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Multisensory Integration in Migraine

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Abstract

Purpose of Review—Migraine attacks consist of head pain and hypersensitivities to somatosensory, visual, auditory and olfactory stimuli. Investigating how the migraine brain simultaneously processes and responds to multiple incoming stimuli may yield insights into migraine pathophysiology and migraine symptoms.

Recent Findings—The presence and intensity of hypersensitivity to one stimulus type are positively associated with the presence and intensity of hypersensitivities to other stimuli and to headache intensity. Furthermore, exposure to visual, auditory and olfactory stimuli can trigger migraine attacks. These relationships suggest a role for multisensory integration in migraine.

Summary—Multisensory integration of somatosensory, visual, auditory and olfactory stimuli by the migraine brain may be an important concept for understanding migraine.

Keywords

Migraine; Multisensory Integration; Sensitization; Cutaneous Allodynia; Migraine Pathophysiology

Introduction

Migraine attacks consist of moderate to severe headache, nausea and/or vomiting, and hypersensitivities to somatosensory, visual, auditory and olfactory stimuli. Hypersensitivities to stimuli are most prominent during individual migraine attacks. However, many migraineurs have less prominent but persistent hypersensitivities to stimuli between migraine attacks (i.e. interictally). Hypersensitivities result in common migraine symptoms such as cutaneous allodynia, photophobia, phonophobia, and osmophobia.

Hypersensitivities to individual stimuli and the headache of migraine are not independent symptoms. Exposure to a specific stimulus results not only in hypersensitivity to that stimulus, but may also result in further enhancement of hypersensitivities to other stimuli (e.g. exposure to light leads to greater hypersensitivity to touch of the skin) and may contribute to worsening headache intensity. Understanding the interactions that occur when

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processing multiple external stimuli and the interactions between processing of these stimuli and activation of the trigeminal system may help to explain migraine symptoms and mechanisms by which exposure to visual, auditory and olfactory stimuli can trigger full-blown migraine attacks. Thus, investigation of migraine symptoms and their underlying mechanisms should take an integrative approach.

The term “multisensory integration” as used in this manuscript refers to the process by which the brain has the ability to co-process and co-modulate different modes of incoming stimuli in order to derive a single perception of one’s environment. Rather than processing each mode of sensory stimuli in isolation (e.g. visual inputs, auditory inputs, olfactory inputs) and deriving individual sensory perceptions, multisensory integration allows the human brain to consider multiple sensory stimuli simultaneously and construct a unified perception of the environment based upon these simultaneous inputs.

In this manuscript, data demonstrating migraineurs’ aberrant unisensory processing of somatosensory, visual, auditory and olfactory stimuli will be briefly reviewed. A potential role of multisensory integration in migraine is then discussed.

Aberrant Unisensory Processing in Migraine

People with migraine process and perceive individual modes of sensory stimuli differently than people without migraine. Typically, migraineurs are hypersensitive to somatosensory, visual, auditory and olfactory stimuli. In the following sections, evidence for atypical unimodal sensory processing in migraine is discussed.

Somatosensory

The majority of migraineurs has physiologic evidence for somatosensory hypersensitivity (i.e. reduced cutaneous pain thresholds) and have symptoms of somatosensory hypersensitivity (i.e. cutaneous allodynia) during migraine attacks. During migraine, migraineurs have lower pain thresholds to thermal and mechanical cutaneous stimuli compared to the interictal period. [1] Cutaneous hypersensitivity is found within trigeminally-innervated body locations (e.g. forehead) as well as outside of the trigeminal distribution (e.g. upper and lower extremities). Symptoms of cutaneous allodynia occur in approximately 2/3 of migraineurs during a migraine attack. [2–4] Allodynic migraineurs perceive normally non-painful stimuli to be painful, and thus may feel pain with light touch of the skin, wearing tight collars or neckties, shaving the face, wearing earrings, and brushing the hair. Symptoms of extracephalic allodynia, typically involving the upper extremity, are present in up to 26.5% of migraineurs with allodynia. [5]

