. The latter include fluctuations of blood oxygen levels. Hypoxic vasodilation is one of the essential mechanisms of blood perfusion regulation [30, 31], which particularly applies to cerebral circulation [32, 33]. Hypoxia, in association with cerebral vasodilation, has been shown to trigger migraine [34]. Most migraine triggers lead to direct or indirect vasodilation [35, 36], probably via induction of metabolic processes that cause hypoxia or result from it [37]. This includes reduced barometric pressure [36, 38] that may produce hypoxia [39]. Cerebral hypoxic vasodilation in migraine can explain observations of cerebral hypoperfusion during migraine attacks [40–43]. Hypoxemia may accompany patent foramen ovale (foramen Botalli) associated with atrial right-to left shunt [44], one of the risk factors of migraine [45]. Also, the rhinogenic etiology of primary headaches [46–48] may be due to hypoxemia caused by airway obstruction.

Relevantly, many effective means of migraine treatment can be associated with direct or indirect abolishment of vasodilation. Transcutaneous neurostimulation techniques [49] may involve electricity-induced vasoconstriction, both directly and via neural pathways [50]. Notably, local vasoconstriction can spread to other vascular areas [51, 52]. Oxygen has been shown to be effective in the treatment of primary headaches including migraine and cluster headache [53], which may be due to the cerebral vasoconstrictive effects of hyperoxemia [54, 55, 53]. This as well applies to the success of interictal oxygen therapy in a series of migraineurs with patent cardiac foramen ovale [56]. It is also of relevance that the 5-HT and CGRP receptor-targeting medication of migraine [57], as well as some natural means such as cold therapy [58], have a vasoconstrictive effect.

Neurovascular Entrapment at Trigger Points and Trigger Sites

Trigger points have been associated with hypersensitive spots in taut muscle bands and *referred* pain upon pressure [59–61]. Anatomical studies have revealed that myofascial trigger points correspond to sites where nerves enter muscles [62–65]. These nerves are accompanied by corresponding vessels [66–70], which makes the so-called perforating triad (nerve, artery, and vein) surrounded by fascia [61]. Such anatomical arrangement has been postulated to cause neural entrapment [61]. At trigger points, nerve compression may be produced both by muscle activity and by vessel dilation. Positive results of botulinum injection in trigger point zones in some neuropathic conditions [71, 72] (as well as in migraine [72, 73]) may be due to local muscle paralysis and consequent loosening of the myofascial ring that surrounds the "perforating triad."

The term of trigger sites in migraine surgery is somewhat different from the above definition of trigger points. While the tight vicinity between nerves and vessels is also an essential feature of the extracranial trigger sites, neurovascular entrapment here is primarily associated with adjacent myo-fibro-osseous structures [2] other than the fascia around the typical neurovascular perforators of muscles. Only the septonasal site [46] and patent cardiac foramen ovale [45] do not clearly fit the entrapment concept. Dysfunction at these sites, however, may cause hypoxemia and consequent vasodilatory compression of cranial nerves, as discussed in the preceding section.

Intracranial occurrence of neurovascular compression of almost all cranial nerves except olfactory has been well documented [74–76, 77•]. The main focus of migraine surgeons is multiple extracranial head sites where the sensory nerves are accompanied by corresponding arteries and veins [78, 79] (which is a general rule [80]). Neurovascular compression, however, may not be limited to extracranial areas. Cranial foramina and fissures that convey cranial nerves along vessels are potential sites of neural entrapment. Intracranially, branches of the trigeminal and other cranial nerves closely adhere to vessels [81]. This seems to apply to the tiny collaterals of the intracranial trigeminal nociceptors that along with emissary veins reach the extracranial periosteum via emissary canals [82–84]. An important possible site of intracranial neurovascular compression of *multiple* cranial nerves is the cavernous sinus. This compartment is surrounded by two dural layers and includes the internal carotid artery [85, 86] (Fig. 1), slight dilation of which may increase intracavernous pressure and result in neural compression within the sinus. Cranial nerve entrapment may also occur at the transition zones where the nerves pierce the dura mater. Spinal dissections have shown that the dura mater blends with the epineurium of spinal nerves [87, 88], which by analogy may apply to cranial nerves as well. The neural-dural transition zone is a tight water-impermeable junction [87], which makes the piercing nerves here susceptible to entrapment. Notably, the trigeminal nerve and ganglion are well vascularized and contain intraneural arteries of considerable size [89]. Logically, intraneural vasodilation may also cause neural compression, if epineurial tissue is tight due to anomalies or fibrosis (Fig. 2). Obviously, this type of neural lesion may occur at any point of the nerve trunk. Thus, extracranial, intracranial, paraneural, and intraneural neurovascular compression is anatomically possible.

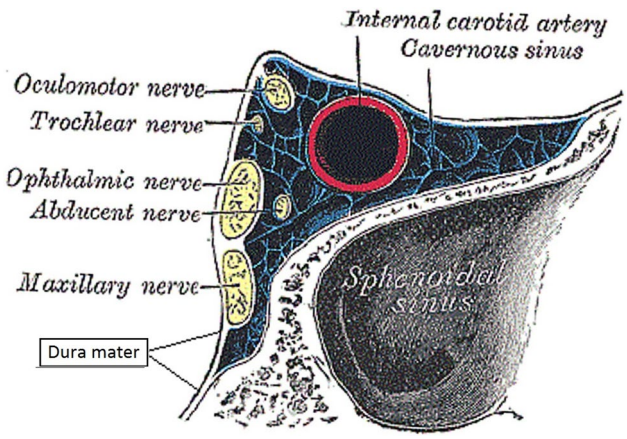

Fig. 1 The cavernous sinus as a possible intracranial site of vasodilatory neurovascular compression. Adapted from Gray and Lewis (Figure 786, public domain) [86]

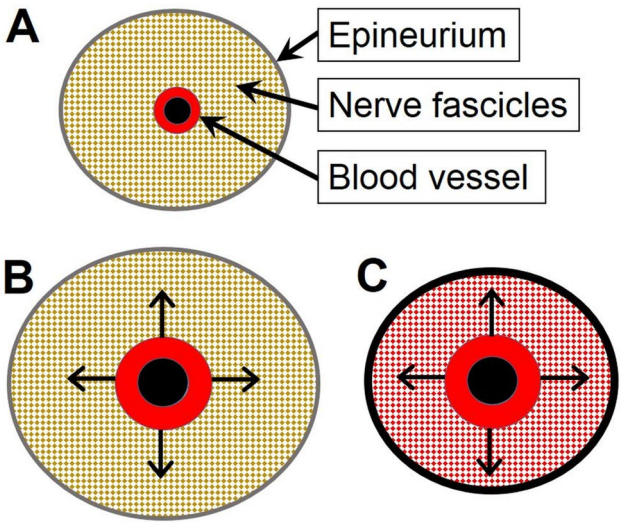

Fig. 2 Hypothetical neurovascular compression due to intraneural vasodilation. **A** Normal neurovascular relationship. **B** Elasticity of the epineurium allows expansion of the intraneural volume and thus prevents intraneural compression after intraneural vasodilation, which, however, **C** can cause intraneural compression if the epineurium is tight

It is known that a focal lesion of the nerve trunk makes its entire length vulnerable (sensitized) to secondary compression, the occurrence of which can lead to double crush syndrome [90, 91]. According to this concept, trigger points can be regarded as secondary sites of compression due to a primary, more proximal neural entrapment. The latter inference can be supported by occurrence of trigger points in thoracic outlet syndrome (TOS) [92]. Theoretically, a reverse situation is also possible: Trigger points may act as primary entrapment sites and lead to proximal neural lesion, because of the initial trigger point-induced sensitization.

Cranial nerves may also be affected by a double crush-type lesion. Recent measurement studies suggest that narrow foramen ovale and rotundum may be secondary sites of trigeminal nerve compression in trigeminal neuralgia [93, 94•, 95]. According to the double crush concept, extracranial trigger sites in migraine may be due to *intracranial* nerve compression, which could account for incomplete improvement and new extracranial trigger sites after deactivation surgery [4, 6]. Multiple extracranial trigger sites in migraine echo with multiple extracephalic trigger points in peripheral neuropathic conditions (notably, in TOS [92]). In theory, development of *intracranial* multiple trigger points is also possible. The dura mater is a dense network of collagen fibers, some of which crisscross each other and are oriented transversely to the longitudinal axis of blood vessels [96]. This may create a perforating triad-like unit in the dura, because trigeminal nerve branches accompany blood vessels [83]. The dural collagen lattices can serve as tunnels for neurovascular entrapment, especially if the trigeminal nerve is presensitized by proximal lesion.

Central Versus Peripheral Neuropathic Origin of Migraine Pain

While it is recognized that trigeminal sensitization drives migraine headaches, an essential matter of contemporary debate remains whether the sensitization originates in the periphery or in the brain [97, 98]. Although this question has been supposed to be the chicken or the egg dilemma [99], there are substantial facts that speak in favor of peripheral genesis of sensitization in migraine.

It is generally agreed that peripheral sensitization induces central sensitization [100–102]. It is not clear, however, whether central sensitization can *persist* without peripheral input. Although, theoretically, autonomous (periphery independent) central sensitization is possible, there is little practical evidence for this concept [103•]. Central neural factors definitely play an important role in migraine [104]. Yet, if trigeminal sensitization were inducible by descending excitation mechanisms alone, then we would likely observe cranial nociceptive hypersensitivity in such conditions as epilepsy, which does not seem to be the case. (However, there are numerous pathophysiological and clinical similarities between epilepsy and migraine [105, 106].) The observed activation of central structures, which has been supposed to serve as a proof of central origin of migraine [98], may in fact arise from peripheral neural input [102]. While cortical spreading depression (CSD) has been suggested to be the central excitatory mechanism responsible for migraine aura and trigeminal system activation [107], there is no straightforward evidence for applicability of this supposition to humans [108]. Furthermore, most of the CSD-relevant animal experiments involve direct physical stimulation of the cerebral cortex following craniotomy [109–112]. Injuries of this magnitude do not commonly occur in migraine. This problem has been attempted to overcome by indirect, optogenetic stimulation of the brain cortex. The latter approach, however, may produce direct excitation of trigeminal nociceptors by light, surgical exposure of the animal skull, and fixation in a stereotaxic frame [113–115]. Sleep deprivation is probably the only model that has shown noninvasive activation of the trigeminal system in animals [116]. However, in sleep-deprived subjects who develop hypersensitivity, peripheral sensitization may be due to proximal neural compression induced by negative postural impact [117] that in turn may be due to fatigue and muscle coordination imbalance [118], as also implied by a sleep deprivation study that has found sensitization of craniofacial muscles [119].

The existence of peripheral input-independent central sensitization in migraine could be reasoned on the basis of the continuing mediating role of CGRP [18, 19] following initial peripheral sensitization. However, CGRP has no direct neurostimulatory potential [120]. Relevant electrophysiological studies are lacking to confirm direct systemic contribution of CGRP to nociceptive sensitization. Notably, a recent experimental study has not found an association between CGRP and neuropathic pain [121]. On the other hand, vasodilatory effects of CGRP may have a role in perpetuating neurovascular compression, which may partly support the descending origin of migraine pain: Initial trigeminal activation may be caused by other means than neural compression. The latter, however, may be required to drive sensitization.

Increased concentrations of neurotransmitters obviously are involved in both peripheral and central sensitization. However, while the physiology of cranial nociceptors seems to be analogous to those of other tissues [122], studies of pharmacological induction of migraine in humans do not mention remote extracephalic pain to accompany induced headache [123–125]. Also, antimigraine triptans do not seem to be effective in noncerebral analgesia [126, 127]. While this may be attributed to the different embryological origin of the trigeminal and dorsal root ganglia [126], a considerable doubt arises concerning the concepts of pure neurochemical initiation of migraine pain.

