Migraine and motion sickness: what is the link?

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ABSTRACT

The brainstem is a structurally complex region, containing numerous ascending and descending fibres that converge on centres that regulate bodily functions essential to life. Afferent input from the cranial tissues and the special senses is processed, in part, in brainstem nuclei. In addition, brainstem centres modulate the flow of pain messages and other forms of sensory information to higher regions of the brain, and influence the general excitability of these cortical regions. Thus, disruptions in brainstem processing might evoke a complex range of unpleasant symptoms, vegetative changes and neurovascular disturbances and that, together, form attacks of migraine. Migraine is linked with various co-morbid conditions, the most prominent being motion sickness. Symptoms such as nausea, dizziness and headache are common to motion sickness and migraine; moreover, migraine sufferers have a heightened vulnerability to motion sickness. As both maladies involve reflexes that relay in the brainstem, symptoms may share the same neural circuitry. In consequence, subclinical interictal persistence of disturbances in these brainstem pathways could not only increase vulnerability to recurrent attacks of migraine but also increase susceptibility to motion sickness. Mechanisms that mediate symptoms of motion sickness and migraine are explored in this paper. The physiology of motion sickness and migraine is discussed, and neurotransmitters that may be involved in the manifestation of symptoms are reviewed. Recent findings have shed light on the relationship between migraine and motion sickness, and provide insights into the generation of migraine attacks.

Keywords: migraine; motion sickness; serotonin

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Abbreviations:

CGRP = calcitonin gene-related peptide; **fMRI** = functional magnetic resonance imaging; **GTN** = glyceryl tinitrate; **5-HT** = serotonin; **NK1** = neurokinin 1; **NTS** = nucleus tractus solitarius; **PAG** = periaqueductal grey; **PET =** Positron emission tomography; **PPE** = plasma protein extravasation.

1. Introduction

The brainstem is structurally and functionally complex, comprising numerous ascending and descending neural pathways and nuclei that regulate functions essential to life (Standring, 2004). Afferent input from the cranial tissues and the special senses is processed, in part, in the brainstem, and brainstem pain modulation centres modify nociceptive sensations before they arrive at their subcortical and cortical destinations. Thus, it is not surprising that recent theories of migraine have focused on the brainstem as a source of the neurovascular disturbances and symptoms that accompany attacks (Lance and Goadsby, 2005; Lambert and Zagami, 2009).

Various co-morbid conditions, which necessarily involve brainstem circuitry, have been linked with migraine such as sleep apnoea (Proceta and Dalessio, 1995), asthma (Medina and Diamond, 1976) and stroke (Lidegaard, 1995), but the closest fit in terms of symptoms would appear to be motion sickness. These symptoms arise due to a mismatch between visual, proprioceptive or vestibular cues of motion, possibly to warn the body of a potential threat to homeostasis. The conflicting central sensory input evokes physiological disturbances that resemble effects of poisoning, and results in pre-emptive nausea and vomiting (Triesman, 1977; Money, 1990). Numerous structures, pathways and mechanisms are implicated in the complex neurophysiology of motion sickness (Crampton, 1990; Harm, 1990; Yates, Miller and Lucot, 1998), but the brainstem appears to play a pivotal coordinating role.

The essential mediator for movement-induced motion sickness is the vestibular apparatus (Yates et al., 1998), as animals and humans with no functional vestibular apparatus do not develop motion sickness during rotation or when placed in low-gravity environments associated with the exploration of space (Crampton, 1990; Igarashi, 1990; Money, 1990). Visually-induced motion sickness does not involve

direct vestibular stimulation but, nevertheless, involves converging sensory inputs (vestibular, visual, somatosensory) that are at variance with sensory integration from the 'neural store' (memory, past experience) (Takedo, Morita, Horii, Nishiike, Kitahara and Uno, 2001). This neural mismatch results in motion sickness.

As headache, nausea, dizziness, drowsiness and perceived changes in body temperature are common to migraine and motion sickness (Marcus, Furman and Baleban, 2005), the same neural pathways may be active in both conditions. The manifestation of these symptoms involves reflexes that relay in the brainstem, possibly in nuclei that become active during migrainous attacks (Weiller, May, Limmroth, Jŭptner, Kaube, Schayck and Diener, 1995). Subclinical excitability in these brainstem reflexes could increase vulnerability to repeated attacks of migraine, and could increase susceptibility to motion sickness. Aspects of motion sickness related to migraine, and the implications of this relationship, are discussed below.

2. Mechanisms of migraine

Migraine is a complex neurological disorder characterized by headache and associated symptoms, including nausea and vestibular disturbances (Headache Classification Subcommittee of the International Headache Society, 2004). Brain imaging studies have recently provided new insights into the mechanism of attacks. However, the neural events that increase susceptibility to migraine and that link trigger factors, such as stress and hormonal changes, with the initiation of attacks, are still poorly understood (Bolay, Reuter, Dunn, Huang, Boas and Moskowitz, 2002; Williamson and Hargreaves, 2001; Lambert and Zagami, 2009).

2.1. Brainstem and hypothalamic involvement

Symptoms of brainstem and hypothalamic disturbance often precede migraine, and focal brainstem activity develops during attacks (Weiller et al., 1995). Positron

emission tomography (PET) indicates that activity in certain brainstem and midbrain nuclei (e.g., nucleus raphe dorsalis, nucleus raphe magnus, locus coeruleus and periaqueductal grey matter) increases in spontaneous attacks of migraine (Weiller et al., 1995; Bahra, Matharu, Buchel, Frackowiak and Goadsby, 2001; Diener, 1997, 1999). Consistent with these findings, Raskin, Hosobuchi and Lamb (1987) observed migraine-like headache in 15 of 175 patients following implantation of electrodes into the midbrain periaqueductal grey or somatosensory region of the thalamus for treatment of intractable pain. In contrast to migraine, attacks of cluster headache and other trigeminal autonomic headaches are associated with hypothalamic rather than brainstem activation (May, Bahra, Büchel, Frackowiak and Goadsby, 1998; Bahra et al., 2001; May, 2003; May, 2009). However, this dissociation may not be clearcut, as Denuelle, Fabre, Payoux, Chollet and Geraud (2007) recently recorded increased activity in the hypothalamus in addition to the pons using $H_2^{15}O$-PET in seven patients during spontaneous attacks of migraine without aura. Activity persisted in these regions after headache was relieved following treatment with sumatriptan. Denuelle et al. proposed that the persistence of hypothalamic activity after headache relief might indicate the activation of a nociceptive generator or an antinociceptive mechanism in the hypothalamus. In particular, the persistence of hypothalamic activity after sumatriptan had relieved the pain might implicate this part of the brain in the generation of migraine attacks, as this would explain the frequent recurrence of headache following treatment with sumatriptan (Weiller et al., 1995).

Increased activity on high resolution PET was also observed in the left dorsal pons, in the thalamus contralateral to pain, and in the right anterior cingulate, posterior cingulate, cerebellum, insula, prefrontal cortex, and temporal lobes during spontaneous migraine headache (Afridi et. al., 2005a). In a related study, Afridi et al.

