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REVIEW

Space motion sickness

James R. Lackner · Paul DiZio

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Abstract Motion sickness remains a persistent problem in spaceflight. The present review summarizes available knowledge concerning the incidence and onset of space motion sickness and aspects of the physiology of motion sickness. Proposed etiological factors in the elicitation of space motion sickness are evaluated including fluid shifts, head movements, visual orientation illusions, Coriolis cross-coupling stimulation, and otolith asymmetries. Current modes of treating space motion sickness are described. Theoretical models and proposed ground-based paradigms for understanding and studying space motion sickness are critically analyzed. Prediction tests and questionnaires for assessing susceptibility to space motion sickness and their limitations are discussed. We conclude that space motion sickness does represent a form of motion sickness and that it does not represent a unique diagnostic entity. Motion sickness arises when movements are made during exposure to unusual force backgrounds both higher and lower in magnitude than 1 g earth gravity.

Keywords Motion sickness · Sensory conflict · Fluid shift · Sensorimotor control · Weightlessness

J. R. Lackner (✉) · P. DiZio
Ashton Graybiel Spatial Orientation Laboratory and Volen Center for Complex Systems, Brandeis University, Waltham, MA 02454-9110, USA
e-mail: lackner@brandeis.edu

P. DiZio
e-mail: dizio@brandeis.edu

Incidence of space motion sickness

A remarkable aspect of human exposure to weightlessness for brief periods, e.g. days, is the relative paucity of severe side effects. "Space motion sickness" and the mal de barquement that occurs after re-entry and landing are the most obvious adverse consequences. Motion sickness first appeared as an operational problem in the second manned Soviet mission (Titov and Caidin 1962) and became a significant concern in later missions, especially with increased flight duration. It emerged as a problem in the American Space Program during the Apollo moon missions with the larger crew compartments then available compared with the cramped crew space in the earlier Mercury ($\approx$1 m^3) and Gemini missions ($\approx$1.5 m^3) (Graybiel 1980; Graybiel et al. 1977; Nicogossian and Uri 1994). The US missions then had the possibility, as had been present already in the Soviet flights, of unrestricted body movements and free floating (Matsnev et al. 1983).

The overall incidence of symptoms of motion sickness in the space shuttle program has been approximately 70% for astronauts in their first space mission but is lower in experienced astronauts (Davis et al. 1988). Symptoms range in severity from drowsiness to nausea and vomiting. Since the beginning of the manned spaceflight era, our understanding of motion sickness has increased and a larger constellation of symptoms and signs is now recognized as being characteristic of motion sickness. Among these is the "sopite syndrome" which refers to the chronic drowsiness, fatigue, mood and personality changes, and lack of initiative associated with long-term exposure to mildly provocative stimulation (Graybiel and Knepton 1976). Symptoms related to the sopite syndrome persist during exposure to provocative situations long after more familiar features, such as

nausea and pallor have abated. Aspects of the sopite syndrome may have been experienced in the pre-Apollo missions without being recognized as being indicative of motion sickness. All the primary signs and symptoms of terrestrial motion sickness, with the exception of pallor, have been observed in space motion sickness.

Symptoms of space motion sickness usually start to develop within the first several hours in weightlessness (Thornton et al. 1987a). After 72–96 h, most astronauts and cosmonauts have either recovered or begun to recover and are able to move about freely without eliciting debilitating symptoms. In terms of incidence of symptoms and recovery, the American and Russian experiences seem comparable (cf. Davis et al. 1988; Harm 1990; Jennings 1998; Matsnev et al. 1983; Homick et al. 1984).

Physiology of motion sickness

Motion sickness is a complex phenomenon. Table 1 presents a diagnostic system that was developed by Graybiel et al. (1968) to rate the severity of motion sickness under laboratory and operational conditions. Nausea and vomiting are synonymous with motion sickness in most people's minds but pallor and cold sweating are also characteristics. Pallor is not a diagnostic sign in spaceflight, however, because of the persisting engorgement of the facial veins owing to the lack of a hydrostatic gradient in weightless conditions. Drowsiness is now recognized to be a common feature of low grade motion sickness, as is headache (Graybiel 1969; Graybiel and Knepton 1976).

For simplicity, motion sickness can be discussed under two primary rubrics: (1) stomach emptying and (2) stress response (cf. Money et al. 1996). The mechanisms of vomiting and its control have been thoroughly explicated by Lang (1992, 1999) and Miller and Yates (Miller 1991; Miller and Grelot 1996; Miller and Leslie 1994; Miller and Wilson 1984; Yates and Miller 1996; Yates et al. 1998). The stress response associated with motion sickness includes psychic, endocrine, and autonomic changes. The conscious or psychic sensations include anxiety, distress, and apprehension even approaching dread. The endocrine responses involve elevations of plasma levels of virtually all of the stress response hormones. Antidiuretic hormone levels are increased several fold and ACTH, cortisol, epinephrine, norephinephrine, prolactin, growth hormone, beta endorphin, and thyroid hormone levels increase as well (Money et al. 1996). Most of these changes are associated with elevated activity of the sympathetic nervous system, as is the increased blood flow in skeletal muscles which may accompany motion sickness (Johnson 1974; Johnson et al. 1993; Sunahara et al. 1987).

Autonomic nervous system responses are variable and inconsistent during motion sickness. For the motion sick person, subjectively salivation seems to increase but actually salivary flow usually decreases (Gordon et al. 1989). Motion sick individuals may not swallow as much saliva as normal, thus producing this apparent contradiction. Heart rate may increase, decrease, or not change with motion sickness and may be influenced by level of severity but this remains uncertain. Tachygastria, electrogastrogram activity in the 7–10 cpm range is reported to accompany motion sickness and has been proposed as an objective measure of motion sickness (Koch 1999; Stern et al. 1985, 1987a, b; 1989, 1990). However, other studies have failed to confirm this relationship and found that (a) tachygastria is primarily associated with heightened anxiety levels, (b) the onset of tachygastria and onset of reported symptoms are not temporally linked, either can occur earlier, (c) motion sickness symptoms can occur without tachygastria, (d) tachygastria can occur without motion sickness symptoms, (e) the degree of tachygastria is not correlated with type or severity of symptoms, (f) tachygastria can persist long after all apparent symptoms of motion sickness have resolved (Cheung and Vaitkus 1998; Kiernan et al. 1997; Lawson 1993). The *R–R* interval, the time between heart beats, is

Table 1 Cardinal symptoms of motion sickness and criteria for grading motion sickness severity (Graybiel et al. 1968)

Category	Pathognomonic (16 points)	Major (8 points)	Minor (4 points)	Minimal (2 points)	AQS (1 point)
Nausea syndrome	Vomiting or retching	Nausea II, III	Nausea I	Epigastric discomfort	Epigastric awareness
Skin		Pallor III	Pallor II	Pallor I	Flushing
Cold sweating		III	II	I	
Increased salivation		III	II	I	
Drowsiness		III	II	I	
Pain					Headache
Central nervous system					Dizziness Eyes closed > II Eyes open III

AQS Additional qualifying symptoms; *III* severe or marked; *II* moderate; *I* slight

reported to become less variable, a sign of sympathetic activity with motion sickness (Koch 1993). Blood pressure behaves inconsistently in motion sick individuals changing up or down or not at all (Graybiel and Lackner 1980b; Johnson 1974). Facial pallor, attributable to decreased blood volume in the venous return, is a prominent feature of motion sickness on earth, as is sweating despite normal environmental temperatures (McClure and Fregly 1972).