Peripheral Nerve Lesion–Induced Sensitization in Migraine

In neurophysiological terms, peripheral sensitization is synonymous with excitation threshold decrease and spontaneous (ongoing) activity of afferent neurons [101, 128]. Ongoing activity has been shown to be dependent on neuroinflammatory input: without the latter ongoing activity fades [129]. The same applies to nociceptive fiber mechanosensitivity [130–132] and cutaneous hypersensitivity [131, 133, 134]. Notably, non-inflammatory axonal transport disruption alone does not induce ongoing activity [129] as in the case of focal neuroinflammation [129, 131, 132] that also impairs intraaxonal circulation [132, 134, 135]. Yet, similarly to neuroinflammation, non-inflammatory axoplasmic block results in cutaneous hypersensitivity [134], as well as in brief transient axonal mechanical sensitivity [129]. This may explain development of hypersensitivity via subtle cranial neurovascular compression in migraine patients.

There are indirect indications that extent of sensitization may be trigger dose- and exposure time-dependent. For example, hypersensitivity tends to last longer after invasive nerve manipulation, such as spared nerve injury [136, 137], than after atraumatic induction of ongoing activity [131, 133]. Most important is that sensitization lasts months after nerve injury [138], but only hours or days after local peripheral tissue injury [101, 139, 140]. Another indirect evidence of input dose-dependent sensitization can be seen in double crush-type neural lesions [90]. Cumulative effects

of systemic neuroinflammation and nerve compression (which involves both axoplasmic transport disruption and focal neuroinflammation [17, 141]) can also be regarded as a double-crush neural injury [117]. Cerebral vasodilation and CGRP concentrations seem to be dependent on the intensity of trigeminal stimulation [24], which implies a corresponding relationship between trigger dose and neurovascular compression of the trigeminal nerve. Notably, simultaneous combined action of several migraine triggers may be necessary to induce a migraine attack [142, 143], and not every prodrome develops into a migraine headache [144, 145]. The phenomena of additive sensitization may be involved in migraine chronification [146].

It is of great importance to migraine pathophysiology that lesions of different cranial nerves may trigger extraterritorial sensitization. Nociceptive hypersensitivity of rat hind limbs can be induced by subdiaphragmatic vagotomy [147–149]. Transection of the C2–C4 spinal nerves induces cutaneous hypersensitivity in the trigeminal zone of rats, which has been suggested to be due to sensitizing effects of astroglial cell activation [150]. Ligation of the buccal branch of the facial nerve also induces facial hypersensitivity, which has been associated with neuroinflammatory mediation [151]. These phenomena are also explainable by numerous anatomical and functional interconnections between the trigeminal, facial, glossopharyngeal, hypoglossal, vagus, and vestibulocochlear nerves [152–157]. The trigeminal nerve is the most complex nerve, branches of which are closely intertwined with other cranial nerves and vessels [81]. Trigeminal innervation areas overlap with innervation of other cranial [154] and spinal nerves [154, 158]. The facial, glossopharyngeal, hypoglossal, and vagus nerves contribute to posterior cranial fossa innervation along with the occipital nerves [158]. Equally important is the transcranial communication between intracranial and extracranial sensory innervation [82–84, 158]. Transaxonal signaling, which seems to be a normal neurophysiological phenomenon [159], and induction of transaxonal degeneration of healthy axons via primary injury of nearby neural fibers [160] should be taken into account as well. Notably, neurovascular compression has been speculated to result in transaxonal (ephaptic) impulse spread [161], possibly due to demyelination that usually accompanies nerve entrapment. Transneuronal sensitization of intact cranial nerves via injury of other cranial nerves is in line with the models of spared nerve injury, which show that intact sensory fibers can be sensitized by compressive or axotomy injury of the neighboring neurons at various levels [136, 162–164]. (While it has been contended that motor fiber lesion is more important for transneuronal sensitization [165], it is noteworthy that in relevant explorations, both motor and sensory fiber damage occur after ventral spinal root injury, because they contain a considerable amount of sensory afferents [166].) The phenomena of indirect sensitization may also involve nerve injury-induced neuroinflammation, which can act at the level of the nerve trunk [131, 134, 133, 167, 168] and ganglia [167, 137, 168], including the trigeminal ganglion [169], as well as at the level of the spinal trigeminal subnucleus caudalis [170, 169]. The pathophysiology of migraine may be dependent on neuroinflammatory processes [171], which can be a consequence of neural lesion. Cranial neural entrapment-induced

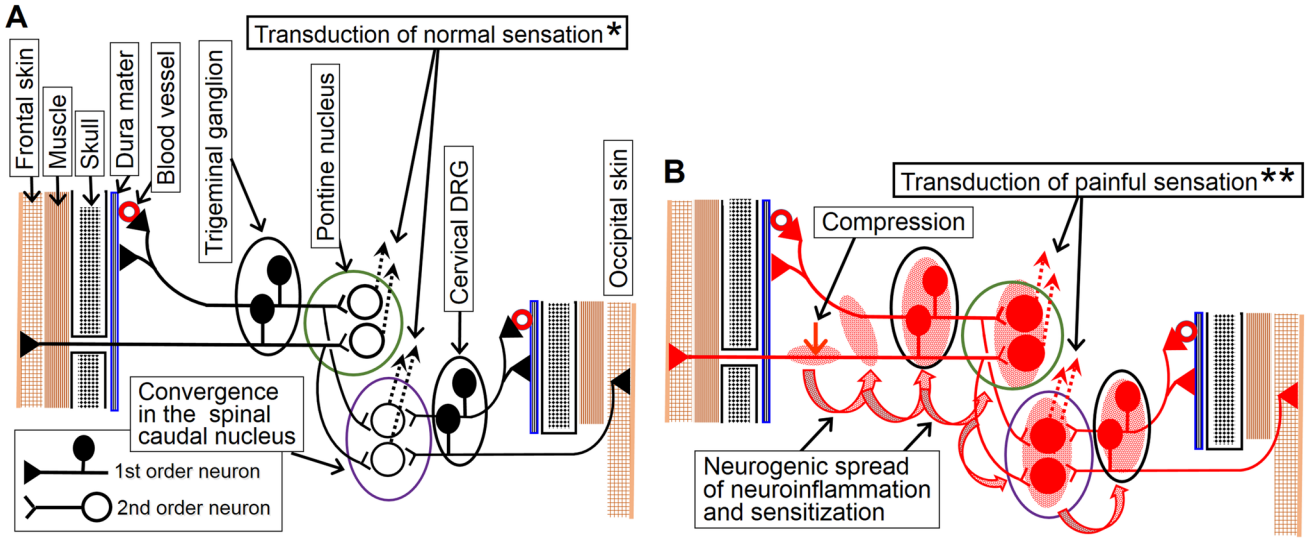

Fig. 3 **A** Simplified diagram of cranial trigeminocervical sensory anatomy and **B** neurogenic spread of focal nerve compression–induced neuroinflammation and consequent sensitization. The first-order neurons schematically represent all types of sensory neurons. This also applies to trigeminal proprioceptive neurons, which have their soma in the mesencephalic nucleus (not shown). DRG = dorsal root ganglion. *Upon non-painful stimulation of sensory terminals (not shown).**Upon painful or certain threshold exceeding non-painful stimulation of sensory terminals (not shown)

focal neuroinflammation may spread both ortho- and antidromically, similarly to neurogenic inflammation [172], which could explain the cascading activation of the trigeminovascular system [173, 171] (Fig. 3), as well as sensitization of multiple cranial nerves with the resultant clinical diversity of migraine [99]. Thus, theoretically, trigeminal pathways can be activated by damage to cranial nerves other than trigeminal.

Schumacher-Wolff Experiment and the Enigma of the Source of Migraine Pain

Schumacher's and Wolff's (S&W) unique exploration of headache response to an artificial increase in cerebrospinal fluid (CSF) pressure (up to 70 cm H2O above physiological levels) included several separate experiments [174], most significant of which are the first two. First, this investigation has convincingly demonstrated that headache induced by histamine, a potent vasodilator, can almost immediately be abolished by considerably raising CSF pressure and elicited again by reducing it (Fig. 4A). Notably, it was possible to repeat this cycle twice and thrice in three and two subjects, respectively. Altogether, this process was observed in seven horizontally positioned patients (presumably non-migraineurs) who required a diagnostic lumbar puncture for unreported reasons. The magnitude of CSF pressure was manipulated by changing the height of the physiological saline column in a rubber tubing connected to the puncture needle. Second, in six subjects with a migraine attack, stepwise artificial elevation of the CSF pressure had no considerable effect on the headache intensity (Fig. 4B). Elevation of CSF pressure also did not reduce headache in another three patients with systemic hypertension.

While this study can be found to have many limitations according to modern protocols, the first Schumacher's and Wolff's conclusion that histamine-induced distension of cerebral vessels causes headache is difficult to refute. The authors mechanistically explained the abolishment of vasodilation-induced acute headache by the drastic increase in CSF pressure and resultant compression of dilated cerebral vessels [174]. This conclusion suggests that excessive vasodilation serves as a mechanical painful stimulus to the vascular trigeminal terminals. Schumacher and Wolff ascribed the failure to abate the spontaneous migraine headaches to the origin of the pain from extracranial arteries (presumably, to their painful vasodilation) and to the fact that these vessels

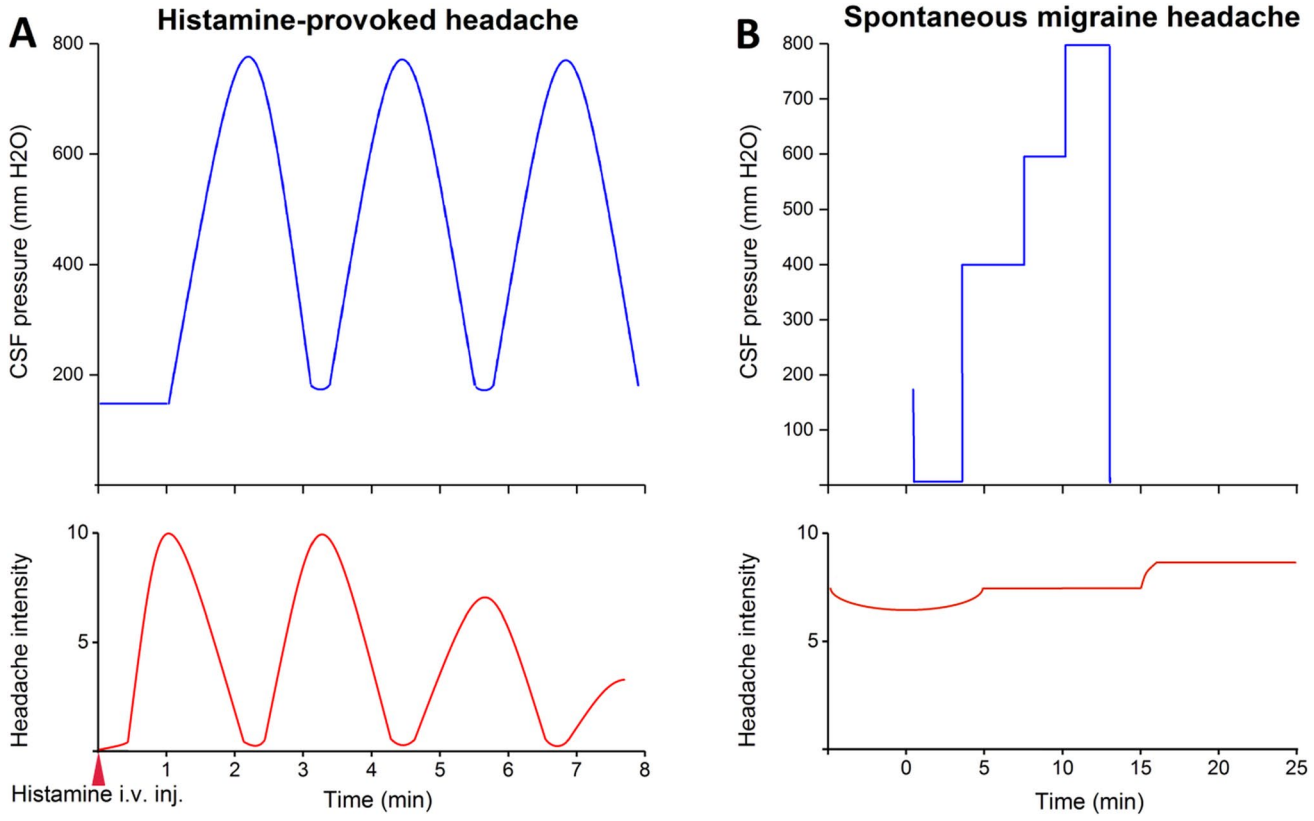

Fig. 4 A modified version of the two graphs of Schumacher's and Wolff's experiment [174]. This side-by-side comparison of headache response to elevation of CSF pressure (represented here by the height of the fluid column in the measurement tube) indicates different nature of **A** histamine-provoked and **B** spontaneous migraine headaches, which may be due to absence or presence of sensitization, respectively

are unreachable to CSF. Today, however, the unresponsiveness of the true migraine headaches to the elevation of intracranial pressure deserves a more complex explanation.