A proportion of people with migraine have less prominent but persistent hypersensitivity to cutaneous stimulation between migraine attacks. Interictal cutaneous pain thresholds are lower in episodic and chronic migraine patients compared to non-migraine controls. [6–7] Interictal episodic and chronic migraineurs are more sensitive to cold and heat stimuli, even in the absence of overt symptoms of cutaneous allodynia. [6] It is anticipated that migraineurs with lower interictal pain thresholds are predisposed to further sensitization and development of allodynia during migraine attacks. [6]

Functional and structural imaging of migraineurs suggests the presence of atypical structure, function, and connectivity of pain matrix regions, aberrations that may relate to abnormal pain processing and thus atypical perceptual judgments of potentially noxious somatosensory stimuli. Atypical function of the brainstem descending pain modulatory system may specifically relate to the development of allodynia in migraineurs. In support of this theory, migraineurs are found to have hypofunctional activation of the nucleus cuneiformis in response to pain and migraineurs with allodynia have atypical functional connectivity of the periaqueductal gray and nucleus cuneiformis compared to migraineurs without allodynia. [8–10]

Visual

Most migraineurs have increased sensitivity to light and other visual stimuli during migraine attacks. Estimates of photophobia prevalence during a migraine range from 50%–90%. [11–12] Exposure to light and visual patterns may cause generalized discomfort and increase the intensity of headache pain. Migraineurs have an increased sensitivity to normal lighting conditions, to bright light (e.g., sunlight), and to flickering lights (e.g., fluorescent lights, computer screen). [13] Even after 72 hours of migraine freedom, migraineurs have significantly lower visual discomfort thresholds compared to non-migraine controls. [14] Compared to controls and patients with tension-type headache, migraineurs have increased interictal sensitivity to white light (unfiltered light), high-wavelength light (red), and low-wavelength light (blue). [15].

Neuroimaging has shown migraineurs to have atypical structure of visual motion processing areas (e.g. cortical thickening and lower fractional anisotropy) and greater activation of visual cortex and motion sensitive temporal cortex regions in response to visual stimulation. [16–18]

Auditory

Phonophobia afflicts approximately 52% to 82% of patients during a migraine attack. [11–12] Exposure to noise may cause generalized discomfort and increase the pain of the migraine headache. Approximately 3/4 of migraine patients report interictal hypersensitivity to sound. [19] Quantitative testing shows that the interictal migraineur is more sensitive to sound compared to the non-migraine control and that the migraine patient is even more sensitive to sound during a migraine attack compared to the interictal period. [14, 19–20]

Olfactory

Prevalence estimates for osmophobia during migraine range from 25%–43%. [21–23] Patients most commonly report osmophobia to scents (e.g., perfumes, deodorants), foods (e.g., coffee, fried foods, onion), and cigarette smoke. [21–22] Interictal olfactory hypersensitivity is present in approximately 35% of migraineurs and about ½ of migraineurs report the presence of odor-triggered migraines. [24]

An interictal PET study of migraineurs with odor hypersensitivity showed that in response to odorants and compared to non-migraine controls, migraineurs had greater activation in the left temporal pole and less activation in frontal, temporo-parietal, posterior cingulate and

locus ceruleus regions. [25] Compared to migraineurs between attacks, those during an attack have greater activation in several olfactory, limbic and pain matrix regions including regions in the amygdala, insula, temporal pole, superior temporal gyrus, cerebellum, and rostral pons. [26]

Is Migraine a Disorder of Multisensory Integration?

There is ample evidence supporting that migraineurs have atypical unimodal processing of somatosensory, visual, auditory and olfactory stimuli. In the following paragraphs, multisensory integration is defined and the potential importance of multisensory integration in migraine is discussed.

