Visual Vertigo, Motion Sickness and Disorientation in vehicles

Bronstein, A.M., Golding, J.F. and Gresty, M.A.

This is an author's accepted manuscript of an article published in the Seminars in Neurology DOI: 10.1055/s-0040-1701653. The final definitive version is available online at:

https://dx.doi.org/10.1055/s-0040-1701653

Visual Vertigo, Motion Sickness and Disorientation in vehicles

Bronstein, A.M., Golding, J.F. and Gresty, M.A.

Bronstein AM, Golding JF, Gresty MA. Visual Vertigo, Motion Sickness and Disorientation in vehicles. **Seminars in Neurology.** (accepted 24 Sep 2019)

Visual Vertigo, Motion Sickness and Disorientation in vehicles

Bronstein AM, Golding JF, Gresty MA

Adolfo M. Bronstein
Division of Brain Sciences,
Imperial College London
Charing Cross Hospital
London W6 8RF, UK
Email: a.bronstein@imperial.ac.uk

John F. Golding
Psychology, School for Social Sciences,
University of Westminster
115 New Cavendish St, London W1W 6UW, U.K.
Email: goldinj@westminster.ac.uk

Michael A Gresty
Division of Brain Sciences
Imperial College London
Charing Cross Hospital
London W6 8RF, UK
Email: m.gresty@imperial.ac.uk

Abstract

The normal vestibular system may be adversely affected by environmental challenges which have characteristics that are unfamiliar or ambiguous in the patterns of sensory stimulation they provide. A disordered vestibular system lends susceptibility even to quotidian environmental experiences as the sufferer becomes dependent on potentially misleading, non-vestibular sensory stimuli. In both cases the sequela may be dizziness, incoordination, imbalance and unpleasant autonomic responses. Many forms of visual environmental motion, particularly busy places such as supermarkets, readily induce inappropriate sensations of sway or motion and imbalance referred to as *visual vertigo.* All people with intact vestibular function can become motion sick although individual susceptibility varies widely and is partially determined by inheritance. Motorists learn to interpret sensory stimuli in the context of the car stabilised by its suspension and guided by steering. A type of motorist disorientation occurs in some individuals that develop a heightened awareness of false perceptions of car orientation, readily experiencing stereotypical symptoms of threatened rolling over on corners and veering on open highways or in streaming traffic. This article discusses the putative mechanisms, consequences and approach to managing patients with visual vertigo, motion sickness and motorist disorientation syndrome in the context of chronic dizziness and motion sensitivity.

Introduction

The vestibular apparatus is the prime, indeed only organ evolved specifically to signal orientation in space. It is therefore, unsurprising, that unusual, non-physiological stimulation and disorders of vestibular function give rise to a variety of symptoms ranging from vertigo, through imbalance and in-co-ordination to autonomic distress. The interpretation, corroboration and calibration of vestibular signals is dependent on environmental context; importantly visual and somatosensory cues to orientation. Consequently, challenging visual and mechanical motion in the environment may have adverse effects on vestibular function producing dizziness and visual disorientation.

Visual Vertigo

Panoramic visual motion normally accompanies head movement giving rise to visual motion signals which calibrate and help interpret vestibular signals of head movement and orientation. In normal subjects visual motion alone may occasionally induce sensations of self-motion, 'vection', as in the 'railway train' illusion. However, as a means of compensation, some patients with vestibular disease develop an overreliance on environmental visual cues leading to 'visual dependency'. This is a characteristic also found in people with a certain psychological susceptibility. Visual vertigo may itself become a major, disabling symptom, particularly when part of the functional (i.e., non-organic) syndrome of PPPD (persistent perceptual postural dizziness).

Visual vertigo is an inappropriate response to motion of the visual environment due to overreliance or misinterpretation of visual cues due to a sensory (vestibular) disturbance or functional disorder. Finally, although vehicle control becomes an overlearned skill, dis-adaptation in certain individuals renders them susceptible to the instability of the driving environment causing a 'motorists disorientation' with components of both motion sickness and visual vertigo.

Interaction of vestibular and visual mechanisms

The vestibular and visual systems complement each other in eliciting slow phase eye movements in order to stabilise visual images on the retina. Pursuit-optokinetic eye movements are elicited by visual motion whereas vestibular eye movements (vestibulo-ocular reflex, VOR) are elicited by head motion. These two systems work synergistically when a person rotates with eyes open while gazing at the surrounding environment, for instance a passenger looking out of a bus which is turning (Figure 1). However, they are said to be in conflict ('visuo-vestibular conflict') when a person looks at a visual object that rotates with him/her, e.g. a passenger reading a book on a bus. In this case, instead of collaborating with the VOR, the visual input actually suppresses the VOR (VOR suppression).

The interaction between vestibular and visual inputs is not only present in physiological circumstances. Indeed, the first line of defence against a pathological nystagmus due to a labyrinthine lesion is to resort to VOR suppression mechanisms so that visual stability can be partly restored (Figure 2). Similarly, where there is absent (1) or altered visual input as in congenital nystagmus (2) or when there is external ophthalmoplegia (3), vestibular function and perception is modified. It is thus not surprising that vestibular lesions can cause visual symptoms and that visual input influences vestibular symptoms.

Clinical picture of visual vertigo

Many patients with a current or previous vestibular disorder report worsening or triggering of dizziness and imbalance in certain visual environments. These patients dislike moving visual surroundings, as encountered in traffic, crowds, disco lights and car-chase scenes in films. Typically, such symptoms develop when in busy visual surroundings such as supermarket aisles. The development of these symptoms in some patients with vestibular disorders has long been recognised (4,5,6) and given various names such as Visuo-Vestibular Mismatch (7,8) or Visual Vertigo (9,10). This syndrome should not be confused with oscillopsia. Oscillopsia is a visual perception of movement, bouncing or oscillation of the visual percept. In visual vertigo, the trigger is visual commotion but the symptom is of a vestibular kind such as dizziness, vertigo, disorientation and unsteadiness.

The symptoms of visual vertigo frequently develop after a vestibular insult. Any vestibular disorder, peripheral or central, can lead to visual vertigo but patients with migraine, particularly vestibular migraine, are extremely prone to developing visual vertigo. A typical patient is a previously asymptomatic person who suffers an acute peripheral disorder (e.g. vestibular neuritis) and that after an initial period of recovery of a few weeks, he/she discovers that the dizzy symptoms do not fully disappear. Furthermore, symptoms are aggravated by looking at moving or repetitive images, as described above. Patients may also develop anxiety or frustration because symptoms do not go away or because medical practitioners tend to disregard them.

The origin and significance of the symptoms of visual vertigo in vestibular patients has been the subject of research. We know that tilted or moving visual surroundings have a pronounced influence on these patients' perception of verticality and balance, over and above what can be expected from an underlying vestibular deficit (9,10). This increased responsiveness to visual stimuli is called 'visual dependency'. Patients with central vestibular disorders and patients combining vestibular disorders and congenital squints or squint surgery can also report visual vertigo and show enhanced visuo-postural reactivity (9).

Overall, these findings suggest that the combination of a vestibular disorder and visual dependence in a given patient is what leads to the visual vertigo syndrome. Ultimately, what makes some patients with vestibular disorders develop such visual dependence is not known. The role of the associated anxiety-depression, often observed in these patients, and whether this is a primary or secondary phenomenon is not clear. Earlier evidence indicated that anxiety or depression levels were not higher in visual vertigo patients than in other patients seen in dizziness clinics (10,11). Recently, however, a longitudinal study of unselected patients with acute vestibular neuritis showed that the grouping of visual dependence, psychological dysfunction (anxiety, depression, somatization traits) and autonomic arousal in a single statistical factor was able to predict long term symptoms and handicap (12). So this work does suggest an interrelation between long term vestibular symptoms, psychological symptoms and visual vertigo.

The more important differential diagnosis in a patient presenting to clinic with visual vertigo is, however, one of a purely psychological disorder or panic attacks (13). Neurologists or neuro-otologists are usually happy to treat a patient with visual vertigo as a secondary complication of vestibular disease but not necessarily so if the patient’s presentation appears primarily as psychiatric. An accepted set of criteria to distinguish between psychological and vestibular symptoms is not completely agreed presently (13,14,15), although the delineation of PPPD as a functional vestibular syndrome has been a major practical development in neuro-otology (see below). In principle, however, a patient who has never had a clear history of vestibular disease, with no findings on vestibular examination and with visual triggers restricted to a single particular environment (e.g. a specific supermarket) would be more likely to have a primary psychological disorder.

