Contributions of aversive environmental stress to migraine chronification: Research update of migraine pathophysiology

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Abstract
Clinical studies have suggested that internal and/or external aversive cues may produce a negative affective-motivational component whereby maladaptive responses (plasticity) of dural afferent neurons are initiated contributing to migraine chronification. However, pathophysiological processes and neural circuitry involved in aversion (unpleasantness)-producing migraine chronification are still evolving. An interdisciplinary team conducted this narrative review aimed at reviewing neuronal plasticity for developing migraine chronicity and its relevant neurocircuits and providing the most cutting-edge information on neuronal mechanisms involved in the processing of affective aspects of pain and the role of unpleasantness evoked by internal and/or external cues in facilitating the chronification process of migraine headache. Thus, information presented in this review promotes the understanding of the pathophysiology of chronic migraine and contribution of unpleasantness (aversions) to migraine chronification. We hope that it will bring clinicians’ attention to how the maladaptive neuroplasticity of the emotion brain in the aversive environment produces a significant impact on the chronification of migraine headache, which will in turn lead to new therapeutic strategies for this type of pain.

Key Words: Migraine chronification; Aversive environmental stress; Migraine pathophysiology; Migraine headache; Roles of unpleasantness; Emotion brain

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INTRODUCTION

Migraine is the third most prevalent disease and the second most severe disabling disorder worldwide\(^1\). In the United States, it is estimated that over 45 million people are actively afflicted by migraine. Of these, about 4% of them develop chronic migraine annually\(^2\). The International Headache Society clinically characterizes chronic migraine as recurrent unilateral throbbing headache attacks of moderate to severe intensity and associated symptoms (including facial allodynia, nausea, vomiting, phonophobia and photophobia) occurring episodically for more than 15 d every month for 3 consecutive months\(^3\). Before or at the same time as a headache, migraineurs could have aura, \textit{i.e.} a transient visual, sensory, or other central nervous system symptoms\(^4\). Clinical retrospective data show that the development of chronicity (chronification) is frequently related to a wide variety of internal and external triggers, such as physical and/or mental stress, hormonal fluctuations, sleep disturbances, meal skipping, sensory overload, \textit{etc.} Also, such a chronic disorder is associated with greater psychiatric and medical comorbidities\(^5\). Pathophysiologically, maladaptive responses (plasticity) of dural afferent neurons of the ophthalmic division in the trigeminal ganglia are evident to be an underlying mechanism for migraine headache. This plasticity is modulated by descending pathways from the higher brain centers\(^6\). Thus, it is proposed that internal and/or external aversive cues produce a negative affective-motivational component whereby maladaptive responses are initiated contributing to migraine chronification. However, our understanding of pathophysiological processes and neural circuitry involved in aversion (unpleasantness)-producing migraine chronification is still evolving. In this article, neuronal plasticity for developing migraine chronicity and relevant neurocircuits were reviewed and discussed. Specifically, we focused on providing the most cutting-edge information on neuronal mechanisms involved in the processing of affective aspects of pain and the role of unpleasantness evoked by internal and/or external cues in facilitating the chronification process of migraine headache. New information collected from both preclinical and clinical studies on these aspects may advance our understanding on the chronic migraine pain mechanisms and lead to new strategies for pain treatment.

LITERATURE REVIEW

An interdisciplinary team conducted this narrative review. MEDLINE and Cochrane databases were reviewed to identify publications relevant to chronic migraine pathophysiology, unpleasantness (aversion), and synaptic plasticity. Publications were selected based on author expertise to summarize our current understanding of the impact of aversive environmental stress on chronic migraine.
MIGRAINE PATHOPHYSIOLOGY

It is well established by a great deal of research work that migraine pathophysiology involves altered excitability of many brain regions, intracranial arterial dilatation, recurrent activation (sensitization) of the trigeminovascular pain pathway, and consequential structural and functional changes in genetically susceptible individuals\(^6\). The headache of a migraine attack is the major complaint from the migraine sufferers and is thought to originate from activation of nociceptors innervating meninges, large cerebral arteries, and sinuses. Activation of these structures by mechanical, electrical, or chemical (inflammatory “soup” or infectants) stimulation contributes to migraine headache and its most common associated symptoms including nausea, throbbing pain, photophobia, and phonophobia\(^6\). The nociceptive innervation of the meninges and intracranial vasculature consists of unmyelinated and thinly myelinated axons (C- and Aδ fibers) that contain vasoactive neuropeptides, mainly substance P and calcitonin gene-related peptide contributing to neurogenic inflammation. These peripheral nociceptive terminals originate in the trigeminal ganglion and reach the dura mainly through the ophthalmic branch of the trigeminal nerve (V1) and, to a lesser extent, through the maxillary (V2) and mandibular (V3) divisions\(^6\). Innervation of the dura is also supplied by neurons in the upper cervical dorsal root ganglia\(^6\). Central processes of meningeal sensory afferents enter the brainstem via the trigeminal tract and at the same time sends out collaterals that terminate in the spinal trigeminal nucleus caudalis (Sp5C) and upper cervical spinal cord (C1-3), called trigeminocervical pathway. The projections of intracranial (visceral) and extracranial (somatic) primary afferents onto Sp5C neurons are involved in the perception of referred pain in the periorbital and occipital regions (orofacial allodynia)\(^6\). Ascending projections of Sp5C neurons to several cortical and subcortical areas contribute to a wide variety of symptoms like migraine headache, phonophobia, photophobia, osmophobia, nausea, irritability, fatigue, sleepiness, and exaggerated emotional responses\(^6,12\).