Neurovascular Compression-Induced Allodynia as the True Nature of Migraine Headache

A contemporary view of S&W experiment suggests that migraine and cerebral vasodilation-induced headaches are of different nature. Naturally, Schumacher and Wolff could not know anything about peripheral and central sensitization [175], which must have been present in their migraine patients but absent in the subjects with artificially induced headaches. Sensitization clinically presents as hypersensitivity that includes hyperalgesia (i.e., an increased sensitivity to painful stimuli) and allodynia (i.e., painful sensations to non-painful stimuli). For the cerebral cortex to perceive pain in the absence of sensitization, the terminals of peripheral nociceptors must be stimulated by painful stimuli produced by noxious events, such as, tissue injury or inflammation. Normally, in migraineurs, there are no obvious active or potential lesional processes that could produce painful stimuli. Some theories of migraine suggest that it is central neural activity-induced neurogenic inflammation of the dura and intracranial vasculature that causes headache [173, 171]. However, inflammatory mechanisms of migraine lack unequivocal experimental support [176]. While neurogenic inflammation may contribute to pain by sensitizing nociceptors [172], it has not been shown that such inflammation can act as a direct nociceptive input. Multiple repeated attacks of migraine do not seem to produce considerable structural brain changes [176, 177], which one would expect as a consequence of inflammation [178]. Logically, if there are no intracranial processes that could produce painful stimuli, then it is non-painful stimuli that cause migraine headaches. By definition, this means that migraine headache is intracranial allodynia due to trigeminal sensitization [179, 180], which seems to be more likely due to compressive cranial nerve lesion than to some other noxious events, as discussed in the relevant sections above.

Cranial allodynia in migraineurs is common [99, 181•, 182] and presents not only as skin allodynia [183–186] but also as visual allodynia (photophobia) [187, 188]. Allodynia is believed to involve interneuronal disinhibition and consequent collateralization of the non-nociceptive pathway into the sensitized nociceptive route that is an anatomical substrate of hyperalgesia [175]. Importantly, interneuronal disinhibition may require reduced afferent input via peripheral neural injury [189, 190•], which in migraine can occur via cranial neural entrapment.

While it is thought that meningeal sensory response is only nociceptive [122, 191], there is sufficient functional anatomical research that supports allodynic nature of migraine headache. Experimental observations show that the dura is sensitive to non-painful stimuli produced by application of von Frey monofilaments [122, 192], which are used to detect allodynia. The dura possesses mechanosensitive innervation by low-threshold A-neurons [191], including A-beta neurons, which are commonly non-nociceptive, and nociceptive A-delta neurons [173, 193], which may have a non-nociceptive subpopulation [194]. Dural nociceptive C-fibers [191] may also be involved in non-nociceptive transmission [194]. The A-delta neurons have Ruffini-like terminals at the sites of confluence of sinuses, at the superficial cerebral vein entrance into the sagittal sinus, and at the coronal sutures; the A-delta fibers terminate jointly with the C-fibers in capillaries and postcapillary venules [195, 196]. The dural Ruffini terminals are thought to detect tension [195, 196], similarly to their non-nociceptive counterparts in the skin [197]. Also, there are recently discovered cerebral perivascular interneurons that seem to take part in mechanoreception [198].

Conjecturally, not only nociceptive but also non-nociceptive neurons can be sensitized, because experimental research indicates that ongoing activity can develop in all types of sensory fibers [129, 199]. Sensitized mechanoreceptors require relatively less intense stimuli to produce neural impulses, which can explain intracranial allodynia due to normally non-painful intracranial vasodilation, elevation of intracranial pressure, and arterial pulsation [179]. (Throbbing pain in tissue infections, e.g., in pulpitis [200], may have an allodynic component.) Allodynia can well account for exacerbation of migraine headache during coughing, bending down, and the Queckenstedt maneuver (Q-test) [201–204], which lead to intracranial venous dilation that normally is non-painful. Thus, non-painful intracranial mechanical stimuli, which are always present in the form of intracranial pressure fluctuations, may be sufficient to produce allodynic headaches and their varying subjective perceptions in migraine patients.

What then about the histamine-induced headache in S&W experiment [174], as well as in modern models of artificial headache induction? S&W study indicates that intracranial vasodilation, as a stimulus for immediate headache in healthy subjects, should probably be of greater extent than that revealed by recent imaging studies of induced headache in migraineurs [205, 206], who are known to have relatively low headache threshold [181•]. It is likely that increased CSF pressure in S&W experiment did not diminish migraine pain because of continuing intracranial allodynia, which could have been caused by vasodilation-induced neural compression at extracranial as well as intracranial sites. Allodynia may have been persisting even after vasodilation was abolished either spontaneously or artificially, because sensitization does not fade abruptly [101, 129, 131, 133, 134, 136, 138] (see the next section for more elaboration). Noteworthy in this respect is that anti-migraine triptans,

which are known for their vasoconstrictive properties [207], are not effective in migraineurs with established allodynia [208]. Furthermore, it is roughly known that depending on the pharmacological substance the time point of occurrence of artificial headache varies [123]. While immediate headaches may be due to pharmacologically induced painful intracranial vasodilation, gradual worsening of headaches in the course of migraine attack [209] can be explained by slow development of symptomatic sensitization [101, 208] (or exacerbation of background subsymptomatic sensitization) following subtle vasodilation-induced neurovascular compression. Determining the detailed time course of cranial vasodilation during migraine headaches could bring more light into S&W findings.

Provoked headaches are worse in migraineurs than in healthy controls [123]. This is in agreement with neurovascular compression-induced sensitization, because it can lower sensory threshold in migraine patients, both ictally and interictally [181•, 210]. Certainly, in artificial headache, not only vascular but also direct neural activation should be considered, as implied by, e.g., multiple effects of nitroglycerin [125], which, however, does not seem to have immediate algesic effect. By inverted analogy, the same may apply to the mechanisms of some anti-migraine drugs, as in the case of triptans [208].

Intracranial Allodynic Stimuli

Sensitization alone without certain stimuli does not mean pain. The abolishment of histamine-induced headache in the non-migraineurs in S&W study [174] indicates that, in the absence of sensitization, even supra-physiological elevation of CSF is not painful. On the other hand, the slight intensification of headache in S&W migraine patients (Fig. 4B) may have been due to the mechanical stimulating effect of CSF pressure elevation and consequent worsening of preexisting allodynia. Increased intracranial pressure has been documented in some migraine patients [211–213]. In presence of sensitization, elevated intracranial pressure, even within normal ranges, may act as a threshold-exceeding stimulus for allodynia (and contribute to neural compression). As an allodynic stimulus, elevated intracranial pressure can explain the common occurrence of pressure pain perception in migraineurs [209, 214]. Of note, while migraine treatment with trepanation and craniotomy [215] has historically been regarded as a misconception, there are modern-day indications that surgical intracranial decompression may be beneficial to migraine patients [216, 217]. Ancient cranial trepanations may have been performed for headache treatment, because the geographical distance between sites where trepanned skulls have been found [218] suggests that this procedure may have developed independently in different ancient cultures. Multiple sites and different historical times of cranial paleo surgery also imply that intracranial decompression may have provided at least temporary relief of persistent headaches.

Cerebral vasoactivity, along with intracranial pressure, may act as threshold-exceeding allodynic stimuli and may be the cause of throbbing pain [209, 214]. Vasoactivity can explain why migraine pain is not invariably diffuse but may occur at varying cephalic locations [214, 219], may be throbbing, and may spread from one region to another [214]. Headache spreading indicates spatial spread of occurrence of threshold-exceeding allodynic stimuli. This is in line with fluctuations of brain perfusion, which seems to be never perfectly symmetric and uniform throughout the brain, both in healthy subjects [220, 221] and in migraineurs [222–225]. The circumscribed zones of hypoperfusion and hyperperfusion during migraine attack [223] may involve local vasoconstriction and vasodilation. Imaging studies have also revealed transient venous asymmetry during migraine attacks [226] and the "index vein" in migraine with aura [227]. Of note, vasodilation can spread from an initial focus to other areas via the mechanism of conducted vasodilation [228]. An analogous phenomenon is associated with vasoconstriction [51, 52].

Nerve Entrapment and Laterality of Migraine Headache

Migraine headaches can be unilateral, bilateral, and side-switching [219], which may correspond to occurrence of neurovascular entrapment at only one or at both sides of the head. One of the anatomical reasons for one-sided trigeminal entrapment may be that the skull is never ideally symmetric [229]. Association of anatomical asymmetry with unilateral migraine headache has been recently shown [230•]. Unilateral or bilateral headache may result from synergy of one-sided or both-sided neurovascular entrapment with certain factors that facilitate laterality of intracranial sensitization. For example, compressive neuropathies of the upper extremity, which have been found to occur often in migraine patients [231, 232], may contribute to one-sided trigeminal sensitization via extremity nerve lesion, because of the anatomical closeness and possible convergence of trigeminal and cervicospinal pathways. Alternating laterality of migraine pain may be associated with cyclic activity of hemispheres and lateralized rhythmic activity of autonomic nervous system [233–235]. This may facilitate induction of one-sided intracranial sensitization in synchrony with neurovascular entrapment, which alone may not be sufficient for symptomatic sensitization. Important in this respect is asymmetry of the oscillating nasal vasomotor activity (i.e., vasoconstriction and vasodilation) [236, 237] and its side-shift, which can occur spontaneously or via certain stimulation [236, 237]. Asymmetry here means different amplitudes of vasomotor oscillations, which in relative effect produce vasodilation

on one side and vasoconstriction on the other [236, 237]. This phenomenon has been explained by rhythmic asymmetry of oscillating activity of sympathetic neurons in the brainstem [235]. Nasal vasoconstriction has also been speculated to occur synchronically with ipsilateral cerebral vasoconstriction [235]. Notably, the nasal cycle may transform [238] and even be absent [239, 240]; it can be influenced by age, posture, exercise, and other factors, including olfaction [241]. Possible triggering of headaches by latent recurrent infections [242], in particular by one-sided activity of herpes simplex, which is known to invade the trigeminal ganglion [243, 244], may also influence laterality of migraine attacks. Position during sleep may laterally affect regional blood circulation [245] and thus cause one-sided neurovascular compression. It is also of consideration that cervicogenic headache, which can overlap with clinical features of migraine and can be unilateral as well as bilateral [246], may be caused by postural one-sided or both-sided occipital nerve compression and consequent trigeminal activation.

Neural Compression and Phasic Nature of Migraine

Cyclic features of migraine [181] and gradual intensification of pain after the onset of migraine attack [209] could be explained by the fact that symptomatic trigeminal sensitization takes a certain time to develop [101, 208]. Ongoing activity reaches its peak at about 4–5 days after induction of peripheral neuritis [129]. This tendency is also applicable to cutaneous hypersensitivity induced by direct compressive nerve lesion [137, 138], spared nerve injury [164, 136, 170, 137], and local neuroinflammation [131, 133, 134]. Also, sensitization *gradually* fades without supporting noxious input [101, 129, 131, 133, 134, 136, 138]. Such temporal intermittency of sensitization intensity could explain interictal increase and ictal decrease in sensory thresholds [181•]. Furthermore, as discussed above, development of sensitization is triggered dose-dependent: Cranial neurovascular entrapment may not occur if trigger intensity is not sufficient to induce vasodilation. The dose-dependence of sensitization implies that *subsymptomatic* interictal sensitization (or latent sensitization [18]) may exist in some migraineurs, which can account for the hypothetical persistence of the premonitory phase in chronic migraine [247]. Also, rhythmic neural activity and in particular its accidental synchrony with neurovascular entrapment may influence interchangeable occurrence of ictal and interictal spells.