Reciprocally, a patient with no pre-morbid features of psychological dysfunction who after a vestibular insult may develop car tilting illusions when driving (16) or dizziness when looking at various moving visual scenes (traffic, crowds, movies) is more likely to have the visual vertigo syndrome.

The syndrome of persistent perceptual postural dizziness (PPPD or 3PD), which is exceedingly common in specialist clinics, has been recently defined and diagnostic criteria have been proposed (17). In summary, patients report dizziness, unsteadiness, or non-spinning vertigo on most days for prolonged periods of time, but may wax and wane in severity. Persistent symptoms occur without specific provocation, but are often exacerbated by upright posture, active or passive motion, moving visual stimuli or complex visual patterns. The disorder is triggered by events that cause vertigo, unsteadiness, dizziness, or problems with balance including acute, episodic, or chronic vestibular syndromes, other neurologic or medical illnesses, and psychological distress. It can be seen that visual vertigo, as discussed in the preceding paragraphs, can feature in patients with PPPD but visual vertigo can exist without PPPD and, vice versa, PPPD can exist without visual vertigo.

Treatment of visual vertigo

There are three aspects in the treatment of patients with the visual vertigo syndrome. The first is specific measures for the underlying vestibular disorder, e.g. Meniere’s disease, BPPV, migraine, but discussing these is beyond the scope of this article. However, given that a specific etiological diagnosis cannot be confirmed in many patients with chronic dizziness symptomatic treatment as discussed below should not be delayed.

Secondly, patients benefit from general vestibular rehabilitation with a suitably trained audiologist or physiotherapist. These exercise-based programs can be either generic, like the original Cawthorne-Cooksey approach (18) or, preferably, customised to the patient's needs. All regimes involve progressive eye, head and whole body movements (bending, turning) as well as walking exercises (19, 20, 21).

Finally, specific measures should be introduced in the rehabilitation program for visual vertigo patients in order to reduce their hyper-sensitivity to visual motion. The aim is to promote desensitisation and increase tolerance to visual stimuli and to visuo-vestibular conflict. Patients are therefore exposed, under the instruction of the vestibular physiotherapist, to optokinetic stimuli which can be delivered via projection screens, head mounted virtual reality systems, video monitors, ballroom planetariums or optokinetic rotating systems (22). Initially patients watch these stimuli whilst seated, then standing, walking, initially without and then with head movements, in a progressive fashion (Figure 3). Research has shown that these patients benefit from repeated and gradual exposure to such visual motion training programs; both the dizziness and associated psychological symptoms improve over and above conventional vestibular rehabilitation (23).

Although no controlled trials for drug treatment of visual vertigo have been conducted, some evidence that Acetazolamide may be useful has been presented (24). As visual vertigo is prominent in patient with vestibular migraine, it could be argued that the Acetazolamide related improvement is due to its general antimigraine properties (25). Finally, as visual vertigo may be a component of PPPD clinicians should assess whether additional counselling, psychotherapy or psychopharmacological treatment, in particular antidepressants, may be required (for review, see 26,27).

Motion Sickness

Susceptibility to motion sickness is ubiquitous and possessed by all individuals with intact vestibular function. This proneness has become more problematic for more susceptible individuals in modern vehicular and visual environments. The primary signs and symptoms of motion sickness are nausea and vomiting. Other commonly related symptoms include stomach awareness, sweating and facial pallor (so-called 'cold sweating'), increased salivation, sensations of bodily warmth, dizziness, drowsiness, headache, loss of appetite and increased sensitivity to odours. Motion sickness can be provoked by a wide range of situations - in cars, tilting trains, funfair rides, aircraft, weightlessness in outer-space, virtual reality and simulators. The term 'motion sickness' embraces car-sickness, air-sickness, space-sickness, sea-sickness, etc. (28). The increasing use of new visual technologies such as virtual reality (29) and driverless autonomous vehicles (30) may increase the general public exposure to environments capable of provoking motion sickness.

Physiological responses associated with motion sickness vary between individuals. For the stomach, gastric stasis occurs and increased frequency and reduced amplitude of the normal electro-gastric rhythm (31). Other autonomic changes include sweating and vasoconstriction of the skin causing pallor (less commonly skin vasodilation and flushing in some individuals), with the simultaneous opposite effect of vasodilation and increased blood flow of deeper blood vessels, changes in heart rate which are often an initial increase followed by a rebound decrease, and inconsistent changes in blood pressure (28). A whole host of hormones are released, mimicking a generalised stress response, amongst which vasopressin is thought to be most closely associated with the time course of motion sickness (32). The observation of cold sweating suggests that motion sickness may disrupt aspects of temperature regulation (33), a notion consistent with the observation that motion sickness reduces deep core body temperature during cold water immersion, accelerating onset of hypothermia (34).

Motion sickness is unpleasant but also under some circumstances it may have adverse consequences for performance and even survival. Motion sickness preferentially causes decrements on performance of tasks which are complex, require sustained performance and offer the opportunity of the person to control the pace of their effort (35). For pilots and aircrew it can slow training in the air and in simulators and even cause a minority to fail training altogether (28). Approximately 70% of novice astronauts will suffer space sickness in the first 24 hours of flight. The possibility of vomiting while in a spacesuit in microgravity is potentially life threatening, consequently precluding extravehicular activity for the first 24 hours of spaceflight (36). For survival-at-sea, such as in in life rafts, seasickness can reduce survival chances by a variety of mechanisms, including reduced morale and the ‘will to live’, failure to consistently perform routine survival tasks, dehydration due to loss of fluids through vomiting (28), and possibly due to the increased risk of hypothermia (34).

Causes and Reasons for Motion Sickness

Any proposed mechanism for motion sickness must account for the observation that the physical intensity of the stimulus is not necessarily related to the degree of nauseogenicity. Indeed with optokinetic (visual motion) stimuli there is no real motion. A person sitting at the front in a wide screen cinema experiences self-vection and ‘cinerama sickness’ but there is no physical motion of the body. In this example, the vestibular and somatosensory systems are signalling that the person is sitting still, but the visual system is signalling illusory movement or self-vection. Consequently, the generally accepted explanation is based on some form of sensory conflict or sensory mismatch. The sensory conflict or sensory mismatch is between actual versus expected invariant patterns of vestibular, visual & kinaesthetic inputs (37). Brainstem and cerebellar neurons whose activity corresponds to what might be expected of putative 'sensory conflict' neurons have been identified (38). Benson (28) categorised neural mismatch into two main types: (i) conflict between visual and vestibular inputs or (ii) mismatch between the semicircular canals and the otoliths. A simplified model was proposed by Bos and Bles (39) that there is only one conflict: between the subjective expected vertical and the sensed vertical. However, despite this apparent simplification the underlying model is necessarily complex and finds difficulty in accounting for the observation that motion sickness can be induced by types of optokinetic stimuli which pose no conflict concerning the earth vertical (40). A useful set of rules was proposed by Stott (41), which if broken, will lead to motion sickness: *Rule 1*. Visual-vestibular: motion of the head in one direction must result in motion of the external visual scene in the opposite direction; *Rule 2*. Canal-otolith: rotation of the head, other than in the horizontal plane, must be accompanied by appropriate angular change in the direction of the gravity vector; Rule *3*. Utricle-saccule: any sustained linear acceleration is due to gravity, has an intensity of 1 *g* and defines 'downwards'. In other words, the visual world should remain space stable, and gravity should always point down and average over a few seconds to 1 *g*.

The above describes what might be termed the 'how' of motion sickness in terms of mechanisms. By contrast it is necessary to look elsewhere for an understanding of the 'why' of motion sickness. Motion sickness itself could have evolved from a system designed to protect from potential ingestion of neurotoxins by inducing vomiting when unexpected central nervous system inputs are detected, the "toxin detector" theory of Treisman (42). This system would be activated by modern methods of transport that cause mismatch. This theory is consistent with the observation that people who are more susceptible to motion sickness are also more susceptible to emetic toxins, chemotherapy sickness, and post-operative nausea and vomiting (PONV) (43). In addition this theory has been experimentally tested with evidence of reduced emetic response to challenge from toxins after bilateral vestibular ablation (44). Less popular alternatives to the toxin detector hypothesis propose that motion sickness could be the result of aberrant activation of vestibular-cardiovascular reflexes (45); or that it might originate from a warning system that evolved to discourage development of perceptual motor programmes that are inefficient or cause spatial disorientation (46); or that motion sickness is a unfortunate consequence of the physical proximity of the motion detector (vestibular) and vomiting circuitry in the brainstem (47).