In the laboratory, motion sickness is relatively easy to identify and to quantify because laboratory experiments typically involve highly provocative stimulation. The objective is to elicit symptoms quickly so that different stimulation conditions and groups of subjects can be compared. Under operational conditions, e.g. on shipboard or in an aircraft, it is more difficult to assess motion sickness symptoms and severity because of lack of control over activity levels, environmental conditions, and patterns of vehicle motion. There have been persistent attempts to identify physiological concomitants of motion sickness that could be used to objectively grade its severity. The success of these endeavors has been limited because neither the central nervous system pathways subserving motion sickness nor the central nervous system sites involved in the evocation of nausea are fully known, although imaging studies (Balaban 1999) implicate regions of the hypothalamus and frontal lobes. By contrast, through the studies of Yates and Miller a great deal is known about the CNS control and coordination of vomiting (Yates 1998; Yates et al. 1998, 1999; Miller and Wilson 1984; Yates and Miller 1996), and of vestibular influences on autonomic function (Miller and Grelot 1996; Yates 1996, 2004; Yates and Bronstein 2005; Yates et al. 1998, 2000, 2002). The vestibular pathways and CNS mechanisms underlying motion sickness involve a multitude of neurotransmitters and receptor types which complicates attempts to develop pharmacological countermeasures. Miller and Grelot (1996) and Yates et al. (1998) provide excellent reviews.

Humans with complete bilateral labyrinthine loss are usually completely insusceptible to experiencing nausea and vomiting in response to provocative physical motion (Graybiel and Johnson 1963; Money 1970; Money et al. 1996; Reason and Brand 1975). They are susceptible to fatigue but whether this is a reflection of the sopite syndrome is uncertain. Moreover, individuals with one-sided loss are less susceptible than normal subjects to provocative stimulation (Graybiel and Niven 1953). However, Johnson et al. (1999) have found, unlike Cheung et al. (1991), that individuals with vestibular loss can experience nausea in response to optokinetic stimulation although they have an elevated threshold relative to people with normal vestibular function. Animal models of motion sickness and nausea typically rely on vomiting as an index of motion sickness but some species do not vomit, e.g., rats and rabbits. Dogs show susceptibility similarities to humans, but behave differently in terms of their responses to drugs that are effective antiemetics in the human (Money 1990). In non-vomiting species, immobility and swallowing of non-nutritive substances (pica behavior) are taken as signs of motion sickness.

Etiological factors in space motion sickness

Fluid shift hypothesis

The absence of hydrostatic pressure in the circulatory system in weightlessness leads to a substantial rostral redistribution of blood and lymph. Lung vital capacity decreases by hundreds of cc's owing to the engorgement of the pulmonary circulation; the facies exhibit a persisting pitting edema; and, with continued exposure, the total volume of circulating blood is reduced owing to homeostatic mechanisms that interpret the increased activity of carotid and aortic arch baroreceptors as reflecting too large a blood volume (Moore and Thornton 1987; Thornton et al. 1987a). During re-entry after spaceflight with the return of hydrostatic pressure in the circulatory system, the decreased blood volume produces a tendency for vaso-vagal syncope (Noskov and Grigoriev 1994; Yates and Kerman 1998; Yates et al. 2003).

Fluid shifts are potential factors in space motion sickness because they might affect the relative balance of endolymphatic and perilymphatic pressures in the labyrinth (cf. Parker et al. 1983) creating a situation akin to labyrinthine hydrops (Meneire's disease) or they might increase intracranial pressure (Kakurin et al. 1976; Matsnev et al. 1983; Noskov and Grigoriev 1994). Both these conditions can produce nausea and vomiting. "Motion sickness" could result because abnormally high intralabyrinthine pressures would lead to unusual patterns of vestibular activity or because increased cerebral spinal fluid pressures would activate brainstem emetic "centers". The fluid shift hypothesis is appealing because shifts of hundreds of cc's occur in spaceflight and many investigators feel this phenomenon cannot be without functional consequences. However, on earth, fluid shifts occur whenever an animal or human changes its orientation. When a person is standing upright, hydrostatic pressure is greatest because the height of the fluid column is then dependent on the length of the major longitudinal

blood vessels of the body. When the body is supine, hydrostatic pressure approaches zero because the fluid column height is effectively the diameter of the major blood vessels. Thus, postural changes relative to gravity always influence the regional distribution of blood and lymph in the body.

In the course of evolution, animals have developed mechanisms of autoregulation for maintaining cerebral blood flow within very narrow limits despite fluctuations in perfusion pressure related to changes in body orientation. The need for autoregulation is readily apparent in the giraffe, an animal that has been widely used in studies of cerebral blood flow. Without autoregulation, cerebral blood flow and intracranial pressure would vary profoundly in the giraffe as it raises and lowers its head (Patterson et al. 1975; Patterson and Graybiel 1974; Van Citters et al. 1968). Tree climbing snakes have similar demands on their cerebral blood flow regulation and have developed mechanical specializations (i.e. a more rostrally located heart and less compliant skin) as well as autoregulation mechanisms to control cerebral blood flow (Badeer 1998; Lillywhite 1996).

Spaceflight observations on fluid shifts

Several spaceflight studies have addressed the issue of fluid shifts and their role in space motion sickness. Thornton concluded from his personal observations on fluid shifts and motion sickness in space shuttle flight STS-8 and from studies carried out under his aegis in other shuttle missions that fluid shifts are not an important factor in space motion sickness (Thornton et al. 1987a). Shifts develop after insertion into orbit and persist until the end of the mission. They give rise to discomfort because of sinus and facial distension but do not affect susceptibility to motion sickness in any obvious way nor do they parallel the time course of motion sickness. Auditory evoked potentials and eye movement recordings are normal contrary to what would be expected for labyrinthine hydrops or increased intracranial pressure. Oman (1987) and Oman et al. (1986, 1990) conducted systematic motion sickness monitoring in Spacelab 1. The astronauts all experienced discomfort from the engorgement of the veins of the face which persisted throughout the mission. After correlating in-flight symptom development and abatement in relation both to voluntary activity levels and to fluid shift time courses, Oman and his colleagues concluded that fluid shifts are at best a minor factor in space motion sickness. They identified head movements, especially in pitch, as being particularly provocative. Later systematic studies by Oman on the International Microgravity Laboratory mission led to the same conclusions (Oman 1998). Simanonok and Charles (1994) have reported a potential positive relationship between fluid shifts and space motion sickness. Their correlational study did not include an assessment of astronaut activity levels in relation to symptom development but they did find that astronauts who were most susceptible to space motion sickness exhibited the largest post-flight decreases in electro-cardiographic measures of right ventricle, diastolic volume. They raise the possibility that fluid shifts might decrease the threshold for vestibular stimulation to elicit motion sickness. Noskov and Grigoriev (1994) found that diuretics alleviate some of the subjective discomfort and congestion associated with being in weightlessness but not the motion sickness.

Ground-based studies of the fluid shift hypothesis

Parker (1977), who monitored simultaneously endolymphatic pressure in a semicircular canal and cerebral spinal fluid pressure in a ventricle of the guinea pig, found no changes related to modulations in fluid shift magnitude. Parker et al. (1983) measured auditory thresholds and tympanic impedance in the human during head-down body tilt as an indirect assessment of the effects of fluid shifts on inner ear function. Using a 30°, head-down, body tilt to mimic weightlessness, they found slight decrements in auditory sensitivity at higher frequencies and significant changes in impedance. This magnitude of head-down tilt creates a headward directed hydrostatic pressure approximately 50% of that acting footward in a standing individual. Montgomery et al. (1993) used 6° head-down body tilts to see how, relative to measurements at the upright, audiometric thresholds, tympanometric values, and auditory evoked potentials would be affected. No changes were observed despite the congestion and discomfort subjects reported during the head-down tilt.

Two behavioral studies of fluid shifts and motion sickness susceptibility involved "barbecue spit rotation" (Graybiel and Lackner 1977, 1979). In this situation, as the body rotates, the otolith organs of the inner ear are continuously re-oriented in relation to the gravitational force vector. Such stimulation when prolonged induces motion sickness in most subjects. One study exposed blindfolded subjects to constant velocity rotation at 30 rpm while they were either in the head-horizontal, head 10° up, or head 10° down orientations, and estimated the relative magnitude of fluid shift by measuring lung vital capacity (Graybiel and Lackner 1977). The fluid shifts were significantly different across all conditions and in relation to measures at the

upright, but no differences in susceptibility or in pattern or severity of symptoms were present. In the other study, subjects were rotated at 30 rpm while in the 10° head-down position (an orientation where the resulting fluid shift should be slightly greater than that to be expected in weightlessness) either immediately after being placed in the test position or 6 h later (Graybiel and Lackner 1979). The 6-h period was chosen because space motion sickness is often reported within that interval. The experimental results showed a significant tendency, $P < 0.05$, for subjects to tolerate rotation longer before experiencing symptoms after having been head-down for 6 h prior to the onset of rotation.