Development of neural plasticity in the trigeminovascular pain pathway has been evidently shown to be the underlying migraine pathophysiology. Brief chemical stimulation with inflammatory agents on the dura of rodents can lead to peripheral sensitization of the primary afferent neurons in the trigeminal ganglion and dorsal root ganglia of C2/C3 and central sensitization of the second order neurons in the Sp5C (known as trigeminocervical complex)\(^6\). Central sensitization may extend to the thalamic (third order) neurons. This is proven clinically by finding an exaggerated activation of the cortical and subcortical areas during ictal period of migraine attack in human migraineurs triggered by nitroglycerin and experimentally by finding the increased responses of sensitized thalamic neurons of rats to cephalic and extracephalic skin stimuli after exposing their dura receptive field to inflammatory soup\(^6\). These strongly support there are endogenous inflammatory mediators released during migraine attacks to activate and sensitize peripheral and central trigeminovascular neurons by the mechanism of neurogenic inflammation\(^6,13\).

Peripheral sensitization mediates the throbbing perception of the headache, whereas sensitization of second-order neurons in the Sp5C mediates cephalic allodynia as well as muscle tenderness\(^6\). In most chronic migraineurs, episodic attacks are associated closely with the triggering of sensitization of the trigeminovascular pain pathway. These neural plastic responses to episodic attacks are initially adaptive and physiological but later become maladaptive and pathological, which would eventually create a vicious cycle leading to the chronicity of migraine headache\(^6\). However, it still remains debatable how episodic attacks are triggered and initiated. So far the most widely accepted view is that migraines are preceded by visual, motor, or somatosensory symptoms known as aura that is characterized by a visual perception of light flashes moving across the visual field.

Aura has been suggested to be closely linked to a reversible, transient cortical event, called cortical spreading depression (CSD)\(^6\). Electrophysiologically, CSD is a slowly propagating wave (2-6 mm/min) from membrane depolarization of neurons and glia followed by a prolonged inhibition (15-30 min) of cortical activity\(^4\). This distinctive electrophysiological phenomenon has been correlated with the visual aura that precedes the onset of headache in migraine\(^6,19\). Neurochemically, triggering of CSD has been shown to lead to the local release of ATP, glutamate, potassium, hydrogen ions, calcitonin gene-related peptide, and nitric oxide by neurons, glia, or vascular cells\(^6\). These molecules in turn diffuse toward the surface of the cortex to irritate persistently (activate) dorsal nociceptors, triggering a consequential neurogenic inflammation (vasodilatation, plasma protein extravasation, and mast cell degranulation). The release of pro-inflammatory molecules in the meninges due to
nociceptor activation contribute to the pain of migraine\[^{[16,17]}\]. Further, the plastic changes in the trigeminocervical pathway by CSD was suggested by showing that CSD induces an increase of c-fos expression in the Sp5C and that neural firing of meningeal nociceptors and central trigeminocervical neurons in the Sp5C are enhanced by CSD\[^{[18]}\]. One of the molecular mechanisms has been proposed by the finding that CSD propagation induces the opening of neuronal Panx1 megachannels leading to a downstream cascade of events that include the release of pro-inflammatory molecules in the meninges\[^{[19]}\]. These would serve as the triggers of episodic attacks of migraines. Thus, abnormal cortical excitability plays a pivotal role in the predisposition to develop neural plasticity contributing to the recurrent trigeminovascular and/or dural nociceptor activation. These pathophysiological processes are likely associated with the transition of migraine from acute to chronic disorder (chronification).

**CONTRIBUTION OF THE UNPLEASANTNESS (AVersion) TO MIGRAINE PAIN**

A number of internal and external cues are suggested to be triggers of episodic attacks of migraines in approximately 75% of patients. These include physical and/or mental stress, menstruation, hormonal fluctuations, noise, odors, heat, headache/neck movement, neck pain, and sensory overload\[^{[20,21]}\]. However, whether these factors are the causes of CSD causing migraine attacks remains to be investigated. It has long been known that negative emotions-induced unpleasantness produces a significant impact on pain perception\[^{[22]}\]. Patients experiencing pain caused by many diseases often reported a higher degree of unpleasantness (or aversion) that are reflected as varying degrees of affective symptoms, such as fear, anxiety, anger, depression, and aversion to pain associated environments. Moreover, the negative affect or “bothersome”-like pain significantly impacts the quality of life of the sufferers and leads to the common comorbidities of psychiatric disorders such as depression\[^{[23]}\]. Clinical studies have provided important evidence that pain-related aversion experiences seem to be not related to pain intensity but to be significantly influenced by the psychological environment in which pain is perceived\[^{[24]}\].