(2005b) administered glyceryl trinitrate (GTN) intravenously to 24 migraine sufferers and 8 healthy controls. All migraine sufferers experienced mild headache during the GTN infusion, which eventually developed into typical migraine headache. $H_2{}^{15}O$-PET revealed brainstem activation in the dorsal lateral pons during the migraine attack. Activation was ipsilateral to the side of headache in the right- and left-sided groups, and bilateral with a left-sided tendency in the bilateral group. Based on these findings, Afridi et al. proposed that the lateralization of pain in migraine may reflect lateralized brain dysfunction.

In general, such findings have led to the concept that the midbrain and brainstem is the migraine "generator". Specifically, it was proposed that an abnormality might lead to an imbalance in brainstem regulation of cerebral blood vessels and pain in migraine sufferers (Weiller et al., 1995). Consistent with this notion, PET revealed activation of cerebral structures corresponding to the rostral brainstem and intra- and extracranial blood vessels during an attack of migraine without aura following administration of 1.2g GTN in a man with a history of migraine and cluster headache (Bahra et al., 2001). Bahra and colleagues proposed that vasodilatation may be neurally-driven from brainstem activation (there was no apparent activation in the hypothalamus). As noted above, however, the hypothalamus might also be involved in the generation of migraine (Denuelle et al., 2007), perhaps via activation of hypothalamic nuclei and their connections with those in the brainstem (Lance, 1989).

2.2. The trigeminovascular system in migraine

As the brain itself is largely insensitive to pain, intracranial pain is probably generated from intracranial blood vessels (Lance and Goadsby, 2005). These vessels are supplied with sympathetic, parasympathetic and sensory nerve fibres (Edvinsson and Uddman, 2005). Intense activation of trigeminal pain pathways in cluster

headache and migraine may initiate parasympathetic reflexes in the superior salivatory nucleus, resulting in the release of the vasodilator vasoactive intestinal polypeptide and the manifestation of facial symptoms such as ipsilateral flushing and lacrimation (Edvinsson and Uddman, 2005; Knight, 2005). In the extreme, the intracranial vasodilatation evoked by these reflexes may compress sympathetic vasoconstrictor fibres that travel with the internal carotid artery through the carotid canal, ultimately releasing sympathetic vasoconstrictor tone and aggravating vasodilatation. In such instances, compression of perivascular trigeminal nociceptive fibres in the carotid canal could act as a secondary source of pain.

The trigeminal nerve contains sensory and motor components but the sensory component, in particular, appears to be associated with migraine pathophysiology (Williamson and Hargreaves, 2001; Borsook, Burstein, Moulton and Becerra, 2006). The trigeminal nerve, the fifth and largest of the cranial nerves, has three divisions: the ophthalmic, maxillary and mandibular. The sensory fibres of all three divisions enter the brainstem and project to nuclei in the pons or medulla, or enter the spinal trigeminal tract. Sensory information from the face and forehead, including pain, thermal and tactile sensations, are conveyed to higher brain centres via this nerve.

Branches of the trigeminal nerve also innervate cerebral blood vessels and the dura mater. Specifically, a collection of cell bodies in the trigeminal ganglion regulates blood flow in the pain-sensitive large cranial vessels and dura mater (O'Conner and van der Kooy, 1986; May and Goadsby, 1999), the pia mater (Mayberg, Langer, Zervas and Moskowitz, 1981), forebrain and the rostral basilar artery (Arbab, Wiklund and Svendgaard, 1986). Nerve fibres that project from the peripheral and central arms of the trigeminovascular system provide pathways for the transmission of pain signals from cranial vessels to brain centres involved in pain

sensation (Borsook et al., 2006), thereby providing the framework for trigeminal nociceptive activity to dilate cranial vessels. This may operate by two means: a trigeminal-parasympathetic reflex that dilates extracranial blood vessels; and a neurogenic inflammatory process that involves release of neuropeptides such as calcitonin gene-related peptide (CGRP) from trigeminal nerve terminals (Lambert, Bogduk, Goadsby, Duckworth and Lance, 1984; Goadsby, Lambert and Lance, 1986). An interaction between trigeminal-parasympathetic vasodilatation and neurogenic inflammation could then establish a vicious circle, driven by trigeminal nociceptive discharge. What initially triggers the trigeminovascular reflex in migraine is unclear but one possibility could be the release of inflammatory mediators within the brain parenchyma or supporting tissues. After the provoking stimulus is removed, sensitization of trigeminal nerve fibres evoked by the inflammatory response may cause pain to persist (Macfarlane, 1993).

Neuropeptides released during neurogenic inflammation activate mast cells, vascular endothelial cells and platelets, resulting in the further release of extracellular inflammatory mediators. This chemical cascade of activated cells and inflamed tissue may lead to hyperalgesia and pain (Moskowitz, 1993; Silberstein, 2003). Neurogenic inflammation could also contribute to the scalp tenderness associated with migraine headache. Tenderness to mechanical stimulation of the scalp persists for up to a week after episodes of migraine (Drummond, 1987), implying that pain mechanisms such as neurogenic inflammation and central sensitization outlast the headache itself and may act as a latent source of pain during the headache-free period.

Neurogenic inflammation is characterized by two distinct processes – plasma protein extravasation (PPE) and neurogenic vasodilatation. Peroutka (2005) evaluated data from animal models of neurogenic inflammation in relation to the human

condition. PPE is mediated by tachykinins (e.g., substance P) and endothelin-3 whereas neurogenic vasodilatation is mediated primarily by CGRP. Peroutka noted that inhibitors of PPE identified in animal studies were ineffective in the acute treatment of migraine. However, CGRP antagonists have met with greater success (Ho et al., 2008; Olesen et al., 2004), suggesting that neurogenic vasodilatation, rather than PPE, plays a key role in migraine pathophysiology.

Migraine has long been considered a vascular headache (Wolff, 1948; Lance, 1993; Williamson and Hargreaves, 2001). Dilatation of extracranial vessels during attacks (Drummond and Lance, 1983; Iversen, Nielsen, Olesen and Tfelt-Hansen, 1990) may be mediated, at least in part, by release of CGRP from trigeminal nerve terminals as levels were found to be elevated in the external jugular vein (Goadsby, Edvinsson and Ekman, 1990). In animal models of the migraine aura, focal injury or chemicals applied to the cerebral cortex initiate a wave of neural discharge that spreads slowly across the cortex, followed in its wake by depression of neural activity. This wave of "spreading depression" activates trigeminal nerves that innervate meningeal and cerebral blood vessels, leading to PPE and vasodilatation in the dura mater (Moskowitz, 1984). CGRP-containing sensory receptors activated by spreading depression in the anterior and/or posterior circulation may be responsible for the pain component of certain attacks (Vincent and Hadjikhani, 2007). A similar process in the cerebellum might account for symptoms such as dysarthria, ataxia, and dizziness during attacks of migraine (Vincent and Hadjikhani, 2007).