Multisensory Integration

“Multisensory Integration” describes the brain’s ability to co-process and co-modulate multiple sensory stimuli in order to develop a unified perception of one’s environment. This is opposed to the brain processing stimuli of each modality (e.g. auditory, visual, olfactory, somatosensory) completely in isolation, deriving a separate perception of the environment within each modality, and only then summing each perception to derive a comprehensive perception of the environment. It is easy to imagine the evolutionary advantage of multisensory integration over unisensory processing. For example, the human trying to survive in the wild is likely to have greater success if he can quickly determine the threat from a predator based upon the combined and co-modulated perception of the predator according to what he sees, hears, smells and feels. As Stein and Stanford state, the “integrated product” that is the result of combining sources of information “reveals more about the nature of the external event and does so faster and better than would be predicted from the sum of its individual contributors.” [27] In support of this statement, multiple stimuli delivered in close temporal and spatial proximity result in greater neural activation than the sum of each stimuli delivered independently. [28] There is evidence for multisensory integration of somatosensory, visual, auditory and olfactory stimuli.

Integration of sensory inputs of different modalities involves co-modulation of sensory inputs by other sensory inputs. For example, what a person hears can be directly altered by what a person sees. Examples of such modulation include spatial ventriloquism, auditory driving/auditory flash-illusion, and the McGurk effect. In the auditory flash-illusion, a single flash of light is perceived as two flashes when it is paired with two beeps. [29–30] In the McGurk effect, watching the lips of someone speaking changes what a person hears, even when the sound being produced by the speaker remains unchanged. Thus, when watching and listening to a person rhythmically vocalizing “bah, bah, bah”, you hear “bah, bah, bah”. However, if that person continues to vocalize “bah, bah, bah” but their lips make movements of “fah, fah, fah”, you will hear “fah, fah, fah”. (If you find this hard to believe, then watch the video clip of the BBC Horizon programme on YouTube demonstrating the McGurk effect [31]) Although auditory flash-illusion and the McGurk effect are examples of how multisensory integration results in misperceptions, they demonstrate the power of multisensory integration when evaluating sensory inputs. Multisensory integration may also result in multisensory enhancement and thus improved perceptions of the environment. Multisensory integration may reduce the interval between encoding of sensory stimuli and

motor responses to such stimuli (for example allowing a person to more quickly escape from danger) and may speed sensory processing by enhancing the initial subthreshold component of a typical response to unisensory stimulation. [27, 32] Human experiments have demonstrated that exposure to one mode of sensory stimuli may enhance the perception of other types of stimuli. For example, motor responses to visual cues are faster if the visual cue is preceded by an ipsilateral auditory stimulus (<300 ms between the auditory cue and onset of visual target). [33–34] As another example, exposure to a brief sound enhances the perceived intensity of a subsequent flash of light. [35] This enhancement in perceived visual intensity is independent of the location of the auditory cue. Furthermore, exposure to low-intensity sounds enhances the detection of simultaneous but task-irrelevant light. [36]

Numerous cortical brain regions and subcortical regions contain neurons that receive inputs from several different senses and are thus considered to be multisensory convergence zones. Multisensory convergence zones exist within the superior colliculus, basal ganglia, premotor cortex, posterior parietal cortex, inferior prefrontal cortex and posterior superior temporal sulcus. [27, 37] Increasingly, there are data suggesting the presence of multisensory influences on brain areas traditionally considered to be sensory specific. Driver and Noesselt suggest several “rival” explanations for these findings: 1) an extreme view that all brain areas are multisensory or at least contain multisensory interneurons; 2) there are transitional multisensory zones adjacent to sensory-specific cortex; and 3) multisensory influences on sensory-specific cortex are due to feedback influences from multisensory convergence zones. [37]

Is Multisensory Integration an Important Concept in Migraine?

Since headache and hypersensitivity symptoms of migraine co-occur and since the presence and severity of one symptom can impact the presence and intensity of other migraine symptoms, it is inadequate to consider each migraine symptom in isolation. Consideration of the entire symptom complex and investigation into how each symptom impacts other migraine symptoms may lead to a better clinical and scientific understanding of migraine.