Signs of Peripheral Nerve Damage in Migraine

Axonal abnormalities of the zygomaticotemporal branch of the trigeminal nerve in migraineurs have been confirmed by electron microscopy [248]. Recent relevant neuroimaging studies have also observed microstructural changes of the trigeminal nerve root [249, 250]. Trigeminal nerve damage in migraineurs, as well as in tension-type and cluster headache patients, is further evidenced by sensory disturbances of the face [251]. Cranial allodynia in migraine [186, 185, 187, 188, 183, 184] is a significant indication of trigeminal nerve lesion. Association of allodynia with occurrence of extracephalic symptoms [252] may be an indication of the degree of trigeminal nerve damage.

Gray and white matter alterations that have been found in migraineurs [253–255] may be due to reduced sensory input [256, 257], which obviously requires trigeminal nerve lesion. Notably, classical (primary) trigeminal neuralgia, which is associated with neurovascular compression [258], involves both gray matter changes [259, 260] and trigeminal nerve atrophy [260]. Likewise, in carpal tunnel syndrome, alterations of gray matter [261, 262] as well as of white matter [261, 263] have been found. Similar brain changes in neuropathic pain [264–266], including radiculopathy [267], may also be due to peripheral nerve damage.

Neural injury in migraine may be difficult to detect because of the subtle, transient nature of neurovascular compression. Unfortunately, autopsy studies of trigeminal neuron counts in migraineurs are lacking.

Why Are There Migraine Headaches?

Why do migraine headaches not invariably occur in everyone exposed to migraine triggers? This is a key question in testing speculative pathophysiological mechanisms of migraine. It is known that migraineurs have lower migraine threshold compared to healthy individuals [181•], i.e., migraineurs require relatively weaker triggers to elicit headache. Genetic mechanisms have been supposed to be responsible for the neural hyperexcitability in migraineurs [176, 177, 268]. On the other hand, migraine is clearly an acquired condition, as implied by epidemiologic age-related studies [1, 269, 270]. Certain anatomical circumstances in migraineurs, in contrast to non-migraineurs, may enable vasodilation to cause neurovascular entrapment and consequent sensitization. The current report suggests that realization of genetic predisposition to migraine occurs via inheritance of entrapment-prone relationships between neurovascular and fibro-osseous structures. This supposition finds support in, e.g., observations of induction of migraine by trauma [271] and by acquired, as well as by genetic, vasculopathies [272].

Cranial nerves belong to the peripheral nervous system, and there are many analogies of nociceptive transmission between all pain types. Why then do we not see migraine-like pain in extracephalic regions where neurovascular compression can

also occur (e.g., in the thoracic outlet)? Apart from the distinct features of neurobiology of cranial nerves and their proximity to the cerebral cortex, other anatomo-functional differences between cranial and extracephalic entrapment should be considered. First, all cranial nerves, differently from peripheral extracephalic nerves, pass through tight bony openings. Increased pressure within these sites cannot be completely ameliorated by elasticity of the surrounding tissue. Second, whereas cranial nerves are almost static, extracephalic nerves are relatively mobile, which enables frequent change of the compression point with an effect of preventing disturbance of neural blood and axoplasmic flow. Therefore, vasodilation may not be sufficient to cause extracephalic neural entrapment, which usually involves constant pressure by paraneural fibrous structures (but see also a relevant discussion in [117]). Third, as the cranium is a tightly closed compartment, an increased intracranial pressure simultaneously affects multiple neural structures at multiple sites. Consequent subclinical activation of non-trigeminal nerves may contribute to symptomatic trigeminal sensitization via neurogenic mechanisms addressed above.

Neurovascular Compression and other Primary Headaches

In general, the above evidence of neuropathic etiology of migraine is applicable to other primary headaches, primarily because the trigeminocervical complex is a common anatomical substrate of all headaches [273, 158]. The distinct clinical features of primary headaches may be due to different sites and modes of neurovascular compression, as well as due to varying combinations of multiple entrapment sites of the trigeminal and other cranial nerves. For example, nummular headaches [274] can be well explained by focal neurovascular compression of sensory trigeminal collaterals by transcranial veins within the emissary canals. Considering the perplexity of the cranial sensory anatomy, it is not surprising that primary headaches present with numerous concomitant symptoms. Primary headaches, in particular migraine and tension-type headaches, share not only common anatomical but also pathophysiological [275–277] and clinical [145, 278–280] features. Nitroglycerin can induce corresponding headache types in patients with migraine, tension-type headache, and cluster headache [281], which suggest that neurovascular compression by vasodilation may be entailed in all these conditions. Vasoconstriction as a cause of neurovascular compression may also be involved, e.g., as in trigeminal neuralgia [258]. The multitude of cranial neurovascular entrapment-prone sites may account for the high frequency of primary headaches.

Conclusions

Indirect evidence suggests that etiopathogenesis of migraine involves vasodilation-induced compression of the trigeminal nerve. The concept of anatomically predisposed cranial neurovascular compression can provide a reasonable alternative to the current explanations of origin of sensitization in migraine. Allodynic rather than purely nociceptive nature of migraine and other primary headaches fits better the current anatomo-physiological knowledge. Even per se non-painful transient vasodilation may cause trigeminal nerve compression at entrapment-prone sites, which can lead to intracranial sensitization and consequent allodynia. Trigeminal compression-induced focal neuroinflammation may spread as a neurogenic neuroinflammation via anatomofunctional interconnections of cranial and upper cervical nerves, which can result in sensitization of multiple cranial nerves; an inverse process is theoretically possible as well. While central excitatory processes contribute to trigeminal hypersensitivity, symptomatic sensitization of trigeminal pathways is more likely to occur in ascending than in descending manner. Alternating intensity of sensitization as well as accidental synchrony between trigger dose-dependent neurovascular compression and other triggering and anatomical factors may account for laterality and phasic nature of migraine headache. Failures of surgical *extracranial* neurovascular decompression in migraine may be due to unreleased intracranial, intraneural, and double crush-type neurovascular compression. Aiming research at the neurovascular mechanisms of intracranial allodynia, including experimental imitation of neurovascular compression and determination of detailed time course of cerebral vasoactive changes in migraineurs, may help to resolve the longstanding dispute concerning the role of vasodilation in migraine.

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References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17:954–76.
2. Bink T, Duraku LS, Ter Louw RP, Zuidam JM, Mathijssen IMJ, Driessen C. The cutting edge of headache surgery: a systematic review on the value of extracranial surgery in the treatment of chronic headache. Plast Reconstr Surg. 2019;144:1431–48.
3.• ElHawary H, Barone N, Baradaran A, Janis JE. Efficacy and safety of migraine surgery: a systematic review and meta-analysis of outcomes and complication rates. Ann Surg. 2022;275:e315–23. **This systematic review shows efficacy of migraine treatment by extracranial nerve decompression.**
4. Henriques S, Almeida A, Peres H, Costa-Ferreira A. Current evidence in migraine surgery: a systematic review. Ann Plast Surg. 2022;89:113–20.
5.• Biondi DM. Is migraine a neuropathic pain syndrome? Curr Pain Headache Rep. 2006;10:167–78. **One of the few articles that conceptually discusses migraine as a neuropathic condition.**
6. Gfrerer L, Hulsen JH, McLeod MD, Wright EJ, Austen WG. Migraine surgery: an all or nothing phenomenon? Prospective evaluation of surgical outcomes. Ann Surg. 2019;269:994–9.
7. Vincent AJPE, van Hoogstraten WS, Maassen Van Den Brink A, van Rosmalen J, Bouwen BLJ. Extracranial trigger site surgery for migraine: a systematic review with meta-analysis on elimination of headache symptoms. Front Neurol. 2019;10:89.
8. Muehlberger T. How does migraine surgery work? Migraine Surg Clin Guide Theory Pract. Cham: Springer International Publishing; 2018. p. 73–105.
9. Edmeads J. Editorial review: migraine: new views on an old theory. Can J Neurol Sci J Can Sci Neurol. 1984;11:363–4.
10. Shevel E. The extracranial vascular theory of migraine–a great story confirmed by the facts. Headache. 2011;51:409–17.
11. Goadsby PJ. The vascular theory of migraine–a great story wrecked by the facts. Brain J Neurol. 2009;132:6–7.
12. Amin FM, Asghar MS, Hougaard A, Hansen AE, Larsen VA, de Koning PJH, et al. Magnetic resonance angiography of intracranial and extracranial arteries in patients with spontaneous migraine without aura: a cross-sectional study. Lancet Neurol. 2013;12:454–61.
13. Shevel E. Intracranial and extracranial arteries in migraine. Lancet Neurol. 2013;12:847.
14. Janis JE, Hatef DA, Reece EM, McCluskey PD, Schaub TA, Guyuron B. Neurovascular compression of the greater occipital nerve: implications for migraine headaches. Plast Reconstr Surg. 2010;126:1996–2001.
15. Janis JE, Hatef DA, Ducic I, Ahmad J, Wong C, Hoxworth RE, et al. Anatomy of the auriculotemporal nerve: variations in its relationship to the superficial temporal artery and implications for the treatment of migraine headaches. Plast Reconstr Surg. 2010;125:1422–8.
16. Raposio E, Raposio G, Del Duchetto D, Tagliatti E, Cortese K. Morphologic vascular anomalies detected during migraine surgery. J Plast Reconstr Aesthetic Surg JPRAS. 2022;75:4069–73.
17. Rempel D, Dahlin L, Lundborg G. Pathophysiology of nerve compression syndromes: response of peripheral nerves to loading. J Bone Joint Surg Am. 1999;81:1600–10.
18. Iyengar S, Ossipov MH, Johnson KW. The role of calcitonin gene-related peptide in peripheral and central pain mechanisms including migraine. Pain. 2017;158:543–59.
19. Iyengar S, Johnson KW, Ossipov MH, Aurora SK. CGRP and the trigeminal system in migraine. Headache. 2019;59:659–81.
20. Russell FA, King R, Smillie S-J, Kodji X, Brain SD. Calcitonin gene-related peptide: physiology and pathophysiology. Physiol Rev. 2014;94:1099–142.
21. Zheng L-F, Wang R, Xu Y-Z, Yi X-N, Zhang J-W, Zeng Z-C. Calcitonin gene-related peptide dynamics in rat dorsal root ganglia and spinal cord following different sciatic nerve injuries. Brain Res. 2008;1187:20–32.
22. Toth CC, Willis D, Twiss JL, Walsh S, Martinez JA, Liu W-Q, et al. Locally synthesized calcitonin gene-related peptide has a critical role in peripheral nerve regeneration. J Neuropathol Exp Neurol. 2009;68:326–37.
23. Zochodne DW. Local blood flow in peripheral nerves and their ganglia: resurrecting key ideas around its measurement and significance. Muscle Nerve. 2018;57:884–95.
24. Li C, White TG, Shah KA, Chaung W, Powell K, Wang P, et al. Percutaneous trigeminal nerve stimulation induces cerebral vasodilation in a dose-dependent manner. Neurosurgery. 2021;88:E529–36.
25. Stjärne P, Lacroix JS, Anggård A, Lundberg JM. Release of calcitonin gene-related peptide in the pig nasal mucosa by antidromic nerve stimulation and capsaicin. Regul Pept. 1991;33:251–62.
26. Kunkler PE, Ballard CJ, Oxford GS, Hurley JH. TRPA1 receptors mediate environmental irritant-induced meningeal vasodilatation. Pain. 2011;152:38–44.
27. Petzold GC, Albeanu DF, Sato TF, Murthy VN. Coupling of neural activity to blood flow in olfactory glomeruli is mediated by astrocytic pathways. Neuron. 2008;58:897–910.
28. Lecrux C, Bourourou M, Hamel E. How reliable is cerebral blood flow to map changes in neuronal activity? Auton Neurosci Basic Clin. 2019;217:71–9.
29. Drew PJ. Neurovascular coupling: motive unknown. Trends Neurosci. 2022;45:809–19.
30. Umbrello M, Dyson A, Feelisch M, Singer M. The key role of nitric oxide in hypoxia: hypoxic vasodilation and energy supply-demand matching. Antioxid Redox Signal. 2013;19:1690–710.
31. Allen BW, Stamler JS, Piantadosi CA. Hemoglobin, nitric oxide and molecular mechanisms of hypoxic vasodilation. Trends Mol Med. 2009;15:452–60.
32. Hoiland RL, MacLeod DB, Stacey BS, Caldwell HG, Howe CA, Nowak-Flück D, et al. Hemoglobin and cerebral hypoxic vasodilation in humans: evidence for nitric oxide-dependent and S-nitrosothiol mediated signal transduction. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab. 2023;271678X231169579.
33. Hoiland RL, Bain AR, Rieger MG, Bailey DM, Ainslie PN. Hypoxemia, oxygen content, and the regulation of cerebral blood flow. Am J Physiol Regul Integr Comp Physiol. 2016;310:R398-413.
34. Arngrim N, Schytz HW, Britze J, Amin FM, Vestergaard MB, Hougaard A, et al. Migraine induced by hypoxia: an MRI spectroscopy and angiography study. Brain J Neurol. 2016;139:723–37.
35. Martin VT, Vij B. Diet and headache: part 2. Headache. 2016;56:1553–62.
36. Kesserwani H. Migraine triggers: an overview of the pharmacology, biochemistry, atmospherics, and their effects on neural networks. Cureus. 2021;13: e14243.
37. Grech O, Mollan SP, Wakerley BR, Fulton D, Lavery GG, Sinclair AJ. The role of metabolism in migraine pathophysiology and susceptibility. Life Basel Switz. 2021;11:415.
38. Britze J, Arngrim N, Schytz HW, Ashina M. Hypoxic mechanisms in primary headaches. Cephalalgia Int J Headache. 2017;37:372–84.