Fluid shifts and space motion sickness: conclusions

Neither spaceflight nor ground-based studies provide support for fluid shifts being an important factor in space motion sickness. Space motion sickness also does not have the clinical characteristics that would be expected if it were attributable to labyrinthine hydrops or abnormal cranial pressure (Reschke et al. 1994; Thornton et al. 1987a). Patients with labyrinthine hydrops often have drop attacks, elevation of auditory thresholds, acute rotary vertigo, paroxysmal episodes of dizziness, nausea and vomiting, and nystagmus (Baloh and Honrubia 1990). A paroxysmal episode may last from several minutes to several hours, occasionally as long as 24 h. Increased cerebral spinal fluid pressure can evoke nausea and vomiting irrespective of activity levels. It is also notable that prolonged bed rest studies which use recumbency to mimic weightlessness do not evoke the panoply of signs and symptoms characteristic of space motion sickness despite the rostral fluid shifts generated.

Role of head movements in evoking space motion sickness

Astronauts and cosmonauts have consistently reported that head movements tend to elicit and exacerbate symptoms of space motion sickness. Titov first reported this (Titov and Caidin 1962) and it was noted in the Apollo and Skylab missions (Graybiel 1980) and throughout the space shuttle missions. Controlled experiments to evaluate how different kinds of natural head and body movements influence susceptibility to motion sickness in spaceflight have not yet been carried out. Observations en passant (e.g. Thornton et al. 1987a, b; Oman et al. 1986) indicate that at least initially pitch head movements are most stressful, and yaw least, in bringing on symptoms.

Oman et al. (1986, 1990) have made key in-flight measurements of motion sickness incidence in relation to activity levels in Spacelab 1. Some of the participating astronauts wore accelerometers that allowed their head movements to be monitored. Early in their missions the astronauts found pitch and roll head movements to be provocative, especially pitch movements, and limited their head movements when symptoms developed. The astronauts who moved their heads most vigorously prior to symptom onset were those who later experienced the most severe symptoms. Establishing firm body contact with a surface tended to alleviate their symptoms. By mission day 4, symptoms of motion sickness abated and the astronauts were again able to make unrestricted head movements.

The Spacelab astronauts also found that being in unusual orientations, e.g. inverted relative to other astronauts or to architectural features of the spacecraft, could bring on or exacerbate symptoms of motion sickness. Episodes of sudden vomiting also occurred. However, as Oman et al. (1986, 1990) emphasize, prior to these episodes, prodromal signs of sickness were usually present, i.e. the astronauts were already sensitized. This pattern is also characteristic of terrestrial motion sickness. Golding and Stott (1997b) found that laboratory subjects remain abnormally sensitive to provocative stimuli for up to 3–4 h after all apparent symptoms have abated. Following parabolic flight maneuvers, subjects who have been motion sick but who are seemingly symptom free may exhibit sudden vomiting when the aircraft rapidly decelerates on landing (Lackner and Graybiel 1986a, b).

The Spacelab astronauts were tested in parabolic flight 4 days after re-entry from orbital flight and 1-year later. In the first parabolic flight, all could make head movements without evoking symptoms; 1 year later head movements did elicit symptoms. This pattern points to an immediate post-spaceflight desensitization for certain types of stimulation. Their ensemble of in-flight and post-flight observations led Oman et al. (1990) to conclude that space motion sickness shares relevant features with terrestrial motion sickness. Many tests of orientation and sensory function were conducted with the Spacelab astronauts pre- and post-flight to see whether any would be of predictive value for space motion sickness. None were, but Oman et al. (1990) present an insightful analysis of the difficulties and complexities associated with predicting susceptibility.

Role of head movements in evoking motion sickness in low and high force environments

The question arises whether there is something special about head movements eliciting motion sickness in

weightless conditions or whether head movements in any non-earth force background would elicit symptoms. In other words, is space motion sickness a unique diagnostic entity? This issue has been systematically evaluated in parabolic flight experiments where the flight path generates alternating periods of high force, approximately 1.8 g peak, and weightlessness, each lasting about 20–25 s (Lackner and Graybiel 1984, 1985). Figure 1 illustrates the flight path and associated force levels. Some individuals become sick through exposure to such cyclic alterations in force level even when they are seated with head fixed. This makes it necessary to measure their baseline susceptibility to the force variations per se prior to experimental observations being carried out. This was done by first exposing subjects to two, 40 parabola flights separated by several days during which they were strapped in position to prevent body movements and wore orthopedic neck collars to prevent head movements. Depending on the number of motion sickness symptoms experienced in their two flights, individuals were classified as Category I, insusceptible; Category II, moderately susceptible; Category III, highly susceptible. After categorization was completed, the influence of yaw, pitch, and roll head movements on susceptibility was evaluated by having subjects make head movements in the 0 g phase of each parabola until nausea was reached or 40 parabolas had been completed. Within and across susceptibility categories, the following results were obtained: symptoms of motion sickness appeared earlier and with greater overall severity when pitch head movements were made, yaw head movements were least provocative, and roll movements were of intermediate stressfulness. Movements were more provocative when vision was permitted.

Lackner and Graybiel (1985) had subjects make head movements in pitch and in yaw in the 1.8 g phases of parabolas. The experimental findings were similar to those obtained in free fall. Head movements in pitch were much more stressful than in yaw, and the presence of vision further heightened susceptibility. The main difference was that head movements made in 1.8 g were much more stressful than those in 0 g. Many subjects participated in both experimental series and all showed this pattern. These results demonstrate that motion sickness results when head movements are made in non-1 g force environments regardless whether force level is increased or decreased and suggest that space motion sickness is not a unique diagnostic entity.