Individual differences in motion sickness susceptibility

Individuals vary widely in their susceptibility, and there is evidence from twin studies that a large proportion of this variation is accounted for by genetic factors with heritability estimates around 55-70% (48). A large-scale genome study has isolated 35 single-nucleotide polymorphisms (SNPs) associated with motion sickness susceptibility, demonstrating that multiple genes are involved (49). Some groups of people have particular risk factors. Infants and very young children are immune to motion sickness with motion sickness susceptibility beginning from around 6 to 7 years of age (37) and peaking around 9 to 10 years (50). Following this peak susceptibility, there is a subsequent decline of susceptibility during the teenage years towards adulthood around 20 years. This doubtless reflects habituation.

Women appear somewhat more susceptible to motion sickness than men; women show higher incidences of vomiting and reporting a higher incidence of symptoms such as nausea (51). This increased susceptibility is likely to be objective and not subjective because women vomit more than men; surveys of passengers at sea indicate a 5 to 3 female to male risk ratio for vomiting (52). Although susceptibility varies over the menstrual cycle, peaking around menstruation, it is unlikely that this can fully account for the greater susceptibility in females because the magnitude of fluctuation in susceptibility across the cycle is only around one third of the overall difference between male and female susceptibility (53). The elevated susceptibility of females to motion sickness or indeed to post-operative nausea and vomiting or chemotherapy induced nausea and vomiting (43, 54), may serve an evolutionary function. Thus, more sensitive sickness thresholds in females may serve to prevent exposure of the foetus to harmful toxins during pregnancy. Individuals who have complete bilateral loss of labyrinthine (vestibular apparatus) function are largely immune to motion sickness. However this may not be true under all circumstances since there is evidence that some bilateral labyrinthine defective individuals are still susceptible to motion sickness provoked by visual stimuli (visual vertigo) designed to induce self-vection during pseudo-Coriolis stimulation, i.e. pitching head movements in a rotating visual field (55).

Certain groups with medical conditions may be at elevated risk. Many patients with vestibular pathology and disease and vertigo can be especially sensitive to any type of motion. The known association among migraine, motion sickness sensitivity, and Meniere’s disease dates back to the initial description of the syndrome by Prosper Meniere in 1861. The reason for the elevated motion sickness susceptibility in migraineurs is not known but may be due to altered serotonergic system functioning (56). Patients with vestibular migraine are especially susceptible to motion sickness (57). Motion sickness susceptibilities are shown for various vestibular disorders and migraine versus healthy controls (58) see Figure 4.

A rapid estimate of an individual's susceptibility can be made using Motion sickness Susceptibility Questionnaires (sometimes called Motion History Questionnaires). A typical questionnaire is shown in Table 1, which has been validated for exposure to motion stimuli in the laboratory and in transport environments (59). An overall indicator of susceptibility, may be calculated as the MSSQ score = (total sickness score) x (18) / (18 - number of motion types not experienced); this formula corrects for differing extent of exposure to different motion stimuli in individuals. For the normal population, the median MSSQ score is 11.3, where higher scores indicate greater susceptibility and vice versa.

Mal de Debarquement

Whittle (60) provided an early description of *Mal de Debarquement* Syndrome (MdDS), after the landing and during the advance of the troops of William of Orange in Torbay in 1688. *"As we marched here upon good Ground, the Souldiers would stumble and sometimes fall because of a dissiness in their Heads after they had been so long toss'd at Sea, the very Ground seem'd to rowl up and down for some days, according to the manner of the Waves'*. MdDS is the sensation of unsteadiness and tilting or rocking when a sailor returns to land. A similar effect is observed in astronauts returning to 1 *g* on Earth after extended time in weightlessness in space. This can lead to illusory motion as, if still on a boat, but, unlike motion sickness, there is little or no nausea. MdDS symptoms usually resolve within a few hours as individuals readapt to the normal land environment. Individuals susceptible to MdDS may have reduced reliance on vestibular and visual inputs and increased dependence on the somatosensory system for the maintenance of balance (61). In a minority of individuals symptoms persist and can be troublesome. Customised vestibular exercises have been proposed as a treatment (62). Some temporary relief can be obtained by re-exposure to motion but this is not a viable treatment. Standard anti-motion sickness drugs appear ineffective but benzodiazepines appear to offer some relief (63). Transcranial Magnetic Stimulation (TMS) is a potential treatment (64). MdDS is discussed elsewhere in this issue.

Behavioural countermeasures to reduce motion sickness.

Habituation offers the surest counter measure to motion sickness but by definition is a long-term approach. Habituation is superior to anti-motion sickness drugs, and it is free of side effects (65). The most extensive habituation programmes, often denoted “motion sickness desensitisation,” are run by the military with success rates exceeding 85% (28) but can be extremely time consuming, lasting many weeks. Critical features include: (a) the massing of stimuli (exposures at intervals greater than a week almost prevents habituation), (b) use of graded stimuli to enable faster recoveries and more sessions to be scheduled, which may help avoid the opposite process of sensitization, and (c) maintenance of a positive psychological attitude to therapy (66). Sleep loss should be avoided since not only can it increase motion sickness sensitivity but more importantly impedes the rate of adaptation over successive motion exposures (67).

Habituation may be specific to a particular stimulus, for example tolerance to car travel may confer no protection to seasickness. Anti-motion sickness drugs are of little use in this context, since both laboratory (68) and sea studies (69) show that although such medication may speed habituation compared to placebo in the short term, in the longer term it is disadvantageous. This is because when the anti-motion sickness medication is discontinued, the medicated group relapses and is worse off than those who were habituated under placebo.

Immediate short-term behavioural counter measures include reducing head movements, aligning the head and body with GIF, the gravito-inertial forces, (70, 71) or laying supine (72). However, such protective postures may be incompatible with task performance. It is usually better to be in control, i.e. to be the driver or pilot rather than a passenger (73). Obtaining a stable external horizon reference is helpful (74). Controlled regular breathing has been shown to provide increased motion tolerance, and may involve activation of the known inhibitory reflex between respiration and vomiting (66). Supplemental oxygen may be effective for reducing motion sickness in patients during ambulance transport, but it is ineffective in healthy individuals, this apparent paradox being explained by the suggestion that supplemental oxygen may work by ameliorating a variety of internal states that sensitize for motion sickness rather than against motion sickness *per se* (75).

Some report acupuncture and acupressure to be effective against motion sickness (76) however other well controlled trials find no evidence for their value (77). High frequency head vibration can provide some reduction in motion sickness and a similar technique of noisy vestibular stimulation by vibration reduced visually induced motion sickness (VIMS), the effectiveness being best when time-coupled to periods of visual motion (78). Although electrical stimulation of the vestibular apparatus, usually termed ‘galvanic vestibular stimulation’ (GVS) can cause vertigo and nausea, the opposite effect has been proposed, that it may provide a novel, countermeasure for motion sickness (78).   Similarly, galvanic cutaneous stimulation has been shown to reduce symptoms during driving simulation. Transcranial electrical stimulation has been shown to reduce motion sickness evoked by physical motion and visual motion (78). However the practicality of all of these vibratory and electrical stimulation techniques against motion sickness remains to be proven in the real world outside of the laboratory.

For habitual smokers acute withdrawal from nicotine provides significant protection against motion sickness (79). Indeed this finding may explain why smokers are at reduced risk for postoperative nausea & vomiting (PONV) whereas non-smokers have elevated risk; the temporary nicotine withdrawal peri-operatively and consequent increased tolerance to sickness from any source may explain why smokers have reduced risk for PONV (79). It has been suggested that ginger (main active agent gingerol) acts to calm gastrointestinal feedback, but studies of its effects on motion sickness have been equivocal making it an unlikely potent anti-motion sickness agent (80). The findings for any effects of diet are contradictory. For example, a study suggesting that protein-rich meals may inhibit motion sickness (81) may be contrasted with a study which drew the opposite conclusion that any meal of high protein or dairy foods 3-6 h prior to flight should be avoided to reduce airsickness susceptibility (82).

Pharmacological countermeasures

Drugs currently used against motion sickness may be divided into the categories: anti-muscarinics (e.g. scopolamine), H_1 anti-histamines (e.g. dimenhydrinate), and sympathomimetics (e.g. amphetamine) and have improved little over 50 years (83). Commonly used anti-motion sickness drugs are shown in Table 2. Other more recently developed anti-emetics are not effective against motion sickness, including D_2 dopamine receptor antagonists, and $5HT_3$ antagonists used for side effects of chemotherapy, (84). Nor do the neurokinin 1 antagonist anti-emetics appear effective against motion sickness (85). This is probably because their sites of action may be at vagal afferent receptors or the brainstem chemoreceptor trigger zone (CTZ), whereas anti-motion sickness drugs act elsewhere perhaps at the vestibular brainstem nuclei.