39. Savourey G, Launay J-C, Besnard Y, Guinet A, Travers S. Normo- and hypobaric hypoxia: are there any physiological differences? Eur J Appl Physiol. 2003;89:122–6.
40. Zanette EM, Agnoli A, Roberti C, Chiarotti F, Cerbo R, Fieschi C. Transcranial Doppler in spontaneous attacks of migraine. Stroke. 1992;23:680–5.
41. Denuelle M, Fabre N, Payoux P, Chollet F, Geraud G. Posterior cerebral hypoperfusion in migraine without aura. Cephalalgia Int J Headache. 2008;28:856–62.
42. Viola S, Viola P, Litterio P, Buongarzone MP, Fiorelli L. Pathophysiology of migraine attack with prolonged aura revealed by transcranial Doppler and near infrared spectroscopy. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2010;31(Suppl 1):S165-166.
43. Kellner-Weldon F, El-Koussy M, Jung S, Jossen M, Klinger-Gratz PP, Wiest R. Cerebellar hypoperfusion in migraine attack: incidence and significance. AJNR Am J Neuroradiol. 2018;39:435–40.
44. Mojadidi MK, Ruiz JC, Chertoff J, Zaman MO, Elgendy IY, Mahmoud AN, et al. Patent foramen ovale and hypoxemia. Cardiol Rev. 2019;27:34–40.
45. Liu K, Wang BZ, Hao Y, Song S, Pan M. The correlation between migraine and patent foramen ovale. Front Neurol. 2020;11: 543485.
46. Lee M, Erickson C, Guyuron B. Intranasal pathology in the migraine surgery population: incidence, patterns, and predictors of surgical success. Plast Reconstr Surg. 2017;139:184–9.
47. Hu S, Helman S, Filip P, Cabin J, Colley P. The role of the otolaryngologist in the evaluation and management of headaches. Am J Otolaryngol. 2019;40:115–20.
48. Lee K-I, In SM, Kim J-Y, Hong J-Y, Han K-D, Kim J-S, et al. Association of nasal septal deviation with the incidence of anxiety, depression, and migraine: a national population-based study. PLoS ONE. 2021;16: e0259468.
49. Evers S. Non-invasive neurostimulation methods for acute and preventive migraine treatment—a narrative review. J Clin Med. 2021;10:3302.
50. Brinton M, Mandel Y, Schachar I, Palanker D. Mechanisms of electrical vasoconstriction. J Neuroengineering Rehabil. 2018;15:43.
51. Emerson GG, Segal SS. Electrical activation of endothelium evokes vasodilation and hyperpolarization along hamster feed arteries. Am J Physiol Heart Circ Physiol. 2001;280:H160-167.
52. Segal SS, Welsh DG, Kurjiaka DT. Spread of vasodilatation and vasoconstriction along feed arteries and arterioles of hamster skeletal muscle. J Physiol. 1999;516(Pt 1):283–91.
53. Mo H, Chung SJ, Rozen TD, Cho S-J. Oxygen therapy in cluster headache, migraine, and other headache disorders. J Clin Neurol Seoul Korea. 2022;18:271–9.
54. Floyd TF, Clark JM, Gelfand R, Detre JA, Ratcliffe S, Guvakov D, et al. Independent cerebral vasoconstrictive effects of hyperoxia and accompanying arterial hypocapnia at 1 ATA. J Appl Physiol Bethesda Md. 1985;2003(95):2453–61.
55. Hirunpattarasilp C, Barkaway A, Davis H, Pfeiffer T, Sethi H, Attwell D. Hyperoxia evokes pericyte-mediated capillary constriction. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab. 2022;42:2032–47.
56. Wang M, Lan D, Dandu C, Ding Y, Ji X, Meng R. Normobaric oxygen may attenuate the headache in patients with patent foramen ovale and migraine. BMC Neurol. 2023;23:44.
57. Zobdeh F, Ben Kraiem A, Attwood MM, Chubarev VN, Tarasov VV, Schiöth HB, et al. Pharmacological treatment of migraine: drug classes, mechanisms of action, clinical trials and new treatments. Br J Pharmacol. 2021;178:4588–607.
58. Hsu Y-Y, Chen C-J, Wu S-H, Chen K-H. Cold intervention for relieving migraine symptoms: a systematic review and meta-analysis. J Clin Nurs. 2023;32:2455–65.
59. Alvarez DJ, Rockwell PG. Trigger points: diagnosis and management. Am Fam Physician. 2002;65:653–60.
60. Baeumler P, Hupe K, Irnich D. Proposal of a diagnostic algorithm for myofascial trigger points based on a multiple correspondence analysis of cross-sectional data. BMC Musculoskelet Disord. 2023;24:62.
61. Gautschi RU. Trigger points as a fascia-related disorder. In: Schleip R, Stecco C, Driscoll M, Huijing PA, editors. Fascia Tens Netw Hum Body. Elsevier; 2022. p. 329–40.
62. Akamatsu FE, Saleh S, Pinesi HT, Rodrigues KR, Zandoná CB, Andrade M, et al. Anatomical basis of the myofascial trigger points of the trapezius muscle. Int J Morphol. 2013;31:915–20.
63. Akamatsu FE, Yendo TM, Rhode C, Itezerote AM, Hojaij F, Andrade M, et al. Anatomical basis of the myofascial trigger points of the gluteus maximus muscle. BioMed Res Int. 2017;2017:4821968.
64. Wada JT, Akamatsu F, Hojaij F, Itezerote A, Scarpa JC, Andrade M, et al. An anatomical basis for the myofascial trigger points of the abductor hallucis muscle. BioMed Res Int. 2020;2020:9240581.
65. Procópio Pinheiro R, Gaubeur MA, Itezerote AM, Saleh SO, Hojaij F, Andrade M, et al. Anatomical study of the innervation of the masseter muscle and its correlation with myofascial trigger points. J Pain Res. 2020;13:3217–26.
66. Yang D, Morris SF. Trapezius muscle: anatomic basis for flap design. Ann Plast Surg. 1998;41:52–7.
67. Scheufler O, Farhadi J, Kovach SJ, Kukies S, Pierer G, Levin LS, et al. Anatomical basis and clinical application of the infragluteal perforator flap. Plast Reconstr Surg. 2006;118:1389–400.
68. Tansatit T, Chokrungyaranont P, Sanguansit P, Wanidchaphloi S. Anatomical study of the superior gluteal artery perforator (S-GAP) for free flap harvesting. J Med Assoc Thail Chotmaihet Thangphaet. 2008;91:1244–9.
69. Sarrafian S, Kelikian A. Nerves. In: Kelikian AS, editor. Sarrafian's anatomy of the foot and ankle: descriptive, topographic, functional. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2011. p. 381–427.
70. Kaya B, Apaydin N, Loukas M, Tubbs RS. The topographic anatomy of the masseteric nerve: a cadaveric study with an emphasis on the effective zone of botulinum toxin A injections in masseter. J Plast Reconstr Aesthetic Surg JPRAS. 2014;67:1663–8.
71. Argoff CE. A focused review on the use of botulinum toxins for neuropathic pain. Clin J Pain. 2002;18:S177-181.
72. Oh H-M, Chung ME. Botulinum toxin for neuropathic pain: a review of the literature. Toxins. 2015;7:3127–54.
73. Becker WJ. Botulinum toxin in the treatment of headache. Toxins. 2020;12:803.
74. Møller AR. Vascular compression of cranial nerves. I. History of the microvascular decompression operation. Neurol Res. 1998;20:727–31.
75. McLaughlin MR, Jannetta PJ, Clyde BL, Subach BR, Comey CH, Resnick DK. Microvascular decompression of cranial nerves: lessons learned after 4400 operations. J Neurosurg. 1999;90:1–8.
76. Sirko A, Chekha K, Mizyakina K. Cranial nerve hyperfunction syndromes. modern approaches to diagnosis and treatment (review). Georgian Med News. 2020;6:113–20.
77.• Szmyd B, Sołek J, Błaszczyk M, Jankowski J, Liberski PP, Jaskólski DJ, et al. The underlying pathogenesis of neurovascular compression syndromes: a systematic review. Front Mol Neurosci. 2022;15: 923089. **This article discusses neurovascular compression syndromes of cranial nerves and thus can serve as an anatomical basis for the neurovascular entrapment concept of migraine.**
78. Barbaro F, Bassi E, Toni R. Surgical anatomy of the vascularization and innervation of the human scalp. In: Raposio E,