CGRP is a powerful dilator of cranial blood vessels (Edvinsson, Ekman, Jansen, McCulloch and Uddman, 1987). This may be an important source of pain in migraine, as Ho and colleagues (2008) found that the vasoconstrictive effect of a CGRP antagonist (telcagepant) was as effective as the anti-migraine drug zolmitriptan in

treating migraine headache. These findings support the view that migraine headache may be a disorder characterized by distension of cerebral blood vessels. Additionally, the throbbing quality of migraine headache, the sometimes conspicuous dilatation of extracranial vessels, and the recognized pain sensitivity of cranial blood vessels, further imply that migraine may be linked to trigeminovascular mechanisms (Lance, 1993). Lance proposed that an unstable trigeminovascular reflex, in conjunction with a fault within pain control pathways, might underlie the pathogenesis of migraine.

Despite the appealing logic of increased cranial blood flow resulting in migraine headache, vasodilatation does not necessarily equate to headache. For example, the headache of migraine with aura frequently begins while regional cerebral blood flow is diminished (Olesen, Friberg, Skyhøj Olsen, Iversen, Lassen, Andersen and Karle, 1990). Furthermore, the presence of severe headache during the vasoconstrictive state that follows subarachnoid haemorrhage suggests that vasodilatation is an 'epiphenomenon' to nociceptive discharge rather than the cause of it (Macfarlane, 1993). A recent study by Schoonman and co-workers (2008) has further challenged the view that migraine headache is necessarily associated with dilatation of cranial vessels. Headache developed in 20 migraineurs several hours after intravenous administration of GTN. A sensitive and non-invasive imaging technique, 3-Tesla magnetic resonance angiography, was used to measure blood flow in the basilar and internal carotid arteries and to estimate the diameter of the external carotid and major intracranial arteries. No change was observed in the diameter of blood vessels or in basilar and internal carotid artery blood flow during attacks provoked by GTN. In sum, it seems reasonable to conclude that disturbances in the extracranial circulation may aggravate, but not necessarily initiate, the headache during attacks of migraine (Drummond and Lance, 1983).

Susceptibility to migraine presumably is due to an underlying innate 'migraine threshold', delicately balanced between excitation and inhibition of neural networks that mediate symptoms of migraine. A pain modulation pathway that extends from the midbrain periaqueductal gray matter incorporates the serotonergic nucleus raphe magnus in the medulla and locus coeruleus in the pons (Lance and Goadsby, 2005). Stimulation of the locus coeruleus leads to changes in intracranial and extracranial blood flow and the discharge of noradrenaline from the adrenal medulla (Goadsby, 1985), which may be a catalyst for the discharge of serotonin systemically (Lance and Goadsby, 2005). Together, these changes may trigger symptoms of migraine.

The periaqueductal grey (PAG), the locus coeruleus and the raphe nuclei are major components of the descending pain modulation pathways. Weiller et al. (1995) found that regional cerebral blood flow in the distribution of the PAG, locus coeruleus and raphe nuclei was greater during migraine, even after pain-relieving treatment, than during the headache-free interval. Although it seems likely that the PAG is linked to the generation of headache, more rigorous research is required to establish whether activation of this area is a cause or consequence of headache. It may be that brainstem activation during attacks is due to trigeminal neuronal discharge (Moskowitz, 1993) rather than driving the increase in trigeminal nerve activity.

2.3. Migraine triggers

Stimulation of the special senses increases the intensity of headache and other symptoms of migraine during (Linde, 2006) and outside attacks (Kowacs, Piovesan, Werneck, Tatsui, Lange, Ribas and da Silva, 2001), and can also trigger attacks (Debney, 1984; Scharff, Turk and Marcus, 1995; Granston and Drummond, 2005). Conversely, head pain increases discomfort to sensory stimulation in migraine sufferers (Drummond and Woodhouse, 1993; Drummond, 1997). Even seemingly

innocuous visual and auditory stimulation commonly aggravates migraine headache (Goadsby, 2001), consistent with the notion of an underlying disturbance of gating mechanisms in the brainstem.   Hypersensitivity of the special senses during migraine attacks may be due to loss of normal inhibitory controls, resulting in increased sensory discomfort and aggravation of headache (Drummond, 1997). This sensitivity to light and noise persists to some extent during the headache-free interval (Drummond, 1986; Vanagaite et al., 1997; Vingen et al., 1998).

Stress, a commonly recognized trigger of migraine (Passchier, 1994; Reynolds and Hovanitz, 2000), may also initiate or intensify attacks, perhaps by acting on an unstable pain control system (Lance, 1993). In particular, stimulation from higher brain centres, such as the cortex or hypothalamus during stress or emotion, or excessive afferent input from the special senses or cranial vessels, may compromise the pain control system in individuals vulnerable to migraine. Other migraine triggers (e.g., hormonal variations or alcohol) could also act upon the pain control system to increase vulnerability to attacks.

2.4. Hyperexcitable nociception in migraine sufferers

Goadsby (2001) suggested that the source of pain in migraine may be more to do with the "abnormal perception of the normal" than the activation of nociceptive pathways in the usual way that pain is generated. For example, disruption of pain modulating processes may contribute to photophobia and phonophobia by removing normal inhibitory gating mechanisms. This release of inhibitory control might also result in sensitization of central nociceptive pathways.

By-and-large, the cranial nociceptive system appears to be more excitable in migraine sufferers than in headache-free controls. For example, vulnerability to headache induced by consumption of cold foods such as ice cream is greater than

usual in migraine sufferers (Raskin and Knittle, 1976; Drummond and Lance, 1984; Fuh et al., 2003; Selekler, Erdogan, and Budak, 2004). Similarly, the prevalence of stabbing, ice pick-like pains is greater in migraine sufferers than controls, and these pains are likely to recur at the usual site of headache (Raskin and Schwartz, 1980; Drummond and Lance, 1984). Drummond and Cuomo-Granston (Drummond and Granston, 2003, 2004, 2005; Granston and Drummond, 2002, 2005; Cuomo-Granston, 2008, 2009) reported that migraine sufferers were more sensitive to painful stimulation of the temple with ice than controls, and more readily developed headache. Head pain intensified photophobia in migraine sufferers but not controls (Drummond and Woodhouse, 1993; Drummond, 1997), an effect that might be relevant to the mechanism of photophobia during attacks. Temporal summation to painful mechanical stimulation of the supraorbital region was found to be greater in migraine sufferers than controls, consistent with induction of wind-up in second-order trigeminal nociceptive neurons (Weissman-Fogel et al., 2003). Moreover, trigeminal nociceptive blink reflexes were hyperexcitable in migraine sufferers during the headache-free interval (Sandrini et al., 2002; Katsarava et al., 2003), and demonstrated evidence of sensitization during attacks (Kaube et al., 2002).

In patients with strictly unilateral migraine, pressure-pain thresholds were found to be lower and pericranial tenderness greater on the symptomatic than nonsymptomatic side during the headache-free interval, and pressure-pain thresholds were lower on both sides than in controls (Fernandaz-de-las-Penas et al., 2008). In addition, pain to palpation over the supraorbital nerve was greater on the symptomatic than nonsymptomatic side of the forehead in patients with strictly unilateral migraine (Fernandaz-de-las-Penas et al., 2009). Caputi and Firetto (1997) also detected mechanical hyperalgesia in the interictal period at distal emergence points of the

supraorbital and greater occipital nerves of migraine sufferers. They reported that the frequency and intensity of migrainous attacks decreased following analgesic blockade of these nerves, particularly in individuals sensitive to pressure at these points. Together, these findings suggest that nociceptive discharge in hyperexcitable cranial nerves may increase susceptibility to migraine.

