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MIGRAINE (R COWAN, SECTION EDITOR)

Migraine is Associated With Altered Processing of Sensory Stimuli

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Abstract Migraine is associated with derangements in perception of multiple sensory modalities including vision, hearing, smell, and somatosensation. Compared to people without migraine, migraineurs have lower discomfort thresholds in response to special sensory stimuli as well as to mechanical and thermal noxious stimuli. Likewise, the environmental triggers of migraine attacks, such as odors and flashing lights, highlight basal abnormalities in sensory processing and integration. These alterations in sensory processing and perception in migraineurs have been investigated via physiological studies and functional brain imaging studies. Investigations have demonstrated that migraineurs during and between migraine attacks have atypical stimulus-induced activations of brainstem, subcortical, and cortical regions that participate in sensory processing. A lack of normal habituation to repetitive stimuli during the interictal state and a tendency towards development of sensitization likely contribute to migraine-related alterations in sensory processing.

Keywords Migraine · Sensory processing · Migraine triggers · Electrophysiology · Functional neuroimaging

This article is part of the Topical Collection on *Migraine*

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Introduction

Migraine attacks typically consist of intense unilateral throbbing headaches that are associated with sensitivities to light, sound, odors, and cutaneous stimulation, as well as nausea and vomiting with or without accompanying auras [1]. It is becoming quite clear that the migraine-susceptible brain is unique not only in its ability to produce these symptoms of the migraine attack, but also in how it processes sensory information [2].

Several studies have demonstrated that migraineurs differ in their processing and perception of unimodal and multimodal sensory inputs.[3•] During the migraine attack, migraineurs develop an enhanced perception of painful and non-painful somatosensory, visual, auditory, and olfactory sensations. Between migraine attacks, atypical sensory perception persists, with migraineurs often demonstrating low discomfort thresholds to various experimentally applied stimuli. In addition, migraine is associated with atypical integration of information from different sensory modalities presented simultaneously (i.e. multisensory integration).

Atypical cortical excitation, sensitization, and habituation probably underlie migraine-related deviations in sensory perception [2]. Data from physiological studies substantiate functional differences in sensory processing between migraineurs and non-migraineurs [4–13]. Additionally, advanced functional imaging techniques reveal functional networks and individual brain regions involved in aberrant sensory processing in migraineurs [14–17]. Ultimately, discovering the mechanisms responsible for migraine-related alterations in sensory processing is critical for developing a more comprehensive description of migraine pathophysiology and perhaps for identifying biomarkers and new targets for migraine therapy. This article reviews the evidence from clinical, physiological, and imaging studies that investigated differences in sensory processing between migraineurs and non-migraineurs.

Unimodal Special Sensory Processing in Migraineurs

Auditory

Migraineurs have hypersensitivity to auditory stimuli, altered perception of sound, hyperacusis, activation of migraine attacks with auditory triggers, and aversion of noise during migraine attacks [18]. Approximately two-thirds of migraineurs report sensitivity to sound between migraine attacks [18]. In a study examining interictal discomfort to sound and auditory pain thresholds in 65 migraine and 80 control subjects, a lower proportion of migraineurs (6 % versus 44 %, p=0.0001) endured maximal intensity sound stimulation (in this case 111.3 dB) without some form of irritation as compared to headache-free controls [18]. A higher proportion of migraine subjects reported pain at maximal stimulation (69 % versus 25 %, p=0.0001) compared to controls. Likewise, migraine subjects reported lower auditory discomfort thresholds [18]. Migraineurs report that noise, such as traffic noise, can trigger migraine attacks [19]. Sensitivity to sound increases during a migraine attack. Approximately 70 – 90 % of migraine patients report sensitivity to or aversion to noise during a migraine attack. [18, 20•]

The neuroanatomical substrate for sound hypersensitivity probably involves activation of dura-sensitive thalamic neurons that project to auditory cortex. Dura-sensitive thalamic neurons of the posterior and lateral nuclei have diverse cortical projections including projections to primary auditory and auditory association cortices.[20•, 21] There are otologic comorbidities of migraine that point to a potential disruption in the ability to process auditory stimuli. Recent data suggest that migraineurs are at increased risk of sensorineural hearing loss [22] and that migraineurs demonstrate differences in cochlear hair cell activation that may involve both sensory afferent and brainstem efferent olivovestibulocochlear mechanisms. [23]

