Multisensory Integration in Migraine: Recent Developments

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Abstract

There are well-documented unimodal sensory differences in migraine compared to control groups both during, and between migraine attacks. There is also some evidence of multisensory integration differences in migraine groups compared to control groups, however the literature on this topic is more limited. There are interesting avenues in the area of visual-vestibular integration, which might have practical implications e.g. motion sickness and nausea in migraine. Recent work has been investigating the possibility of visual-auditory integration in migraine, and found possible differences in the susceptibility to the sound-induced flash illusion in particular, which could give insights into relative excitability of different areas of the cortex, and also into mechanisms for the illusions themselves. This review updates the most recent literature and also highlights potentially fruitful areas of research to understand one of the most common neurological disorders.

Keywords: Migraine; Visual; Auditory; Sound-induced flash illusions; Vestibular; Vertigo

Introduction

Migraine is a common neurological disorder (Steiner et al., 2003). Migraine attacks can be very debilitating (Stovener et al., 2007), and the overall cost to the individual and to society is large. The International Headache Society diagnostic criteria for migraine (Headache Classification Subcommittee of the International Headache Society, 2013) require at least two of the following four criteria: unilateral location (only one side of the head), pulsating quality to the headache, the headache has moderate to severe pain intensity, and the headache is aggravated by physical activity.

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The headache is to be accompanied be at least one of the following: nausea and/or vomiting; photophobia (a heightened sensitivity to light) and phonophobia (a heightened sensitivity to sounds). There are large idiosyncratic differences in the manifestation of the disorder (e.g. Sacks, 1992), and migraine is a cycling disorder, with differences within an individual fluctuating over time (e.g. Khalil, 1991). There is no objective way of measuring migraines, for example, by recording brain activity directly, and so diagnosis often relies on self-report over a long period of time, which may be relatively unreliable. Misdiagnosis between different headache disorders is probable, and there are even cases of occipital epilepsy being misdiagnosed as migraine (Panayiotopolos, 1999).

Migraine is characterised by differences in sensory processing. The International Headache Society (Headache Classification Subcommittee of the International Headache Society, 2013) classification criteria includes photophobia (aversion to light) and phonophobia (aversion to sound) during the attack itself in order to qualify as a migraine. Differences in sensory processing have been found between attacks (interictally) as well. Whilst the bulk of the research so far has been unimodal (within one sensory system) there is also the possibility that there are multisensory differences in migraine. This review explores the literature on multisensory processing in migraine.

A Brief Consideration of Unimodal Sensory Differences in Migraine

Migraine aura is one of the most obvious sensory phenomena associated with migraine: a sensory hallucination preceding the onset of the headache itself, which can be in any modality, but is most commonly visual (Steiner et al., 2003). Other hallucinations reported include vestibular and auditory (Cal and Bahmad, 2008), auditory and olfactory (Miller et al., 2015). There is also osmophobia (sensitivity to smells) reported during the migraine attack and 84% of individuals reporting olfactory hallucinations have migraine (Coleman et al., 2011).

There are differences in visual processing in migraine groups compared to control groups on performance measured in between migraine attacks (interictally). Specifically, there is poorer performance on the whole in migraine (interictally measured) compared to control groups for visual (for a review, see O'Hare and Hibbard, 2016) and auditory tasks (Agessi et al., 2014). There is also evidence of olfactory dysfunction in migraine compared to controls (Hirsch, 1992).

In summary, there are differences in sensory processing between migraine and control groups. In general, although migraine groups appear to be more sensitive to sensory stimulation compared to headache-free groups, migraine groups tend to show poorer performance on sensory tasks. Of particular interest to multisensory research, there are associations between the senses in migraine groups, particularly in the aura stage of the attack. Demarquay et al., (2006) showed that those with

migraine reporting more olfactory hypersensitivity (based on a questionnaire and rating odours) were also those reporting increased visual sensitivity and greater attack frequency, than those without odour sensitivity. This could be due to a variety of reasons: one possibility is that migraine is more excitable in general compared to controls, another possibility is that excitation in one sensory area, (in this case olfactory) increases the overall excitation of other sensory areas, in this case visual. There could also be interactions between the senses, in the form of differences in multisensory integration in migraine groups.

Multisensory integration in migraine

Schwedt (2013a) reviewed the literature looking at audiovisual, pain and auditory, visual and vestibular associations in migraine groups, and to date, this remains the only review of multisensory integration in migraine. However, studies specifically investigating multimodal integration are increasing since Schwedt's (2013a) review.