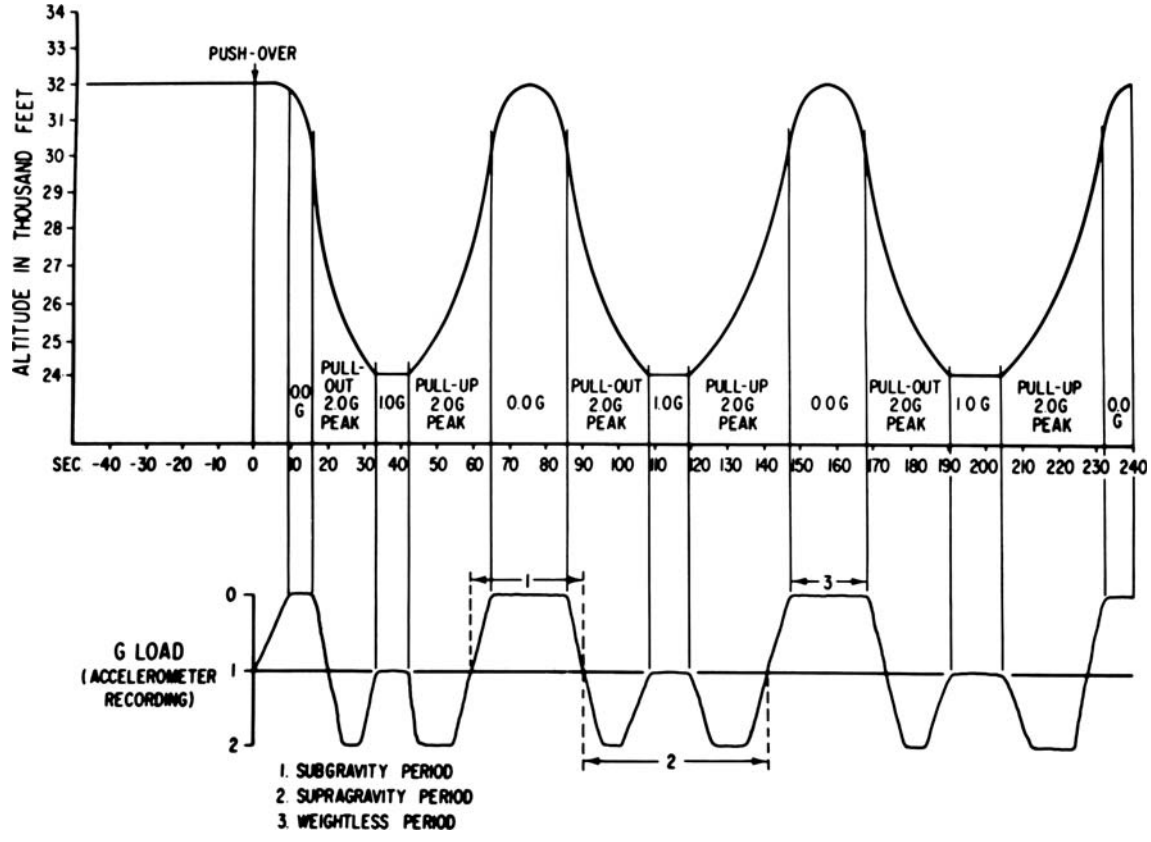

Fig. 1 Schematic flight path and associated force level of an aircraft flying parabolic maneuvers to generate periods of weightlessness and high force

Coriolis cross-coupled angular accelerations and space motion sickness

Coriolis cross-coupled angular accelerations generated by head movements during rotation are extraordinarily provocative and disorienting. Figure 2 illustrates the cross coupling of the semicircular canals which occurs when an individual rotating at constant velocity in a clockwise direction pitches his head forward 45°. For simplicity, the paired sets of semicircular canals are represented as single canals in the pitch, yaw, and roll planes. The "pitch canal" will signal accurately the forward tilt of the head. Simultaneously, the "yaw canal" will receive a counter-clockwise velocity impulse because it is being moved out of the plane of rotation and thus losing momentum; the roll canal will receive a clockwise angular velocity impulse because it is being moved into the plane of rotation. Collectively, the canals will indicate forward pitch about the *y*-axis, counter-clockwise rotation and displacement about the *z*-axis of the head, and clockwise rotation and displacement about the *x*-axis. Subjects find such stimulation extremely nauseating.

Skylab M-131 experiment

Susceptibility to motion sickness during exposure to cross-coupled angular accelerations was assessed in spaceflight on all three manned Skylab missions (Graybiel et al. 1972, 1975, 1977). Pre-flight, the nine participating astronauts were highly susceptible to cross-coupled angular accelerations. In spaceflight, five of the nine astronauts experienced space motion sickness during their first several days in orbit. However, when initially exposed to Coriolis cross-coupling stimulation on or after Mission Day 6, the astronauts were insusceptible to motion sickness. They did not become even slightly sick when they made 150 head movements while rotating at 30 rpm, the peak velocity of the test chair, and then another 150 head movements when the direction of rotation was reversed. Pre-flight, none of the astronauts could make this many head movements without eliciting symptoms even at much lower rotation rates. On return to earth, the astronauts were less susceptible than pre-flight to Coriolis, cross-coupled angular accelerations and remained so for several weeks. The findings are shown in Fig. 3.

These results present a potential quandary. Head movements in free fall elicit symptoms of motion sickness; however, in spaceflight, the astronauts could make head movements while rotating without becoming motion sick. Such head movements are presumably more provocative than head movements made while stationary. Resolving this dilemma is contingent on

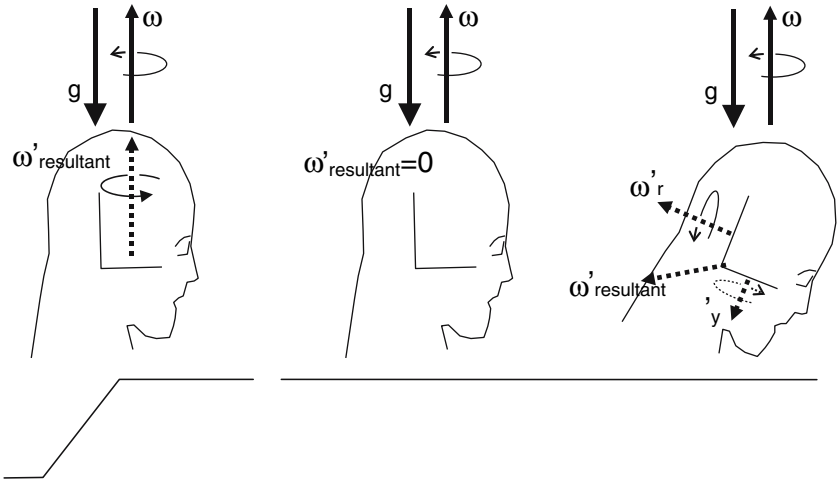

Fig. 2 Vestibular cross-coupled stimulation of idealized roll and yaw semicircular canals elicited by a pitch head movement during clockwise rotation. *Solid arrows* indicate body rotation velocity (ω) and gravity (g). *Black-dashed vectors* represent the afferent activity of individual semicircular canals (ω'_r for roll canal, ω'_p for pitch canal) and their resultant ($\omega'_{resultant}$). The *left panel* shows the yaw canal accurately encoding body angular velocity after a brief acceleration. The center panel illustrates the canals equilibrated to resting discharge levels after constant velocity rotation has been maintained for about a minute (represented by the break in the velocity profile, at the bottom). At this point, the subject will feel stationary if denied vision as well as auditory and wind cues. The steady loading of the otolith organs and somatic mechanoreceptors is consistent with the vertical axis rotation of the body, up to this point. Pitching the head 30° forward (*right panel*) elicits cross-coupled stimulation of the roll and yaw canals which jointly encode rotation about a nearly horizontal axis. The otolith organs receive a transient rightward Coriolis acceleration (not illustrated) during the head movement and immediately return to a state of constant loading by gravity, which is not consistent with the off-vertical axis of canal-encoded rotation which decays slowly. Vestibular responses to the voluntary pitch movement are not illustrated