All anti-motion sickness drugs can produce unwanted side effects, drowsiness being the most common. Promethazine is a classic example (65). Scopolamine may cause blurred vision in a minority of individuals, especially with repeated dosing. The anti-motion sickness combination drug amphetamine+scopolamine (so-called “Scop-dex”) is probably the most effective with the fewest side-effects, at least for short-term use. This is because both scopolamine and amphetamine are proven anti-motion sickness drugs, doubtless acting through different pathways so they have additive efficacy, and their side-effects of sedation and stimulation cancel each other out. Unfortunately for legal reasons the Scop-dex combination is no longer available apart from specialised military use and alternative stimulants such as Modafinil seem ineffective (86).

Oral administration must anticipate motion since motion sickness induces gastric stasis consequently preventing drug absorption by this route (87). Injection overcomes the various problems of slow absorption kinetics and gastric stasis or vomiting. Other routes such as transdermal also offer advantages providing protection for up to 72 hours with low constant concentration levels in blood, thus reducing side effects. However, transdermal scopolamine (Table 2) has a very slow onset time (6-8 h), which be offset by simultaneous administration of oral scopolamine enabling protection from 30 minutes onwards (88). There may be variability in absorption via the transdermal route which alters effectiveness between individuals (89). Buccal absorption is effective with scopolamine but an even faster route is via nasal scopolamine spray. Peak blood levels via the nasal route may be achieved in 10 minutes and this has been shown to be effective against motion sickness (90).

Investigations of new anti-motion sickness drugs include re-examination of old drugs such as phenytoin, as well as the development of new agents. The range of drugs is wide and the list is long. Such drugs include phenytoin, betahistine, chlorpheniramine, cetirizine, fexofenadine, benzodiazepines and barbiturates, the anti-psychotic droperidol, corticosteroids such as dexamethasone, tamoxifen, opioids such as the u-opiate receptor agonist loperamide, neurokinin NK_1 receptor antagonists, vasopressin V_{1a} receptor antagonists, NMDA antagonists, 3-hydroxypyridine derivatives, $5HT_{1a}$ receptor agonists such as the anti-migraine triptan rizatriptan, ghrelin agonists, selective muscarinic M_3/m5 receptor antagonists such as zamifenacin and darifenacin. So far none of these drugs have proven to be of any major advantage over those currently available for motion sickness (91). The reasons are various and include relative lack of efficacy, complex and variable pharmacokinetics, or in those that are effective, unacceptable side-effects. Future development of drugs with highly selective affinities to receptor subtypes relevant to motion sickness may produce an anti-motion sickness drug of high efficacy with few side-effects. A good candidate would be a selective antagonist for the m5 muscarinic receptor (92).

Motorists' (vestibular) disorientation

Motorists' disorientation. Motorists learn to interpret sensory stimuli in the context of the car stabilised by its suspension and guided by steering. However, the sensory stimulation during driving is potentially ambiguous: the forces of cornering may be interpreted as tilt rather than as lateral acceleration and visual flow of the road and traffic can be interpreted to indicate veering, a form of ‘visual vertigo’. There is no consistent pattern of co-morbidity but subjects with vestibular or other sensory disturbances, anxiety or phobia may be more susceptible. Once developed, it is difficult to suppress the tendency to disorientation when driving.

Spatial disorientation while driving

Many readers will have some experience of spatial disorientation in road vehicles for which the underlying causes are almost always identifiable within the known physiology of spatial orientation. Common manifestations are as follows. A more detailed analysis is given in Golding and Gresty (78).

The very steep hill: the perception of extreme inclination is an illusion since the steepest metaled roads in Europe involve only 18–20° of tilt above horizontal. The appearance of gradient derives from visual foreshortening, engine load, misperception of subjective tilt due to seated posture, and redistribution of blood volume from the legs to the trunk (93).

The tilted horizon: the horizon may appear to be tilted when driving caused by both a visual ‘frame effect’ of the road and scenery giving false cues to orientation and also by ocular counter-rolling. The counter-rolling is provoked by the lateral acceleration rounding a bend evoking otolith-ocular reflexes. Lateral acceleration, say to the right evokes ocular counter-rolling to the left which induces an apparent rightwards tilt of the visual world. Illusions of horizon tilt could induce the perception of rolling over in vehicles (94,95) and may be part of the mechanism, evoked later in the chapter, explaining serious, persistent disorientation.

Apparent drift when stationary: this is a version of the “railway illusion” of self-motion in a stationary carriage provoked by the sight of an adjacent train moving.

Illusory drift in a vehicle is often provoked when vehicles moving on either side of one's own stationary vehicle induce 'vection' (cf 'visual vertigo', above).

*Tilting and rolling over***:** a perception of rolling over without actual rotation from vertical is associated with lateral linear acceleration and with rolling of the visual scene (94,95). The lateral, 'centripetal', acceleration experienced when rounding a bend causes a tilt of the gravitoinertial vertical from earth upright in the direction of the centre of rotation. This earth tilted direction of the Gravito Inertial Forces acting on the car is 'physical uprightness': witness the cyclist who leans into the bend to balance his bike. However, the weight and suspension of a four-wheeled vehicle keeps it oriented approximately earth upright. A driver learns to interpret the centripetal acceleration of cornering as a lateral force on his flank but an alternative perception, which is feasible in physics, is that the driver is tilted out of the bend away from the gravitoinertial upright which occurs as a compelling disorientation. This mis-perception is perhaps facilitated by the lack of structure on open highways, masking vibration and noise and banking of the road.

Veering: feeling that the car is threatening to veer to the side of the road occurs typically on open fast roads. A perception veering is a form of vection (cf 'visual vertigo' above) and is probably provoked by the 'optokinetic' stimulation of visual flow which induces a sense of self-motion in the opposite direction to the flow which is some combination of rotation and linear translation. On an open straight highway the dominant rapid optic flow is from the view of the proximal road and roadside whereas optic flow of the distance is of lower angular velocity and not so compelling. A possible perception induced in the driver is of a rotation away from the origin of the visual flow which is interpreted as veering. Veering may also occur when traffic such as large trucks are passing by, or vehicles are entering towards the driver from a slip road. The visual flow of the passing traffic can induce the perception of motion in the opposite direction, which a potential trajectory into that traffic. Susceptibility to vection may be enhanced because somatosensory cues to orientation may be masked by vibration, downregulated because of monotony and adapted because of immobility of the seated driver.

Such disorientation accords with an inappropriate interpretation of the sensory signals that arise from a complex, dynamic environment (96) and can be thought of as a naïve way of interpreting sensory signals, whereas driving is a highly cognitive skill (97) demanding specific selection and interpretation of sensory input. The driver may not be aware of disorientation and may respond to subliminal cues (98) so that steering adjustments can occur before perception of veering.

Motorists complaining of systematic disorientation 'Dizzy Drivers'

Occasional drivers present with complaints of inappropriate perceptions of veering and tilt or rolling over on the highway. These are the dominant features of the 'motorist's vestibular disorientation syndrome' as first described by Page and Gresty (16), but better termed 'motorists disorientation syndrome' (99). The inappropriate perceptions are so systematic that patients have changed cars before realizing that the problem was not that of the vehicle. In some patients the onset of disorientation symptoms is abrupt in a single experience; in others there seems to be a gradual buildup of severity of symptoms until threat of veering or rolling over become a reliable occurrence on all open highways, thereby confining the driver to lesser town and suburban roads.

It is commonplace for passengers to become apprehensive that a vehicle is running out of control, often expressed in the 'back seat driver' attitude. The striking feature of motorist's disorientation is that the driver, used to being in control, is surprised that he perceives the vehicle to be unstable under unremarkable road conditions.

Susceptibility to disorientation was originally thought to be caused by vestibular imbalance (16). It is certainly the case that vestibular disorder causes incorrect orientation in a vehicle (100,101,102). However, subsequent experience showed that few dizzy drivers have identifiable vestibular asymmetry. Almost all have no related organic disorder although many have trait or state anxiety. The following patients are illustrative with further details given in Golding and Gresty (78). In all patients to be described the stereotypical characteristics of disorientation were rolling over and/or veering.

1) A middle aged man experienced symptoms of disorientation when driving which completely disappeared when a hitherto unsuspected 'BPPV' (benign paroxysmal positional vertigo) was identified and resolved by an Epley manoeuvre.

2) After a near crash flying in fog a special forces pilot experienced perceptions of instability in his helicopter which extended to driving his car. He was in a divorce but denied that he was otherwise stressed by operations that had killed a colleague.

3) A middle age man, retraining after an unsuccessful career, began to experience disorientation driving on the highway to a retraining centre. He admitted to considerable anxiety about security and achievement.