**UNPLEASANTNESS COMPONENT OF MIGRAINE PAIN**

Migraine is a subjective multidimensional conscious experience, and the pain processing and perception are significantly affected by negative emotions. In addition to cephalic allodynia and/or hyperalgesia perceived as headache, a negative unpleasant affective-motivational component (aversion) is clinically very important and named as pain aversion\[^{[25]}\]. A number of clinical retrospective data seem to support etiologically that migraine pain is associated with adverse affective and emotional states. For example, the high comorbidity of migraine and depression highlights the importance of negative affect\[^{[26]}\]. Also, migraine patients have been identified to be significantly associated with suicide, and literature has proven that migraine patients have a higher suicide risk (about 2.5 times) than patients without migraine\[^{[27]}\]. It is widely accepted that stress contributes to the severity and frequency of migraine attacks\[^{[28,29]}\]. In laboratory studies using animal models, the reward- and/or penalty-conditioned paradigms, such as conditioned place preference (CPP) and/or conditioned place aversion (CPA), are the common procedures to assess the affective component of pain and then analyze its mechanisms\[^{[30,31]}\]. Animals are conditioned with CPA paradigm where aversive stimuli (like varieties of stress) can “teach” animals to avoid environments (or objects) that are associated with aversive stimuli by psychologically producing negative, unpleasant affect\[^{[32]}\] and by behaviorally inducing avoidance or escape\[^{[33]}\]. Using CPP paradigm, the conditioned animals learn to differentiate the pain- alleviating environment from pain-producing environment. For example, in animals with migraine-like pain induced by inflammatory mediators applied to the dural membrane, administration of lidocaine elicited animals to develop a CPP\[^{[34]}\]. Thus, both CPP and CPA paradigms are demonstrated experimentally to be a useful, effective tool to reveal affective pain and are therefore available to study the psychological mechanisms of affective dimension of pain.
BRAIN REGIONS AND RELEVANT NEURAL CIRCUITRY RESPONSIBLE FOR MIGRAINE PAIN AVERSION

It is well known that pain is processed in discrete but interacting brain structures, which help to produce multidimensional experiences composed of sensory, cognitive, and emotional (subjective) components. However, our understanding of the neural circuitry that mediates the negative affective component of pain is still very limited. The anterior cingulate cortex (ACC) is the region of the brain that has been frequently reported to mediate consistently pain affects and unpleasantness in many types of pain, particularly chronic pain. The ACC, along with the insular cortex and orbitofrontal cortex, is part of a salience network. This network circuit has a central role in the detection of behaviorally relevant salient stimuli (including pain) and the coordination of neural resources. Thus, aberrant salience processing in the salience network may contribute to chronic pain. When brain salience systems become dysregulated or disrupted, they may overly respond to certain types of stimuli because they cannot properly filter and process information. Thus, the dysfunction of the salience network would be a critical mechanism contributing to chronic pain. Functional imaging analysis has firstly been used to capture the activity of the brain in a migraine cycle that includes preictal, ictal, and postictal phases for migraine attacks. Secondly, increasing neuroimaging studies have investigated the brains of migraine patients in responses to painful and other stimuli during interictal periods. Studies have consistently observed increased activation of a network of brain regions collectively known as the “painmatrix” including the primary and secondary somatosensory cortices, ACC, insula, prefrontal cortex, amygdala, thalamus, and others. Also, decreased activation can be observed in areas responsible for pain inhibition (e.g., pons and ventral medulla), thereby suggesting an imbalance between facilitation and inhibition, likely resulting from maladaptive neural plasticity. Some of these brain regions, like the ACC, prefrontal cortex, amygdala, etc., have been shown to specifically contribute to psychological and/or aversive processing of migraine headache. It is evident that migraine patients viewing pain-related words exhibited enhanced activation in the insular cortex and orbitofrontal cortex compared to healthy control subjects. Further, there is a report of structural deficits in the orbitofrontal cortex and increased functional connectivity between the orbitofrontal cortex and ACC in migraineurs. In an animal model of migraine pain induced by application of inflammatory mediators to the dura mater, lesions of the ACC prevented the acquisition for place preference produced by injection of lidocaine into the rostral ventral medulla. The important role of the ACC in the integration of the aversive component of pain was also demonstrated by the evidence that a CPA to formalin-induced pain was absent following the lesion of the ACC. Migraineurs were identified to have structural and functional cerebral abnormalities (e.g., reduced cortical thickness) in the prefrontal cortex, the rostral ACC, the somatosensory cortex, the orbitofrontal cortex, and insular cortex. In addition to cortical thinning, the functional activity of both the ACC and the insular cortex was significantly reduced in patients with chronic migraine.