There are several lines of evidence to support the notion that multisensory integration is an important concept in migraine:

1. The presence and intensity of one migraine symptom is associated with the presence and intensity of other migraine symptoms.
 - Migraine headache intensity correlates positively with the presence of photophobia, phonophobia and osmophobia. [38]
 - The intensity of photophobia and phonophobia associate positively with the intensity of headache pain. [38]
 - Exposing the migraineur to noise can trigger headache and increase migraine pain intensity. [39] In one study, 94% of migraine subjects reported that sound increased their headache intensity. [40]

- Migraineurs with olfactory hypersensitivity are more likely to have odor-induced migraines, more frequent migraine attacks, and are more likely to have visual hypersensitivity. [24]
- Migraineurs with allodynia have lower sound aversion thresholds compared to migraineurs without allodynia. [41]
- Migraineurs have lower sound discomfort thresholds when experiencing a migraine headache compared to migraineurs without headache. [40]
- Increasing severity of pain is associated with greater sensitivity to sound. [40]

2. In migraineurs, experimental trigeminal pain leads to reductions in visual discomfort thresholds and greater activation of visual cortex in response to light.

Interictal migraineurs have lower light discomfort thresholds compared to non-migraine controls. Exposing interictal migraineurs to trigeminal pain, (e.g. by applying an ice-block to the center of the forehead), results in further reductions in visual discomfort thresholds in migraineurs. [42–43] However, exposing control subjects to the same noxious stimulation has no effect on their visual discomfort thresholds. Furthermore, PET imaging of interictal migraineurs in response to light with and without concomitant application of trigeminal pain demonstrates greater activation of visual cortex in the presence of concomitant pain compared to exposure to light without trigeminal pain. [44]

3. Exposure to bright light reduces pain thresholds within trigeminally innervated locations and potentiates activation of visual cortex in migraineurs.

Pain thresholds tend to be lower in interictal migraineurs compared to non-migraine control subjects. Exposing the interictal migraineur to light causes further reductions in pain thresholds, a phenomena not observed in non-migraine subjects. [42, 45] Pain thresholds drop when noxious stimulation is given over the emergence of the supraorbital, infraorbital, mental and greater occipital nerves and over the temporal muscles.

4. Olfactory stimulation causes greater activation of limbic structures and the rostral pons in migraineurs.

Exposing a migraineur to olfactory stimuli (e.g. rose odor) during a migraine attack results in stronger activation (compared to control subject activation) of several regions that play roles in pain processing, olfactory processing, and processing of other sensory stimuli including: amygdala, insular cortex, temporal pole, superior temporal gyrus, rostral pons and cerebellum. [26] These results suggest that the migraine brain has increased sensitivity to odors during the migraine attack and that exposure to odors can activate brain regions responsible for processing of other types of sensory stimuli.

5. Aberrant activation and connectivity of multisensory convergence zones in migraine neuroimaging studies.

Functional imaging studies of migraine have identified aberrant activation and atypical functional connectivity with a region in the temporal pole, a region that may be a multisensory convergence zone responsible for processing visual, olfactory and auditory stimuli. [25, 46] For example, noxious heat stimulation of the skin results in greater activation in the anterior temporal pole in interictal migraineurs (compared to controls) with even greater activation during migraine compared to the interictal period. [46] Furthermore, a temporal pole region has enhanced functional connectivity to pain processing regions and to other multisensory convergence zones in migraineurs. [46]

6. *Triggering of migraine attacks by auditory, olfactory, and visual stimuli.*

Approximately 40% of migraineurs have migraine attacks triggered by visual stimuli, 50%-75% have attacks triggered by noise, and 50% report that perfumes or other odors trigger their migraines. [13, 47–48] Exposure to odors during a migraine results in activation of a region in the rostral pons, a region that has been implicated in the headache of migraine and a region that has been considered as a possible “migraine generator”. [26, 49–50] Activation of a rostral pons region following exposure to odor could explain how odors trigger migraine attacks.

7. Repeated dural inflammation induces phonophobia and allodynia in rats.

Recurrent inflammatory stimulation of the rat dura leads to decreases in the intensity of sound required to elicit the startle reflex (i.e. sound hypersensitivity) and results in periorbital allodynia, both occurring in close temporal proximity. [51]

Conclusions

By definition, migraine consists of multiple sensory symptoms that include a combination of somatosensory, visual, auditory and olfactory symptoms. The presence and intensity of one migraine symptom positively correlates with the presence and intensity of other migraine symptoms. When studying migraineurs in the lab, exposure to one mode of sensory stimulation alters the sensitivity to concurrent sensory stimuli of other modalities. Finally, exposure to visual, auditory and olfactory stimuli may trigger a migraine attack. These observations suggest a role for multisensory integration in migraine pathophysiology.