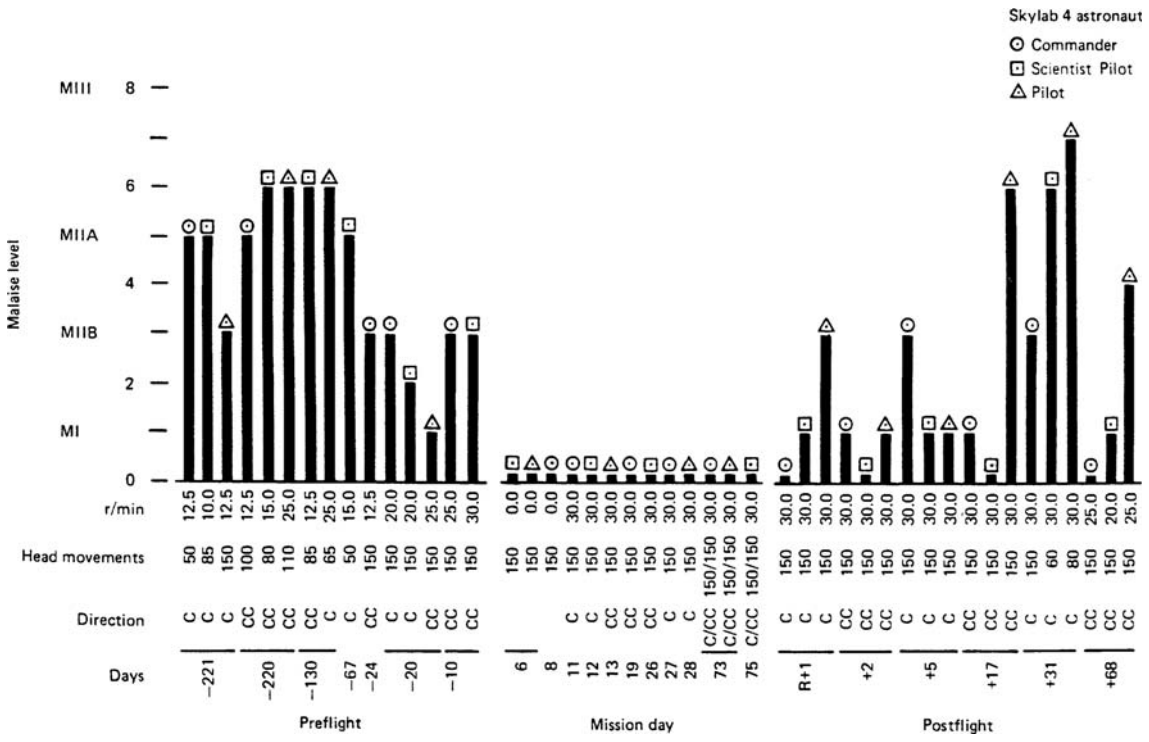

Fig. 3 Results of the Skylab M-131 experiment for three Skylab 4 astronauts. The *columns* represent the severity of motion sickness on the Graybiel scale (see Table 1). The *rows* of numbers along the bottom indicate the angular velocity of body rotation, the number of head movements performed, rotation direction, and flight day (*solid line* pre-flight; *R+* post-flight)

realizing that in the Skylab missions the first head movements during rotation were made on or after Mission Day 6 when natural head movements were no longer provocative. Other factors contributing to the decreased sensitivity to Coriolis stimulation in spaceflight are described below.

Motion sickness and Coriolis cross-coupling stimulation in 0 and 1.8 g

Susceptibility to motion sickness during Coriolis cross-coupling stimulation has been measured in the free fall and high force phases of parabolic flight maneuvers to determine how background force level affects performance (Lackner and Graybiel 1986a, b). Subjects were tested blindfolded, while rotating at 20 rpm and making pitch head movements in sets of eight until they reached a motion sickness endpoint of nausea, or had completed 40 sets. The experimental results were unequivocal: all subjects were more susceptible to motion sickness during exposure to high force levels than in free fall. The Category I and II subjects (see Role of head movements in evoking motion sickness in low and high force environments) were less susceptible to motion sickness in free fall than in the laboratory. Category III subjects, who are susceptible during exposure to parabolas per se, were slightly less susceptible to Coriolis stimulation in free fall than in the laboratory.

Subjects also rated the apparent intensity and provocativeness of constant levels of Coriolis cross-coupling stimulation during parabolic flight maneuvers. All subjects showed the same patterns: comparable physical levels of Coriolis cross-coupling stimulation were more intense, disorienting, and provocative in 1.8 g background force levels than in 1 g, and head movements made in 0 g were much less intense and nauseogenic than in 1 g. In addition, the aberrant head and body motion (tilt and turning about several axes) experienced when head movements were made during straight and level flight was greatly enhanced in 1.8 g. In 0 g, subjects experienced pitch of their heads with little or no rotation about other axes. In another experiment, subjects made head movements during rotation in the transitions from 0 to 1.8 g or from 1.8 to 0 g (Lackner and Graybiel 1985, 1986a, b). Every subject experienced the same pattern. Head movements made during the 0 to 1.8 g transitions were more intense and provocative than those in the 1.8 to 0 g transitions. The influence of gravitoinertial force level on the apparent intensity and provocativeness of Coriolis stimulation was thus *virtually immediate*.

Vestibulo-ocular responses to Coriolis stimulation as a function of gravitoinertial force level

Coriolis, cross-coupling stimulation elicits reflexive eye movements because of the impulsive stimulation of the semicircular canals when the head is tilted out of the axis of body rotation. DiZio et al. (1987a) measured the vestibulo-ocular response to constant levels of Coriolis stimulation in straight-and-level flight and in the high force and free-fall phases of parabolic flight maneuvers. In 0 g, the average slow phase eye velocity of the nystagmus elicited decreased, as did beat frequency relative to 1 g values, although peak slow phase velocity was unaffected. The time constant of nystagmus slow phase velocity decreased in 0 and 1.8 g relative to 1 g baseline values, although to a lesser extent in 1.8 g than in 0 g. This modulation of reflexive eye movement responses was systematic and highly significant statistically. Importantly, it did neither parallel the subjective nor the motion sickness responses to Coriolis stimulation which although likewise attenuated in 0 g are greatly enhanced in 1.8 g relative to 1 g values (Lackner and Graybiel 1986a, b). This dichotomy means that the central influences of semicircular canal stimulation on perception and motion sickness are distinct from their influence on oculomotor control.

DiZio et al. (1987b) also recorded vestibulo-ocular responses to impulsive deceleration from constant velocity rotation in parabolic flight. Precisely the same angular stimulation was delivered in 0, 1, and 1.8 g. The peak velocity of the resulting vestibular nystagmus was the same in all phases of parabolic flight; but, the time constant of decay of slow phase eye velocity was lower in 1.8 g than in 1 g and lower still in 0 g. The value in 0 g was only slightly above the allometrically computed time constant for the horizontal semicircular canals. Nystagmus time constants were shortened or "dumped" by post-rotary head tilts in 1 and 1.8 g but not in 0 g (DiZio and Lackner 1988). These findings indicate that velocity storage (Cohen et al. 1977), the central integration of semicircular canal signals, is attenuated at least during initial exposure to non-terrestrial gravitoinertial force backgrounds, and much more so in 0 g than in 1.8 g. Oman and Balkwill (1993) found similar results for nystagmus dumping and aftereffect durations in the Spacelab SLS-1 crew confirming diminished velocity storage in weightlessness. Oman et al. (1996) tested four SLS-2 astronauts and found decreases in velocity storage for all four. But, for two of them, the least experienced in spaceflight, velocity storage later returned toward pre-flight levels. Head movements in pitch did not dump the velocity storage.

Altered integration of semicircular canal signals in weightlessness

Converging evidence from parabolic flight experiments points to perception of the vertical and of body angular displacement both being affected by exposure to weightlessness. The perception of the subjective vertical (Bryan et al. 2004) was tested with subjects recumbent in a bed-like apparatus that allowed them to be set at different yaw angles with respect to the gravitational vertical. The blindfolded subjects haptically indicated the vertical as an aircraft performed parabolic maneuvers. Settings of the vertical did not differ for 1.8 and 1 g force levels. This is unlike the case for pitch and roll body tilts where increased shear on the otolith organs leads to a greater apparent body tilt relative to gravity (Correia et al. 1968; Miller et al. 1965). After transition into weightlessness subjects quickly felt horizontal and set the joystick perpendicular to their frontal plane (parallel to their midline). The symmetric touch and pressure cues imposed by the restraint system of the apparatus likely account for the subjects feeling horizontal when weightless.

These findings were extended in a parabolic flight experiment in which recumbent subjects were dynamically rotated to different yaw orientations relative to gravity while continuously tracking the apparent vertical with a joystick (Lackner et al. 2006). Subjects turned while in a 1 or 1.8 g force level, moved the joystick systematically to the direction opposite their tilt, but when the aircraft entered 0 g, they moved the joystick to be virtually perpendicular to their frontal plane (parallel to their midline) and reported feeling horizontal. When they were tilted to a new static angle while in 0 g, they failed to perceive a change in body orientation. The semicircular canal stimulation generated when subjects were rotated to a new orientation was always at least an order of magnitude above canal thresholds on earth for eliciting perception of a positional change. The failure to sense angular displacement indicates that spatial integration of canal afferent signals is disturbed or that the apparent vertical defined by somatosensory information overrides the canal cues.