4) Two taxi drivers and one roadside assistance mechanic, all had similar abrupt onset of persistent disorientation when highway driving. One was provoked crossing a high bridge, a second when exiting a roundabout causing her steer into oncoming traffic. None had identifiable organic disorder or raised anxiety.

4) When deserted by her husband, a mother with several children began to experience disorientation, even on local roads, when driving to work and trying to manage child care.

Prevalence

In a London tertiary referral clinic, specializing in and balance disorders (A. M. Bronstein, personal observation), 4–5 patients per year are seen with specific complaints of driving, amongst 450–500 new patients referred with complaints of dizziness. The sufferers have been adults of both sexes, and rarely with a history of psychiatric or relevant organic disorder.

The absence of comprehensive surveys of ‘dizzy motorists’ in the medical literature, following the original study is surprising since a recent article in a weekly magazine, aimed at housewives indicates a general awareness of the problem. Thus: Tanya Byron, writing in ‘Good Housekeeping’ (October 2018 pp 98-99) advises on ‘….fear of motorway driving’, highlighting the role of anxiety and phobia. She advises an otological screen for vestibular disorder and recommends appropriate cognitive behaviour therapy. The widespread awareness of motorists’ disorientation, despite the paucity of scientific literature may be because of sufferers’ fail to seek medical opinion for fear of disqualification from driving.

Treatment

The treatment model for rehabilitation of motorists’ disorientation is based on rehabilitation of flying disorientation and motion sickness (103,104) and comprises desensitization and retraining within framework of cognitive therapy: viz

- Exclusion of neurological/vestibular/psychiatric disorder and treatment of high anxiety.
- Explanation of how disorientation may occur as described above.

- Progressive desensitization commencing with short duration exposures driving slowly on local roads progressing to faster trips on the highway. The protagonist gives himself a verbal briefing of the planned journey, talks himself through the driving manoeuvres and stopping for 'time out' if he becomes overstressed, in which case anxiolytic controlled breathing and postural relaxation may help. The verbal appraisal highlights cognitive context. For examples: if he feels his lane is too narrow a check that the vehicle ahead negotiates the lane with ease assures the driver that he can follow; if he feels veering he checks the steering wheel and sides of the vehicle against lane markings.
- A log should be kept of the rehabilitation as reinforcing evidence of progress.

Desensitization by 'immersion' is inappropriate; a patient who persisted with long driving sessions on a therapist's recommendation incurred a serious RTI road traffic incident which she attributed to accumulating disorientation. Patients who have complied with this therapeutic program have recovered the ability to drive but can readily decompensate. However it seems that once a motorist has experienced disorientation it becomes difficult to "quarantine" (105) inappropriate interpretations of the sensory stimulation during driving and he may readily revert to disorientation.

Implications for road safety

The authors have encountered only one serious accident resulting from a case of motorist's disorientation together with one report of veering creating a potential for collision. It is likely that few incidents are reported because disorientation is so alarming that the driver slows or stops. Currently, there are no *specific* guidelines on fitness to drive while susceptible to motorists' disorientation, although the advisability of both flying and driving with active BPPV, in which head tilts can provoke disabling dizziness, has been raised (101).

In the road safety literature a high proportion of road traffic incidents are attributed to lapses of attention without adequate consideration of the role of spatial orientation. It should be stressed that a main factor in tuning attention and regulating vigilance is state of spatial orientation: viz driving fast on a highway may be unremarkable whereas viewing nearby, fast traffic from the roadside is alarming (78).

Classification and relationship to other disorientation syndromes

Motorist's disorientation has been classified with (14,106) 'Phobic Postural Vertigo' and more recently 'Persistent Postural Dizziness' (17, 107) which is a functional 'vestibular system' disorder. However, phobia is not typical of the majority of cases, as neither is contextual postural vertigo. Furthermore, some patients have a structural vestibular disorder which can account for misperceptions of orientation. Hence, such vague classifications are not helpful, particularly since the stereotypical symptoms of disoriented motorists can be explained by known physiological mechanisms. The missing element in understanding motorists' disorientation is the precise mechanism causing the driver to abandon the learned framework of sensory interpretation during driving and adopt an alternative interpretation of the sensory input.

References

1 Seemungal BM, Glasauer S, Gresty MA, Bronstein AM. Vestibular perception and navigation in the congenitally blind. J Neurophysiol 2007;97:4341-56

2 Okada T, Grunfeld E, Shallo-Hoffmann J, Bronstein AM. Vestibular perception of angular velocity in normal subjects and in patients with congenital nystagmus. Brain 1999;122:1293-303

3 Grunfeld EA, Shallo-Hoffmann JA, Cassidy L et al. Vestibular perception in patients with acquired ophthalmoplegia. Neurology 2003;60:1993-5

4 Hoffman RA, Brookler KH. Underrated neurotologic symptoms. Laryngoscope 1978;88:1127-38

5 Hood JD. Unsteadiness of cerebellar origin: an investigation into its cause. J Laryngol Otol 1980;94:865-76

6 Bronstein AM. Under-rated neuro-otological symptoms. Hoffman and Brookler 1978 revisited. Brit Med Bull 63: 213-21

7 Longridge NS, Mallinson AI, Denton A. Visual vestibular mismatch in patients treated with intra-tympanic gentamicin for Meniere's disease. J Otolaryngol 2002;31:5-8

8 Jacob RG. Panic disorder and the vestibular system. Psychiatr Clin North Am 1988;11:361-74

9 Bronstein AM. Visual vertigo syndrome: clinical and posturography findings. J Neurol Neurosurgery Psychiatry 1995;59:472-476

10 Guerraz M, Yardley L, Bertholon P et al. Visual vertigo: symptom assessment, spatial orientation and postural control. Brain 2001;124:1646-56

11 Pavlou M, Davies RA, Bronstein AM. The assessment of increased sensitivity to visual stimuli in patients with chronic dizziness. J Vestib Res 2006;16:223-31

12 Cousins S, Kaski D, Cutfield N, Arshad Q, Ahmad H, Gresty MA, Seemungal BM, Golding J, Bronstein AM. Predictors of clinical recovery from vestibular neuritis: a prospective study. Ann Clin Transl Neurol. 2017 Mar 22;4(5):340-346. doi: 10.1002/acn3.386

13 Furman JM, Jacob RG. Psychiatric dizziness. Neurology 1997;48:1161-6

14 Brandt T. Phobic postural vertigo. Neurology 1996;46:1515-9

15 Bronstein AM, Gresty MA, Luxon LM, Ron MA, Rudge P, Yardley L. Phobic postural vertigo. Neurology 1996;46:1515-9

16 Page NG, Gresty MA. Motorist's vestibular disorientation syndrome. J Neurol Neurosurg Psychiat 1985;48:729-35

17 Staab JP, Eckhardt-Henn A, Horii A, Jacob R, Strupp M, Brandt T, Bronstein A.Diagnostic criteria for persistent postural-perceptual dizziness (PPPD): Consensus document of the committee for the Classification of Vestibular Disorders of the Bárány Society. J Vestib Res. 2017;27(4):191-208. doi: 10.3233/VES-170622.

18 Cawthorne T. The rationale of physiotherapy in vertigo and facial palsy. Physiotherapy 1952;38:237-41

19 Black FO, Pesznecker SC. Vestibular adaptation and rehabilitation. Curr Opin Otolaryngol Head Neck Surg 2003;11:355-60

20 Pavlou M, Shummway-Cook A, Horak F, Yardley L, Bronstein AM. Rehabilitation of balance disorders in the patient with vestibular pathology. In: Bronstein AM, Brandt T, Woollacott M, Nutt J, ed. Clinical Disorders of Balance and Gait Disorders, London: Edward Arnold Publishers;2004:317-43

21 Bronstein AM, Lempert T. Dizziness: a practical approach to diagnosis and management. Cambridge Clinical Guides: Cambridge University Press; 2nd Edition, 2017.

22 Vitte E, Semont A, Berthoz A. Repeated optokinetic stimulation in conditions of active standing facilitates recovery from vestibular deficits. Exp Brain Res 1994;102:141-8.

23 Pavlou M, Lingeswaran A, Davies RA, Gresty MA, Bronstein AM. Simulator based rehabilitation in refractory dizziness. J Neurol 2002; 251:983-995.

24 Sluch IM, Elliott MS, Dvorak J, Ding K, Farris BK. Acetazolamide: A New Treatment for Visual Vertigo. Neuroophthalmology. 2017 Aug; 41(6):315-320. doi: 0.1080/01658107.2017.1326944.