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References

1. Burstein R, Yarnitsky D, Goor-Aryeh I, et al. An association between migraine and cutaneous allodynia. *Ann Neurol*. 2000; 47:614–624. [PubMed: 10805332]
2. Ashkenazi A, Silberstein S, Jakubowski M, Burstein R. Improved identification of allodynic migraine patients using a questionnaire. *Cephalalgia*. 2007; 27:325–329. [PubMed: 17376108]
3. 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; 70:1525–1533. [PubMed: 18427069]

4. Lipton RB, Bigal ME, Ashina S, Burstein R, Silberstein S, Reed ML. Cutaneous allodynia in the migraine population. *Ann Neurol*. 2008; 63:148–158. [PubMed: 18059010]
5. Mathew NT, Kailasam J, Seifert T. Clinical recognition of allodynia in migraine. *Neurology*. 2004; 63:848–852. [PubMed: 15365135]
6. Schwedt TJ, Krauss MJ, Frey K, Gereau RW. Episodic and chronic migraineurs are hypersensitive to thermal stimuli between migraine attacks. *Cephalalgia*. 2011; 31:6–12. [PubMed: 20974609]
7. 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; 104:693–700. [PubMed: 12927642]
8. Moulton EA, Burstein R, Tully S, Hargreaves R, Becerra L, Borsook D. Interictal dysfunction of a brainstem descending modulatory center in migraine patients. *PLoS ONE*. 2008; 3:e3799. [PubMed: 19030105]
9. Mainero C, Zhang W-T, Kumar A, Rosen B, Sorensen AG. Mapping the spinal and supraspinal pathways of dynamic mechanical allodynia in the human trigeminal system using cardiac-gated fMRI. *Neuroimage*. 2007; 35:1201–1210. [PubMed: 17336547]
10. Schwedt TJ, Larson-Prior L, Coalson RS, Nolan T, Mar S, Ances BM, Benzinger T, Schlaggar BL. Allodynia and descending pain modulation in migraine: a resting state functional connectivity analysis. *Headache*. 2012; 52:P66.
11. Russell MB, Rasmussen BK, Fenger K, Olesen J. Migraine without aura and migraine with aura are distinct clinical entities: a study of four hundred and eighty-four male and female migraineurs from the general population. *Cephalalgia*. 1996; 16:239–245. [PubMed: 8792035]
12. Wober-Bingol C, Wober C, Karwautz A, Auterith A, Srim M, Zebeholzer K, Aydinkoc K, Kienbacher C, Wanner C, Wessely P. Clinical features of migraine: a cross-sectional study in patients aged three to sixty-nine. *Cephalalgia*. 2004; 24:12–17. [PubMed: 14687007]
13. Friedman DI, De ver Dye T. Migraine and the environment. *Headache*. 2009; 49:941–952. [PubMed: 19545255]
14. Main A, Dowson A, Gross M. Photophobia and phonophobia in migraineurs between attacks. *Headache*. 1997; 37:492–495. [PubMed: 9329231]
15. Main A, Vlachonikolis I, Dowson A. The wavelength of light causing photophobia in migraine and tension-type headache between attacks. *Headache*. 2000; 40:194–199. [PubMed: 10759921]
16. Vincent M, Pedra E, Mourao-Miranda J, Bramati IE, Henrique AR, Moll J. Enhanced interictal responsiveness of the migrainous visual cortex to incongruent bar stimulation: a functional MRI visual activation study. *Cephalalgia*. 2003; 23:860–868. [PubMed: 14616927]
17. Antal A, Polania R, Saller K, Morawetz C, Schmidt-Samoa C, Baudewig J, Paulus W, Dechent P. Differential activation of the middle-temporal complex to visual stimulation in migraineurs. *Cephalalgia*. 2010; 31:338–345. [PubMed: 20693230]
18. Granziera C, DaSilva AFM, Snyder J, Tuch DS, Hadjikhani N. Anatomical alterations of the visual motion processing network in migraine with and without aura. *PLoS Medicine*. 2006; 3:e402. [PubMed: 17048979]
19. Vingen JV, Pareja JA, Storen O, White LR, Stovner LJ. Phonophobia in migraine. *Cephalalgia*. 1998; 18:243–249. [PubMed: 9673802]
20. Ashkenazi A, Mushtaq A, Yang I, Oshinsky ML. Ictal and interictal phonophobia in migraine – a quantitative controlled study. *Cephalalgia*. 2009; 29:1042–1048. [PubMed: 19735532]
21. De Carlo D, Dal Zotto L, Perissinotto E, Gallo L. Osmophobia in migraine classification: a multicentre study in juvenile patients. *Cephalalgia*. 2010; 30:1486–1494. [PubMed: 20974611]
22. Zanchin G, Dainese F, Trucco M, Mainardi F, Mampreso E, Maggiani F. Osmophobia in migraine and tension-type headache and its clinical features in patients with migraine. *Cephalalgia*. 2007; 27:1061–1068. [PubMed: 17681021]
23. Kelman L. Osmophobia and taste abnormality in migraineurs: a tertiary care study. *Headache*. 2004; 44:1019–1023. [PubMed: 15546266]
24. Demarquay G, Royet JP, Giraud P, Chazot G, Valade D, Ryvlin P. Rating of olfactory judgements in migraine patients. *Cephalalgia*. 2006; 26:1123–1130. [PubMed: 16919063]