The amygdala is another important brain region contributing to the mediation of the aversive component of pain because there is overwhelming evidence demonstrating the comorbidity of psychiatric illness with migraine. Also, more than 47% of migraineurs are comorbid with mood and anxiety disorders. The development of disease comorbidity and the progression to chronic migraine are proposed to be a result of stress-induced neuronal plasticity heavily integrated with stress, affect, and pain. An interesting finding by Akcali et al. suggests that synaptic plasticity within the amygdala may contribute to migraine pain. Their study demonstrated that (1) topical application of N-methyl-D-aspartate to the central amygdala led to a high expression of c-fos in the amygdaloid neurons and CSD; and (2) sumatriptan attenuated c-fos expression that was thought to result from the induction of CSD. An in vitro electrophysiological recording on the amygdala-hippocampus-cortex slices further indicated that CSD modulates synaptic transmission of the lateral amygdala producing synaptic plasticity. Human imaging data showed that migraine patients during spontaneous and untreated attacks had significantly higher blood oxygen level-dependent signal intensities in the limbic structures (amygdala and insular cortices). These findings suggest strongly a pathophysiological mechanism how the CSD is linked to negative emotions-induced unpleasantness, which in turn contributes to migraine pain. Since there is broad transmission from the amygdala to other brain structures facilitating stress and pain response, it is proposed that the sensitization of the amygdala may underlie the progression of migraine symptoms that are comorbid.
THE ROLE OF UNPLEASANTNESS (AFFECTIVE) IN THE CHRONIFICATION OF MIGRAINE HEADACHE

The transition from acute migraine to chronic status of migraine is called “migraine chronification”. It is estimated that approximately 4% of patients with acute migraine develop and become chronic migraineurs. So far the pathophysiology of migraine chronification still remains elusive. Some mechanisms have been proposed including (1) altered trigeminal and cranial autonomic system function; (2) thalamic contribution to central sensitization; (3) dysfunction of the descending pain-modulating network; and (4) medication-associated central sensitization. These proposed views share a common mechanism, i.e. sensitization of migraine pain related pathways. As mentioned above, sensitization of trigeminovascular system and higher brain centers contributes to the neuronal plasticity that should be the key to the progression of migraine. Therefore, it is proposed that frequent or persistent exposure to unpleasant (affective) events leads to a synaptic plasticity in these pain pathways, leading to chronicity. Nevertheless, the exact pathophysiological mechanism remains to be clarified, because this sensitization is affected by multiple internal and external triggers. Patients with migraine often show a “lack of habituation”, i.e. no decrease or even an increase in response following frequent or persistent stimulation. Clinically, this habituation deficit seen in migraine patients has been demonstrated using several tests, including visual evoked potentials, somatosensory and auditory evoked potentials, blink reflex, and laser evoked potentials. This migraine-related deficit in habituation phenomenon is suggested to be one of the mechanisms underlying interictal deficits in habituation and the associated changes accompanying migraine chronification. Clinical observations on patients with chronic migraine showed that the habituation pattern during interictal periods is similar to that during a migraine attack. This should explain such chronic disorder as a status of never-ending migraine.

Studies at cellular and molecular levels using animal models have provided insights into the mechanisms that lead to and sustain chronic pain. Synaptic plasticity has been reported in several cortical and sub-cortical regions that are known to be involved in the processing of pain aversion. Of these higher centers, synaptic plasticity has been most extensively studied in the ACC. Hyperactivation of the ACC is involved in signaling the unpleasantness associated with pain, especially individuals with neuropathic pain and chronic pain conditions. Further, activation of the ACC has also been linked to emotional or psychological pain. For example, experimentally induced sadness, social exclusion, or rejection led to an increase in activity in this cortical region. Thus, the ACC mediates various negative effects, including the unpleasantness of pain in the course of pain chronification.