There are multiple possibilities for why multisensory integration might be different in migraine. One possibility is differences in midbrain areas, where multisensory neurons are located. The superior colliculus is a site of multisensory neurons in the midbrain, which also has connections to the trigeminal nerves (Harting et al., 1997). The superior colliculus projects to cortical areas, including the parietal, temporal and occipital areas (Selzer et al., 1994), and conversely there is evidence that superior colliculus activity is modulated by cortical areas, for example those around the sylvian fissure (Jiang et al., 2001). In addition, the superior colliculus is a light-sensitive site (Boehnke and Munoz, 2008), and also associated with the control of circadian rhythms (Marchant and Morin, 1998). As light sensitivity is a feature of migraine, and sleep disturbances are listed as a possible trigger (Inamorato et al., 1993), this would imply involvement of the superior colliculus in migraine. However, although this provides evidence that it is possible for multisensory information to be shared between these locations, it is not evidence that the information from different sensory modalities is actually shared at these sites (Meredith, 2002).

It has been suggested that migraine attacks might damage cortical structures, for example the visual cortex (Chronicle and Mulleners, 1994). A thicker cortex might be due to damage (Messina et al., 2013), and increased thickness in the temporal pole in migraine has been reported (Schwedt et al., 2015). There is evidence to suggest that migraine with aura is associated with increased white matter lesions (Kurth et al., 2011), which supports the suggestion that migraine might be a progressive disorder (Lipton and Pan, 2004). If this is indeed the case, then it might be expected that

symptoms change in severity over time, and also that there are secondary symptoms arising as a consequence of the disorder.

Alternatively, migraine sensory differences could be due to differences in processing in the cerebral cortex itself, for example hyperexcitation in the cortex. It might be the case that if an individual with migraine is more sensitive in one modality, this might also be the case in another modality. Schwedt's (2013a) review of multisensory integration in migraine identified the temporal pole and rostal pons as locations of increased activity in migraine groups that might have significant implications for sensory processing. The evidence for each of these possible explanations for differences in multisensory integration in migraine will be considered here.

Somatosensory integration: Pain and the other senses

Pain is an important feature of migraine (Lipton et al., 2001). Schwedt (2013a) made the point that pain and light sensitivity are linked in migraine groups. In the case of migraine, research suggests that the response to visual stimulation increased whilst experiencing painful stimuli. This was achieved by applying ice to the forehead of individuals with migraine, and measuring the level of light at which discomfort was reported. The level of light that was tolerated before discomfort was reported was reduced when ice was applied to the forehead (Drummond and Woodhouse 1993). In addition, mechanically-induced pain increased the susceptibility to discomfort from light (Drummond, 1997). Conversely, migraine patients are less tolerant of painful stimuli after light stimulation (Kowasc et al., 2001).

There is evidence that auditory stimulation increases sensitivity to pain in those with migraine (Vanagaite et al., 1998; Martin et al., 2005, Ashkenazi et al., 2010). Contrary to this, there is evidence that combining sound and electrophysiological stimulation can increase the tolerance to pain in migraine groups (Trinka et al., 2002). This might be due to the warning changing the criterion in this study, as pain was measured based on self-report. Expectation and pain have a complex relationship; however an individual's tolerance to pain can be increased when there is a reliable predictor, or warning of pain (Ploghaus et al., 2003). It is possible that the concurrent sound might have allowed patients to prepare themselves, and thus be more resilient to pain.

Somatosensory heat stimulation to cause pain increases activity to temporal pole (Moulton et al., 2011), which is an area associated with multisensory integration that shows increased activity in migraine groups compared to controls (Schwedt, 2013a). In normal populations, somatosensory sensitivity is greater with either concurrent visual, or vestibular stimulation (Ferre et al., 2015), and the somatosensory cortex is important in multisensory integration (Petrusic et al., 2015). The

somatosensory cortex is thicker in migraine compared to control groups (DaSilva et al., 2007; Kim et al., 2014), and the functional connectivity of pain pathways different in migraine compared to control groups (Schwedt et al., 2014a, Schwedt et al., 2014b, Schwedt et al., 2013b). However, this does not show whether the changes in structure and connectivity are due to repeated exposure to pain in the form of headache, if the migraine patient is more susceptible to pain, or if the structural differences themselves are the causes of the migraine disorder. Petrusic et al., (2014) showed that teenagers with migraine commonly report both visual and somatosensory symptoms during migraine aura (all reported visual symptoms, 60% reported somatosensory). Teenagers with migraine are unlikely to have had the disorder for long enough for them to develop secondary problems from the disorder, and so it seems that the visual and somatosensory symptoms might be an inherent part of the disorder itself.