25. Demarquay G, Royet JP, Mick G, Ryvlin P. Olfactory hypersensitivity in migraineurs: a H₂¹⁵O-PET study. *Cephalalgia*. 2008; 28:1069–1080. [PubMed: 18727640]
- **26. Stankewitz A, May A. Increased limbic and brainstem activity during migraine attacks following olfactory stimulation. *Neurology*. 2011; 77:476–482. This study showed the migraine brain to have increased sensitivity to odors during the migraine attack and that exposure to odors can activate brain regions responsible for processing of other types of sensory stimuli and can activate a rostral pons region that may participate in the generation of migraine attacks. [PubMed: 21775739]
27. Stein BE, Stanford TR. Multisensory integration: current issues from the perspective of the single neuron. *Nature Reviews Neuroscience*. 2008; 9:255–266.
28. Meredith MA, Stein BE. Interactions among converging sensory inputs in the superior colliculus. *Science*. 1983; 221:389–391. [PubMed: 6867718]
29. Shams L, Kamitani Y, Thompson S, Shimojo S. Sound alters visual evoked potentials in humans. *Neuroreport*. 2001; 12:3849–3852. [PubMed: 11726807]
30. Shams L, Kamitani Y, Shimojo S. Illusions. What you see is what you hear. *Nature*. 2000; 408:788. [PubMed: 11130706]
31. [Accessed 05 March 2013] Try The McGurk Effect! - Horizon: Is Seeing Believing? - BBC Two. 2010. <http://www.youtube.com/watch?v=G-IN8vWm3m0>
32. Rowland BA, Quessy S, Stanford TR, Stein BE. Multisensory integration shortens physiological response latencies. *The Journal of Neuroscience*. 2007; 27:5879–5884. [PubMed: 17537958]
33. McDonald JJ, Ward LM. Involuntary listening aids seeing: evidence from human electrophysiology. *Psychol Sci*. 2000; 11:167–171. [PubMed: 11273425]
34. Schmitt M, Postma A, de Haan E. Interactions between exogenous auditory and visual spatial attention. *Q J Exp Psychol*. 2000; 53:105–130.
35. Stein BE, London N, Wilkinson LK, Price DD. Enhancement of perceived visual intensity by auditory stimuli: a psychophysical analysis. *J Cog Neurosci*. 1996; 8:497–506.
36. Lovelace CT, Stein BE, Wallace MT. An irrelevant light enhances auditory detection in humans: a psychophysical analysis of multisensory integration in stimulus detection. *Cognitive Brain Research*. 2003; 17:447–453. [PubMed: 12880914]
37. Driver J, Noesselt T. Multisensory interplay reveals crossmodal influences on ‘sensory-specific’ brain regions, neural responses, and judgements. *Neuron*. 2008; 57:11–23. [PubMed: 18184561]
38. Kelman L, Tanis D. The relationship between migraine pain and other associated symptoms. *Cephalalgia*. 2006; 26:548–553. [PubMed: 16674763]
39. Martin PR, Todd J, Reece J. Effects of noise and a stressor on head pain. *Headache*. 2005; 45:1353–1364. [PubMed: 16324168]
40. Vanagaite Vingen J, Pareja JA, Storen O, White LR, Stovner LJ. Phonophobia in migraine. *Cephalalgia*. 1998; 18:243–249. [PubMed: 9673802]
41. Ashkenazi A, Yang I, Mushtaq A, Oshinsky ML. Is phonophobia associated with cutaneous allodynia in migraine? *J Neurol Neurosurg Psychiatry*. 2010; 81:1256–1260. [PubMed: 20562466]
42. Drummond PD. Photophobia and autonomic responses to facial pain in migraine. *Brain*. 1997; 120:1857–1864. [PubMed: 9365375]
43. Drummond PD, Woodhouse A. Painful stimulation of the forehead increases photophobia in migraine sufferers. *Cephalalgia*. 1993; 13:321–324. [PubMed: 8242724]
44. Bouilloche N, Denuelle M, Payoux P, Fabre N, Trotter Y, Geraud G. Photophobia in migraine: an interictal PET study of cortical hyperexcitability and its modulation by pain. *J Neurol Neurosurg Psychiatry*. 2010; 81:978–984. [PubMed: 20595138]
45. Kowacs PA, Piovesan EJ, Werneck LC, Tatsui CE, Lange MC, Ribas LC, da Silva HP. Influence of intense light stimulation on trigeminal and cervical pain perception thresholds. *Cephalalgia*. 2001; 21:184–188. [PubMed: 11442552]
- *46. Moulton EA, Becerra L, Maleki N, Pendse G, Tully S, Hargreaves R, Burstein R, Borsook D. Painful heat reveals hyperexcitability of the temporal pole in the interictal and ictal migraine states. *Cerebral Cortex*. 2011; 21:435–448. In this fMRI study, noxious heat stimulation of the skin resulted in greater activation of the anterior temporal pole in interictal migraineurs compared to controls, with even greater activation during migraine compared to the interictal period. This