Olfaction

Various odors, including pungent odors, perfumes, food smells, cigarette smoke, and cleaning detergents, can be bothersome to migraineurs [24, 25]. Migraineurs report sensitivity to odors during and between migraine attacks [25, 26]. Interictally, migraineurs can detect the odor of vanillin, a pure olfactory nerve stimulant, at weaker concentrations compared with non-migraine healthy controls [26]. Acetone, which stimulates both olfactory nerve endings and trigeminal nerve endings innervating the nasal mucosa, is detected at lower concentrations in migraineurs who report osmosensitivity during their migraines as compared to healthy controls [26]. While not included in the International Classification of Headache Disorders criteria of migraine due to its low sensitivity, osmophobia is present in about 25 % of migraineurs during their migraine attacks [25].

About 50 % of migraineurs report that odors can trigger their migraine attacks [27]. Chemical stimulation and sensitization of trigeminal afferents innervating the nasal mucosa may partially explain this phenomenon. Likewise, trigeminal afferents may converge on second order neurons in the brainstem or hypothalamus that also receive olfactory input. A functional magnetic resonance imaging study detected odor-induced activation of a region in the rostral pons in ictal migraineurs (possibly containing the “migraine generator”), perhaps indicating a mechanism by which odors could trigger a migraine attack [28]. Similar to the increased incidence of sensorineural hearing loss in migraineurs, there may be an increased risk of anosmia in migraineurs [26]. However, the mechanisms underlying this loss of sensory perception and its link to abnormal sensory processing between and during migraine attacks are unclear.

Vision

Migraineurs process and perceive visual information atypically.[20•] Most migraineurs report increased sensitivity to light between migraine attacks (75 %) [29] and light-induced aggravation of headache during a migraine attack (60 – 90 %).[20•, 30] As with auditory stimuli, migraineurs have reduced visual discomfort thresholds as compared to non-migraineurs [30, 31]. Various visual stimuli can trigger a migraine attack, including exposure to sunlight, flashing or flickering lights, television, computer screens, and patterned lights [19].

The observation that blind migraineurs with complete optic nerve damage do not experience photophobia, while photophobia is preserved in blind migraineurs with intact optic nerves, suggests that optic nerve signals are necessary for the experience of photophobia.[20•] Light activates posterior thalamic neurons via retinal ganglion cell input; some of these thalamic neurons also have dural receptive fields. These light and dural responsive posterior thalamic neurons project to cortical regions that participate in processing of painful stimuli and to cortical regions responsible for processing visual stimuli. Increased cortical input from this dural and retinal-thalamocortical pathway might amplify the perception of pain in the presence of visual stimulation and amplify the perception of visual stimuli in the presence of pain [32–34]. Additionally, trigeminovascular brainstem neurons that receive convergent ocular nociceptive and dural inputs may be sensitized during a migraine attack.[20•]

Unimodal Somatosensory Processing in Migraineurs

Allodynia and Hyperalgesia

Migraineurs display enhanced perceptions of somatosensory stimuli that are normally painful and of those that are normally non-noxious. Approximately 60 – 70 % of migraineurs develop cutaneous allodynia during the migraine attack [35–37]. That is, they describe normally non-noxious stimulation of the skin as painful. For allodynic migraineurs, shaving, showering, wearing earrings and glasses, and brushing hair can cause pain [35]. Mechanical and thermal stimuli rated as non-painful during the interictal period are reported as painful in both cephalic and extracephalic regions during a migraine attack [38–40]. Additionally, cutaneous allodynia during migraine has been associated with other unique features of migraine including sensitivities to light and sound [35]. Compared to healthy people, thermal pain thresholds and mechanical pain thresholds are lower in migraineurs between attacks as well [41, 42]. Interictally, migraineurs have a higher pain rating in response to suprathreshold electrical stimulation of the trigeminal region as compared to controls, suggestive of trigeminal hyperalgesia, that is, an exaggerated perception of a pain in response to stimuli in the noxious range [43]. In addition, migraineurs experience increased pain in response to repetitive electrical stimulation of the trigeminal area, indicating a lack of habituation [43]. Neuronal sensitization, which is a long-lasting increased excitation of neurons in response to a given stimulus, can explain the allodynia and hyperalgesia experienced during and between migraine attacks. Cephalic allodynia likely results from sensitization of trigeminal nucleus caudalis neurons that receive convergent signals from the dura and cutaneous regions of the face, whereas extracephalic allodynia probably results from more widespread sensitization of thalamic and cortical neurons [35].