editor. Atlas Surg Ther Migraine Tens-Type Headache. Cham: Springer International Publishing; 2020. p. 5–11.
79. Konschake M. Surgical anatomy of craniofacial nerves regarding migraine surgery. In: Raposio E, editor. Atlas Surg Ther Migraine Tens-Type Headache. Cham: Springer International Publishing; 2020. p. 13–8.
80. Gamboa NT, Taussky P, Park MS, Couldwell WT, Mahan MA, Kalani MYS. Neurovascular patterning cues and implications for central and peripheral neurological disease. Surg Neurol Int. 2017;8:208.
81. Joo W, Yoshioka F, Funaki T, Mizokami K, Rhoton AL. Microsurgical anatomy of the trigeminal nerve. Clin Anat N Y N. 2014;27:61–88.
82. Kosaras B, Jakubowski M, Kainz V, Burstein R. Sensory innervation of the calvarial bones of the mouse. J Comp Neurol. 2009;NA-NA.
83. Schueler M, Neuhuber WL, De Col R, Messlinger K. Innervation of rat and human dura mater and pericranial tissues in the parieto-temporal region by meningeal afferents. Headache. 2014;54:996–1009.
84. Zhao J, Levy D. The sensory innervation of the calvarial periosteum is nociceptive and contributes to headache-like behavior. Pain. 2014;155:1392–400.
85. Mahalingam HV, Mani SE, Patel B, Prabhu K, Alexander M, Fatterpekar GM, et al. Imaging spectrum of cavernous sinus lesions with histopathologic correlation. Radiogr Rev Publ Radiol Soc N Am Inc. 2019;39:795–819.
86. Gray H, Lewis WH. Anatomy of the human body. 20th ed. Philadelphia: Lea & Febiger; 1918.
87. Wiltse LL. Anatomy of the extradural compartments of the lumbar spinal canal. Peridural membrane and circumneural sheath. Radiol Clin North Am. 2000;38:1177–206.
88. McCabe JS, Low FN. The subarachnoid angle: an area of transition in peripheral nerve. Anat Rec. 1969;164:15–33.
89. Ćetković M, Štimec BV, Mucić D, Dožić A, Ćetković D, Reçi V, et al. Arterial supply of the trigeminal ganglion, a micromorphological study. Folia Morphol. 2020;79:58–64.
90. Dellon AL, Mackinnon SE. Chronic nerve compression model for the double crush hypothesis. Ann Plast Surg. 1991;26:259–64.
91. Upton AR, McComas AJ. The double crush in nerve entrapment syndromes. Lancet Lond Engl. 1973;2:359–62.
92. Novak CB, Mackinnon SE. Thoracic outlet syndrome. Orthop Clin North Am. 1996;27:747–62.
93. Liu P, Zhong W, Liao C, Liu M, Zhang W. Narrow foramen ovale and rotundum: a role in the etiology of trigeminal neuralgia. J Craniofac Surg. 2016;27:2168–70.
94.• Li S, Liao C, Qian M, Yang X, Zhang W. Narrow ovale foramina may be involved in the development of primary trigeminal neuralgia. Front Neurol. 2022;13:1013216. **This study presents evidence that narrow cranial foramen ovale can be a secondary site of trigeminal nerve compression.**
95. Li S, Liao C, Zhang W. The potential role of a narrow foramen rotundum and foramen ovale in the development of concomitant continuous pain in trigeminal neuralgia. Med Hypotheses. 2023;177:111110.
96. Hamann MC, Sacks MS, Malinin TI. Quantification of the collagen fibre architecture of human cranial dura mater. J Anat. 1998;192(Pt 1):99–106.
97. Do TP, Hougaard A, Dussor G, Brennan KC, Amin FM. Migraine attacks are of peripheral origin: the debate goes on. J Headache Pain. 2023;24:3.
98. Edvinsson L, Haanes KA. Views on migraine pathophysiology: where does it start? Neurol Clin Neurosci. 2020;8:120–7.
99. Villar-Martinez MD, Goadsby PJ. Pathophysiology and therapy of associated features of migraine. Cells. 2022;11:2767.
100. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain. 2009;10:895–926.
101. Malick A, Burstein R. Peripheral and central sensitization during migraine. Funct Neurol. 2000;15(Suppl 3):28–35.
102. Olesen J, Burstein R, Ashina M, Tfelt-Hansen P. Origin of pain in migraine: evidence for peripheral sensitisation. Lancet Neurol. 2009;8:679–90.
103.• Brazenor GA, Malham GM, Teddy PJ. Can central sensitization after injury persist as an autonomous pain generator? A comprehensive search for evidence. Pain Med Malden Mass. 2022;23:1283–98. **This article shows that central sensitization cannot persist without peripheral input.**
104. Barbanti P, Brighina F, Egeo G, Di Stefano V, Silvestro M, Russo A. Migraine as a cortical brain disorder. Headache. 2020;60:2103–14.
105. Bauer PR, Tolner EA, Keezer MR, Ferrari MD, Sander JW. Headache in people with epilepsy. Nat Rev Neurol. 2021;17:529–44.
106. Nye BL, Thadani VM. Migraine and epilepsy: review of the literature. Headache. 2015;55:359–80.
107. Carneiro-Nascimento S, Levy D. Cortical spreading depression and meningeal nociception. Neurobiol Pain Camb Mass. 2022;11: 100091.
108. Borgdorff P. Arguments against the role of cortical spreading depression in migraine. Neurol Res. 2018;40:173–81.
109. Zhang X, Levy D, Noseda R, Kainz V, Jakubowski M, Burstein R. Activation of meningeal nociceptors by cortical spreading depression: implications for migraine with aura. J Neurosci Off J Soc Neurosci. 2010;30:8807–14.
110. Zhang X, Levy D, Kainz V, Noseda R, Jakubowski M, Burstein R. Activation of central trigeminovascular neurons by cortical spreading depression. Ann Neurol. 2011;69:855–65.
111. Zhao J, Levy D. Modulation of intracranial meningeal nociceptor activity by cortical spreading depression: a reassessment. J Neurophysiol. 2015;113:2778–85.
112. Zhao J, Levy D. Cortical spreading depression promotes persistent mechanical sensitization of intracranial meningeal afferents: implications for the intracranial mechanosensitivity of migraine. eNeuro. 2016;3:ENEURO.0287–16.2016.
113. Harriott AM, Chung DY, Uner A, Bozdayi RO, Morais A, Takizawa T, et al. Optogenetic spreading depression elicits trigeminal pain and anxiety behavior. Ann Neurol. 2021;89:99–110.
114. Houben T, Loonen IC, Baca SM, Schenke M, Meijer JH, Ferrari MD, et al. Optogenetic induction of cortical spreading depression in anesthetized and freely behaving mice. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab. 2017;37:1641–55.
115. Pi C, Tang W, Li Z, Liu Y, Jing Q, Dai W, et al. Cortical pain induced by optogenetic cortical spreading depression: from whole brain activity mapping. Mol Brain. 2022;15:99.
116. Kim S, Park J. Sleep deprivation, headache, and Fos immunohistochemistry. In: Rajendram R, Preedy VR, Patel VB, Martin CR, editors. Neurobiol Physiol Psychol Pain. Elsevier; 2022. p. 203–15.
117. Macionis V. Chronic pain and local pain in usually painless conditions including neuroma may be due to compressive proximal neural lesion. Front Pain Res. 2023;4.
118. Paillard T. Detrimental effects of sleep deprivation on the regulatory mechanisms of postural balance: a comprehensive review. Front Hum Neurosci. 2023;14:1146550.
119. Kristiansen ES, Nielsen LS, Christensen SS, Botvid SHC, Nørgaard Poulsen J, Gazerani P. Sleep deprivation sensitizes human craniofacial muscles. Somatosens Mot Res. 2017;34:116–22.
120. Messlinger K. The big CGRP flood - sources, sinks and signalling sites in the trigeminovascular system. J Headache Pain. 2018;19:22.
121. Ishida K, Tanaka S, Shen D, Matsui S, Fuseya S, Shindo T, et al. Calcitonin gene-related peptide is not involved in neuropathic

pain induced by partial sciatic nerve ligation in mice. Neurosci Lett. 2022;778: 136615.
122. Bove GM, Moskowitz MA. Primary afferent neurons innervating guinea pig dura. J Neurophysiol. 1997;77:299–308.
123. Ashina M, Hansen JM, Á Dunga BO, Olesen J. Human models of migraine - short-term pain for long-term gain. Nat Rev Neurol. 2017;13:713–24.
124. Greco R, Demartini C, De Icco R, Martinelli D, Putortì A, Tassorelli C. Migraine neuroscience: from experimental models to target therapy. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2020;41:351–61.
125. Demartini C, Greco R, Zanaboni AM, Sances G, De Icco R, Borsook D, et al. Nitroglycerin as a comparative experimental model of migraine pain: from animal to human and back. Prog Neurobiol. 2019;177:15–32.
126. Messlinger K, Balcziak LK, Russo AF. Cross-talk signaling in the trigeminal ganglion: role of neuropeptides and other mediators. J Neural Transm Vienna Austria. 1996;2020(127):431–44.
127. Ahn AH, Basbaum AI. Where do triptans act in the treatment of migraine? Pain. 2005;115:1–4.
128. Bove GM, Dilley A. The conundrum of sensitization when recording from nociceptors. J Neurosci Methods. 2010;188:213–8.
129. Satkeviciute I, Goodwin G, Bove GM, Dilley A. Time course of ongoing activity during neuritis and following axonal transport disruption. J Neurophysiol. 2018;119:1993–2000.
130. Dilley A, Bove GM. Resolution of inflammation-induced axonal mechanical sensitivity and conduction slowing in C-fiber nociceptors. J Pain. 2008;9:185–92.
131. Bove GM, Ransil BJ, Lin H-C, Leem J-G. Inflammation induces ectopic mechanical sensitivity in axons of nociceptors innervating deep tissues. J Neurophysiol. 2003;90:1949–55.
132. Greening J, Dilley A. Peripheral mechanisms of chronic upper limb pain: nerve dynamics, inflammation and neurophysiology. In: Fernandez de las Penas C, Cleland JA, Huijbregts PA, editors. Neck Arm Pain Syndr. Elsevier; 2011. p. 476–95.
133. Satkeviciute I, Dilley A. Neuritis and vinblastine-induced axonal transport disruption lead to signs of altered dorsal horn excitability. Mol Pain. 2018;14:1744806918799581.
134. Dilley A, Richards N, Pulman KG, Bove GM. Disruption of fast axonal transport in the rat induces behavioral changes consistent with neuropathic pain. J Pain. 2013;14:1437–49.
135. Armstrong BD, Hu Z, Abad C, Yamamoto M, Rodriguez WI, Cheng J, et al. Induction of neuropeptide gene expression and blockade of retrograde transport in facial motor neurons following local peripheral nerve inflammation in severe combined immunodeficiency and BALB/C mice. Neuroscience. 2004;129:93–9.
136. Decosterd I, Woolf CJ. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. Pain. 2000;87:149–58.
137. Noh M, Mikler B, Joy T, Smith PA. Time course of inflammation in dorsal root ganglia correlates with differential reversibility of mechanical allodynia. Neuroscience. 2020;428:199–216.
138. Bennett GJ, Xie Y-K. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain. 1988;33:87–107.
139. Arendt-Nielsen L, Andersen OK. Capsaicin in human experimental pain models of skin, muscle and visceral sensitization. In: Malmberg AB, Bley KR, editors. Turn Heat Pain TRPV1 Recept Pain Inflamm. Basel: Birkhäuser-Verlag; 2005. p. 117–44.
140. Brennan TJ. Pathophysiology of postoperative pain. Pain. 2011;152:S33-40.
141. Schmid AB, Fundaun J, Tampin B. Entrapment neuropathies: a contemporary approach to pathophysiology, clinical assessment, and management. Pain Rep. 2020;5: e829.
142. Peris F, Donoghue S, Torres F, Mian A, Wöber C. Towards improved migraine management: determining potential trigger factors in individual patients. Cephalalgia Int J Headache. 2017;37:452–63.
143. Martinelli D, Pocora MM, De Icco R, Putortì A, Tassorelli C. Triggers of migraine: where do we stand? Curr Opin Neurol. 2022;35:360–6.
144. Sheftell F, Cady R. Migraine without aura. In: Bigal ME, Lipton RB, editors. Migraine Headache Disord. New York, NY: Taylor & Francis Group; 2006. p. 173–88.
145. Cady RK. The convergence hypothesis. Headache. 2007;47(Suppl 1):S44-51.
146. de Ru JA, Filipovic B, Lans J, van der Veen EL, Lohuis PJ. Entrapment neuropathy: a concept for pathogenesis and treatment of headaches—a narrative review. Clin Med Insights Ear Nose Throat. 2019;12:1179550619834949.
147. Khasar SG, Miao FJ, Jänig W, Levine JD. Vagotomy-induced enhancement of mechanical hyperalgesia in the rat is sympathoadrenal-mediated. J Neurosci Off J Soc Neurosci. 1998;18:3043–9.
148. Khasar SG, Miao JP, Jänig W, Levine JD. Modulation of bradykinin-induced mechanical hyperalgesia in the rat by activity in abdominal vagal afferents. Eur J Neurosci. 1998;10:435–44.
149. Furuta S, Shimizu T, Narita M, Matsumoto K, Kuzumaki N, Horie S, et al. Subdiaphragmatic vagotomy promotes nociceptive sensitivity of deep tissue in rats. Neuroscience. 2009;164:1252–62.
150. Kobayashi A, Shinoda M, Sessle BJ, Honda K, Imamura Y, Hitomi S, et al. Mechanisms involved in extraterritorial facial pain following cervical spinal nerve injury in rats. Mol Pain. 2011;7:12.
151. Lewis SS, Grace PM, Hutchinson MR, Maier SF, Watkins LR. Constriction of the buccal branch of the facial nerve produces unilateral craniofacial allodynia. Brain Behav Immun. 2017;64:59–64.
152. Tseng CY, Lue JH, Lee SH, Wen CY, Shieh JY. Evidence of neuroanatomical connection between the superior cervical ganglion and hypoglossal nerve in the hamster as revealed by tract-tracing and degeneration methods. J Anat. 2001;198:407–21.
153. Păduraru D, Rusu MC. The anatomy of the intralingual neural interconnections. Surg Radiol Anat SRA. 2013;35:457–62.
154. Bičanić I, Hladnik A, Džaja D, Petanjek Z. The anatomy of orofacial innervation. Acta Clin Croat. 2019;58:35–42.
155. Adair D, Truong D, Esmaeilpour Z, Gebodh N, Borges H, Ho L, et al. Electrical stimulation of cranial nerves in cognition and disease. Brain Stimulat. 2020;13:717–50.
156. Wang X, Meng D, Wang L, Chen G. The clinical characteristics and surgical treatment of glossopharyngeal neuralgia with pain radiating to the innervated area of the trigeminal nerve. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg. 2021;79:786.e1-786.e8.
157. Henssen DJHA, Derks B, van Doorn M, Verhoogt N, Van Cappellen van Walsum A-M, Staats P, et al. Vagus nerve stimulation for primary headache disorders: an anatomical review to explain a clinical phenomenon. Cephalalgia Int J Headache. 2019;39:1180–94.
158. Terrier L-M, Fontaine D. Intracranial nociception. Rev Neurol (Paris). 2021;177:765–72.
159. Spead O, Poulain FE. Trans-axonal signaling in neural circuit wiring. Int J Mol Sci. 2020;21:5170.
160. Assunção FB, Scoppetta TLPD, Yonekura Inada BS, Martins LDA, Narvaez EO, Soldatelli MD, et al. Secondary neurodegeneration: a general approach to axonal and transaxonal degeneration. Neurographics. 2021;11:111–26.
161. Lee MH, Park JS. Pathogenesis of hemifacial spasm. In: Park K, Park JS, editors. Hemifacial Spasm. Singapore: Springer Singapore; 2020. p. 21–5.
162. Wu G, Ringkamp M, Hartke TV, Murinson BB, Campbell JN, Griffin JW, et al. Early onset of spontaneous activity in uninjured C-fiber nociceptors after injury to neighboring nerve fibers. J Neurosci Off J Soc Neurosci. 2001;21:RC140.

163. Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron. 2006;52:77–92.
164. Tal M, Bennett GJ. Extra-territorial pain in rats with a peripheral mononeuropathy: mechano-hyperalgesia and mechano-allodynia in the territory of an uninjured nerve. Pain. 1994;57:375–82.
165. Liu X-G, Pang R-P, Zhou L-J, Wei X-H, Zang Y. Neuropathic pain: sensory nerve injury or motor nerve injury? Adv Exp Med Biol. 2016;904:59–75.
166. Hildebrand C, Karlsson M, Risling M. Ganglionic axons in motor roots and pia mater. Prog Neurobiol. 1997;51:89–128.
167. Ji R-R, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and central sensitization in chronic and widespread pain. Anesthesiology. 2018;129:343–66.
168. Estera LA, Walsh SP, Headen JA, Williamson RE, Kalinski AL. Neuroinflammation: breaking barriers and bridging gaps. Neurosci Res. 2021;S0168010221002224.
169. Kubíčková L. Neuroinflammation in the trigeminal system. [Brno]: Masaryk University; 2021.
170. Okada-Ogawa A, Suzuki I, Sessle BJ, Chiang C-Y, Salter MW, Dostrovsky JO, et al. Astroglia in medullary dorsal horn (trigeminal spinal subnucleus caudalis) are involved in trigeminal neuropathic pain mechanisms. J Neurosci Off J Soc Neurosci. 2009;29:11161–71.
171. Biscetti L, Cresta E, Cupini LM, Calabresi P, Sarchielli P. The putative role of neuroinflammation in the complex pathophysiology of migraine: from bench to bedside. Neurobiol Dis. 2023;180: 106072.
172. Chiu IM, von Hehn CA, Woolf CJ. Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. Nat Neurosci. 2012;15:1063–7.
173. Ramachandran R. Neurogenic inflammation and its role in migraine. Semin Immunopathol. 2018;40:301–14.
174. Schumacher GA, Wolff HG. Experimental studies on headache: A. Contrast of histamine headache with the headache of migraine and that associated with hypertension B. Contrast of vascular mechanisms in preheadache and in headache phenomena of migraine. Arch Neurol Psychiatry. 1941;45:199.
175. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152:S2-15.
176. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: a disorder of sensory processing. Physiol Rev. 2017;97:553–622.
177. Burstein R, Noseda R, Borsook D. Migraine: multiple processes, complex pathophysiology. J Neurosci Off J Soc Neurosci. 2015;35:6619–29.
178. Edvinsson L, Haanes KA, Warfvinge K. Does inflammation have a role in migraine? Nat Rev Neurol. 2019;15:483–90.
179. Goadsby PJ. Migraine, allodynia, sensitisation and all of that ... Eur Neurol. 2005;53 Suppl 1:10–6.
180. Belopasova AV, Dobrynina LA, Gubanova MV, Suslina AD. Achievements of recent decades in the diagnosis and study of migraine pathogenesis. Hum Physiol. 2020;46:870–9.
181.• Peng K-P, May A. Migraine understood as a sensory threshold disease. Pain. 2019;160:1494–501. **Presents evidence for a variety of sensory changes in migraine, which relates to peripheral neural lesion.**
182. Suzuki K, Suzuki S, Shiina T, Kobayashi S, Hirata K. Central sensitization in migraine: a narrative review. J Pain Res. 2022;15:2673–82.
183. Maleki N, Szabo E, Becerra L, Moulton E, Scrivani SJ, Burstein R, et al. Ictal and interictal brain activation in episodic migraine: Neural basis for extent of allodynia. PLoS ONE. 2021;16: e0244320.
184. Mínguez-Olaondo A, Quintas S, Morollón Sánchez-Mateos N, López-Bravo A, Vila-Pueyo M, Grozeva V, et al. Cutaneous allodynia in migraine: a narrative review. Front Neurol. 2021;12: 831035.
185. Lovati C, D'Amico D, Bertora P, Rosa S, Suardelli M, Mailland E, et al. Acute and interictal allodynia in patients with different headache forms: an Italian pilot study. Headache. 2008;48:272–7.
186. Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. Ann Neurol. 2000;47:614–24.
187. Kowacs PA, Utiumi MA, Piovesan EJ. The visual system in migraine: from the bench side to the office. Headache. 2015;55(Suppl 1):84–98.
188. Perenboom MJL, Zamanipoor Najafabadi AH, Zielman R, Carpay JA, Ferrari MD. Quantifying visual allodynia across migraine subtypes: the Leiden Visual Sensitivity Scale. Pain. 2018;159:2375–82.
189. Todd AJ. Plasticity of inhibition in the spinal cord. In: Schaible H-G, editor. Pain Control. Berlin, Heidelberg: Springer Berlin Heidelberg; 2015. p. 171–90.
190.• Hughes DI, Todd AJ. Central nervous system targets: inhibitory interneurons in the spinal cord. Neurother J Am Soc Exp Neurother. 2020;17:874–85. **This review includes discussion of how reduced peripheral afferent input causes interneuronal disinhibition, which is required for development of allodynia.**
191. Levy D, Strassman AM. Mechanical response properties of A and C primary afferent neurons innervating the rat intracranial dura. J Neurophysiol. 2002;88:3021–31.
192. Bartsch T, Goadsby PJ. Increased responses in trigeminocervical nociceptive neurons to cervical input after stimulation of the dura mater. Brain J Neurol. 2003;126:1801–13.
193. Strassman AM, Weissner W, Williams M, Ali S, Levy D. Axon diameters and intradural trajectories of the dural innervation in the rat. J Comp Neurol. 2004;473:364–76.
194. Abraira VE, Ginty DD. The sensory neurons of touch. Neuron. 2013;79:618–39.
195. Andres KH, von Düring M, Muszynski K, Schmidt RF. Nerve fibres and their terminals of the dura mater encephali of the rat. Anat Embryol (Berl). 1987;175:289–301.
196. Fricke B, Andres KH, Von Düring M. Nerve fibers innervating the cranial and spinal meninges: morphology of nerve fiber terminals and their structural integration. Microsc Res Tech. 2001;53:96–105.
197. Crawford LK, Caterina MJ. Functional anatomy of the sensory nervous system: updates from the neuroscience bench. Toxicol Pathol. 2020;48:174–89.
198. Larriva-Sahd J, León-Olea M, Vargas-Barroso V, Varela-Echavarría A, Concha L. On the existence of mechanoreceptors within the neurovascular unit of the mammalian brain. Brain Struct Funct. 2019;224:2247–67.
199. Nascimento AI. Sensory neurons have an axon initial segment that initiates spontaneous activity in neuropathic pain [Thesis]. [Porto, Portugal]: University of Porto; 2022.
200. Massler M, Pawlak J. The affected and infected pulp. Oral Surg Oral Med Oral Pathol. 1977;43:929–47.
201. Doepp F, Schreiber SJ, Dreier JP, Einhäupl KM, Valdueza JM. Migraine aggravation caused by cephalic venous congestion. Headache. 2003;43:96–8.
202. Chou C-H, Chao A-C, Lu S-R, Hu H-H, Wang S-J. Cephalic venous congestion aggravates only migraine-type headaches. Cephalalgia Int J Headache. 2004;24:973–9.
203. Chou C-H, Fuh J-L, Hu H-H, Wu J-C, Wang S-J. Throbbing pain is related to Queckenstedt's test effect in migraine patients. Cephalalgia. 2009;29:373–8.
204. Chou C-H, Fuh J-L, Wang S-J, Hu H-H, Wu J-C, Cheng Y-T. Queckenstedt's test headache response is associated with increased jugular venous flow volume during migraine attack. Ultrasound Med Biol. 2011;37:23–8.
205. Christensen CE, Younis S, Lindberg U, de Koning P, Tolnai D, Paulson OB, et al. Intradural artery dilation during experimentally induced migraine attacks. Pain. 2021;162:176–83.

