Chapter 11
Pain Perception and Migraine

Martin Uglem

11.1 Migraine Pain

Migraine is a heterogeneous disease with a spectrum of symptoms accompanying the headache pain. The classic migraine headache is characterized by a moderate to severe unilateral throbbing pain. Several other sensory symptoms add to the burden of the headache pain, the most common being nausea and light, sound, and smell hypersensitivity.

Migraineurs may experience symptoms hours to days before the headache attack, as well as symptoms that outlast the headache [1]. Some migraineurs can even predict migraine headaches based on preceding non-headache symptoms. Common prodromal symptoms are tiredness, concentration difficulties, neck stiffness, and increased sensory sensitivity [2, 3]. Migraineurs could report prodromal symptoms several days before the headache started, but analysis showed that the predictive value of these symptoms was rather low until the last 12–24 h before an attack [3].

Allodynia, defined as "pain due to a stimulus that does not normally provoke pain" [4], appears to be an important clinical correlate for altered pain processing in migraine. Allodynia may be assessed by questionnaire, by bedside assessment, or by more detailed experimental quantification as further discussed below. Simple clinical assessment of allodynia may include examination with cotton swab, pinprick, and thermal stimuli, i.e., normally non-painful stimulations [5]. When evaluated by questionnaire, about 50–70% of migraineurs report allodynia during headache, and allodynia is associated with frequency and severity of migraine [6–9]. Seo and Park [10] explored the clinical significance of allodynia compared with photo-, phono-, and osmophobia and

M. Uglem (✉)
Department of Neuromedicine and Movement Science, NTNU - Norwegian University of Science and Technology, Trondheim, Norway

Department of Neurology and Clinical Neurophysiology, St. Olavs Hospital, Trondheim, Norway
e-mail: martin.uglem@ntnu.no

G. Coppola, W.-T. Chen (eds.), *Neurophysiology of the Migraine Brain*,
Headache, https://doi.org/10.1007/978-3-030-56538-1_11

found that both the prevalence of chronic migraine or medication overuse headache, disease duration, and headache intensity were increased in migraineurs with allodynia compared to migraineurs without allodynia, regardless of concomitant hypersensitivity to light, sound, or smell. Accordingly, the presence of allodynia is clearly associated with quality of life and increases the burden of the disease.

A case report showed that, during a migraine attack, allodynia started on the same side of the head as the headache and then spread to the other side of the head and finally to the arm with a progressive increase in magnitude [11]. The authors suggested that this represented activation of peripheral nociceptive neurons, followed by sensitization of second-order spinothalamic neurons and lastly third-order thalamocortical neurons [11]. In one study, at least one of heat, cold, or mechanical ipsilateral trigeminal allodynia was present in 79% of migraineurs 3–4 h into an attack [12]. Only five of those 33 subjects had ipsilateral trigeminal allodynia without contralateral or non-trigeminal allodynia, and two had contralateral but no ipsilateral allodynia [12], thus not providing any clear evidence of sequential activation of first- to second- to third-order trigeminal neurons.

Activation of nociceptive neurons innervating pial, arachnoid, and dural blood vessels and large cerebral arteries and sinuses, combined with a change in central pain modulation, is believed to give rise to the migraine headache [13]. Dysfunction of central nervous system structures involved in modulation of excitability and pain may activate and sensitize the trigeminovascular pain pathway [14–16]. However, the driving force behind this cycling activation is still unknown. Findings from functional imaging studies suggest involvement of hypothalamic, thalamic, and brainstem networks [17–22].

11.2 Experimental Pain

A strictly objective measure of pain perception is not available. Neurophysiological tests can measure *nociception*, the neural process of encoding noxious stimuli [4], but the degree of nociceptive activity does not necessarily comply with subjective pain perception. To quantify pain semi-objectively, a battery of psychophysical neurophysiological tests may be used, commonly defined as quantitative sensory tests (QST). A QST protocol is considered a useful method for psychophysical assessment of sensory detection and pain perception [23]. The protocol may include assessment of detection thresholds, pain thresholds, suprathreshold pain, and pain modulation. Modalities used may be pressure (deep mechanical), tactile (superficial mechanical brush, pins, or filaments), vibration (not used for pain), thermal (heat and cold), electrical (bypassing receptors), visual (light), auditory (sound), and chemical (for the nasal or oral mucosa). Pain thresholds are defined by the external stimulus, e.g., in degrees Celsius for thermal stimuli. An important limitation to the QST is that the tests require cooperation from the subject to define the moment a stimulus is detected, perceived as painful, or to rate the degree of pain experienced in suprathreshold pain experiments.