There is also evidence of massage to the occipital areas alleviating a migraine attack (Piovesan et al., 2007). If migraine can be alleviated by a simple therapy such as massage then this would be immensely beneficial to both the patient and the healthcare system. However, as with pain and concurrent auditory stimulation, it appears that there might be different ways of stimulation that result in different effects in the patient, thus further work is needed in order to develop non-invasive therapies, in particular, identifying the mechanism behind any beneficial effects.

Visual-auditory integration

Yang et al., (2014) studied visual-audio integration in migraine by varying the inter-stimulus interval of visual and auditory stimuli to investigate the length of the integration window. There was evidence of greater integration window in migraine compared to control groups when the visual stimulus was presented before the auditory signal consistent with the idea that these populations are hyperexcitable (Yang et al., 2014). Audiovisual stimuli lead to suppression effects: longer intervals (200 - 300ms) between audio and visual stimuli tend to result in suppression of the second stimulus, as the two are no longer thought to be linked (Meredith et al., 1987). Yang et al., (2014) demonstrated less suppression from audio stimuli on visual stimuli in migraine compared to control groups when there was this longer inter-stimulus interval, also consistent with the idea of hyperexcitation in migraine.

There is research on the integration of visual and auditory information in migraine, commonly using multisensory illusions, for example the ‘sound-induced flash illusion’, or 'flash-beep illusion'. Presenting two beeps with one flash tends to make participants more likely to misperceive a single flash as two flashes (fission illusion). Conversely, presenting a single beep with two flashes tends to

result in participants being more likely to report a single flash (fusion illusion). It is thought that susceptibility to the sound-induced flash illusion depends on the relative activity in the auditory and visual processing areas (Mishra et al., 2007). The relative excitation can even be manipulated: Bologini et al., (2011) demonstrated using anodal (thought to be excitatory) transcranial direct current stimulation (tDCS) the susceptibility to fission illusions decreases, concluding that if excitatory tDCS is given to the occipital areas then perceptual weighting to these areas increases relative to auditory areas. This illusion has been suggested to be a useful tool to explore migraine sensory processing (Maccorca et al., 2013), as susceptibility to one or other illusion will show a dominance for one modality over another, due to differences in excitation over the different areas.

Brighina et al., (2014) demonstrated less susceptibility to sound-induced flash illusions in episodic migraine in the ictal (headache) phase. Chronic migraine showed less susceptibility to the illusion throughout testing sessions. This shows an increased ability to discriminate between the stimuli during the ictal phase of a migraine attack (or much of the time, in the case of chronic migraine), however in the non-ictal phase temporal integration seems to operate over a longer time interval in migraine compared to control groups. It is possible that the results of the Yang et al., (2014) and Brighina et al., (2014) studies could be explained by a dominance for the visual cortex: an increase in visual cortex excitability relative to auditory cortex excitability. Alternatively, it could be the case that the longer time window for integration in migraine compared to control groups is due to the gating of sensory information. This will be discussed in more detail below.

Di Marco et al., (2015) showed that children with migraine show no difference in sound-induced flash illusions compared to controls, however, children tended to report more illusions overall compared to adults. This could suggest that multisensory disorders develop as migraine progresses, increasing the weighting to vision and thus increasing the susceptibility to the illusion. Alternatively this result might be because the test is subjective, and children are more suggestible than adults, rather than there being differences with their sensory faculties.

Visual-vestibular integration

Migraine is also associated with differences in vestibular information processing - there is a specific subtype called vestibular migraine, described most commonly by patients as feelings of "unsteadiness" and balance problems, as well as sensations of spinning and rocking (Cohen et al., 2011). A disturbance of visual-vestibular input can result in an experience of vertigo. Vertigo is defined by Brandt (2013) as "spatial disorientation, misperception of motion, and postural imbalance induced by unusual visual stimulation or visual dysfunction". Vertigo, also described as