Cutaneous allodynia and hyperalgesia develops in the distal extremities during the later stages of migraine headache (Burstein, Cutrer, and Yarnitsky, 2000; Burstein, Collins and Jakubowski, 2004; Burstein and Jakubowski, 2004; Levy, Jakubowski and Burstein, 2004; Yarnitsky, Goor-Aryeh, Bajwa, Ransil, Cutre, Sottile and Burstein, 2003). The progression of hyperalgesia from the site of headache to more distal regions implies that sensitization spreads rostally in nociceptive networks as the attack progresses (Burstein et al., 2000). Moreover, pressure-pain thresholds were found to be lower on both sides in migraine sufferers than in controls both over the supraorbital nerves and over peripheral nerve trunks in the upper extremities during the headache-free interval (Fernandaz-de-las-Penas et al., 2009), consistent with persistent generalized sensitization of nociceptive networks in migraine.

2.5. Convergence of nociceptive input in the nucleus tractus solitarius (NTS)

The nucleus tractus solitarius (NTS) receives converging visceral, spinal and trigeminal nociceptive inputs, and is critically involved in medullary reflexes controlling cardiovascular, respiratory and gastrointestinal functions (Benarroch, 2006). In a review of the literature, Boscan, Kasparov and Paton (2002) illustrated the potential for integration of visceral and somatic afferents within the NTS. The immediate response gene *c-fos* plays a role in the alteration of cellular responses to pain signals (Hunt, Pini and Evans, 1987). Boscan et al. cited evidence that cardio-respiratory afferent regions in the NTS receive direct projections from the spinal cord

and express *c-fos* immunoreactivity in response to noxious stimulation of limbs (spinal input), cornea (trigeminal input) and stomach (visceral input). Boscan et al. further studied the interaction between nociceptive and baroreceptive activity in the NTS of rats involving mechanical stimulation of the paw, electrical stimulation of the brachial nerve, and paced microinjections of $GABA_A$ antagonist bicuculline methiodide, substance P, and the neurokinin 1 (NK_1) receptor antagonist CP-99,994 into the NTS. They concluded that somatic nociceptive afferents activate NK_1 receptors which, in turn, enhance the release of GABA in the NTS. This activation inhibits the baroreceptor cardiac reflex and may facilitate the tachycardia and pressor response associated with pain. Based on their electrophysiological findings, Boscan et al. suggested that nociceptive inputs converge on the NTS via multiple afferent pathways. Additionally, other brainstem and midbrain regions, such as the rostal ventrolateral medulla, trigeminal nuclei, parabrachial complex and the PAG, may relay nociceptive information to the NTS.

Similarly, convergence of multiple inputs to the NTS may influence autonomic responses, such as vomiting, to visceral stimuli. For example, activation of vagal and sympathetic afferents during myocardial ischaemia evokes nausea, vomiting, inhibitory cardiac responses (e.g., bradycardia and hypotension) and excitatory cardiac responses (e.g., tachycardia and hypertension) (Longhurst, Tjen-A-Looi and Fu, 2001). Gastrointestinal disturbances and inhibitory cardiovascular responses are thought to be mediated by vagal efferents whereas excitatory cardiovascular responses are regulated by sympathetic efferents. During the vomiting process brainstem outputs include sweating and increased heart rate, a sympathetic response; increased salivation, a parasympathetic response; and motor responses involving contraction of abdominal muscles (Horn, 2008). The association between nausea and the various

responses associated with vomiting is not well understood, but it seems reasonable to assume that nausea involves communication between the brainstem centres that coordinate these responses and forebrain areas such as the extended amygdala (Horn, Ciucci and Chaudhury, 2007), which regulates responses to stress, conditioned flavor aversion and, possibly, anticipatory nausea and vomiting during chemotherapy.

Reciprocal interaction between the NTS and the trigeminal nociceptive system (e.g., Menetrey and Basbaum, 1987; Zerari-Mailly, Buisseret, Buisseret-Delmas, and Nosjean, 2005) could explain why symptoms such as headache develop during the motion sickness induced by optokinetic stimulation, particularly in migraine sufferers (Drummond and Granston, 2004, 2005; Drummond, 2002; Granston and Drummond, 2005; Cuomo-Granston, 2008, 2009). Drummond (2002) found that nausea and headache were greater in migraine sufferers than controls after optokinetic stimulation, and scalp tenderness increased in the most nauseated subjects. Thus, the disturbances responsible for nausea might also sensitize central trigeminal nociceptors or release inhibitory controls on their discharge.

3. The association between motion sickness and migraine

Motion sickness is associated with migraine in children (Barabas, Matthews and Ferrari, 1983; Jan, 1998) and adults (Cutre and Baloh, 1992; Kuritzky, Ziegler and Hassanein, 1981). In fact, approximately two-thirds of migraine sufferers are prone to motion sickness (Baloh, 1997). Genetic factors may underlie the tendency to motion sickness (Reavley, Golding, Cherkas, Spector and MacGregor, 2006; Stern, 1996) and the neuro-otological symptoms of migraine (Baloh, 1997), but whether the same genes are involved in both conditions is uncertain.

Bijveld, Bronstein, Golding and Gresty (2008) found that subjects exposed to visual cues of motion while stationary developed headache more frequently than

during off-vertical axis rotation. They suggested that mechanisms responsible for headache during visual motion might be similar to those of migraine. In a study of 42 migraine sufferers and 39 headache-free controls of similar age- and sex-distribution, a greater proportion of migraine sufferers reported that traveling in cars and buses, reading in the car, playing on playground equipment such as roundabouts, and watching wide-screen movies and movement simulators induced motion sickness (Drummond, 2005a). Moreover, migraine sufferers were more susceptible than controls to symptoms evoked by visual simulation of movement (Drummond, 2002; Drummond and Granston, 2004), implying that migraine is associated with abnormal central integration of visual and vestibular cues.

Females are generally more prone to motion sickness than males (Golding, 2006; Grunfeld and Gresty, 1998), and are especially vulnerable during menstruation (Golding, Kadzere and Gresty 2005). Curiously, female predominance also applies to migraine (Celic, Ekuklu, Tokuc and Utku, 2005; Rasmussen, 1995; Lipton, Stewart, Diamond, Diamond, and Reed, 2001), and menstruation increases vulnerability to migraine. Grunfeld and Gresty (1998) found an association between these female weighted maladies. Female yacht crewmembers who experienced migraine reported greater susceptibility to motion sickness than other crewmembers. Additionally, motion sickness and headache peaked during the ovulatory or menstrual phases of the menstrual cycle, though migraine and motion sickness did not always occur together. Grunfeld and Gresty commented that as symptoms common to both of these disorders are remarkably similar, some of the women may not have distinguished whether their symptoms were due to migraine or motion sickness.