Multisensory Processing and Integration

Multisensory integration refers to the co-processing and co-modulation of information from different sensory modalities in order to assess the surrounding environment by forming a unified perception [44]. This unified perception of the environment produced by integrating and co-modulating information from multiple sensory domains reveals more to the individual than would a simple summation of information from each sensory domain individually [45]. There are cortical and subcortical regions that subserve the function of multimodal sensory integration. Multisensory integration involves visual, auditory, olfactory, and somatosensory stimuli– sensory modalities that are processed abnormally in migraine.

In addition to atypical unimodal processing, migraine is likely associated with aberrant multisensory integration. The interplay between pain, somatosensory, visual, auditory, and olfactory stimuli is responsible for several clinical characteristics of the migraine attack. For example, exposure to stimuli from one sensory modality, such as sound or light, can impact sensations within another sensory modality, like pain. Migraineurs commonly report that exposure to visual, olfactory and auditory stimuli enhance the intensity of their headache pain [46, 47]. Furthermore, the intensity of photosensitivity and phonosensitivity positively correlate with headache intensity [46]. There is a clustering of hypersensitivity symptoms in migraine, with presence of olfactory hypersensitivity predicting presence of visual hypersensitivity and presence of cutaneous allodynia associating with phonosensitivity [27, 48]. This interplay amongst migrainous hypersensitivities may result from activation of subcortical brain regions that receive convergent inputs and then project broadly to various cortical brain regions involved in unimodal pain, visual, auditory, and olfactory processing as well as hetermodal processing areas responsible for integration of multiple sensory modalities.[49, 20•]

Electrophysiologic Studies of Sensory Processing in Migraine

Electrophysiologic recordings in migraineurs help quantify and characterize abnormalities in cortical excitability. Several visual evoked potential studies have found migraineurs to have atypical symmetry and amplitude of the initial negative and positive cortical responses to visual stimuli [5–9]. There may be differences in the latency of brainstem auditory evoked responses in migraineurs during the interictal state as well [4, 10, 50]. High frequency oscillations of the somatosensory evoked potential also vary in migraneurs as compared to healthy controls, representing differences in activation of thalamocortical pathways [11].

One of the most consistent findings, irrespective of the stimulus modality, is an impairment of habituation in interictal migraineurs as compared to healthy controls. Habituation is defined by diminished responsiveness to subsequent recurring stimuli [51]. The counterpart of habituation is sensitization, a process in which the perception of sensory stimuli is amplified. These adaptive mechanisms utilize changes in synaptic strength to facilitate or dampen stimulation-induced responses, thereby preferentially focusing the attention of cortical processing to new or unique sensory stimuli over that of background “noise” [51]. Multiple studies demonstrate that interictal migraineurs have a lack of normal habituation and that they develop sensitization in response to recurrent visual, auditory, and

somatosensory stimuli. In migraineurs, the evoked potentials recorded from primary sensory cortices in response to visual or auditory stimulation increases with repetition [8, 52]. This lack of habituation is characteristic of the interictal state of migraine [13, 51]. Similar results have been generated for primary somatosensory cortex and brainstem responses using brainstem auditory evoked potentials [51]. The lack of habituation in migraineurs spans multiple modalities and involves cortical, thalamocortical, and brainstem circuits. Interestingly, this phenomenon of decreased habituation appears to normalize just before and during a migraine attack [12]. Magnetic evoked potentials are higher amplitude in migraineurs as compared to healthy controls [53]. Lastly, transcranial magnetic stimulation studies investigating motor thresholds and thresholds for generation of phosphenes with stimulation of occipital cortex suggest that migraineurs have greater cortical excitability than non-migraine controls [54]. Taken together, these studies demonstrate that migraineurs have a lack of habituation during the interictal period and increased cortical excitability both during and between migraine attacks.