Long-lasting synaptic plasticity mostly seen in the form of long-term potentiation (LTP) and mediated by excitatory amino acid receptors and their relevant downstream signaling molecules is the major pathophysiological change responsible for chronic pain. Increasing evidence suggests that LTP recorded in the ACC is causally associated with chronic pain. Pharmacological studies on the ACC synaptic plasticity by using in vitro electrophysiological recordings reveal that LTP exists in at least four different forms: N-methyl-D-aspartate receptor-dependent, L-type voltage-gated calcium channel-dependent, late-phase LTP, and presynaptic LTP. Some of these LTPs may coexist to be involved in chronic pain or affective (e.g., fear) memory. The development of pain chronicity seems to be encoded temporally by LTP in the ACC: (1) Synaptic responses in the ACC are potentiated at the time that allodynia develops seen in rodent models of chronic inflammatory pain, neuropathic pain, bone cancer pain, and chronic visceral pain, and LTP is persistently expressed when pain symptom develops; and (2) Although acute nociception is short-lasting, it can trigger persistent synaptic changes associated with the formation of affective memory. Thus, acute pain may engage synaptic plastic mechanisms in the ACC to encode physiologically relevant information about pain-evoked cognitive impairment, which might contribute to the chronification of pain. With the known widespread connectivity among the ACC, as well as other subcortical limbic regions known as “emotion brain” and noiceptive pathways, it may be presumed that the ACC would integrate the processing of pain with the associated emotional and affective events, contributing to the migraine chronification. Internal and/or external environmental stressors would serve as aversive triggers to stimulate these limbic brain areas and
cause a negative affective state that significantly changes pain sensation, which is the main source of pain aversion. When aversive stimuli become frequent or persistent, the emotional brain may develop sensitization, i.e. hyper responsiveness. It thus is proposed that central sensitization of emotional brain will be generated through affective learning of aversive environment, which can trigger recurrence of migraine and contributes to the development of migraine chronicity.

**SIGNIFICANCE OF STUDYING THE ROLE OF AVERSE ENVIRONMENTS IN MIGRAINE CHRONIFICATION**

Insights into the plasticity of emotion brain induced by aversive environment are prerequisites to the understanding of the neural basis of chronic migraine headache and how this chronic event develops due to the maladaptive changes in mood and cognitive function caused by environmental stress. Traditionally, the trigeminal ganglia are trigeminovascular structures and are still seen as “gold” targets for controlling migraine pain. However, when the pain becomes chronic, the situation does not always seem to be the case, because more and more evidence shows that some central changes will occur in the course of chronification. Just like aversion memory and other affective learning processes, it is too late to interfere at the periphery if such “bad” memory takes place in the brain. Therefore, clinicians and laboratory researchers should pay more and more attention to how the maladaptive neuroplastic changes of the emotion brain in aversive environment promote the development of the chronic pain state. The results of this study may provide potential new targets for the treatment of this chronic disorder.

**CONCLUSION**

Migraine pathophysiology in the transition from acute to chronic pain is complex and multifactorial and involves altered excitability of many brain regions, intracranial arterial dilatation, recurrent activation (sensitization) of the trigeminovascular pain pathway, and consequential structural and functional changes in genetically susceptible individuals. Chronic migraine is closely associated with adverse affective and emotional states. Frequent or persistent exposure to unpleasant (affective) events leads to a synaptic plasticity in these pain pathways, leading to chronicity. The achievements from clinical and laboratory studies may provide potential new targets for the treatment of this chronic disorder.

**REFERENCES**

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1211-1259 [PMID: 28919117 DOI: 10.1016/S0140-6736(17)32154-2]
2. Migraine Research Foundation. Migraine Facts - Migraine Research Foundation. Available from: https://migraineresearchfoundation.org/about-migraine/migraine-facts/
3. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013; 33: 629-808 [PMID: 23771276 DOI: 10.1177/0333102413485658]
4. Niles AN, Dour HJ, Stanton AL, Roy-Byrne PP, Stein MB, Sullivan G, Sherbourne CD, Rose RD, Craske MG. Anxiety and depressive symptoms and medical illness among adults with anxiety disorders. *J Psychosom Res* 2015; 78: 109-115 [PMID: 25510186 DOI: 10.1016/j.jspychres.2014.11.018]
5. Burgos-Vega C, Moy J, Dussor G. Meningeal afferent signaling and the pathophysiology of migraine. *Prog Mol Biol Transl Sci* 2015; 131: 537-564 [PMID: 25744685 DOI: 10.1016/bs.pmbts.2015.01.001]
6. Noseda R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. *Pain* 2013; 154 Suppl 1: S44-S53 [PMID: 23891892 DOI: 10.1016/j.pain.2013.07.021]
7. Lai TH, Protsenko E, Cheng YC, Loggia ML, Coppola G, Chen WT. Neural Plasticity in Common Forms of Chronic Headaches. *Neural Plast* 2015; 205985 [PMID: 26366304 DOI: 10.1155/2015/205985]
8. Olesen J, Burstein R, Ashina M, Tfelt-Hansen P. Origin of pain in migraine: evidence for peripheral
sensitisation. Lancet Neurol 2009; 8: 679-690 [PMID: 19539239 DOI: 10.1016/S1474-4422(09)70090-0]

9. Levy D, Strassman AM. Mechanical response properties of A and C primary afferent nerve fibers innervating the rat intracranial dura. J Neurophysiol 2002; 88: 3021-3031 [PMID: 12466427 DOI: 10.1152/jn.00292.2002]

10. Keller JT, Saunders MC, Beduk A, Jollis JG. Innervation of the posterior fossa dura of the cat. Brain Res Bull 1985; 14: 97-102 [PMID: 3872702 DOI: 10.1016/0361-9230(85)90181-9]