Female sex hormones may, at least in part, predispose susceptible individuals to motion sickness (Golding, 2006) and migraine (Rasmussen, 1995). Hormonal

influences on migraine susceptibility are under much discussion (Herzog, 2007; Loder, Rizzoli and Golub, 2007; MacGregor, Chia, Vohrah and Wilkinson, 1990; Martin, Wernke, Mandell, Ramadan, Kao, Bean, Liu, Zoma and Rebar, 2005; Newman, 2007; Dzoljic, Sipetic, Vlajinac, Marinkovic, Brzakovic, Pokrajac and Kostic, 2002; MacGregor, 1999; Martin and Behbehani, 2006a; 2006b; Silberstein and Merriam, 2000; Gupta, 2004; Gupta, 1994). However, sex hormones do not account entirely for susceptibility to motion sickness as this usually develops prior to puberty. Additionally, susceptibility to motion sickness gradually declines into adulthood, which may indicate habituation to the symptomatic effects of motion over time (Golding, 2006).

The disconcerting nature of motion sickness is a stressful experience for most people. Therefore, as Graaf and Gresty (1998) propose, stress responses may influence the neurochemistry of motion sickness and increase individual susceptibility.

3.1. Vestibular instability

Vertigo and dizziness are cardinal features both of migraine and motion sickness (Marcus, Furman and Baleban, 2005). The presence of these otoneurologic symptoms indicates activation of vestibular pathways. Dizziness and vertigo often accompany migraine attacks (von Brevern, Zeise, Neuhauser, Clarke and Lempert, 2005; Cutrer and Baloh, 1992; Lance, 2000) and are frequently reported during the headache-free interval (Kuritzy, Ziegler and Hassanein, 1981; Lempert and Neuhauser, 2009; Cha et al., 2009). Indeed, around 25% of migraine sufferers experience episodes of vertigo (Baloh, 1997). Collectively, these symptoms suggest that neural connections within vestibular pathways are compromised in migraine sufferers.

Defective calcium channel genes and subunits have been isolated in familial hemiplegic migraine (Baloh, 1997; Gardner, 1999, 2006; Peroutka, Wilhoit and Jones, 1997) and in families with episodic vertigo and ataxia (Baloh, 1997). Mutations in one such gene (CACNA1A) lead to alterations of calcium channel activity in brain cells and, in turn, neurotransmission, which may explain cortical and subcortical neural excitability in individuals with migraine (Gardner, 2006). Furthermore, mutations in CACNA1A may also depress levels of serotonin via effects on ion homeostasis and gene expression (Estevez, 2006). Mutations linked to familial hemiplegic migraine in the genes SLC1A3 and SCN1A have also been identified (Dichgans, Freilinger, Eckstein, Babinin, Lorenz-Depiereuz, Biskup, Ferrari, Herzog, van den Maagdenberg, Pusch and Strom, 2005; Jen, Wan, Palos, Howard and Baloh, 2005). In a recent study, Graves and colleagues (2008) identified three new premature stop codon mutations specific to exon 37A in CACNA1A associated with the expression of episodic ataxia type 2 and, in one family, with the co-occurrence of migraine and ataxia (diagnosed initially as basilar migraine). These mutations may have implications with respect to cerebellar function and symptoms such as vertigo.

Baloh (1997) proposed that an inherited mechanism, similar to that discovered in rare forms of migraine, may account for otoneurologic symptoms that are experienced in the more common varieties of migraine. In particular, a defective calcium (ion) channel, primarily expressed in the brain and inner ear, could lead to reversible hair cell depolarization (following calcium/potassium displacement), resulting in the otoneurologic symptoms experienced during, and outside, attacks.

3.2. Gastrointestinal hypersensitivity

Nausea is generally described as an unpleasant wave-like sensation in the throat, epigastrium or abdomen that often precedes but does not always culminate in

vomiting. The physiological basis of nausea is uncertain, but may involve communication between afferent pathways involved in vomiting (e.g., the chemoreceptor trigger zone, gastrointestinal visceral afferents and/or the labyrinth) (Takeda et al., 1993) and forebrain regions that integrate this sensory input with past experiences and concurrent sensory-motor and emotional activity (Horn et al., 2007). Alternatively, nausea may arise from preparatory activation of motor pathways involved in vomiting in the nucleus NTS and the dorsal motor nucleus of the vagus – the so-called "vomiting" or "emetic" centre (Dahlof and Hargreaves, 1998; Mitchelson, 1992; Takedo et al., 2001). However, it is worth noting that anti-emetics such as the NK_1 and $5-HT_3$ receptor antagonists suppress vomiting more effectively than nausea (Sanger and Andrews, 2006), indicating only partial overlap of mechanisms.

Vagal and sympathetic afferents and vestibular inputs from the labyrinth make direct synaptic contact with the motor pathways involved in vomiting. Vagal afferents that supply the gastrointestinal system project directly to the NTS (Lee, Hohman, Cai, Regalia and Helke, 2001). Vestibular inputs to the NTS were found to come directly from medial and inferior vestibular nuclei in the cat (Yates et al., 1994) and rabbit (Balaban and Beryozkin, 1994). The chemoreceptor trigger zone, located in the area postrema at the floor of the fourth ventricle on the upper surface of the medulla, detects emetic signals via circulating chemical stimuli in plasma and cerebral spinal fluid (Yates, Grėlot, Kermon, Balaban, Jakuš and Miller, 1994). The so-called "vomiting centre" may also receive indirect input via the cerebellum as cerebellovestibular connections project to superior, medial and inferior vestibular nuclei (Standring, 2005). Vomiting involves the sudden and violent expulsion of stomach contents, caused by powerful persistent contraction of abdominal and chest

muscles. Motor pathways involved in the coordination of vomiting originate in the dorsal motor nucleus of the vagus, a general efferent nucleus and the largest parasympathetic nucleus in the brainstem. Approximately 80% of its neurons give rise to the preganglionic efferent parasympathetic fibres of the vagus nerve which, among other targets, supplies the muscles involved in vomiting.

Nausea is more common than vomiting both in migraine (Lance and Goadsby, 2005; MacGregor, 1999) and motion sickness (Benson, 2002). Although nausea and vomiting can be distressing, it is feasible that momentary relief might follow vomiting as it is the body's primary mechanism to rid itself of real or suspected toxins. Anecdotally, this relief is sometimes associated with a reduction in headache during attacks of migraine (Horton, 2010), perhaps through reciprocal communication between the NTS and trigeminal nucleus caudalis.

Nausea is associated with visceral pain following intra-abdominal operations (Andrews, 1992; Mitchelson, 1992) and with irradiation of the abdomen (Gerstner, 1960), possibly because afferent pathways to the NTS and reticular formation are activated following the handling of viscera during operative procedures or because of tissue damage to viscera following radiation therapy (Blair, 1985; Barber and Yuan, 1989). Additionally, head irradiation may raise intracranial pressure due to local oedema and inflammation, which then appears to stimulate nausea and vomiting. Kowalski and colleagues (2006) pointed out that studies investigating nausea generally have focused on mechanisms leading to the subjective experience rather than on neurophysiological activity. In particular, there is a dearth of research with respect to functional imaging of brain activity during nausea and vomiting. As the brain's emetic response is inadequately delineated, cortical imaging techniques such as functional magnetic resonance imaging (ƒMRI) may provide insights into the neural

mechanisms and time course of the emetic experience. *f*MRI may indeed provide useful physiological correlates in much the same way as positron emission tomography has clarified dose-response relationships in the development of pharmacological treatments targeting substance P-NK$_1$ receptors in the NTS and area postrema in the control of the vomiting reflex in animals and chemotherapy induced nausea and vomiting in humans (Hargreaves, 2006).