Several physiologic studies have demonstrated a likely role of multisensory integration in production and interaction of migraine symptoms. Exposing migraineurs to light while measuring pain thresholds within locations innervated by the trigeminal nerve results in more sensitivity to painful stimuli than if the light is absent [31, 55]. Exposure to light does not change pain thresholds in non-migraine controls. Similarly, application of pain within the trigeminal nerve territory causes increased sensitivity to light in migraineurs, but not healthy controls [55, 56]. In animal studies, recurrent inflammatory stimulation of the dura (a potential animal model of migraine) leads to increased sound hypersensitivity and cutaneous allodynia [57].

Functional and Structural Neuroimaging of Sensory Processing Regions in Migraine

Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies in migraineurs have identified atypical stimulus-induced activations and functional connections between various regions of the brain that participate in sensory processing [15, 16, 58]. While there are differences in the patterns of brain activations and functional connectivity between studies likely related to the heterogeneity of the migraine population, differences in severity of illness, attack frequency, migraine duration, and therapy, these studies collectively show that there are ictal and interictal differences in sensory processing between migraineurs and non-migraineurs.

Interictal Pain Evoked Brain Activations in Migraineurs

Painful stimuli activate similar brain regions in migraineurs as compared to controls [59]. Regions within brainstem, thalamus, insular cortex, cingulate, somatosensory, premotor, and prefrontal cortices, basal ganglia, cerebellum, hippocampus, and parahippocampus are activated in response to painful stimulation in migraineurs and controls [59, 60]. These regions, often collectively called the "pain matrix", are responsible for the multiple aspects of pain processing including ascending and descending modulation, affective-motivational, sensory discriminative, integrative, and cognitive aspects [59, 61]. However, the extent to which these regions are activated differ in migraineurs compared to headache-free controls. Between attacks, migraineurs demonstrate greater thermal pain-induced activation of dorsolateral prefrontal cortex, postcentral gyrus, temporal pole, middle cingulate gyrus, anterior cingulate gyrus, lentiform nucleus, hippocampus, fusiform gyrus, parahippocampal gyrus, and subthalamic nucleus [59] compared to headache-free controls [59, 60, 62]. Meanwhile, controls have greater thermal pain-induced activation of precentral gyrus, secondary somatosensory cortex, superior temporal gyrus, pons, and ventral medulla as compared to interictal migraineurs [59, 62, 63]. Migraineurs who have allodynia during migraine attacks have less interictal activation of the nucleus cuneiformis in response to painful thermal stimuli compared to healthy controls [63]. Since the nucleus cuneiformis is a key region of the descending pain modulatory system, a system that is predominantly pain inhibiting, hypoactivation of this region suggests that lack of pain inhibition contributes to the development of allodynia during a migraine attack.

That there is increased pain evoked activation of prefrontal, postcentral, and cingulate gyri in migraineurs may suggest accentuated discriminative, cognitive, and emotional pain processing in response to painful stimuli as compared to controls. Similarly, reduced activation of pontine and ventral medullary structures may signify reduced descending pain modulation in migraineurs. Together, these findings support the notion that migraineurs experience enhanced pain perception, perhaps due to an imbalance of pain facilitation and pain inhibition.

Resting State Changes in Metabolism and Functional Connectivity in Migraineurs

In the absence of external stimuli, there are cortical metabolic differences in migraineurs as compared to headache-free controls. 18 F-fluorodeoxyglucose PET studies demonstrate hypometabolism of the insula, anterior and posterior cingulate, superior temporal, premotor, prefrontal, and primary somatosensory cortices in migraineurs as compared to controls during the headache-free resting state [64]. This set of

brain regions is similar to the set of brain regions that is hyperactive during pain-evoked stimulation in migraineurs. Therefore, these derangements in metabolism may reflect their overactivity during evoked stimulation and contribute to abnormal pain processing in migraineurs.