The thermal part of a QST protocol is particularly helpful in diagnosing small fiber neuropathy, mostly as hypoesthesia and hypoalgesia but also allodynia and hyperalgesia. A pain threshold below the normal range is interpreted as allodynia. Hyperalgesia, defined as "increased pain from a stimulus that normally provokes pain" [4], may be shown by increased pain intensity score to suprathreshold pain stimulation. Both allodynia and hyperalgesia may be due to peripheral sensitization, central sensitization, or both, although by separate and multiple mechanisms [24]. In example, failure of the central pain inhibition system to properly attenuate noxious stimulation may result in hyperalgesia, while failure to inhibit crosstalk between sensory modalities may result in allodynia [25]. More sophisticated QST measures may be applied to assess endogenous pain inhibitory function and endogenous pain facilitatory processes [26]. Conditioned pain modulation utilizes two concurrent noxious stimuli at separate body parts in a "pain inhibits pain" model to measure central pain inhibition. Temporal summation of pain uses repetitive nociceptive stimuli at a frequency of more than three per second to assess pain facilitation. Decreased conditioned pain modulation and increased temporal summation of pain indirectly indicates central sensitization. Thus, different QST findings might provide insights in the underlying pathophysiology.

11.3 Experimental Pain and Migraine

Several studies have investigated responses to experimental pain in migraine. Most of these studies compared responses from migraineurs in the interictal phase and controls, but some also compared responses between migraine phases, migraineurs with or without aura, or episodic and chronic migraine [27, 28].

A recent meta-analysis of QST and migraine identified 109 articles eligible for qualitative analyses [29]. Nahman-Averbuch et al. [29] provided a comprehensive overview of pressure, mechanical, heat, cold, and electrical detection and pain thresholds, as well as suprathreshold pain and pain modulation. The meta-analysis showed lower pressure and heat pain thresholds and higher suprathreshold cold pain ratings in migraineurs compared to controls. Another meta-analysis of pressure pain thresholds over the cranio-cervical region demonstrated comparative results, i.e., lower pressure pain thresholds in migraineurs compared to controls [30]. The studies included in both meta-analyses compared mainly migraineurs in the interictal phase with controls. However, when studies had measurements from multiple migraine phases, the data were collapsed and analyzed as a merged migraine group compared to controls. Thus, the meta-analyses compared migraineurs to controls irrespective of migraine phase, although the findings mainly are representative for the interictal phase. In general, migraineurs seem to be slightly more sensitive to painful stimuli between attacks compared to controls, although the effects are small [27, 28]. Also, some studies have shown increased temporal summation [31, 32] and less efficient conditioned pain modulation [33, 34] in migraineurs in the interictal phase compared to controls, suggesting central

sensitization. No experimental pain test has so far proved reliable in distinguishing between persons with and without migraine. However, a multitude of factors may influence sensitivity in individual patients and contribute to the variation between studies. As discussed below, some of the variations may be explained by cyclical alterations related to proximity to the previous and next attack and some by migraine subtypes.

11.3.1 Pain Perception by Migraine Phase

Only a few longitudinal studies have examined experimental pain sensitivity in the preictal phase (Table 11.1). Neither pain intensity ratings by laser stimulation [35] nor pain scores to painful intranasal ammonia stimulation [19] seem to be

Table 11.1 Pain perception by migraine phase

	Preictal	Ictal	Postictal
Studies showing hypersensitivity			
Longitudinal			
Burstein 2000 [12]		*42* HPT, CPT, MPT	
De Tommaso 2002 [41]		*10* LPI	
Sand 2008 [36]	*11* HPT, CPT		
Moulton 2011 [42]		*8* HPT	
Uglem 2017 [38]	*27* (HPI[a])	*20* CPT, HPI	
Cross-sectional			
Vanagaite 1997 [43]		*19* LPT	
Vingen 1998 [44]		*19* SPT	
Studies without significant alterations			
Longitudinal			
Uglem 2017 [38]	*27* HPT, CPT	*20* HPT	*13* HPT, CPT, HPI
Uglem 2017 [35]	*26* LPI	*19* LPI	*13* LPI
Cross-sectional			
Stankewitz 2011 [19]	*10* API	*13* API	
Stankewitz 2013 [64]		*10* API	
Engstrøm 2013 [37]	*9* HPT, CPT, PPT		*8* HPT, CPT, PPT
Correlations between pain and time to next attack			
Schwedt 2015 [39]	HPT decreased toward the next attack		
Uglem 2017 [38]	HPI increased toward the next attack (no change in HPT or CPT)		