Eighty-two percent of children identified as having cyclic vomiting syndrome manifest symptoms typical of migraine. Interestingly, in children susceptible to migraine-associated cyclic vomiting, motion sickness was more likely to trigger vomiting and other migrainous symptoms than in children with non-migraine cyclic vomiting - 10% *versus* 0% (Li, Murray, Heitlinger, Robbins and Hayes, 1999). In longitudinal studies, children with a history of recurrent vomiting of unknown cause were found to be at increased risk of migraine in adulthood (Jan, 1998; Jan, Camfield, Gordon and Camfield, 1997). Furthermore, children with a history of motion sickness, migraine, or family history of migraine were more likely to vomit after mild head injury (Jan et al., 1997). The overlap between vomiting, migraine and motion sickness seen in childhood suggests that the gastrointestinal system is hyper-excitable in vulnerable individuals from an early age.

Abdominal migraine is associated with nausea and vomiting and typically recurs in infancy, childhood, and adolescence (Headache Classification Subcommittee of the International Headache Society, 2004), then apparently evolves into more typical migraine during puberty and early adulthood (Blau and MacGregor, 1995; d'Onofrio, Cologno, Buzzi, Petretta, Caltagirone, Casucci and Bussone, 2006). Recently, d'Onofrio et al. (2006) described a rare case of a woman who fulfilled the diagnostic criteria for late onset abdominal migraine. Abdominal pain attacks began in her

adolescence and persisted until age 21. Thereafter she experienced migraine headache accompanied by nausea, photophobia and phonophobia. However, the transition from childhood abdominal migraine to adult migraine has been challenged by Blau and MacGregor (1995), who claimed that the majority of migraine sufferers do not experience abdominal discomfort during migraine attacks. Despite these contrary views, the link between gastrointestinal disturbance and head pain in migraine is certainly well documented (Blau, 1993; Botney, 1981; Olesen, 1978; Rasmussen, Jensen and Olesen, 1991).

Nausea and vomiting may develop in migraine headache because of close functional interconnections between the trigeminovascular system and the NTS (Knight, 2005). Drummond and Cuomo-Granston (Drummond and Granston, 2004, 2005; Granston and Drummond, 2002; Cuomo-Granston, 2008, 2009) observed that migraine sufferers developed nausea in the presence of head pain whereas controls remained asymptomatic. Migraine sufferers initially developed headache following painful stimulation of the temple, and nausea developed gradually as the procedure progressed. Optokinetic stimulation enhanced the incremental upsurge of nausea evoked by head pain, presumably because motion sickness increased the excitability of emetic or trigeminal nociceptive circuits (Drummond and Granston, 2005). A similar synergistic relationship between nausea and headache could develop during attacks of migraine. Since serotonin (5-HT) specific anti-migraine compounds alleviate nausea and headache, this may indicate an action via 5-HT$_{1B/1D}$ receptors in the NTS. Indeed, the 5-HT$_{1B/1D}$ receptor agonists eletriptan and naratriptan were found to inhibit activity in NTS neurons that responded to electrical stimulation of the superior sagittal sinus, a major vein of the dura mater (Hoskin, Lambert, Donaldson, and Zagami, 2004). Thus, serotonergic agonists might not only modulate nociceptive

activity in the trigeminovascular system but also directly suppress the firing rate of NTS neurons that mediate gastrointestinal disturbances.

4. Overlapping mechanisms in migraine and motion sickness

4.1. Gastrointestinal symptoms

Although peripheral pathways mediate the actual vomiting process (Lang, 1999; McMillin, Richards, Mein and Nelson, 1999), nausea and vomiting in migraine (Dahlof and Hargreaves, 1998) and motion sickness (Takeda et al., 2001; Cass, Ankerstjerne, Yetiser, Furman, Balaban, and Aydogan, 1997) are assumed to originate within the central nervous system.   In support of the central generation of nausea in motion sickness, Levine, Chillas, Stern and Knox (2000) found that while gastric tachyarrythmia resolved following administration of 5-HT receptor antagonist antiemetics during optokinetic stimulation, nausea (and other symptoms of motion sickness) still developed.

A hypersensitive 'emetic centre' (reflected by a low threshold for the emetic response) may underlie susceptibility to motion sickness (Takedo et al., 2001). As the same central mechanisms orchestrate emesis, regardless of the triggering condition, and migraine sufferers are prone to motion sickness, 'emetic centre' hypersensitivity could also explain the recruitment of nausea in attacks of migraine. Once established, nausea and headache could escalate in a positive loop.

4.2. Vestibular symptoms

Dizziness or vertigo is frequently reported in the headache-free interval as well as during attacks of migraine (Marano, Marcelli, Di Stasio, Bonuso, Vacca, Manganelli, Marciano and Perretti, 2005; Baloh, 1997; Cutrer and Baloh, 1992), often in association with nausea (Baloh, Foster, Yue and Nelson, 1996; Harris, 1999). The link between headache and dizziness/vertigo may reflect a functional interaction

between the trigeminal and vestibular systems. Lesions associated with vestibular structures commonly produce nystagmus. Marano et al. (2005) reported that spontaneous nystagmus developed more readily in migraine sufferers than in controls following unilateral electrical stimulation of the supraorbital region of the forehead, suggesting that trigeminal nerve activity evoked vestibular dysfunction in migraineurs.

In the case of motion sickness, impulses are relayed from the vestibular nuclei to the cerebellum, and then to the NTS (Mitchelson, 1992). Although motion sickness develops readily in most migraine sufferers, motion sickness is not co-morbid with common peripheral vestibular disorders such as Meniere's disease, benign paroxysmal positional vertigo or vestibular neuritis (Marcus et al., 2005). Thus, the reciprocal relationship between motion sickness and migraine is consistent with the notion that central rather than peripheral pathways involved in their generation are shared. These pathways may include:

- Projections from the trigeminal nucleus caudalis to the vestibular nuclei (Diagne, Valla, Delfini, Buisseret-Delmas and Buisseret, 2006).

- Indirect influences on the vestibular nuclei, mediated by trigeminovascular reflexes that regulate blood flow through the cerebellar and vertebrobasilar vasculature (Vincent and Hadjikhani, 2007).

- Projections from the trigeminal nucleus caudalis and vestibular nuclei to the NTS which, in turn, project to autonomic output pathways (Menėtrey and Basbaum, 1987).

- Rostral projections from the trigeminal nucleus caudalis, vestibular nuclei and NTS to the hypothalamus, thalamus, limbic system and cerebral cortex (Marcus et al., 2005; Menėtrey and Basbaum, 1987), and top-down influences from these

higher brain centres on brainstem processing. The net sum of this central integration may influence the expression and intensity of symptoms such as dizziness, nausea and headache.