In a resting state functional connectivity MRI study, stronger connectivity between the periaqueductal gray and thalamus, insula, supramarginal, precentral, and postcentral gyri was found in interictal migraineurs compared to controls [17]. In a study of patients with chronic migraine, atypical functional connectivity was observed between anterior insula and the periaqueductal gray, pulvinar nucleus, mediodorsal thalamus, cingulate cortex, middle temporal cortex, precuneus, and inferior parietal cortex, and between the amygdala and superior frontal and occipital cortices [58]. There also appears to be stronger connectivity between the temporal pole in migraineurs and the anterior cingulate, insula, somatosensory cortex, thalamus, and caudate nucleus, and between the parahippocampal area and anterior cingulate and prefrontal cortices [60]. The diffuse nature of these atypical functional connectivity patterns amongst sensory processing brain regions may provide the substrate for abnormal processing of diverse sensory stimuli. The pulvinar nucleus, for example, which demonstrates atypical functional connectivity with the periaquaductal grey, is a region that sends divergent projections to heteromodal cortical areas involved in processing pain and visual stimuli [34].

There are also differences in functional connectivity of descending brainstem pain modulatory centers in migraineurs with and without severe ictal allodynia. Migraineurs with severe ictal allodynia have stronger functional connectivity between the periaqueductal grey and the pons, thalamus, cerebellum, posterior insula, inferior temporal, and inferior and superior frontal cortices as compared to migraineurs without ictal allodynia [63]. Not only is there hypoactivation of the nucleus cuneiformis in response to thermal stimuli in migraineurs as compared to controls during the interictal period [63], but migraineurs with severe ictal allodynia have stronger connectivity between the nucleus cuneiformis and the pons, midbrain, ventral medulla, cerebellum, thalamus, precuneus, inferior and superior parietal, inferior and middle frontal, superior temporal, and occipital cortices [42]. Taken together, these studies demonstrate abnormal pain processing and atypical functional connectivity in brainstem modulatory centers and other regions of the brain subserving sensory processing, motor planning, cognition, and affect.

Multisensory Processing in Migraineurs

Functional imaging studies have investigated multisensory processing in migraineurs during the ictal and interictal period. Migraineurs exposed to light have greater activation of visual cortex as compared to controls. This effect is accentuated in the presence of thermal painful stimulation of the face [65]. These data suggest that migraineurs have a cortical hyperexcitability to light and that concomitant painful stimulation further enhances this visual cortex hyperexcitability, demonstrating the co-modulation of visual and somatosensory stimuli in the migraine brain. Similarly, exposing the migraineur to odor during a migraine attack accentuates activation of pain processing and sensory integration areas [28]. During spontaneous migraines, migraineurs demonstrate increased activity in the rostral pons, insula, amygdala, temporal pole, superior temporal gyrus, and cerebellum in response to rose odor when compared to the interictal state [28]. Several fMRI studies have demonstrated enhanced stimulus-induced activation and atypical functional connectivity of the temporal pole, a region that integrates auditory, olfactory, visual, and painful stimuli [60, 66–68]. Furthermore, exposure to visual and olfactory stimuli has been shown to activate brainstem regions, indicating a potential mechanism by which visual and auditory stimuli could trigger migraine attacks [28, 69]. Subcortical regions that receive convergent inputs and project to unimodal and heteromodal brain regions are activated in migraineurs in response to sensory stimulation. These regions include the pulvinar and medial dorsal nucleus of the thalamus [17, 58] and basal ganglia [14].

Conclusions

Migraineurs differ from non-migraineurs in their processing of sensory stimuli. Aberrant cortical excitation, lack of habituation, and sensitization of somatosensory and pain pathways are evident between migraine attacks and may relate to the severity and accompanying symptoms that occur during the attack. Increased sensitivity to sensory stimuli, lower discomfort thresholds to such stimuli, and migraine attack triggering via visual, auditory, and olfactory stimuli serve as evidence for atypical basal functioning of multiple regions in the migraine brain. Neurophysiology studies and functional imaging studies provide evidence that migraineurs have altered sensory processing in both unimodal and multimodal areas. Future studies are needed to further define the mechanisms underlying atypical processing of sensory stimuli in migraineurs between and during migraine attacks.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Andrea M. Harriott declares no potential conflicts of interest.

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