11. Burstein R, Yamamura H, Malick A, Strassman AM. Chemical stimulation of the intracranial dura induces enhanced responses to facial stimulation in brain stem trigeminal neurons. J Neurophysiol 1998; 79: 964-982 [PMID: 9463456 DOI: 10.1152/jn.1998.79.2.964]

12. Noseda R, Kainz V, Jakubowski M, Gooley JJ, Saper CB, Digre K, Burstein R. A neural mechanism for exacerbation of headache by light. Nat Neurosci 2010; 13: 239-245 [PMID: 20062053 DOI: 10.1038/nn.2475]

13. Noseda R, Jakubowski M, Kainz V, Borsook D, Burstein R. Cortical projections of functionally identified thalamic trigeminal neurons: implications for migraine headache and its associated symptoms. J Neurosci 2011; 31: 14204-14217 [PMID: 21976505 DOI: 10.1523/JNEUROSCI.3285-11.2011]

14. Strassman AM, Raymond SA, Burstein R. Sensitization of meningeal sensory neurons and the origin of headaches. Nature 1996; 384: 560-564 [PMID: 8955268 DOI: 10.1038/384a0]

15. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Brain 2014; 137: 232-241 [PMID: 24277718 DOI: 10.1093/brain/awt320]

16. Malhotra R. Understanding migraine: Potential role of neurogenic inflammation. Ann Indian Acad Neurol 2016; 19: 175-182 [PMID: 27293326 DOI: 10.4103/0972-2327.182302]

17. Ramachandran R. Neurogenic inflammation and its role in migraine. Semin Immunopathol 2018; 40: 301-314 [PMID: 29568973 DOI: 10.1007/s00281-018-0676-y]

18. 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): 1703-1709 [PMID: 10908190 DOI: 10.1093/brain/123.8.1703]

19. Vgontzas A, Burch R. Episodic Migraine With and Without Aura: Key Differences and Implications for Pathophysiology, Management, and Assessing Risks. Curr Pain Headache Rep 2018; 22: 78 [PMID: 30291554 DOI: 10.1007/s11916-018-0735-z]

20. Smith JM, Bradley DP, James MF, Huang CL. Physiological studies of cortical spreading depression. Biol Rev Camb Philos Soc 2006; 81: 457-481 [PMID: 16848916 DOI: 10.1017/S1464793106007081]

21. Charles AC, Baca SM. Cortical spreading depression and migraine. Nat Rev Neurol 2013; 9: 637-644 [PMID: 24042463 DOI: 10.1038/nrneurol.2013.192]

22. Close LN, Eftekhar S, Wang M, Charles AC, Russo AF. Cortical spreading depression as a site of origin for migraine: Role of CGRP. Cephalalgia 2019; 39: 428-434 [PMID: 29695168 DOI: 10.1177/0333102418877429]

23. Wahl M, Schilling L, Parsons AA, Kaumann A. Involvement of calcitonin gene-related peptide (CGRP) and nitric oxide (NO) in the pial artery dilatation elicited by cortical spreading depression. Brain Res 1994; 637: 204-210 [PMID: 8180797 DOI: 10.1016/0006-8993(94)91234-3]

24. 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: 855-865 [PMID: 21416429 DOI: 10.1002/ana.22239]

25. Karatas H, Erdener SE, Gursoy-Ozdemir Y, Lule S, Eren-Koçak E, Sen ZD, Dalkara T. Spreading depression triggers headache by activating neuronal Panx1 channels. Science 2013; 339: 1092-1095 [PMID: 23449592 DOI: 10.1126/science.1231897]

26. An YC, Liang CS, Lee JT, Lee MS, Chen SJ, Tsai CL, Lin YK, Yang FC. Effect of Sex and Adaptation on Migraine Frequency and Perceived Stress: A Cross-Sectional Case-Control Study. Front Neurol 2019; 10: 598 [PMID: 31231306 DOI: 10.3389/fneur.2019.00598]

27. Sauro KM, Becker WJ. The stress and migraine interaction. Headache 2009; 49: 1378-1386 [PMID: 19619238 DOI: 10.1111/j.1526-4610.2009.01486.x]

28. Borsook D, Maleki N, Becerra L, McEwen B. Understanding migraine through the lens of maladaptive stress responses: a model disease of allostatic load. Neuron 2012; 73: 219-234 [PMID: 22284178 DOI: 10.1016/j.neuron.2012.01.001]

29. Shala N, Dreshaj S. Association of depression, anxiety and post-traumatic stress disorder with migraine: Data from Kosovo. Neurol Neurochir Pol 2018; 52: 490-494 [PMID: 29580567 DOI: 10.1016/j.jjnnnp.2018.03.003]

30. Buse DC, Manack A, Serrano D, Turkel C, Lipton RB. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. J Neurol Neurosurg Psychiatry 2010; 81: 428-432 [PMID: 20164501 DOI: 10.1136/jnnp.2009.192492]