25 Çelebisoy N, Gökçay F, Karahan C, Bilgen C, Kirazlı T, Karapolat H, Köse T. Acetazolamide in vestibular migraine prophylaxis: a retrospective study. Eur Arch Otorhinolaryngol. 2016 Oct; 273(10):2947-51. doi: 10.1007/s00405-015-3874-4.

26 Trinidade A, Goebel JA. Persistent Postural-Perceptual Dizziness-A Systematic Review of the Literature for the Balance Specialist. Otol Neurotol. 2018 Dec; 39(10):1291-1303. doi: 10.1097/MAO.0000000000002010.

27 Popkirov S, Stone J, Holle-Lee D. Treatment of Persistent Postural-Perceptual Dizziness (PPPD) and Related Disorders. Curr Treat Options Neurol. 2018 Oct 13; 20(12):50. doi: 10.1007/s11940-018-0535-0.

28 Benson AJ. Motion sickness. In: K. Pandolf and R. Burr, eds. Medical Aspects of Harsh Environments vol. 2. Washington, DC: Walter Reed Army Medical Center; 2002: 1048-1083.

29 Keshavarz B, Hecht H, Lawson BD. Visually Induced Motion Sickness. Causes, Characteristics, and Countermeasures. In: K. S. Hale, K. M. Stanney, eds, Handbook of Virtual Environments: Design, Implementation, and Applications (2nd edition). Boca Raton, FL: CRC Press; 2014: 648–697

30 Diels C, Bos JE. Self-driving carsickness. Appl Ergon. 2016; 53 Pt B: 374-82.

31 Stern RM, Koch KL, Leibowitz HW, Linblad IM, Shupert CL, Stewart WR. Tachygastria and motion sickness. Aviat Space Environ Med. 1985; 56:1074–1077.

32 Eversmann T, Gottsmann M, Uhlich E, Ulbrecht G, von Werder K, Scriba PC. Increased secretion of growth hormone, prolactin, antidiuretic hormone and cortisol induced by the stress of motion sickness. Aviat Space Environ Med. 1978; 49: 53-7.

33 Golding JF. Phasic skin conductance activity and motion sickness. Aviat Space Environ Med. 1992; 63:165–171.

34 Cheung B, Nakashima AM, Hofer KD. Various anti-motion sickness drugs and core body temperature changes. Aviat Space Environ Med. 2011; 82: 409-15.

35 Hettinger LJ, Kennedy RS, McCauley ME.Motion and human performance. In: Crampton GH, ed. Motion and Space Sickness. Boca Raton, FL: CRC Press; 1990: 412-41.

36 Heer, M., Paloski, W.H. Space motion sickness: incidence, etiology, and countermeasures. Auton. Neurosci. 2006; 129: 77-79.

37 Reason JT & Brand JJ. Motion Sickness. London: Academic Press; 1975.

38 Oman CM, Cullen KE. Brainstem processing of vestibular sensory exafference: implications for motion sickness etiology. Exp Brain Res 2014; 232: 2483-92.

39 Bos JE, Bles W. Modelling motion sickness and subjective vertical mismatch detailed for vertical motions. Brain Res Bull 1998; 47: 537-542.

40 Bubka A, Bonato F, Urmey S, Mycewicz D. Rotation velocity change and motion sickness in an optokinetic drum. Aviat Space Environ Med 2006; 77: 811-815.

41 Stott JRR. Mechanisms and treatment of motion illness. In: Davis CJ, Lake-Bakaar GV, Grahame-Smith DG, eds. Nausea and vomiting: mechanisms and treatment. Berlin: Springer-Verlag; 1986:110-29.

42 Treisman M. Motion sickness: an evolutionary hypothesis. Science 1997; 197: 493-495.

43 Morrow GR. The effect of a susceptibility to motion sickness on the side effects of cancer chemotherapy. Cancer 1985; 55: 2766-70.

44 Money KE & Cheung BS. Another function of the inner ear: facilitation of the emetic response to poisons. Aviat Space Environ Med 1983; 54: 208-211.

45 Yates BJ, Miller AD, Lucot JB. Physiological basis and pharmacology of motion sickness: an update. Brain Res Bull 1998; 47: 395-406.

46 Guedry FE, Rupert AR, Reschke MF. Motion sickness and development of synergy within the spatial orientation system. A hypothetical unifying concept. Brain Res Bull 1998; 47: 475-480.

47 Oman CM. Are evolutionary hypotheses for motion sickness “just-so” stories? J Vest Res 2012; 22: 117-127.

48 Reavley CM, Golding JF, Cherkas LF, Spector TD, MacGregor AJ. Genetic influences on motion sickness susceptibility in adult females: a classical twin study Aviat Space Environ Med 2006; 77: 1148-52.

49 Hromatka BS, Tung JY, Kiefer AK, et al. Genetic variants associated with motion sickness point to roles for inner ear development, neurological processes and glucose homeostasis. Hum Mol Genet. 2015; 24: 2700-8.

50 Turner M & Griffin MJ. Motion sickness in public road transport: passenger behaviour and susceptibility. Ergonomics 1999; 42: 444-461.

51 Kennedy RS, Lanham DS, Massey CJ & Drexler JM. Gender differences in simulator sickness incidence: implications for military virtual reality systems. SAFE Journal 1995; 25: 69-76.

52 Lawther A, Griffin MJ. A survey of the occurrence of motion sickness amongst passengers at sea. Aviat Space Environ Med 1988; 59: 399-406.

53 Golding JF, Kadzere PN, Gresty MA. Motion Sickness Susceptibility Fluctuates through the Menstrual Cycle. Aviat Space Environ Med 2005; 76: 970-3.

54 Golding JF. Motion sickness susceptibility questionnaire revised and its relationship to other forms of sickness. Brain Res Bull 1998; 47: 507-516.

55 Johnson WH, Sunahara FA, Landolt JP. Importance of the vestibular system in visually induced nausea and self-vection. J Vestib Res 1999; 9: 83-87.

56 Drummond PD. Effect of tryptophan depletion on symptoms of motion sickness in migraineurs. Neurology 2005; 65: 620-2.

57 Boldingh MI, Ljostad U, Mygland A, Monstad P.Vestibular sensitivity in vestibular migraine: VEMPs and motion sickness susceptibility. Cephalalgia 2011; 31: 1211-9.

58 Golding JF, Patel M. Meniere's, migraine, and motion sickness, Acta Oto-Laryngologica, 2017; 137: 495-502.

59 Golding JF. Predicting Individual Differences in Motion Sickness Susceptibility by Questionnaire. Personality and Individual differences, 2006; 41: 237-248.

60 Whittle, J. An exact diary of the late expedition of His Illustrious Highness the Prince of Orange, 1689. Cited in: Pike, J. Tall Ships in Torbay a Brief Maritime History, Bradford on Avon, Wilts, UK: Ex Libris Press; 1986: 35.

61 Nachum Z, Shupak A, Letichevsky V, Ben-David J, Tal D, Tamir A, Talmon Y, Gordon CR, Luntz M. Mal de debarquement and posture: reduced reliance on vestibular and visual cues. Laryngoscope 2004; 114: 581-6.

62 Murdin L, Golding J, Bronstein A .Managing motion sickness. BMJ 2011; 343: 1213-1217.

63 Cha YH. Mal de debarquement. Semin Neurol 2009; 29:520-7.

64 Yuan H, Shou G, Gleghorn D, Ding L, Cha YH. Resting State Functional Connectivity Signature of Treatment Effects of Repetitive Transcranial Magnetic Stimulation in Mal de Debarquement Syndrome. Brain Connect 2017: 617-626.

65 Cowings PS, Toscano WB. Autogenic-feedback training exercise is superior to promethazine for control of motion sickness symptoms. J Clin Pharmacol 2000; 40: 1154-65.

66 Yen Pik Sang F, Billar J, Gresty MA, Golding JF. Effect of a novel motion desensitization training regime and controlled breathing on habituation to motion sickness. Percept Mot Skills 2005; 101: 244-56.

67 Kaplan J, Ventura J, Bakshi A, Pierobon A, Lackner JR, DiZio P. The influence of sleep deprivation and oscillating motion on sleepiness, motion

sickness, and cognitive and motor performance. Auton Neurosci. 2017; 202: 86-96.

68 Wood CD, Manno JE, Manno BR, Odenheimer RC, Bairnsfather LE. The effect of antimotion sickness drugs on habituation to motion. Aviat Space Environ Med 1986; 57: 539-42.

69 van Marion WF, Bongaerts MC, Christiaanse JC, Hofkamp HG, van Ouwerkerk W. Influence of transdermal scopolamine on motion sickness during 7 days' exposure to heavy seas. Clin Pharmacol Ther 1985; 38: 301-5.