dizziness, is commonly associated with migraine, in fact there is a specific disorder called migrainous vertigo (von Brevem et al., 2004), which is characterised by eye movements called positional nystagmus at the acute stage of the disorder (Phillips et al., 2010). Nystagmus is most commonly seen in normal observers when the eyes follow a moving target and then quickly saccade back, repeatedly, for example gazing out of the window of a moving train. This can occur also in the absence of a moving target, and is useful in diagnosing disturbances of the vestibular system, e.g. see Dix-Hallpike Manoeuvre (Dix and Hallpike, 1952). The Dix-Hallpike Manoeuvre involves positioning the head in such a manner that the fluid in the inner ear canals is moved around, which tends to elicit nystagmus from the eyes in the case of a disorder of the vestibular system. Bertholon et al., (2006) report a case of migraine being cause of vertigo in one patient, which was characterised by aegeotropic (upward) left horizontal nystagmus. Boldingh et al., (2013) tested a variety of oculomotor and vestibular responses in two migraine groups: Those with vertigo and those without. The migraine-with-vertigo group showed abnormal results compared to migraine-without-vertigo on both Romberg's test, and the Dix-Hallpike Manoeuvre, both tests of vestibular function. Approximately 2/3 migraine-with-vertigo showed sign of vestibular impairment, but in addition, approximately 1/3 migraine-without-vertigo also showed signs of vestibular impairment (Boldingh et al., 2013), suggesting that vestibular disorder is common in migraine, even in those without vertigo.

Vertigo is due to a mismatch between visual and vestibular information (Brandt, 2013, page 33). There appears to be susceptibility to vertigo in migraine groups, which is not limited to those diagnosed as suffering from migraine-with-vertigo (Boldingh et al., 2013). Additionally, Tomanovic et al., (2010) showed that 13% of those with a vestibular disorder also suffered from migraine. Migrainous vertigo is difficult to discriminate from labyrinthine disorders, such as Menière's disease (Shepard, 2006). Brantberg et al., (2011) suggested that the only real difference to discriminate the two is the hearing loss that is present in Menière's disease but not associated with migrainous vertigo. Lechner et al., (2014) reported that it is possible to discriminate the type of vertigo disorder based on the time course of positional horizontal nystagmus, whether the origin is migraine, or a problem with the ear canal (canalolithiasis). Migraine groups show the symptoms of Menière's disease, without the obvious cause canalolithiasis. This would suggest that there is some trouble with integrating correct sensory signals in the migraine group, rather than a problem with the sensory signals themselves, as is the case in Menière's disease.

In addition to the sensation of vertigo being associated with migraine, visual stimulation can induce motion sickness more in migraine than control groups (Drummond and Granston, 2004).

Additionally, it has been demonstrated that visual input can create differences in postural sway in migraine and control groups (Imaizumi et al., 2014). The stimulus used was the snake illusion, a static pattern that creates a strong illusory motion signal. This was a subtle effect, and only seen after the eyes were closed, not when they remained open, and differences were seen after viewing the pattern, not during the presentation. The increased motion after effect has been reported previously in migraine compared to control groups (Shepherd, 2006). Imaizumi et al. (2014) suggested that the increased susceptibility to postural sway in migraine groups after viewing this pattern was due to difficulty integrating visual and vestibular information, but the authors did not elaborate on a possible mechanism for this. It is possible that a dominance for vision would increase postural sway, if stationary vestibular signals are being 'overruled' by the visual inputs signalling motion.

One potential mechanism has been suggested under different circumstances, by Dell'Osso et al., (2002). This was a report of a case study of a migraine patient, who reported seeing typical scotoma and fortification spectra, before his attack, the difference being these illusions started oscillating sideways. On a separate occasion he reported diplopia (double vision) as well. Dell'Osso et al., (2002) suggested that this was due to a failure to suppress oculomotor efferent copies: When the eyes move, a copy of the motor information from the ocular muscles is relayed back to the brain, so that the eye movement can be discounted from the movement of the retinal image, and if this signal is not adequately suppressed this would lead to substantial distortions in the perception. It could be a failure of efferent copy suppression that might cause the increased illusory motion reported by Imiazumi et al., (2014) on viewing the rotating snakes. Additionally, as the efferent copy is important to the vestibular system, this might be the cause of increased postural sway in migraine. It must be highlighted that this is purely speculation at this point, however if there were a problem with the efferent copy of motor signals from the eye muscles then it should be the case that there are other motor problems in migraine compared to control groups. Migraine is indeed associated with disorders of the motor system: Those with Tourette's syndrome are four times more likely than the general population to experience migraine (d'Onofrio et al., 2012). Migraine and restless leg syndrome, and migraine and hemichorea (involuntary movements) also co-occur more frequently than would be expected by chance (d'Onofrio et al., 2012). These authors suggested the involvement of the extrapyramidal system in migraine, as the onset of Parkinson's disease tends to stop migraine. Therefore, it might be the case not only that the different sensory modalities are active together more in migraine than control groups, but the disorder might also link activity between the sensory and motor systems.