31. Bie B, Brown DL, Naguib M. Synaptic plasticity and pain aversion. Eur J Pharmacol 2011; 667: 26-31 [PMID: 21699892 DOI: 10.1016/j.ejphar.2011.05.080]

32. Ashina S, Serrano D, Lipton RB, Maizels M, Manack AN, Turkel CC, Reed ML, Buse DC. Depression and risk of transformation of episodic to chronic migraine. J Headache Pain 2013; 13: 615-624 [PMID: 23007859 DOI: 10.1007/s10194-012-0479-9]

33. Friedman LE, Gelaye B, Bain PA, Williams MA. A Systematic Review and Meta-Analysis of Migraine and Suicidal Ideation. Clin J Pain 2017; 33: 659-665 [PMID: 27648590 DOI: ]
Liu TH et al. Aversive environmental stress to migraine chronification

10.1097/AJP.0000000000004440

34 Urion L, Zhang Q, Martinez E, Zhou H, Dearosier N, Dale J, Wang J. Assessment of Aversion of Acute Pain Stimulus through Conditioned Place Aversion. *Bio Protoc* 2017; 7 [PMID: 29226182 DOI: 10.21769/BioProtoc.2993]

35 Fuchs PN, Peng YB, Boyette-Davis JA, Uheski ML. The anterior cingulate cortex and pain processing. *Front Integr Neurosci* 2014; 8 [PMID: 24829554 DOI: 10.3389/fint.2014.00035]

36 Caihi C, Cook C, Pickens S. Migraine and reward system-or is it aversive? *Curr Pain Headache Rep* 2014; 18: 410 [PMID: 24671390 DOI: 10.1007/s11916-014-0410-3]

37 Quinette GC. Advances in cortical modulation of pain. *J Pain Res* 2013; 6: 713-725 [PMID: 24092997 DOI: 10.2147/JPR.S45958]

38 DosSantos MF, Moura BS, DaSilva AF. Reward Circuitry Plasticity in Pain Perception and Modulation. *Front Pharmacol* 2017; 8: 790 [PMID: 29290204 DOI: 10.3389/fphar.2017.00790]

39 Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci* 2011; 12: 154-167 [PMID: 21331082 DOI: 10.1038/nrn2994]

40 Lorenz J, Beck H, Bromm B. Cognitive performance, mood and experimental pain before and during morphine-induced analgesia in patients with chronic non-malignant pain. *Pain* 1997; 73: 369-375 [PMID: 9469527 DOI: 10.1016/S0304-3959(97)00123-1]

41 Cauda F, D’Agata F, Sacco K, Duca S, Coticò D, Paolasso I, Isardo G, Geminiani G. Altered resting state attentional networks in diabetic neuropathic pain. *J Neurol Neurosci Psychiatry* 2010; 81: 806-811 [PMID: 19955113 DOI: 10.1136/jnnp.2009.188631]

42 Hadjikhani N, Sanchez Del Rio M, Wu O, Schwartz D, Bakker D, Fischl B, Kwong KK, Cutrer FM, Rosen BR, Tootell RB, Sorensen AG, Moskowitz MA. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci USA* 2001, 98: 4687-4692 [PMID: 11287655 DOI: 10.1073/pnas.071582498]

43 Schwindt TJ, Chiang CC, Chung CD, Dodick DW. Functional MRI of migraine. *Lancet Neurol* 2015; 14: 81-91 [PMID: 25496899 DOI: 10.1016/S1474-4422(14)70193-0]

44 Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain* 2016; 139: 1987-1993 [PMID: 27190019 DOI: 10.1093/brain/aww097]

45 Eck J, Richter M, Straube T, Miltnner WHR, Weiss T. Affective brain regions are activated during the processing of pain-related words in migraine patients. *Pain* 2011; 152: 1104-1113 [PMID: 21377797 DOI: 10.1016/j.pain.2011.01.026]

46 De Felice M, Ebye N, Dodick D, Dussoy GO, Ossipov MH, Fields HL, Porreca F. Capturing the aversive state of cephalic pain preclinically. *Ann Neurol* 2013; 74: 257-265 [PMID: 23686557 DOI: 10.1002/ana.23922]

47 Johansen JP, Fields HL, Manning BH. The affective component of pain in rodents: direct evidence for a contribution of the anterior cingulate cortex. *Proc Natl Acad Sci USA* 2001, 98: 8077-8082 [PMID: 11416168 DOI: 10.1073/pnas.141218998]

48 Gao YJ, Ren WH, Zhang YQ, Zhao ZQ. Contributions of the anterior cingulate cortex and amygdala to pain- and fear-conditioned place avoidance in rats. *Pain* 2004; 110: 343-353 [PMID: 15257585 DOI: 10.1016/j.pain.2004.04.030]