4.3. Vascular disturbances

Vasodilatation of cranial vessels (both extra- and intracranial) has long been regarded as important in the pathophysiology of migraine (Wolff, 1948; Wolff, 1972; Botney, 1981; Moskowitz, 1993; Drummond and Lance, 1983; Lance, 1993; Lance and Goadsby, 2005). As noted in Section 2.2, vasodilatation during attacks of migraine may be driven in a vicious circle by an interaction between nociceptive trigeminal-parasympathetic vasodilatation (Lance et al., 1983) and painful neurogenic inflammation (Moskowitz, 1993; Buzzi and Moskowitz, 2005). Extracranial blood vessels dilate more readily in migraine sufferers than controls during psychological stress (Drummond, 1982), head pain (Drummond, 1997; Drummond and Granston, 2005) and optokinetic stimulation (Drummond and Granston, 2004; Cuomo-Granston, 2008, 2009). This heightened responsiveness could amplify the vascular component of migraine.

Neurogenic inflammation involves a surge of vasoactive neurotransmitters (substance P, neurokinin A, calcitonin gene-related peptide) that provoke vasodilatation and possibly the prolonged pain associated with a migraine attack (Moskowitz, 1993). In this regard, Buzzi, Bonamini and Moskowitz (1995) suggested that headache may be considered a consequence of threatened injury to the brain. Similarly, Edvinsson and Uddman (2005) suggested that the trigeminovascular vasodilator reflex is, in part, generated via CGRP and VIP to offset cerebrovascular constriction.

Motion sickness is commonly associated with facial pallor and cold sweating (Marcus et al., 2005), but may also be associated with increases in skin oxygen and flushing (Harm, Beatty and Reschke, 1987). In a study involving eccentric vertical axis rotation, facial vasodilatation peaked at the commencement of rotation (during vestibular stimulation), even before the onset of motion sickness (Kolev, Möller, Nilsson and Tibbling, 1997). Together, these findings suggest that blood is diverted away from facial capillaries to deeper blood vessels as nausea develops (Marcus et al., 2005). A similar process may account for facial pallor in migraine. In a series of experiments by Golding (1992), phasic skin conductance responses increased progressively in the forehead during provocative motion procedures (reflecting prodromal sweating in nauseated subjects), and decreased in line with subjective recovery as motion sickness resolved. Golding pointed out that the combination of sweating with pallor in motion sickness is an anomaly, as thermoregulatory sweating is generally associated with peripheral vasodilatation. He suggested that the thermoregulatory value of cold sweating in motion sickness might be as a preparatory response to cool the body in anticipation of impending muscular activity. However, the physiological benefit of this response with regard to motion sickness is unclear.

Drummond and Cuomo-Granston (Drummond and Granston, 2004; Cuomo-Granston, 2008, 2009) investigated the association between changes in facial blood flow and symptoms of motion sickness evoked by optokinetic stimulation. Their research involved one central experiment that consisted of six experimental conditions. On separate occasions migraine sufferers and healthy controls were exposed to optokinetic stimulation with or without painful stimulation of the head or limb (Figure 1). During optokinetic stimulation, subjects sat on a stationary chair and watched vertical black and white stripes moving past. This created visual illusions and

a sense of movement: the stripes appeared to take on a 3-dimensional aspect, move further away and grow wider, and to slow down or stop altogether whereas the chair that the subject sat on seemed to spin. The motion sickness evoked by this illusion of movement is associated with nausea, headache and other symptoms of migraine, which are generally more intense in migraine sufferers than controls (Drummond, 2002). Headache developed in migraine sufferers but not controls during optokinetic stimulation, and extracranial vasodilatation was greater in migraine sufferers than controls (Drummond and Granston, 2004). Although the headache intensified when ice was applied to the temple during optokinetic stimulation, there seemed to be no direct correspondence between vasodilatation and headache intensity as the ice did not provoke additional increases in facial blood flow.

The periaqueductal grey (PAG) is involved in pain control and autonomic regulation of the stress response (Behbehani, 1995). Carrive and Bandler (1991) detected extracranial vasodilatation when D.L. homocysteic acid was administered into a restricted portion of the lateral pretentorial PAG in unanesthetized and paralyzed decerebrate cats, a site that evokes a threat display (hisses, howls, retraction of the corners of the mouth and ears) in freely moving cats as part of a defense response. Thus, the extracranial vasodilatation observed by Drummond and Cuomo-Granston (Drummond and Granston, 2004; Cuomo-Granston, 2008, 2009) in migraine sufferers during optokinetic stimulation may have reflected a defense response involving the PAG. In support of this view, anticipation of head pain also evoked an exaggerated extracranial vasodilator response in migraine sufferers (Drummond and Granston, 2005). Increases in sympathetic activity provoked by activation of the defense response may also account for cold sweating during motion sickness.

5. Serotonin, migraine and motion sickness

Pharmacological studies indicate that serotonin (5-HT) may be involved both in migraine and motion sickness. In experiments on cats, 5-HT inhibited the transmission of neural impulses in the lateral vestibular nuclei (Kishimoto, Sasa and Takaori, 1991, 1994). Triptans may evoke analgesic anti-migraine activity in the trigeminal nucleus caudalis, and anti-emetic effects in the NTS, by acting on the numerous 5-HT_1 receptor sites in these locations (Pascual, del Arco, Romon, del Omo, Castro and Pazos, 1996; Hoskin et al., 2004). Serotonin prevents motion-induced emesis in animals (Javid and Naylor, 2006; Okada, Saito and Matsuki, 1996), and 5-HT_{1A} agonists inhibit vomiting during motion sickness in cats (Lucot, 1989; Yates, Miller and Lucot, 1998) and the Asian musk shrew (Okada, Torii, Saito and Matsuki, 1994). However, findings in animal research do not necessarily extrapolate to clinical efficacy in humans (Reid, Sciberras, Gertz, Reinhardt, Lui, Golding and Stott, 1998; Hasler, 1999; Peroutka, 2005). For example, the NK_1 receptor antagonist L-758,298 was found to have motion-related anti-emetic properties in animals (Reid, Palmer, Wright, Clemes, Troakes, Somal, House and Stott, 2000), but proved ineffective in preventing motion-induced nausea in humans (Reid et al., 1998). By necessity, the benchmarks used to determine motion sickness in animals are constrained to vomiting or the consumption of non-nutritive substances such as kaolin (clay), an illness response seen in rats considered comparable to vomiting (Okada et al., 1996; Takeda, Morita, Hasegawa, Horii, Kubo and Matsunaga, 1993). The absence of an animal analogue of nausea limits the degree to which findings from animal research can be translated to humans.

In a pilot study by Marcus and Furman (2006), five migraine sufferers with migrainous vertigo and another five without vestibular symptoms were pretreated

with either the 5-HT$_{1B/D}$ receptor agonist rizatriptan or placebo before vertical axis rotation tests. Rizatriptan inhibited symptoms of motion sickness in migraineurs susceptible to vestibular symptoms during migraine attacks, but not in migraineurs without vestibular symptoms. Whilst these preliminary findings suggest a potential link between serotonin and motion sickness in migraine sufferers, they require confirmation in studies using larger numbers of patients with and without a history of migraine. Baloh (1997) pointed out that anti-migraine treatments such as ergotamine and sumatriptan are probably of little help for the treatment of migraine-associated vertigo, although he did report that several patients found sumatriptan, if taken early, aborted vertigo (Evans and Baloh, 2001). Consistent with this observation, zolmitriptan was found to alleviate migrainous vertigo in a small group of sufferers (Neuhauser, Radtke, Breven and Lempert, 2003).