Implications for the skylab M-131 experiment

The experiments described above on head movements in different background force levels allow a motivated explanation of the Skylab results. The Skylab astronauts were first tested with cross-coupled stimulation at a time by which natural head movements were no longer provocative. Accordingly, one would actually expect the astronauts to be unaffected by Coriolis

cross-coupled stimulation because the provocativeness of Coriolis stimulation is immediately attenuated in free fall and is not much greater than that of head movements per se. The reduced or suppressed integration of canal signals in weightless conditions also means that the abnormal patterns of canal activity present during cross coupling are not fully integrated to produce aberrant positional changes. As a result, disorientation should not be experienced, which is consistent with astronaut reports that head movements during rotation in orbit no longer "tumble their gyros". Disorientation occurs with cross coupling in normal and high force levels because path integration of canal signals is occurring and providing a representation of head motion and path which corresponds to that expected neither from the intended movement nor from the otolith organs.

Otolith asymmetries and space motion sickness

Several investigators have raised the possibility that asymmetries between the otolith organs on the two sides of the head may contribute to space motion sickness (Egorov and Samarin 1970; Gurovskiy et al. 1975). Differences in collective otoconial mass between the paired otolith organs could in principle result in asymmetric shear forces on the otolith membranes on the two sides. However, compensation for asymmetries in vestibular function typically occurs. For example, if one horizontal semicircular canal is destroyed, a horizontal nystagmus will develop, and over time will abate and finally disappear. If the remaining horizontal canal is destroyed, a new nystagmus of opposite sign, known as Bechterev's nystagmus, will appear. Its presence indicates the existence of a central compensation that has developed to restore normal vestibulo-ocular function. Von Baumgarten and colleagues have hypothesized that an analogous compensatory effect occurs under terrestrial conditions in an individual with unbalanced peripheral inputs from the otolith organs to create concordant inputs (von Baumgarten 1986, 1987; von Baumgarten and Thumler 1979; von Baumgarten et al. 1981). Exposure to weightlessness would unmask the persisting central compensation and lead to the development of symptoms of motion sickness because of the resulting asymmetry in signals from the otolith organs.

Ocular counterrolling is an important measure of otolith function (Graybiel 1974; Miller and Graybiel 1974). During tilt of the body in roll, the eyes counterrotate in the opposite direction by a fraction of the body tilt. Ocular counterrolling is a relatively primitive reflex, its gain rarely exceeds 0.1 so it is inadequate to keep the eyes aligned with the environment. By contrast, the modulation of neck, trunk, and limb musculature by otolith-spinal pathways is very important for postural and stance control (Wilson and Melvill Jones 1979). Because of this difference in functional significance of ocular counterrolling and vestibulo-spinal reflexes, individuals with asymmetric otolith function potentially might exhibit asymmetric counterrolls for leftward and rightward body tilts but have centrally compensated vestibulo-spinal pathways (Lackner et al. 1987).

To evaluate the possible role of otolith asymmetries in evoking motion sickness, Lackner et al. (1987) analyzed the ocular counterrolling scores of subjects who had participated in parabolic flight experiments. These subjects had been categorized as insusceptible to the parabolas per se (Category I), moderately susceptible (Category II), or highly susceptible (Category III), see Role of head movements in evoking motion sickness in low and high force environments. On average, the Category II and III subjects had slightly smaller ocular counterrolling amplitudes than the Category I subjects. In addition, they had significantly greater asymmetries in their counterrolls for leftward and rightward body tilts. This finding shows that individuals with asymmetric otolith function tend to be susceptible to motion sickness during changes in gravitoinertial force level. However, these are group differences and some of the Category I subjects had larger counterrolling asymmetries than some of the Category III subjects. This pattern means that one cannot reliably predict a particular individual's susceptibility in parabolic flight on the basis of counterrolling scores. Diamond and Markham measured the ocular counterrolling of a number of veteran astronauts during parabolic flight maneuvers and calculated "torsional disconjugacies" (difference in torsion of the right eye relative to 1 g conditions minus torsion of the left eye for the 0 and 1.8 g force phases of flight) (Diamond and Markham 1988, 1991a, b, 1992; Diamond et al. 1990; Markham and Diamond 1992, 1993). The astronauts who had not been motion sick in orbital flight overall had lower disconjugacy scores in parabolic flight (Markham et al. 2000), but a one-to-one relationship between disconjugacy and susceptibility in spaceflight cannot be drawn.

An issue of key concern is that if there is a central asymmetry in otolith function that is "unmasked" by exposure to weightlessness, then there should be consequences for apparent body orientation as well as for oculomotor control. For example, astronauts should experience a particular individual apparent body tilt whenever they are not moving about because of the unmasked central compensation for the asymmetry between the otolith organs. Such effects have not been

reported. What is clear is that immobilizing the head seems to attenuate and hinder the development of space motion sickness. A significant vestibular asymmetry revealed by exposure to weightlessness would be expected to give rise to symptoms when the head is stationary as well as moving, and this does not seem to be the case.

Treatment of space motion sickness

The drugs primarily used to treat motion sickness have antihistaminic or anticholinergic actions or a combination thereof. Putcha and her colleagues have provided summaries of the antimotion sickness drugs currently used in spaceflight and an analysis of the changes in pharmacodynamics potentially associated with exposure to weightlessness (Graebe et al. 2004; Putcha et al. 1999; Putcha 1999). Oral and buccal delivery of promethazine has been used with some success. Baclofen, which attenuates velocity storage, is currently being evaluated as a potential antimotion sickness therapy (Dai et al. 2006). In parabolic flight, a combination of scopolamine and dexedrine ("scopdex") is often used prophylactically. The scopolamine is used to prevent or attenuate motion sickness and the dexedrine to counteract the soporific action of the scopolamine. In US spaceflights, the commander and pilot cannot take such medications because of FAA regulations to which they are subject.

Antimotion sickness drug injections

Antimotion sickness drugs given orally are often ineffective in suppressing symptoms of motion sickness that have already developed. A motion sick individual may expel some of a drug dose in vomitus. Diminished gastric motility is also one of the signs of motion sickness; consequently, the passage of drugs to absorption sites in the small intestine may be delayed (Money et al. 1996; Thornton et al. 1987c). Drug pharmacokinetics may also be altered in microgravity environments (Harm 1990; Norfleet et al. 1992; Putcha et al. 1999; Davis et al. 1993a, b; Thornton et al. 1987b; Williams 2003). Parenteral administration of antimotion sickness drugs circumvents these problems and provides a rapid way of getting drugs into the blood circulation. Subjects in parabolic flight studies often become severely motion sick, experiencing extreme nausea and multiple bouts of vomiting. Graybiel and Lackner (1987) found that most of these individuals could be greatly relieved of their symptoms by intramuscular injections of promethazine or scopolamine. Many could even resume participating in experiments. In ground-based studies, side effects are usually associated with the use of scopolamine and promethazine at effective dose levels, the most prominent being dry mouth, drowsiness, and with scopolamine, mydriasis (Lucot 1998; Wood et al. 1990). Motion sick subjects in parabolic flight tended not to experience these side effects until after landing and then found them preferable to experiencing repeated bouts of nausea and vomiting. Based on these findings, Graybiel and Lackner (1987) recommended treating severe space motion sickness with injections of promethazine.

This approach was initiated in spaceflight by Bagian, himself an astronaut physician, and his colleagues. It has proven valuable in relieving the symptoms of astronauts disabled by motion sickness (Bagian 1991; Bagian and Ward 1994; Davis et al. 1993a, b). They often recover enough to resume their activities and importantly do not report the severe side effects of drowsiness that are associated with comparable doses of promethazine under ground-based laboratory conditions. Promethazine is often reported to prevent adaptation or to hinder learning. Thus, there is potential concern that promethazine could delay sensory-motor adaptation to the space environment. However, promethazine does not prevent the acquisition of adaptation to provocative vestibular stimulation if goal-directed head movements are made (Dai et al. 2003; Lackner and Graybiel 1994). Consequently, if astronauts resume their natural movements while protected by promethazine, they should continue adapting to the weightless environment. However, if they restrict their movements, adaptation to the weightless environment would be delayed.