A mechanism for multisensory disorders in migraine: integration over time in migraine groups

Sensory integration involves combining signals over time, and there is some indirect evidence to suggest greater integration of sensory signals in those with migraine compared to control groups (DaSilva et al., 2007; Kim et al., 2014; Schwedt et al., 2014a, Schwedt et al., 2014b, Schwedt et al., 2013b). Motion discrimination involves integration of a stimulus over time, and migraine groups are poorer at global motion tasks compared to controls (Antal et al., 2005; McKendrick et al., 2006; Ditchfield et al., 2006; Shepherd et al., 2012; Braunitzer et al., 2012; Tibber et al., 2014). There is evidence to suggest audio-visual integration operates over a longer time window in migraine compared to control groups (Yang et al., 2014). This is of interest as susceptibility to the sound-induced flash illusion is influenced by applying tDCS to modulate the length of the integration window (Cecere et al., 2015), which is thought to be controlled by alpha band oscillations in the cortex. A mechanism for a longer integration window might be related to the frequency and power of the alpha band oscillations, which is thought to control the flow of visual information processing (e.g. Jensen et al., 2014). Alternatively the apparently longer integration window could be due to an imbalance between sensory modalities, for example a dominant visual modality. It is possible that the hyperexcitation found in migraine is due to the alpha band oscillations being slower in migraine compared to headache-free individuals - this would lead to a greater window of time in which stimuli could be integrated together.

Palinopsia is the preservation of images, after the original has disappeared. These hallucinations are not the same as after-images in normal subjects, as they can consist of entire objects, and be much later than the original was seen (Bender et al., 1968). Patients with epilepsy and also those with certain cancers of the brain can report palinopsia (Bender et al., 1968). Neurological patients such as those with migraine also report more cases of palinopsia compared to the general population, and this is especially the case for those with migraine with aura (Belcastro et al., 2011). Although palinopsia itself appears unimodal, it is the time-course of this phenomenon that is of interest. Palinopsia operates over a very long time (in terms of the timescales involved in sensory processing) - the hallucinations can consist of stimuli the patient is currently viewing, or has seen minutes or even hours previously. Why, and how, a stimulus from minutes before should be integrated into the current visual experience remains unexplained, but would require an explanation involving sensory memory processes. However, this phenomenon provides some suggestion that the hyperexcitation thought to be a characteristic in migraine can result in the integration of visual information over a very long time period, considering the timescales usually involved in sensory processing.

Conclusion

There are clear sensory processing differences in migraine compared to control groups both during and in between migraine events. During an attack, migraine groups have an increased sensitivity to sensory stimuli, indeed this is part of the classification criteria for the disorder (Headache Classification Subcommittee of the International Headache Society, 2013). Despite increased sensitivity, there appears to be paradoxically poorer performance in migraine compared to control groups on a range of sensory tasks, e.g. vision (O'Hare and Hibbard, 2016), auditory (Agessi et al., 2014) and olfactory tasks (e.g. Hirsch 1992; Synder and Drummond, 1997). In light of the unimodal differences in sensory performance, it seems logical that there might be differences in multisensory performance in migraine groups. Recent work has demonstrated integration of visual and auditory information in migraine over a longer time window. Vestibular differences are not usually considered in the context of multisensory integration, however, there is an association between vertigo and migraine. As vertigo arises from a mismatch between visual and vestibular information, this is important to consider when investigating multisensory integration in migraine. It might be worth knowing if this information is also integrated in similar brain areas as the other sensory modalities.

Candidate locations have been suggested for the integration of multisensory information in migraine, however, it is important to know what these suggested locations for multisensory integration in the brain are doing with the incoming information. For example, although the temporal pole has been implicated in multisensory information processing, particularly integrating the pain of migraine with other sensory experiences, it is unclear whether this is a point at which information simply converges, or if this location is responsible for the weighting of information from different senses.

There is some evidence for a longer multisensory integration window in migraine groups compared to control groups (e.g. Yang et al., 2014). One possibility for this is alpha band oscillations, alternatively this might be due to dominance of the visual modality over others, for example due to hyperexcitation in the visual cortex. There is evidence that the window of integration of sensory information can be affected by neurostimulatory techniques (Cecere et al., 2015), and tRNS (transcranial random noise stimulation) shows evidence of lasting improvement in sensory performance (Camilleri et al., 2014), this is a possibly fruitful area of research for the development of therapy.

Multisensory integration in migraine is an underexplored area on the whole, given the unimodal differences between migraine and control groups. However, there is evidence of a new interest in this area, suggesting possible differences in multisensory integration in migraine groups compared

to controls. More research is needed to find out the extent of multisensory integration differences, both to develop basic understanding and also new therapies.

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