49 Maleki N, Becerra L, Brawn J, Bigal M, Burstein R, Borsook D. Concurrent functional and structural cortical alterations in migraine. *Cephalalgia* 2012; 32: 607-620 [PMID: 22623760 DOI: 10.1177/0331071612444562]

50 Buse DC, Silberstein SD, Manack AN, Papapetropoulos S, Lipton RB. Psychiatric comorbidities of episodic and chronic migraine. *J Neurol* 2013; 260: 1960-1969 [PMID: 23132299 DOI: 10.1002/ana.00415-012-6725-x]

51 Jette N, Patten S, Williams J, Becker W, Wibe S. Comorbidity of migraine and psychiatric disorders—a national population-based study. *Headache* 2008; 48: 501-516 [PMID: 18070059 DOI: 10.1111/j.1526-4100.2007.00993.x]

52 Akella D, Sayin A, Sara Y, Bolay H. Does single cortical spreading depression elicit pain behaviour in freely moving rats? *Cephalalgia* 2010; 30: 1195-1206 [PMID: 20855365 DOI: 10.1111/j.1468-2984.2010.01830.x]

53 Dehendi S, Speckmann EJ, Pape HC, Gorji A. Cortical spreading depression modulates synaptic transmission of the rat lateral amygdala. *Eur J Neurosci* 2008; 27: 2057-2065 [PMID: 18412626 DOI: 10.1111/j.1460-9568.2008.06188.x]

54 Stankevitz A, May A. Increased limbic and brainstem activity during migraine attacks following olfactory stimulation. *Neurology* 2011; 77: 476-482 [PMID: 21775739 DOI: 10.1212/WNL.0b013e318227e4a8]

55 Chou TM, Chen SP. Animal models of Chronic Migraine. *Curr Pain Headache Rep* 2018; 22: 44 [PMID: 29779126 DOI: 10.1007/s11916-018-0693-5]

56 Lisicki M, Ruiz-Romagnoi E, Piedrabuena R, Giobellina R, Schoenen J, Magis D. Migraine triggers and habituation of visual evoked potentials. *Cephalalgia* 2018; 38: 988-992 [PMID: 28691517 DOI: 10.1177/0331071617720217]

57 Lisicki M, D’Ostilio K, Erpicum M, Schoenen J, Magis D. Sunlight irradiance and habituation of visual evoked potentials in migraine: The environment makes its mark. *Cephalalgia* 2018; 38: 1351-1360 [PMID: 28856911 DOI: 10.1177/0331071417730128]

58 Coppola G, Curra A, Di Lorenzo C, Parisi V, Gorini M, Sava SL, Schoenen J, Pierelli F. Abnormal
cortical responses to somatosensory stimulation in medication-overuse headache. *BMC Neurol* 2010; 10: 126 [PMID: 21192822 DOI: 10.1186/1471-2377-10-126]

59 **Bliss TV**, Collingridge GL, Kaang BK, Zhuo M. Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. *Nat Rev Neurosci* 2016; 17: 485-496 [PMID: 27307118 DOI: 10.1038/nrn.2016.68]

60 **Koga K**, Descalzi G, Chen T, Ko HG, Lu J, Li S, Son J, Kim T, Kwak C, Huganir RL, Zhao MG, Kaang BK, Collingridge GL, Zhuo M. Coexistence of two forms of LTP in ACC provides a synaptic mechanism for the interactions between anxiety and chronic pain. *Neuron* 2015; 85: 377-389 [PMID: 25556835 DOI: 10.1016/j.neuron.2014.12.021]

61 **Bushnell MC**, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci* 2013; 14: 502-511 [PMID: 23719569 DOI: 10.1038/nrn3516]

62 **Yoshino A**, Okamoto Y, Onoda K, Yoshimura S, Kunisato Y, Demoto Y, Okada G, Yamawaki S. Sadness enhances the experience of pain via neural activation in the anterior cingulate cortex and amygdala: an fMRI study. *Neuroimage* 2010; 50: 1194-1201 [PMID: 19969094 DOI: 10.1016/j.neuroimage.2009.11.079]

63 **Zhuo M**. Long-term potentiation in the anterior cingulate cortex and chronic pain. *Philos Trans R Soc Lond B Biol Sci* 2014; 369: 20130146 [PMID: 24298148 DOI: 10.1098/rstb.2013.0146]

64 **Chen T**, Koga K, Descalzi G, Qiu S, Wang J, Zhang LS, Zhang ZJ, He XB, Qin X, Xu FQ, Hu J, Wei F, Huganir RL, Li YQ, Zhuo M. Postsynaptic potentiation of corticospinal projecting neurons in the anterior cingulate cortex after nerve injury. *Mol Pain* 2014; 10: 33 [PMID: 24890933 DOI: 10.1186/1744-8069-10-33]

65 **Tovote P**, Fadok JP, Lithi A. Neuronal circuits for fear and anxiety. *Nat Rev Neurosci* 2015; 16: 317-331 [PMID: 25991441 DOI: 10.1038/nrn3945]