The table shows findings by phase as compared to the interictal phase. The numbers written in italic type represent the number of subjects in the respective phases

API intranasal ammonia pain intensity scores, *CPT* cold pain thresholds, *HPI* heat pain intensity scores, *HPT* heat pain thresholds, *LPI* laser pain intensity scores, *LPT* light-induced pain thresholds, *MPT* mechanical pain thresholds, *PPT* pressure pain thresholds, *SPT* sound-induced pain thresholds

[a]A paradoxical *decrease* in HPI was shown indicating preictal hypoalgesia

altered in the preictal phase compared to the interictal phase. A study by Sand et al. [36] demonstrated decreased heat and cold pain thresholds in the preictal phase compared to the interictal phase. The effect was present when the preictal phase was defined with a 24-h limit, but not with a 72-h limit. Another study that analyzed heat, cold, and pressure pain thresholds with a 48-h preictal limit found no differences [37]. Apparently, different limits may be the source of the discrepant results. However, a follow-up study with a 24-h limit did not reproduce these findings as heat and cold pain thresholds did not change from the interictal to the preictal phase [38]. One explanation might be that preictal recordings were closer to the attack in the study by Sand et al. [36] than in the follow-up study [38], although the latter showed no association between pain thresholds and days to next attack. In contrast, Schwedt et al. [39] found a correlation between heat pain thresholds and time to next attack, as pain thresholds at both the arm and head decreased closer to the attack. Also, pain intensity ratings to suprathreshold heat stimulation have been shown to gradually increase during the interictal period toward the next attack [38]. Thus, studies indicate gradually increasing pain sensitivity in the interictal phase toward the next attack with a more pronounced hyperalgesia during headache.

A study of heat pain intensity scores found an interictal correlation between pain scores and time to next migraine attack and a distinct increase during headache [38]. However, in the 24 h preceding the attack, a subtle decrease of pain scores was present, interpreted as preictal hypoalgesia. These results suggest that significant central events affect processing of pain on the day before headache. Hypothalamic activation has been shown in the preictal phase [17, 18]. Depending on the receptor activated, regions in the hypothalamus may provide either pro- or antinociceptive effects on trigeminal nociception [40]. Thus, it is plausible that preictal hypothalamic activation may cause a transient hypoalgesic effect by increased descending pain modulation. The antinociceptive effect seems to have an effect mainly on suprathreshold pain scores as pain thresholds have been shown to increase or remain unaltered in the preictal phase [36, 38].

Alterations of pain perception are more pronounced in the ictal phase. Studies have shown reduced pain thresholds to either heat, cold, mechanical, visual, and auditory stimulation, increased pain scores to tonic heat, and decreased pain thresholds tested by laser stimulation during attack compared to between attacks (Table 11.1) [12, 38, 41–44]. There are some contradicting findings, but the overall impression is an increased pain sensitivity during headache compared to the interictal phase, which corresponds well with the increase in allodynia and other sensory symptoms during the ictal phase.

Studies of the postictal phase have not shown any differences compared to the interictal phase [35, 37, 38]. When compared to the ictal phase, postictal normalization of cold pain thresholds has been shown [38], indicating a rather fast restoration of pain perception back to interictal levels.

11.3.2 Pain Perception by Migraine Subtypes

Studies comparing experimental pain in migraineurs in the interictal phase and controls have shown variable results, either hypersensitivity or no differences, but never hyposensitivity [27, 28]. Some subgroups may be more hypersensitive than others; for instance, migraineurs with non-sleep-related migraine attacks had lower thermal thresholds than controls [45], while less slow-wave sleep was associated with higher pressure pain thresholds [37].