206. Khan S, Amin FM, Christensen CE, Ghanizada H, Younis S, Olinger ACR, et al. Meningeal contribution to migraine pain: a magnetic resonance angiography study. Brain J Neurol. 2019;142:93–102.
207. Leroux E, Rothrock J. Triptans for migraine patients with vascular risks: new insights, new options. Headache. 2019;59:1589–96.
208. Burstein R, Levy D, Jakubowski M. Effects of sensitization of trigeminovascular neurons to triptan therapy during migraine. Rev Neurol (Paris). 2005;161:658–60.
209. Kelman L. Pain characteristics of the acute migraine attack. Headache. 2006;46:942–53.
210. Di Antonio S, Castaldo M, Ponzano M, Bovis F, Hugo Villafañe J, Torelli P, et al. Trigeminal and cervical sensitization during the four phases of the migraine cycle in patients with episodic migraine. Headache. 2022;62:176–90.
211. De Simone R, Ranieri A, Montella S, Cappabianca P, Quarantelli M, Esposito F, et al. Intracranial pressure in unresponsive chronic migraine. J Neurol. 2014;261:1365–73.
212. De Simone R, Ranieri A, Sansone M, Marano E, Russo CV, Saccà F, et al. Dural sinus collapsibility, idiopathic intracranial hypertension, and the pathogenesis of chronic migraine. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2019;40:59–70.
213. Onder H, Goksungur G. Increased intracranial pressure in migraine? Neuroimaging study on a cohort of migraineurs. Ann Med Res. 2020;27:1554.
214. Barmettler G, Brawn J, Maleki N, Scrivani S, Burstein R, Becerra L, et al. A new electronic diary tool for mapping and tracking spatial and temporal head pain patterns in migraine. Cephalalgia Int J Headache. 2015;35:417–25.
215. Assina R, Sarris CE, Mammis A. The history of craniotomy for headache treatment. Neurosurg Focus. 2014;36:E9.
216. Latimer K, Pendleton C, Rosenberg J, Cohen-Gadol AA, Quiñones-Hinojosa A. Dr. Harvey Cushing's attempts to cure migraine based on theories of pathophysiology. J Neurosurg. 2011;115:924–8.
217. Valdueza JM, Dreier JP, Woitzik J, Dohmen C, Sakowitz O, Platz J, et al. Course of preexisting migraine following spontaneous subarachnoid hemorrhage. Front Neurol. 2022;13: 880856.
218. González-Darder JM. Cranial trepanation in primitive cultures. Neurocir Astur Spain. 2017;28:28–40.
219. Kelman L. Migraine pain location: a tertiary care study of 1283 migraineurs. Headache. 2005;45:1038–47.
220. Clement P, Mutsaerts H-J, Václavů L, Ghariq E, Pizzini FB, Smits M, et al. Variability of physiological brain perfusion in healthy subjects - a systematic review of modifiers. Considerations for multi-center ASL studies. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab. 2018;38:1418–37.
221. Kannakorn I. Dynamic cerebral autoregulation, neurovascular coupling and cerebral haemodynamic parameters: clinical applications [Thesis]. [Leicester, UK]: University of Leicester; 2022.
222. Förster A, Wenz H, Kerl HU, Brockmann MA, Groden C. Perfusion patterns in migraine with aura. Cephalalgia Int J Headache. 2014;34:870–6.
223. Mahammedi A, Wang LL, Vagal AS. Imaging appearance of migraine and tension type headache. Neurol Clin. 2022;40:491–505.
224. Karsan N, Silva E, Goadsby PJ. Evaluating migraine with typical aura with neuroimaging. Front Hum Neurosci. 2023;17:1112790.
225. Pinto SN, Lerner A, Phung D, Barisano G, Chou B, Xu W, et al. Arterial spin labeling in migraine: a review of migraine categories and mimics. J Cent Nerv Syst Dis. 2023;15:117957352311600.
226. Xu WJ, Barisano G, Phung D, Chou B, Pinto SN, Lerner A, et al. Structural MRI in migraine: a review of migraine vascular and structural changes in brain parenchyma. J Cent Nerv Syst Dis. 2023;15:11795735231167868.
227. Scutelnic A, Petroulia V, Schraml L, Jung S, Branca M, Beyeler M, et al. The "index vein" as a sign for migraine aura in the emergency setting. Cephalalgia Int J Headache. 2023;43:3331024221132010.
228. Bagher P, Segal SS. Regulation of blood flow in the microcirculation: role of conducted vasodilation. Acta Physiol Oxf Engl. 2011;202:271–84.
229. McManus IC. The distribution of skull asymmetry in man. Ann Hum Biol. 1982;9:167–70.
230.• Urhan N, Sağlam Y, Akkaya F, Sağlam O, Şahin H, Uraloğlu M. Long-term results of migraine surgery and the relationship between anatomical variations and pain. J Plast Reconstr Aesthetic Surg JPRAS. 2023;82:284–90. **This article shows influence of facial asymmetry to occurrence of unilateral migraine headache and thus supports the anatomical etiology of this condition.**
231. Law H-Z, Amirlak B, Cheng J, Sammer DM. An association between carpal tunnel syndrome and migraine headaches—national health interview survey, 2010. Plast Reconstr Surg Glob Open. 2015;3: e333.
232. Gfrerer L, Lans J, Chartier C, Wenzinger E, Austen WG, Eberlin KR. Migraine headaches in patients with upper extremity compressive neuropathy. Plast Reconstr Surg. 2022;150:1333–9.
233. Werntz DA, Bickford RG, Bloom FE, Shannahoff-Khalsa DS. Alternating cerebral hemispheric activity and the lateralization of autonomic nervous function. Hum Neurobiol. 1983;2:39–43.
234. Shannahoff-Khalsa D. Lateralized rhythms of the central and autonomic nervous systems. Int J Psychophysiol Off J Int Organ Psychophysiol. 1991;11:225–51.
235. Price A, Eccles R. Nasal airflow and brain activity: is there a link? J Laryngol Otol. 2016;130:794–9.
236. Eccles R, Lee RL. Nasal vasomotor oscillations in the cat associated with the respiratory rhythm. Acta Otolaryngol (Stockh). 1981;92:357–61.
237. Bamford OS, Eccles R. The central reciprocal control of nasal vasomotor oscillations. Pflugers Arch. 1982;394:139–43.
238. Tatar A, Altas E. Nasal cycle pattern can transform into another form over time. Electron J Gen Med. 2014;11.
239. Kern EB. The noncycle nose. Rhinology. 1981;19:59–74.
240. Susaman N, Cingi C, Mullol J. Is the nasal cycle real? How important is it? In: Cingi C, Bayar Muluk N, Scadding GK, Mladina R, editors. Chall Rhinol. Cham: Springer International Publishing; 2021. p. 1–8.
241. Pendolino AL, Lund VJ, Nardello E, Ottaviano G. The nasal cycle: a comprehensive review. Rhinol Online. 2018;1:67–76.
242. Vanast WJ, Diaz-Mitoma F, Tyrrell DL. Hypothesis: chronic benign daily headache is an immune disorder with a viral trigger. Headache. 1987;27:138–42.
243. Baringer JR. Herpes simplex infections of the nervous system. Neurol Clin. 2008;26:657–74, viii.
244. Theil D, Derfuss T, Paripovic I, Herberger S, Meinl E, Schueler O, et al. Latent herpesvirus infection in human trigeminal ganglia causes chronic immune response. Am J Pathol. 2003;163:2179–84.
245. Martin-Du Pan RC, Benoit R, Girardier L. The role of body position and gravity in the symptoms and treatment of various medical diseases. Swiss Med Wkly. 2004;134:543–51.
246. Becker WJ. Cervicogenic headache: evidence that the neck is a pain generator. Headache. 2010;50:699–705.
247. Mungoven TJ, Henderson LA, Meylakh N. Chronic migraine pathophysiology and treatment: a review of current perspectives. Front Pain Res Lausanne Switz. 2021;2: 705276.
248. Guyuron B, Yohannes E, Miller R, Chim H, Reed D, Chance MR. Electron microscopic and proteomic comparison of terminal

branches of the trigeminal nerve in patients with and without migraine headaches. Plast Reconstr Surg. 2014;134:796e–805e.
249. Mungoven TJ, Meylakh N, Marciszewski KK, Macefield VG, Macey PM, Henderson LA. Microstructural changes in the trigeminal nerve of patients with episodic migraine assessed using magnetic resonance imaging. J Headache Pain. 2020;21:59.
250. Mungoven TJ, Meylakh N, Macefield VG, Macey PM, Henderson LA. Alterations in brain structure associated with trigeminal nerve anatomy in episodic migraine. Front Pain Res Lausanne Switz. 2022;3: 951581.
251. Malo-Urriés M, Estébanez-de-Miguel E, Bueno-Gracia E, Tricás-Moreno JM, Santos-Lasaosa S, Hidalgo-García C. Sensory function in headache: a comparative study among patients with cluster headache, migraine, tension-type headache, and asymptomatic subjects. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2020;41:2801–10.
252. Altay H, Celenay ST. An investigation of the relationship between cutaneous allodynia and kinesiophobia, gastrointestinal system symptom severity, physical activity and disability in individuals with migraine. Korean J Pain. 2023;36:137–46.
253. Hasan H, Irfan Waheed R, Bin Arif T, Saleem S, Anwar A. Gray and white matter changes in migraineurs: a review of literature. SN Compr Clin Med. 2020;2:2185–96.
254. Kim S-K, Nikolova S, Schwedt TJ. Structural aberrations of the brain associated with migraine: a narrative review. Headache. 2021;61:1159–79.
255. Ashina S, Bentivegna E, Martelletti P, Eikermann-Haerter K. Structural and functional brain changes in migraine. Pain Ther. 2021;10:211–23.
256. Taylor KS, Anastakis DJ, Davis KD. Cutting your nerve changes your brain. Brain J Neurol. 2009;132:3122–33.
257. Osborne NR, Anastakis DJ, Davis KD. Peripheral nerve injuries, pain, and neuroplasticity. J Hand Ther. 2018;31:184–94.
258. Gambeta E, Chichorro JG, Zamponi GW. Trigeminal neuralgia: an overview from pathophysiology to pharmacological treatments. Mol Pain. 2020;16:1744806920901890.
259. Henssen D, Dijk J, Knepflé R, Sieffers M, Winter A, Vissers K. Alterations in grey matter density and functional connectivity in trigeminal neuropathic pain and trigeminal neuralgia: a systematic review and meta-analysis. NeuroImage Clin. 2019;24: 102039.
260. Wang Y, Yang Q, Cao D, Seminowicz D, Remeniuk B, Gao L, et al. Correlation between nerve atrophy, brain grey matter volume and pain severity in patients with primary trigeminal neuralgia. Cephalalgia Int J Headache. 2019;39:515–25.
261. Maeda Y, Kettner N, Sheehan J, Kim J, Cina S, Malatesta C, et al. Altered brain morphometry in carpal tunnel syndrome is associated with median nerve pathology. NeuroImage Clin. 2013;2:313–9.
262. Lu Y-C, Zhang H, Zheng M-X, Hua X-Y, Qiu Y-Q, Shen Y-D, et al. Local and extensive neuroplasticity in carpal tunnel syndrome: a resting-state fMRI study. Neurorehabil Neural Repair. 2017;31:898–909.
263. Xue X, Wu J-J, Hua X-Y, Zheng M-X, Ma J, Ma Z-Z, et al. Structural white matter alterations in carpal tunnel syndrome: a modified TBSS study. Brain Res. 2021;1767: 147558.
264. Geha PY, Apkarian AV. Brain imaging findings in neuropathic pain. Curr Pain Headache Rep. 2005;9:184–8.
265. Lu Y, Liu H, Hua X, Xu J-G, Gu Y-D, Shen Y. Attenuation of brain grey matter volume in brachial plexus injury patients. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2016;37:51–6.
266. Wang J-W, Huang Z-Q, Lu Y-J, Sha K, Li W-M, Zhao J-M. Cerebral gray matter volume changes in patients with neuropathic pain from total brachial plexus injury. Eur Neurol. 2023;86:45–54.
267. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci Off J Soc Neurosci. 2004;24:10410–5.
268. Andreou AP, Edvinsson L. Mechanisms of migraine as a chronic evolutive condition. J Headache Pain. 2019;20:117.
269. Straube A, Andreou A. Primary headaches during lifespan. J Headache Pain. 2019;20:35.
270. Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. J Headache Pain. 2022;23:34.
271. Sufrinko A, McAllister-Deitrick J, Elbin RJ, Collins MW, Kontos AP. Family history of migraine associated with posttraumatic migraine symptoms following sport-related concussion. J Head Trauma Rehabil. 2018;33:7–14.
272. Stam AH, Haan J, van den Maagdenberg AMJM, Ferrari MD, Terwindt GM. Migraine and genetic and acquired vasculopathies. Cephalalgia Int J Headache. 2009;29:1006–17.
273. Edvinsson JCA, Viganò A, Alekseeva A, Alieva E, Arruda R, De Luca C, et al. The fifth cranial nerve in headaches. J Headache Pain. 2020;21:65.
274. Cuadrado M-L. Epicranial headaches part 2: Nummular headache and epicrania fugax. Cephalalgia Int J Headache. 2023;43:3331024221146976.
275. May A, 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 Off J Int Soc Cereb Blood Flow Metab. 1999;19:115–27.
276. Holland P, Goadsby PJ. The hypothalamic orexinergic system: pain and primary headaches. Headache. 2007;47:951–62.
277. Edvinsson L, Uddman R. Neurobiology in primary headaches. Brain Res Brain Res Rev. 2005;48:438–56.
278. Cady R, Schreiber C, Farmer K, Sheftell F. Primary headaches: a convergence hypothesis. Headache. 2002;42:204–16.
279. Al-Karagholi MA-M, Peng K-P, Petersen AS, De Boer I, Terwindt GM, Ashina M. Debate: Are cluster headache and migraine distinct headache disorders? J Headache Pain. 2022;23:151.
280. Frattale I, Ruscitto C, Papetti L, Ursitti F, Sforza G, Moavero R, et al. Migraine and its equivalents: what do they share? A narrative review on common pathophysiological patterns. Life Basel Switz. 2021;11:1392.
281. Tfelt-Hansen PC, Tfelt-Hansen J. Nitroglycerin headache and nitroglycerin-induced primary headaches from 1846 and onwards: a historical overview and an update. Headache. 2009;49:445–56.