70 Golding JF, Bles W, Bos JE, Haynes T, Gresty MA. Motion sickness and tilts of the inertial force environment: active suspension systems versus active passengers. Aviat Space Environ Med 2003; 74: 220-227.

71 Wada T, Konno H, Fujisawa S, Doi S. Can Passengers' Active Head Tilt Decrease the Severity of Carsickness? Effect of Head Tilt on Severity of Motion Sickness in a Lateral Acceleration Environment. Human Factors 2012; 54: 226-234.

72 Golding JF, Markey HM & Stott JRR. The effects of motion direction, body axis, and posture, on motion sickness induced by low frequency linear oscillation. Aviat Space Environ Med, 1995; 66: 1046-51.

73 Rolnick A, Lubow RE. Why is the driver rarely sick? The role of controllability in motion sickness. Ergonomics 1991; 34: 867-879.

74 Bos JE, MacKinnon SN, Patterson A. Motion sickness symptoms in a ship motion simulator: effects of inside, outside, and no view. Aviat Space Environ Med 2005; 76: 1111-8.

75 Ziavra NV, Yen Pik Sang FD, Golding JF, Bronstein AM, Gresty MA. Effect of breathing supplemental oxygen on motion sickness in healthy adults. Mayo Clinic Proceedings 2003; 78: 574-8.

76 Chu H, Li M-H, Juan S-H, Chiou W-Y: Effects of transcutaneous electrical nerve stimulation on motion sickness induced by rotary chair: a crossover study. J Altern Complement Medicine 2012; 18: 494-500.

77 Miller KE, Muth ER. Efficacy of acupressure and acustimulation bands for the prevention of motion sickness. Aviat Space Environ Med 2004; 75: 227-34.

78 Golding JF, Gresty MA. 2019. Motion Sickness and Disorientation in Vehicles. In: Oxford Textbook of Neuro-otology. Chapter 28. Bronstein AM, ed. Oxford University Press. 2019 (In press)

79 Golding JF, Prosyanikova O, Flynn M, Gresty MA. The effect of Smoking Nicotine Tobacco versus Smoking Deprivation on Motion Sickness. Autonomic Neuroscience: Basic and Clinical 2011; 160: 53–58.

80 Palatty PL, Haniadka R, Valder B, et al. Ginger in the prevention of nausea and vomiting: a review. Crit Rev Food Sci Nutr 2013; 53: 659-69.

81 Levine ME, Muth ER, Williamson MJ, Stern RM. Protein-predominant meals inhibit the development of gastric tachyarrhythmia, nausea and the symptoms of motion sickness. Aliment Pharmacol Ther 2004; 19: 583-90.

82 Lindseth G, Lindseth PD. The relationship of diet to airsickness. Aviat Space Environ Med 1995; 66: 537-541.

83 Wood CD, Graybiel A. Evaluation of 16 anti-motion sickness drugs under controlled laboratory conditions. Aerospace Med 1969; 39: 1341-4.

84 Levine ME, Chillas JC, Stern RM, Knox GW. The effects of serotonin (5-HT3) receptor antagonists on gastric tachyarrhythmia and the symptoms of motion sickness. Aviat Space Environ Med 2000; 71: 1111-4.

85 Reid K, Palmer JL, Wright RJ, Clemes SA, Troakes C, Somal HS, House F, Stott JR. Comparison of the neurokinin-1 antagonist GR205171, alone and in combination with the 5-HT3 antagonist ondansetron, hyoscine and placebo in the prevention of motion-induced nausea in man. Br J Clin Pharmacol 2000; 50: 61-4.

86 Hoyt RE, Lawson BD, McGee HA, Strompolis ML, McClellan MA. Modafinil as a potential motion sickness countermeasure. Aviat Space Environ Med 2009; 80: 709-715.

87 Stewart JJ, Wood MJ, Parish RC, Wood CD. Prokinetic effects of erythromycin after antimotion sickness drugs. J Clin Pharmacol 2000; 40: 347-53.

88 Nachum Z, Shahal B, Shupak A, Spitzer O, Gonen A, Beiran I, Lavon H, Eynan M, Dachir S, Levy A. Scopolamine bioavailability in combined oral and transdermal delivery. J Pharmacol Exp Ther 2001; 296: 121-3.

89 Gil A, Nachum Z, Dachir S, Chapman S, Levy A, Shupak A, Adir Y, Tal D. Scopolamine patch to prevent seasickness: clinical response vs. plasma concentration in sailors. Aviat Space Environ Med 2005; 76: 766-70.

90 Simmons RG, Phillips JB, Lojewski RA, Wang Z, Boyd JL, Putcha L. The efficacy of low-dose intranasal scopolamine for motion sickness. Aviat Space Environ Med. 2010; 81: 405-12.

91 Golding JF. Motion Sickness Susceptibility. Autonomic Neuroscience, 2006; 30: 67-76.

92 Golding JF, Wesnes KA, Leaker BR. The Effects of the Selective Muscarinic M3 Receptor Antagonist Darifenacin, and of Hyoscine (scopolamine), on Motion Sickness, Skin Conductance & Cognitive Function. British Journal Clinical Pharmacology, 2018; 84: 1535–1543.

93 Ito Y, Gresty MA. Subjective postural orientation and visual vertical during slow pitch tilt for the seated human subject. Aviat Space Environ Med, 1997 Jan; 68: 3-12.

94 Dichgans J, Held R, Young LR, Brandt T. Moving visual scenes influence the apparent direction of gravity. Science 1972, 178: 1217–9.

95 Previc FH, Kenyon, RV, Boer, ER, Johnson, BH. The effects of background visual roll stimulation on postural and manual control and self-motion perception. Perception Psychophys 1993, 54: 93–107.

96 Probst T, Straube A, Bles W. Differential effects of ambivalent visual-vestibular-somatosensory stimulation on the perception of self-motion. Behav Brain Res, 1985, 16: 71–9.

97 Wertheim AH, Mesland BS, Bles W. Cognitive suppression of tilt sensations during linear horizontal self-motion in the dark. Perception, 2001, 30: 733–41.

98 Mogg K, Bradley B. A cognitive-motivational analysis of anxiety. Behav Res Ther, 1998, 36: 809–48.

99 Gresty MA, Ohlmann TH. Motorists’ Vestibular Disorientation Syndrome Revisited. RTO/NATO. RT-MPO-086. Spatial Disorientation in Military Vehicles, Causes, Consequences and Cures. 2003; 13.1-13.7.

100 Aoki M, Ito Y, Burchill P, Brookes GB, Gresty MA. Tilted perception of the subjective ‘upright’ in unilateral loss of vestibular function. Am J Otol, 1999, 20: 741–7.

101 Gresty MA. BPPV and fitness to fly--or drive. Aviat Space Environ Med. 2008; 79: 541.

102 Benson AJ. Spatial disorientation—common illusions. In: Ernsting J, Nicholson AN, Rainford DJ, eds. Aviation Medicine. 3rd ed. Oxford, England: Butterworth Heinemann; 1999:437–454.

103 Dobie TG, May JG. Cognitive-behavioral management of motion sickness. Aviat Space Environ Med 1994; 65(10 Pt 2):C1–C2 Review.

104 Reid GE. Aviation psychiatry. In: Ernsting J, Nicholson AN, Rainford DJ, eds. Aviation Medicine. 3rd ed. Oxford, England: Butterworth, Heinemann; 1999:397–416.

105 Gresty MA, Waters S, Bray A, Bunday K, Golding JF. Impairment of spatial cognitive function with preservation of verbal performance during spatial disorientation. Curr Biol 2003;13(21):R829–R830.

106 Brandt T, Huppert D, Dieterich M. Phobic postural vertigo: a first follow-up. J Neurol 1994; 241:191–195.

107 Seemungal BM, Passamonti L. Persistent postural-perceptual dizziness: a useful new syndrome. Pract Neurol. 2018 Feb; 18(1):3-4.

Figures & Figure Legends

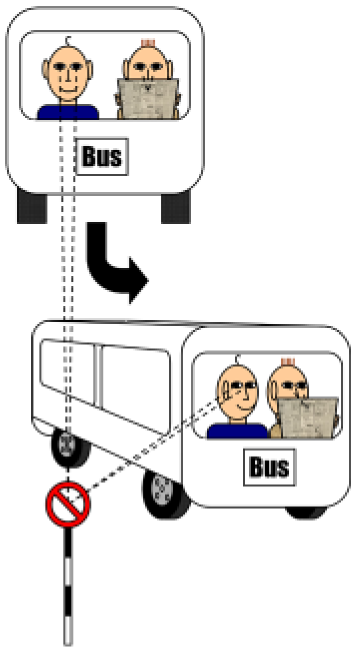

Figure 1: When a passenger looks out of a bus fixating upon a road sign, vestibular (VOR) and visual (pursuit) mechanisms cooperate to stabilise the eyes on the visual target as the bus turns round. In contrast, when a passenger tries to read a newspaper, the VOR takes the eyes off the visual target but pursuit eye movements suppress the VOR so that reading can proceed. In the latter situation visual and vestibular inputs are said to be in conflict. From Bronstein and Lempert 2007 [21], with permission.