Subjects with chronic migraine (more days with than without headache) seem to have more allodynia and lower pain thresholds compared to episodic migraineurs, indicating a relationship between altered pain perception and headache frequency [9, 31, 46–49]. However, other studies have neither shown any differences in mechanical or thermal pain thresholds between chronic and episodic migraine [50] nor a relationship between pressure and thermal pain thresholds and migraine frequency [39, 51]. Disease severity may also be of importance, as headache history duration has been shown to modulate cold pain thresholds [36]. As suggested by Peng and May [27], the increased pain sensitivity in chronic migraine may be due to a higher probability of being tested close to the ictal state compared to episodic migraine with longer interictal periods. Other important factors that may increase pain perception in chronic migraine seem to be increased headache severity and level of drug intake [28].

A twin survey suggested that migraine with and without aura are distinct disorders [52]. On the other hand, the International Classification of Headache Disorders, third edition, states that the same person may have both diagnoses [53]. Nevertheless, the few studies that have compared pain thresholds between migraineurs with and without aura have not shown any differences for thermal [36, 38], electrical [32], light [43], or sound pain thresholds [44]. Russo et al. [54] compared heat pain intensity in groups divided by migraineurs without aura and without ictal allodynia, without aura but with ictal allodynia, with aura but without allodynia, and controls. The study showed no differences between the migraine subgroups or compared to controls and no association between pain intensity and migraine severity. Granovsky et al. [55] compared migraineurs with and without aura and found increased temporal summation of mechanical pain stimulation in migraineurs with aura, but no difference in heat and mechanical pain thresholds, or conditioned pain modulation. Perenboom et al. [56] quantified visual allodynia and demonstrated higher scores in migraine with aura compared to without aura and in chronic compared to episodic migraine. Thus, visual stimulation may be better suited to differentiate between migraine with and without aura compared to thermal and pressure pain, although Vanagaite et al. [43] did not find altered visual pain sensitivity in migraine with aura compared to without aura.

Studies of pain thresholds in children with migraine are scarce, but resemble findings shown in adults [28]. Some studies have shown differences in mechanical pain thresholds [57], pressure pain thresholds [58], and laser-evoked pain thresholds [59] compared to controls, but conflicting results exist [60, 61]. A recent study

demonstrated increased heat pain intensity scores in adolescents with migraine compared to controls, but no difference in conditioned pain modulation [62].

11.4 Conclusion

Pain perception alternates within the migraine cycle (Fig. 11.1). Thresholds gradually decrease toward the next attack with a distinct reduction during headache. What happens during the hours to days before the headache starts is still poorly understood. A few longitudinal studies have shown both decreased pain thresholds and paradoxical decreased pain intensity ratings in the preictal phase. The symptoms