In studies in our laboratory (Drummond, 2005b, 2006), levels of 5-HT within the central nervous system apparently influenced the development of symptoms of migraine and motion sickness. Drummond investigated symptoms of motion sickness (Drummond, 2005b) and sensitivity to light (Drummond, 2006) in migraine sufferers and healthy controls following consumption of an amino acid drink without the serotonin precursor L-tryptophan, to transiently reduce brain serotonin synthesis. In the comparison condition, participants consumed an amino acid drink that included L-tryptophan. Drummond (2005b) found that dizziness, nausea and visual illusions were enhanced in tryptophan-depleted healthy controls during exposure to optokinetic stimulation, to levels comparable to those reported by migraine sufferers. These findings suggest that depleted brain serotonin activity may be involved in vestibulo-ocular disturbances during motion sickness, and that a serotonergic deficit might increase vulnerability to symptoms of migraine. Tryptophan-depleted migraine

sufferers and controls were more sensitive to light, reporting greater glare and light-induced pain than in others without tryptophan depletion (Drummond, 2006). In addition, headache worsened in tryptophan-depleted migraine sufferers, and nausea intensified both in migraine sufferers and controls in the presence of residual motion sickness following exposure to optokinetic stimulation. These findings are consistent with the notion that reduced brain 5-HT synthesis augments migrainous symptoms (Drummond, 2006).

Serotonergic activity has been linked to migraine during (Hasler, 1999; Ladabaum and Hasler, 1999; Silberstein, 1994) and outside attacks (Afra, Proietti Cecchini, Sandor and Schoenen, 2000). However, the precise role of 5-HT is not clear (Evers, Quibeldey, Grotemeyer, Suhr and Husstedt, 1999; Ferrari and Saxena, 1993; Fontes Ribeiro, Cotrim, Morgadinho, Ramos, Seabra Santos and Macedo, 1990). During a migraine attack the trigeminal sensory system presumably activates second-order nociceptive neurons within the brainstem, which relay signals to autonomic brainstem nuclei and higher cortical pain processing centres. In turn, these afferent impulses initiate head pain and serial or parallel activation of sensory and efferent autonomic pathways that trigger nausea and gastrointestinal disturbances (Dahlof and Hargreaves, 1998). Silberstein (1994) proposed that 5-HT modulates rather than mediates sensory responsiveness by acting on serotonergic receptors distributed widely throughout the brain (Millan, 2002). Serotonergic neurons originating in the raphe nuclei of the brain stem have extensive projections to the cortex, hippocampus, basal ganglia, thalamus, cerebellum, and spinal cord. These neurons play a role in controlling levels of arousal and sleep. In addition they modulate sensory input, particularly for pain (Millan, 2002), and could thus influence susceptibility to migraine.

6. Summary and conclusions

Characteristics of the migraine predisposition include:

- susceptibility to vestibular symptoms and motion sickness

- susceptibility to nausea, headache and photophobia induced by facial pain

- persistence of cranial hyperalgesia (scalp and cranial nerve tenderness, ice cream headache, ice pick pain), exaggerated trigeminal-nociceptive reflexes, and possibly hyperalgesia in the distal extremities, between episodes of headache

- persistence of photophobia and phonophobia between headache episodes

- an exaggerated response in extracranial blood vessels to stressful stimuli

Together, these characteristics suggest that migrainous mechanisms persist subclinically during the headache-free interval. Whether this simply represents residual activity from previous episodes or whether this subclinical activity increases susceptibility to further attacks of migraine has not been resolved. However, the expected daily incidence of migrainous attacks increased from 8% to 44% following painful stimulation of the temple during and after optokinetic stimulation (Granston and Drummond, 2005), consistent with the view that heightened activity in pathways responsible for migrainous symptoms increases susceptibility to attacks.

The mechanisms that underlie susceptibility to recurrent attacks of migraine may also increase vulnerability to motion sickness in migraine sufferers. As illustrated in Figure 2, this might include:

- Disruption of brainstem mechanisms that normally inhibit sensory discomfort to light, noise and head pain. This results in the sensitization of trigeminal nociceptive neurons and their rostral projections, and neurons in the NTS that mediate nausea and vomiting.

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- Sensory stimulation that intensifies activity in, and sensitization of, these neural circuits.

- Trigeminovascular reflexes and neurogenic inflammation that develop in response to, then aggravate, the brainstem disturbances responsible for symptoms of migraine. This establishes a vicious circle akin to a neural "wind-up" phenomenon.

Whether the vascular and neurochemical cascade of migraine is evoked by spontaneous discharge of a cyclical brainstem disturbance, or originates in the periphery, is uncertain. However, as a reduction in brain synthesis of 5-HT intensifies dizziness, nausea, photophobia and headache (Drummond 2005b; Drummond, 2006), a central serotonergic disturbance that increases the excitability of the trigeminal nucleus caudalis, NTS and vestibular nuclei may explain the link between motion sickness and migraine.

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<u>Figure legends</u>

Figure 1.   Experimental conditions and sessions.   Bullets indicate the 3 sessions participants attended. Each session involved two conditions (A and B). The order of sessions varied between participants.   The interval between each session was approximately one month.

Figure 2. Mechanisms that may contribute to symptoms of motion sickness and migraine. The key structures in the brainstem that mediate these symptoms include the trigeminal nucleus caudalis, the vestibular nuclei and the nucleus tractus solitarius. Arrows represent activation, whereas the flat terminal linked with pain modulation processes represents inhibition. Disruption of these inhibitory pain modulation processes may increase sensitivity to light, noise and head and/or neck pain, provoke symptoms of migraine and, ultimately, sensitize key brainstem nuclei. Once initiated, the trigeminovascular system could amplify trigeminal nociceptive sensations through a vicious circle involving neurogenic inflammation and extracranial vasodilatation. Reciprocal interactions between the trigeminal nucleus caudalis and the nucleus tractus solitarius may then result in escalation of nausea and headache. In addition, links between the trigeminal nucleus caudalis and the vestibular nuclei might mediate vestibular disturbances. Persistent excitability of these brainstem nuclei could increase vulnerability to symptoms both of motion sickness and migraine.

Session	Condition (A)		Condition (B)
		followed by	
•	optokinetic stimulation alone	→	Ice on temple after optokinetic stimulation
		followed by	
•	Ice on temple before optokinetic stimulation	→	Ice on temple during optokinetic stimulation
		followed by	
•	Hand in ice-water before optokinetic stimulation	→	Hand in ice-water during optokinetic stimulation

migraine

motion sickness

pain modulation processes

sensory stimulation + head or neck pain

sensory conflict

headache

sensory and emotional discomfort

dizziness and vertigo

trigeminal nucleus caudalis

nausea and vomiting

vestibular nuclei

extracranial vasodilatation

neurogenic inflammation

nucleus tractus solitarius