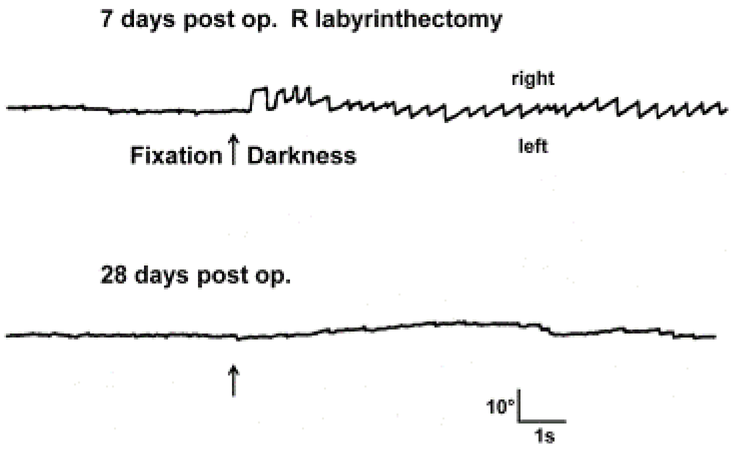

Figure 2: Horizontal electro-oculography in a patient 7 days (top) and one month after a labyrinthectomy (bottom). The nystagmus in the acute phase is almost exclusively seen in the dark. Such suppression of the nystagmus by visual fixation is thought to be akin to normal VOR suppression, as in Figure 1 (bottom).

Figure 3: Optokinetic or visual motion desensitisation treatment for patients with vestibular disorders reporting visual vertigo symptoms. Left: roll (coronal) plane rotating optokinetic disk; Middle: planetarium-generated moving dots whilst the subject walks; Right: 'Eye-Trek' or head-mounted TV systems projecting visual motion stimuli. In this case, in advanced stages of the therapy, the patient moves the head and trunk whilst standing on rubber foam. Based on Pavlou et al 2002 [23], with permission.

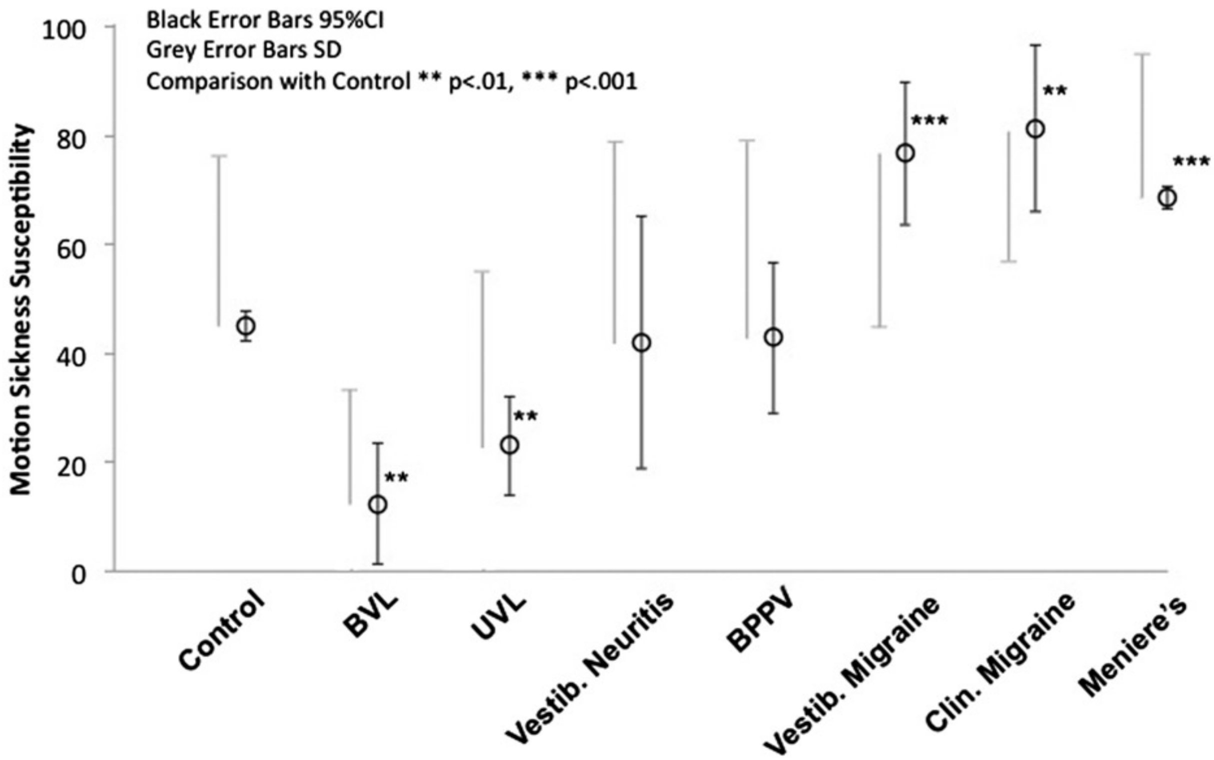

Figure 4: Motion sickness susceptibility is shown for patient groups after the onset of disease together with significances of comparison with age equivalent healthy controls. Higher scores indicate greater motion sickness susceptibility. The 95%CIs are smaller for controls and Meniere's disease as a consequence of larger numbers. BVL: bilateral vestibular loss; UVL: unilateral vestibular loss in compensated (adapted) patients; BPPV: benign paroxysmal positional vertigo. BVL: bilateral vestibular loss; UVL: unilateral vestibular loss; BPPV: benign paroxysmal positional vertigo; Clin. Migraine: patients with severe migraine attending migraine clinics (Adapted from Golding & Patel 2017 [58])

Tables

Table 1: Motion Sickness Susceptibility Questionnaire Short-form (MSSQ-Short) (adapted from Golding 2006 [59])

This questionnaire is designed to find out how susceptible to motion sickness you are, and what sorts of motion are most effective in causing that sickness. Sickness here means feeling queasy or nauseated or actually vomiting.

Your CHILDHOOD Experience Only (before 12 years of age), for each of the following types of transport or entertainment please indicate:

1. **As a CHILD (before age 12),** how often you **Felt Sick or Nauseated** (tick boxes):

	Not Applicable - Never Travelled	**Never Felt Sick**	**Rarely Felt Sick**	**Sometimes Felt Sick**	**Frequently Felt Sick**
Cars					
Buses or Coaches					
Trains					
Aircraft					
Small Boats					
Ships, e.g. Channel Ferries					
Swings in playgrounds					
Roundabouts in playgrounds					
Big Dippers, Funfair Rides					
	t	0	1	2	3

Your Experience over the LAST 10 YEARS (approximately), for each of the following types of transport or entertainment please indicate:

2. **Over the LAST 10 YEARS,** how often you **Felt Sick or Nauseated** (tick boxes):

	Not Applicabl Never Travelle	**Never Felt Sick**	**Rarely Felt Sick**	**Sometimes F Sick**	**Frequently Felt Sick**
Cars					
Buses or Coaches					
Trains					
Aircraft					
Small Boats					
Ships, e.g. Channel Ferries					
Swings in playgrounds					
Roundabouts in playgrounds					
Big Dippers, Funfair Rides					
	t	0	1	2	3

Table 2: Common Anti–Motion Sickness Drugs (Adapted from Benson, 2002 [28])

Drug	**Route**	**Adult Dose**	**Time of Onset**	**Duration of Action (h)**
Scopolamine	oral	0.3–0.6 mg	30 min	4
Scopolamine	injection	0.1–0.2 mg	15 min	4
Scopolamine	transdermal patch	one	6–8 h	72
Promethazine	oral	25–50 mg	2 h	15
Promethazine	injection	25 mg	15 min	15
Promethazine	suppository	25 mg	1 h	15
Dimenhydrinate	oral	50–100 mg	2 h	8
Dimenhydrinate	injection	50 mg	15 min	8
Cyclizine	oral	50 mg	2 h	6
Cyclizine	injection	50 mg	15 min	6
Meclizine	oral	25–50 mg	2 h	8
Buclizine	oral	50 mg	1 h	6
Cinnarizine	oral	15–30 mg	4 h	8