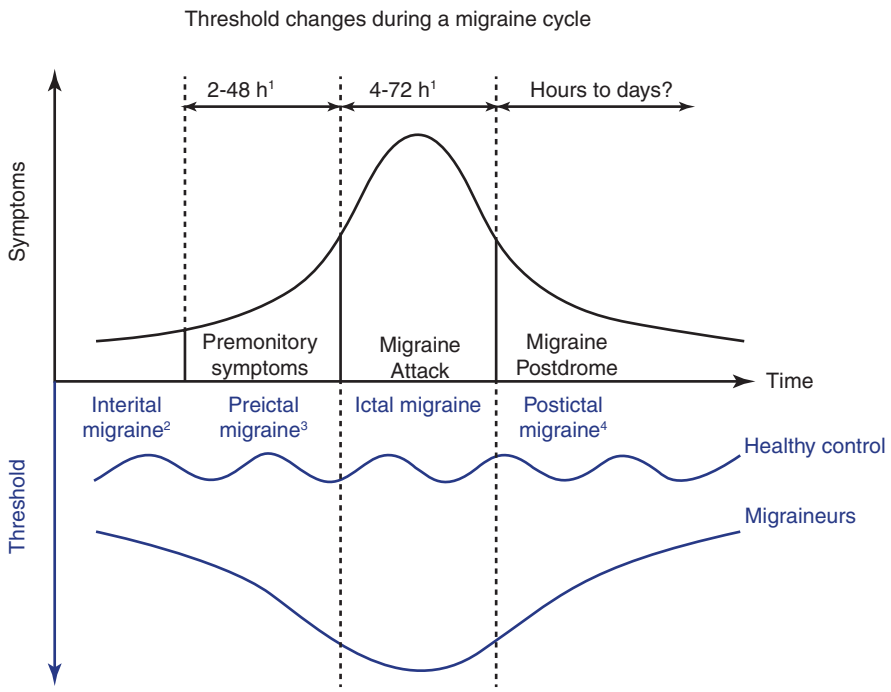

Fig. 11.1 Threshold changes during a migraine cycle. The changes in sensory thresholds over time and their correlation with the clinical symptoms. The undulating threshold in healthy controls reflects the high day-to-day variance as reported in the literature [63]. In this figure, only the phasic changes among migraineurs are depicted; however, the day-to-day variance also stands true to the migraineurs. (1) Definition in the International Classification of Headache Disorders, third edition. (2) No consensus: Certain studies showed lower threshold among migraineurs than healthy controls; others showed no difference. (3) Two studies showed preictal threshold lower than interictal threshold among migraineurs. (4) Hypothetical: No study examined the sensory threshold in the postictal period in comparison with the ictal period (From Peng KP, May A. Migraine understood as a sensory threshold disease. Pain. 2019;160(7):1494–501. doi:https://doi.org/10.1097/j.pain.0000000000001531. Reprinted with permission)

associated with the preictal and ictal phase, in addition to recent functional imaging findings, may suggest thalamocortical alterations by hypothalamic modulation as a generator of the observed preictal hypoalgesia. Findings of cyclical alterations of pain perception support the theory that migraine is a cyclic disorder of the central nervous system related to global alterations of brain excitability and homeostasis.

References

1. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629–808. https://doi.org/10.1177/0333102413485658.
2. Houtveen JH, Sorbi MJ. Prodromal functioning of migraine patients relative to their interictal state—an ecological momentary assessment study. PLoS One. 2013;8(8):e72827. https://doi.org/10.1371/journal.pone.0072827.
3. Giffin NJ, Ruggiero L, Lipton RB, Silberstein SD, Tvedskov JF, Olesen J, et al. Premonitory symptoms in migraine: an electronic diary study. Neurology. 2003;60(6):935–40. https://doi.org/10.1212/01.wnl.0000052998.58526.a9.
4. IASP. IASP terminology. IASP – International Association for the Study of Pain. 2017. https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698.
5. Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. Lancet Neurol. 2014;13(9):924–35. https://doi.org/10.1016/S1474-4422(14)70102-4.
6. Mathew NT, Kailasam J, Seifert T. Clinical recognition of allodynia in migraine. Neurology. 2004;63(5):848–52. https://doi.org/10.1212/01.wnl.0000137107.27585.f7.
7. Lipton RB, Bigal ME, Ashina S, Burstein R, Silberstein S, Reed ML, et al. Cutaneous allodynia in the migraine population. Ann Neurol. 2008;63(2):148–58. https://doi.org/10.1002/ana.21211.
8. Bigal ME, Ashina S, Burstein R, Reed ML, Buse D, Serrano D, et al. Prevalence and characteristics of allodynia in headache sufferers: a population study. Neurology. 2008;70(17):1525–33. https://doi.org/10.1212/01.wnl.0000310645.31020.b1.
9. Louter MA, Bosker JE, van Oosterhout WP, van Zwet EW, Zitman FG, Ferrari MD, et al. Cutaneous allodynia as a predictor of migraine chronification. Brain. 2013;136(Pt 11):3489–96. https://doi.org/10.1093/brain/awt251.
10. Seo JG, Park SP. Clinical significance of sensory hypersensitivities in migraine patients: does allodynia have a priority on it? Neurol Sci. 2019;40(2):393–8. https://doi.org/10.1007/s10072-018-3661-2.
11. Burstein R, Cutrer MF, Yarnitsky D. The development of cutaneous allodynia during a migraine attack clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. Brain. 2000;123(Pt 8):1703–9. https://doi.org/10.1093/brain/123.8.1703.
12. Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. Ann Neurol. 2000;47(5):614–24.
13. Goadsby PJ. The vascular theory of migraine—a great story wrecked by the facts. Brain. 2009;132(Pt 1):6–7. https://doi.org/10.1093/brain/awn321.
14. Vecchia D, Pietrobon D. Migraine: a disorder of brain excitatory-inhibitory balance? Trends Neurosci. 2012;35(8):507–20. https://doi.org/10.1016/j.tins.2012.04.007.
15. Noseda R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization and modulation of pain. Pain. 2013;154(Suppl 1):S44–53. https://doi.org/10.1016/j.pain.2013.07.021.
16. Messlinger K. Migraine: where and how does the pain originate? Exp Brain Res. 2009;196(1):179–93. https://doi.org/10.1007/s00221-009-1756-y.

17. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Brain. 2014;137(Pt 1):232–41. https://doi.org/10.1093/brain/awt320.
18. Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. Brain. 2016;139(Pt 7):1987–93. https://doi.org/10.1093/brain/aww097.
19. Stankewitz A, Aderjan D, Eippert F, May A. Trigeminal nociceptive transmission in migraineurs predicts migraine attacks. J Neurosci. 2011;31(6):1937–43. https://doi.org/10.1523/JNEUROSCI.4496-10.2011.
20. Schulte LH, May A. Of generators, networks and migraine attacks. Curr Opin Neurol. 2017;30(3):241–5. https://doi.org/10.1097/WCO.0000000000000441.
21. May A. Understanding migraine as a cycling brain syndrome: reviewing the evidence from functional imaging. Neurol Sci. 2017;38(Suppl 1):125–30. https://doi.org/10.1007/s10072-017-2866-0.
22. Denuelle M, Fabre N, Payoux P, Chollet F, Geraud G. Hypothalamic activation in spontaneous migraine attacks. Headache. 2007;47(10):1418–26. https://doi.org/10.1111/j.1526-4610.2007.00776.x.
23. Svensson P, Baad-Hansen L, Pigg M, List T, Eliav E, Ettlin D, et al. Guidelines and recommendations for assessment of somatosensory function in oro-facial pain conditions—a taskforce report. J Oral Rehabil. 2011;38(5):366–94. https://doi.org/10.1111/j.1365-2842.2010.02196.x.
24. Lolignier S, Eijkelkamp N, Wood JN. Mechanical allodynia. Pflugers Archiv Eur J Physiol. 2015;467(1):133–9. https://doi.org/10.1007/s00424-014-1532-0.
25. Sandkuhler J. Models and mechanisms of hyperalgesia and allodynia. Physiol Rev. 2009;89(2):707–58. https://doi.org/10.1152/physrev.00025.2008.
26. Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. Expert Rev Neurother. 2012;12(5):577–85. https://doi.org/10.1586/ern.12.41.
27. Peng KP, May A. Migraine understood as a sensory threshold disease. Pain. 2019;160(7):1494–501. https://doi.org/10.1097/j.pain.0000000000001531.
28. Russo A, Coppola G, Pierelli F, Parisi V, Silvestro M, Tessitore A, et al. Pain perception and migraine. Front Neurol. 2018;9:576. https://doi.org/10.3389/fneur.2018.00576.
29. Nahman-Averbuch H, Shefi T, Schneider VJ 2nd, Li D, Ding L, King CD, et al. Quantitative sensory testing in patients with migraine: a systematic review and meta-analysis. Pain. 2018;159(7):1202–23. https://doi.org/10.1097/j.pain.0000000000001231.
30. Castien RF, van der Wouden JC, De Hertogh W. Pressure pain thresholds over the craniocervical region in headache: a systematic review and meta-analysis. J Headache Pain. 2018;19(1):9. https://doi.org/10.1186/s10194-018-0833-7.
31. Weissman-Fogel I, Sprecher E, Granovsky Y, Yarnitsky D. Repeated noxious stimulation of the skin enhances cutaneous pain perception of migraine patients in-between attacks: clinical evidence for continuous sub-threshold increase in membrane excitability of central trigeminovascular neurons. Pain. 2003;104(3):693–700. https://doi.org/10.1016/s0304-3959(03)00159-3.
32. Gierse-Plogmeier B, Colak-Ekici R, Wolowski A, Gralow I, Marziniak M, Evers S. Differences in trigeminal and peripheral electrical pain perception in women with and without migraine. J Headache Pain. 2009;10(4):249–54. https://doi.org/10.1007/s10194-009-0118-2.
33. Nahman-Averbuch H, Granovsky Y, Coghill RC, Yarnitsky D, Sprecher E, Weissman-Fogel I. Waning of "conditioned pain modulation": a novel expression of subtle pronociception in migraine. Headache. 2013;53(7):1104–15. https://doi.org/10.1111/head.12117.
34. Sandrini G, Rossi P, Milanov I, Serrao M, Cecchini AP, Nappi G. Abnormal modulatory influence of diffuse noxious inhibitory controls in migraine and chronic tension-type headache patients. Cephalalgia. 2006;26(7):782–9. https://doi.org/10.1111/j.1468-2982.2006.01130.x.
35. Uglem M, Omland PM, Stjern M, Gravdahl GB, Sand T. Habituation of laser-evoked potentials by migraine phase: a blinded longitudinal study. J Headache Pain. 2017;18(1):100. https://doi.org/10.1186/s10194-017-0810-6.