The use of promethazine injections to treat space motion sickness has been severely criticized based on laboratory studies in which volunteer subjects have been exposed to tests of alertness, manual dexterity, sensorimotor coordination, and motion sickness susceptibility after receiving intramuscular injections of promethazine (Cowings et al. 2000). Subjects showed significant decrements on the performance tasks and greatly impaired alertness. In addition, unlike the observations of Graybiel and Lackner (1987), and Bagian and colleagues (Bagian 1991; Bagian and Ward, 1994; Davis et al. 1993a, b) no protection against motion sickness was observed. Cowings et al. (2000) concluded that drug injections should be discontinued in spaceflight and autogenic feedback training (AFT) substituted. It is notable, however, that in parabolic flight and spaceflight conditions, drug injections are

used only when individuals are already motion sick and unable to carry on their tasks.

In the Cowings et al. (2000) study, the drug injections were given at the beginning of the test day. Over the next 4.5 h, the volunteers were evaluated on the performance measures. Then, they were exposed to provocative vestibular stimulation by having them make head movements during rotation. The effective dose duration of the promethazine used was specified to be 4.5–6 h which means that the performance tests were made during the period of drug efficacy and the motion sickness tests were conducted during the period of diminished or absent protection. The findings are thus not surprising. Caution is also necessary in comparing astronauts to laboratory subjects participating voluntarily for pay in activities that they can terminate at any time. Astronauts often have trained for years before receiving a flight opportunity. Prior to a mission they train extensively on the specific tasks they will have to carry out until these tasks become virtually second nature. Once into a mission they cannot leave the situation if they become indisposed.

Autogenic feedback training

Autogenic feedback training has been proposed by Cowings and her colleagues as a way to prevent space and terrestrial motion sickness (Cowings and Toscano 1982, 2000; Cowings et al. 1977, 1986, 1995, 2000; Toscano and Cowings 1982). They report that as individuals become motion sick they show self-consistent patterns of physiological changes that constitute a personal trait and that remain unchanged across multiple provocative exposures (Cowings et al. 1995; Staut et al. 1995). In AFT, an individual is trained to recognize various bodily sensations so as to detect changes in heart rate, respiration, skin temperature, and other parameters. With feedback training, subjects learn to control these factors, and Cowings et al. report that they thereby become resistant to motion sickness.

AFT studies typically involve physical effort on the subject's part, the execution of many head movements during rotation, thereby generating Coriolis, cross-coupling stimulation of the semicircular canals (see Coriolis cross-coupled angular accelerations and space motion sickness). Cowings et al. have compared AFT training to sham training on a cognitive task for some subjects, and to no treatment for other subjects. Subjects made sets of head movements during rotation at progressively higher rotation velocities until completing the test profile or stopping because of motion sickness. With repeated exposures, subjects in the AFT group showed improvement being able to "tolerate" more rotations and head movements while the other groups failed to show any evidence whatsoever of improvement over repeated exposures. This same pattern has been consistently reported by the Cowings group using this experimental paradigm. AFT groups show improvement, non-AFT groups do not. However, it is surprising that sham and no-treatment control groups fail in these studies to show improvement with repeated incremental exposure to Coriolis cross-coupling stimulation. Placebo groups in drug studies show improvement over non-treatment groups during this form of exposure and the latter also improve with repeated exposures (Wood and Graybiel 1968; Wood et al. 1990). In fact, virtually identical exposure conditions, but without AFT, are used in treatment programs to desensitize subjects to motion sickness (e.g. Cramer et al. 1976; Graybiel et al. 1969; Golding and Stott 1995; Reason and Graybiel 1970).

Jozsvai and Pigeau (1996) have also evaluated the efficacy of AFT itself in suppressing symptom development. They initially exposed subjects to Coriolis cross-coupling stimulation to determine their baseline susceptibility; then divided them into three groups matched for susceptibility. One group received AFT with accurate feedback about their autonomic nervous system responses, another AFT group received false feedback, and the third group received no treatment. The three groups in this comprehensive study did not differ in their performance, thus indicating no benefit of the AFT. In addition, studies in which motion sickness is passively induced by means of sudden decelerations from constant velocity rotation (Graybiel and Lackner 1980a, b) or caloric stimulation (Costa et al. 1995) have unlike the Cowings studies found no regular or self-consistent physiological patterns for individuals across test situations nor between severity of motion sickness and either average values or directional variations in physiological parameters (Cheung and Vaitkus 1998: Cheung et al. 1990; Doweck et al. 1997; Golding and Stott 1997a; Harm and Schlegel 2002; Mullen et al. 1998; Costa et al. 1995).

In summary, current studies provide little hope that space motion sickness can be prevented or attenuated by AFT. This failure is disappointing because it would be valuable to have an alternative to antimotion sickness drugs. Such an alternative is especially important for long duration spaceflight where the radiation levels encountered will diminish the shelf life of drugs (J. Clark, personal communication).

Theories and ground-based models of space motion sickness

Theories of space motion sickness

We lack a fully adequate theory of why motion sickness occurs. "Evolutionary theories" posit that it has survival significance (Treisman 1977). Motion sickness by this perspective serves to empty the stomach and expel ingested toxins, and to decrease body activity. How this response could have developed evolutionarily is unclear. The time course of the emetic response may also be too slow to be of functional significance. Nevertheless, dogs that are surgically labyrinthectomized no longer show a vomiting response to some but not all drugs that earlier induced emesis in them (Money and Cheung 1983). Vestibular overstimulation theories have largely been abandoned because often the most gentle stimuli can be more provocative than more intense ones, e.g. susceptibility to motion sickness during vertical oscillation is greater around 0.2 Hz than 1 Hz (Guignard and McCauley 1990; O'Hanlon and McCauley 1974).

Sensory conflict theories are currently the most accepted explanations of motion sickness (Oman 1982, 1984, 1990, 1998; Reason 1970; Reason and Brand 1975). The basic notion is that motion sickness arises when different sensory systems give conflicting information about the ongoing motion of the body, or the expected sensory feedback from intended movements does not correspond with that actually generated. Such theories have great generality because motion sickness is a disorder associated with motion and almost all situations involving body motion potentially involve some form of sensory "conflict".

Bles and Bos have proposed that all motion sickness including space motion sickness result from situations in which "... the sensed vertical as determined on the basis of integrated information from the eyes, the vestibular system ... is at variance with the subjective vertical as expected from previous experience" (Bles et al. 1998, Bles 1998; Bos and Bles 1998; de Graaf et al. 1998). This sensory conflict hypothesis specifically invokes the vertical as having special significance. Unfortunately, it cannot accommodate typical laboratory conditions for studying motion sickness in which there is not a conflict with the vertical, e.g. passive visual stimulation in optokinetic drums (Hu and Stern 1998; Hu et al. 1999; Stern et al. 1987a; Lackner and Teixeira 1977; Teixeira and Lackner 1979), decelerations from constant velocity rotation (Graybiel and Lackner 1980a, b), vertical oscillation (Wright et al. 2005), and head mounted visual displays with visual updating contingent on head tracking (DiZio and Lackner 2000, 2002).

Although the eliciting elements in space motion sickness are not fully understood a wide range of factors contribute including altered vestibular function under both dynamic and static conditions. Exposure to weightlessness changes the resting activity of the otolith organs because of the unloading of the utricular and saccular membranes. On earth, head orientation influences otolith activity in terms of gravity generated shear forces. These shear forces will be absent and it is unclear what the resting patterns of utricle and saccule discharge will be like in weightless conditions. The patterns of vestibular activity associated with voluntary as well as passive head movements will also be unlike those associated with similar changes in head orientation on earth.

In addition, because the body is weightless in orbital flight, sensory-motor control of the entire body will be drastically altered in terms of the patterns of muscular activation necessary to achieve changes in body configuration and in the associated patterns of sensory feedback (see Lackner and DiZio 2000a for an explanation of the physics of the situation). Body orientation and locomotion are controlled by hand and footholds, and by pushing off. On earth, modifications of the motor control patterns controlling body posture and locomotion can, even in the presence of normal patterns of vestibular input, produce motion sickness and postural control disruption (Lackner and DiZio 1989). Figure 4 provides a schematic representation of some of the factors involved in space motion sickness and adaptation to new force environments.