temporal pole region, a region that may have a role in multisensory integration, has enhanced functional connectivity to pain processing regions and to other multisensory convergence zones in migraineurs. [PubMed: 20562317]

47. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia*. 2007; 27:394–402. [PubMed: 17403039]
48. Martin PR, Reece J, Forsyth M. Noise as a trigger for headaches: relationship between exposure and sensitivity. *Headache*. 2006; 46:962–972. [PubMed: 16732842]
49. Weiller C, May A, Limmroth V. Brain stem activation in spontaneous human migraine attacks. *Nat Med*. 1995; 1:658–660. [PubMed: 7585147]
50. Afridi SK, Matharu MS, Lee L. A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate. *Brain*. 2005; 128:932–939. [PubMed: 15705611]
51. Oshinsky ML, Gonzalez DM, Maxwell C. Repeated dural inflammation induces phonophobia. *Cephalalgia*. 2009; 29:116.

Key Points

1. In addition to headache and nausea/vomiting, migraine attacks consist of hypersensitivities to somatosensory, visual, auditory and olfactory stimuli.
2. Migraine is associated with aberrant unimodal processing of somatosensory, auditory, visual, and olfactory stimuli.
3. The presence and intensity of one migraine symptom modulates the presence and intensity of other migraine symptoms.
4. Investigation of how the migraine brain co-processes and co-modulates multiple sensory stimuli (i.e. multisensory integration) may yield insights into migraine mechanisms and migraine symptoms beyond the insights gained from investigation of unimodal processing.