36. Sand T, Zhitniy N, Nilsen KB, Helde G, Hagen K, Stovner LJ. Thermal pain thresholds are decreased in the migraine preattack phase. Eur J Neurol. 2008;15(11):1199–205. https://doi.org/10.1111/j.1468-1331.2008.02276.x.
37. Engstrom M, Hagen K, Bjork MH, Stovner LJ, Gravdahl GB, Stjern M, et al. Sleep quality, arousal and pain thresholds in migraineurs: a blinded controlled polysomnographic study. J Headache Pain. 2013;14(1):12. https://doi.org/10.1186/1129-2377-14-12.
38. Uglem M, Omland PM, Nilsen KB, Tronvik E, Stovner LJ, Hagen K, et al. Does pain sensitivity change by migraine phase? A blinded longitudinal study. Cephalalgia. 2017;37(14):1337–49. https://doi.org/10.1177/0333102416679955.
39. Schwedt TJ, Zuniga L, Chong CD. Low heat pain thresholds in migraineurs between attacks. Cephalalgia. 2015;35(7):593–9. https://doi.org/10.1177/0333102414550417.
40. Bartsch T, Levy MJ, Knight YE, Goadsby PJ. Differential modulation of nociceptive dural input to [hypocretin] orexin a and B receptor activation in the posterior hypothalamic area. Pain. 2004;109(3):367–78. https://doi.org/10.1016/j.pain.2004.02.005.
41. de Tommaso M, Guido M, Libro G, Losito L, Sciruicchio V, Monetti C, et al. Abnormal brain processing of cutaneous pain in migraine patients during the attack. Neurosci Lett. 2002;333(1):29–32. https://doi.org/10.1016/s0304-3940(02)00967-9.
42. Moulton EA, Becerra L, Maleki N, Pendse G, Tully S, Hargreaves R, et al. Painful heat reveals hyperexcitability of the temporal pole in interictal and ictal migraine States. Cerebral Cortex (New York, NY: 1991). 2011;21(2):435–48. https://doi.org/10.1093/cercor/bhq109.
43. Vanagaite J, Pareja JA, Storen O, White LR, Sand T, Stovner LJ. Light-induced discomfort and pain in migraine. Cephalalgia. 1997;17(7):733–41. https://doi.org/10.1046/j.1468-2982.1997.1707733.x.
44. Vingen JV, Pareja JA, Storen O, White LR, Stovner LJ. Phonophobia in migraine. Cephalalgia. 1998;18(5):243–9. https://doi.org/10.1111/j.1468-2982.1998.1805243.x.
45. Engstrom M, Hagen K, Bjork M, Gravdahl GB, Sand T. Sleep-related and non-sleep-related migraine: interictal sleep quality, arousals and pain thresholds. J Headache Pain. 2013;14(1):68. https://doi.org/10.1186/1129-2377-14-68.
46. Cooke L, Eliasziw M, Becker WJ. Cutaneous allodynia in transformed migraine patients. Headache. 2007;47(4):531–9. https://doi.org/10.1111/j.1526-4610.2006.00717.x.
47. Kitaj MB, Klink M. Pain thresholds in daily transformed migraine versus episodic migraine headache patients. Headache. 2005;45(8):992–8. https://doi.org/10.1111/j.1526-4610.2005.05179.x.
48. Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R. Frequency of headache is related to sensitization: a population study. Pain. 2006;123(1–2):19–27. https://doi.org/10.1016/j.pain.2006.01.040.
49. Sohn JH, Kim CH, Choi HC. Differences in central facilitation between episodic and chronic migraineurs in nociceptive-specific trigeminal pathways. J Headache Pain. 2016;17(1):35. https://doi.org/10.1186/s10194-016-0637-6.
50. Schwedt TJ, Krauss MJ, Frey K, Gereau RW. Episodic and chronic migraineurs are hypersensitive to thermal stimuli between migraine attacks. Cephalalgia. 2011;31(1):6–12. https://doi.org/10.1177/0333102410365108.
51. Florencio LL, Giantomassi MC, Carvalho GF, Goncalves MC, Dach F, Fernandez-de-Las-Penas C, et al. Generalized pressure pain hypersensitivity in the cervical muscles in women with migraine. Pain Med (Malden, MA). 2015;16(8):1629–34. https://doi.org/10.1111/pme.12767.
52. Russell MB, Ulrich V, Gervil M, Olesen J. Migraine without aura and migraine with aura are distinct disorders. A population-based twin survey. Headache. 2002;42(5):332–6. https://doi.org/10.1046/j.1526-4610.2002.02102.x.
53. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. Cephalalgia. 2018;38(1):1–211. https://doi.org/10.1177/0333102417738202.

54. Russo A, Tessitore A, Bruno A, Siciliano M, Marcuccio L, Silvestro M, et al. Migraine does not affect pain intensity perception: a cross-sectional study. Pain Med (Malden, MA). 2018;19(8):1657–66. https://doi.org/10.1093/pm/pnx174.
55. Granovsky Y, Shor M, Shifrin A, Sprecher E, Yarnitsky D, Bar-Shalita T. Assessment of responsiveness to everyday non-noxious stimuli in pain-free migraineurs with versus without aura. J Pain. 2018;19(8):943–51. https://doi.org/10.1016/j.jpain.2018.03.008.
56. 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(11):2375–82. https://doi.org/10.1097/j.pain.0000000000001343.
57. Zohsel K, Hohmeister J, Oelkers-Ax R, Flor H, Hermann C. Quantitative sensory testing in children with migraine: preliminary evidence for enhanced sensitivity to painful stimuli especially in girls. Pain. 2006;123(1–2):10–8. https://doi.org/10.1016/j.pain.2005.12.015.
58. Ferracini GN, Stuginsk-Barbosa J, Dach F, Speciali JG. A comparison pressure pain threshold in pericranial and extracephalic regions in children with migraine. Pain Med (Malden, MA). 2014;15(4):702–9. https://doi.org/10.1111/pme.12353.
59. de Tommaso M, Sciruicchio V, Ricci K, Montemurno A, Gentile F, Vecchio E, et al. Laser-evoked potential habituation and central sensitization symptoms in childhood migraine. Cephalalgia. 2016;36(5):463–73. https://doi.org/10.1177/0333102415597527.
60. Anttila P, Metsahonkala L, Mikkelsson M, Aromaa M, Kautiainen H, Salminen J, et al. Muscle tenderness in pericranial and neck-shoulder region in children with headache. A controlled study. Cephalalgia. 2002;22(5):340–4. https://doi.org/10.1046/j.1468-2982.2002.00352.x.
61. Metsahonkala L, Anttila P, Laimi K, Aromaa M, Helenius H, Mikkelsson M, et al. Extracephalic tenderness and pressure pain threshold in children with headache. Eur J Pain. 2006;10(7):581–5. https://doi.org/10.1016/j.ejpain.2005.08.005.
62. Nahman-Averbuch H, Leon E, Hunter BM, Ding L, Hershey AD, Powers SW, et al. Increased pain sensitivity but normal pain modulation in adolescents with migraine. Pain. 2019;160(5):1019–28. https://doi.org/10.1097/j.pain.0000000000001477.
63. Sand T, Nilsen KB, Hagen K, Stovner LJ. Repeatability of cold pain and heat pain thresholds: the application of sensory testing in migraine research. Cephalalgia. 2010;30(8):904–9. https://doi.org/10.1177/0333102409356023.
64. Stankewitz A, Schulz E, May A. Neuronal correlates of impaired habituation in response to repeated trigemino-nociceptive but not to olfactory input in migraineurs: an fMRI study. Cephalalgia. 2013;33(4):256–65. https://doi.org/10.1177/0333102412470215.