Ground-based models of space motion sickness

Many ground-based models of space motion sickness involve creating sensory conflicts in terms of abnormal patterns of vestibular stimulation and/or unusual visual stimulation. Such approaches include caloric irrigation, galvanic vestibular stimulation (Severac 1992), "preadaptation training" (Parker et al. 1985; Parker and Parker 1990), and centrifugation (Albery and Martin 1996; Bles et al. 1997; Ockels et al. 1990). Caloric and galvanic studies involve stimulating the vestibular receptors to elicit symptoms of motion sickness and postural imbalance. Prolonged exposure to increased g-levels has also been proposed as a model. In one study, test subjects including cosmonauts from MIR missions were exposed to 3 g acceleration levels along the naso-occipital body axis for up to 3 h on a centrifuge (Bles et al. 1997). Afterward, most experienced symptoms of motion sickness when they made head

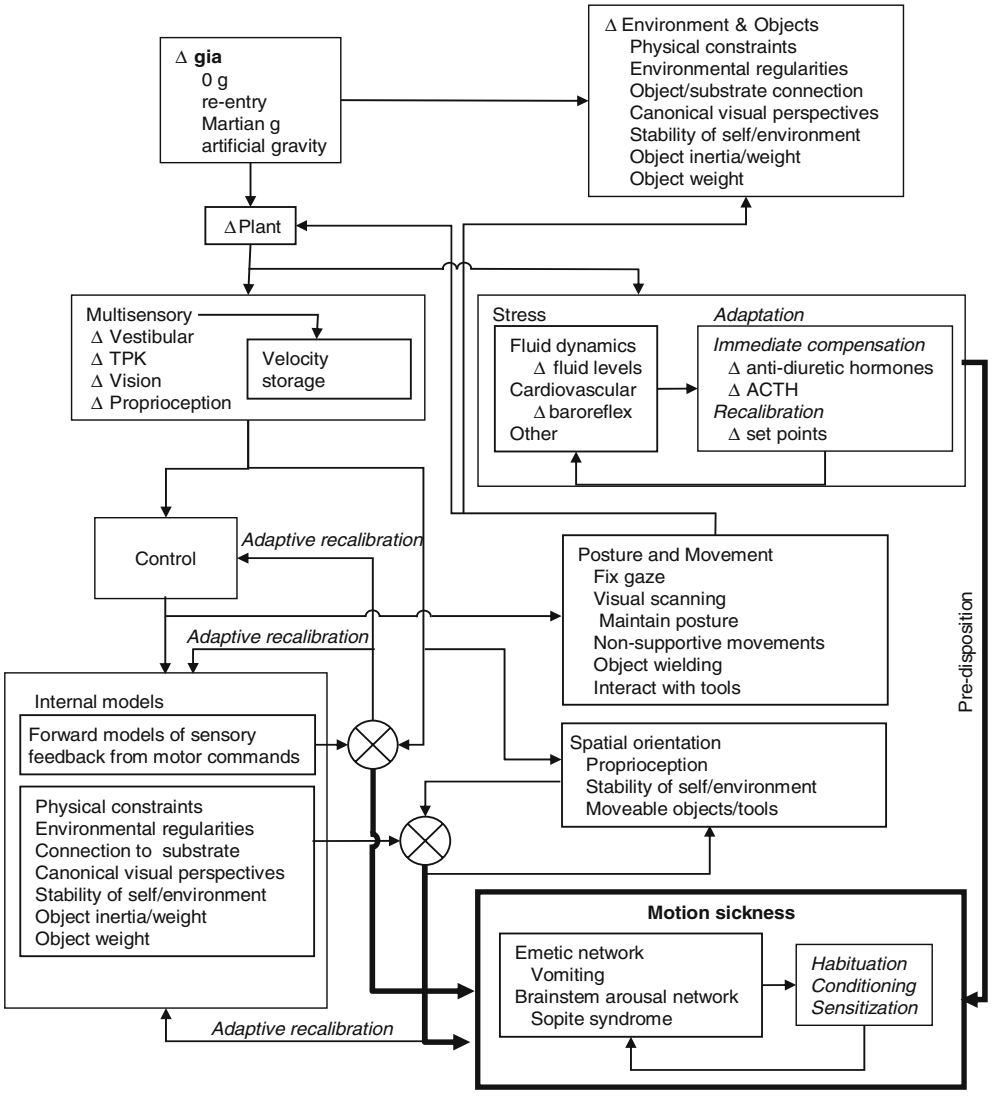

Fig. 4 Schematic of processes involved in space motion sickness. At the *top left* is the physical stimulus for the whole process, a change (*open triangle*) in gravitoinertial acceleration (*gia*), for example, from terrestrial 1 g gravity to orbital spaceflight, 0 g. The *heavy arrows* embody the idea that space motion sickness is strongly correlated with processes involved in adaptation of spatial orientation and sensorimotor control of whole body posture and movement and autonomic adaptation to other stressors evoked by changes in gia. Spatial orientation and sensorimotor control involve many subsystems that utilize internal models, motor command copies, and reafferent feedback (sensory signals contingent on self-movement). Perturbations of orientation and movement control activate adaptive processes that re-weight sensory feedback signals, recalibrate motor output, and revise internal models. Motion sickness is most severe when the orientation and autonomic regulation systems are undergoing rapid recalibration. After adaptation to 0 g orbital spaceflight a new transition, for example to Martian g, artificial g, or re-entry to 1 g conditions can elicit motion sickness anew

movements and were ataxic. The cosmonauts reported that their symptoms were comparable to those they had experienced in their spaceflight 3 years earlier. Motion sickness symptoms and postural imbalance were also elicited in subjects exposed to +1.8 g_z acceleration for 90 min (Albery and Martin 1996). Subjects who made periodic voluntary head movements while exposed to prolonged rotation on a short arm centrifuge also experienced symptoms of motion sickness and exhibited post-rotational postural disturbances (Kaufman et al. 2001). These subjects in addition to receiving abnormal otolith stimulation because of the centrifugal rotation also underwent Coriolis cross-coupling stimulation when they tilted their heads. Thus, they were exposed to multiple provocations.

The rationale for these different approaches is that motion sickness and postural disequilibrium are associated with space motion sickness and the space adaptation syndrome. Consequently, conditions that also produce such effects may serve as a ground-based

model without the need for spaceflight. The assumption is that similar signs and symptoms equal similar etiology. However, similarity of symptoms of motion sickness in different contexts does not necessarily equate to similar etiology and underlying mechanisms and does not justify substitution of contexts. An extreme example will make this clear. Patients undergoing chemotherapy or radiation therapy for treatment of cancer can exhibit many of the signs and symptoms of motion sickness and postural disequilibrium. Nevertheless, one would not propose these treatments as a terrestrial model of space motion sickness. An overnight train ride through rugged terrain in a sleeper compartment also can result in postural and locomotory disturbances that at least superficially share many of the characteristics of postural re-entry disturbances.

The pre-adaptation trainer, or PAT Dome, has been used in attempts to assess susceptibility and to pre-adapt astronauts to the unusual patterns of visual stimulation that they will encounter in spaceflight (Harm and Parker 1994). This device projects unusual visual scene orientations to the observer and induces orientation illusions. When astronauts-free float in spaceflight they experience many body orientations in relation to the architectural verticals and horizontals of the spacecraft that would not be possible on earth. Sometimes they also experience a compelling sense of being upside down, and some episodes of inversion seem to trigger sudden vomiting (Oman et al. 1990). The rationale for the PAT device is that pre-exposure to such conflicting visual scenes may attenuate or eliminate space motion sickness.

Parabolic flight has been extensively used as a ground-based approach to understanding space motion sickness. An important concern is whether information about motion sickness gained from parabolic flight experiments is directly relevant to understanding the etiology of space motion sickness and the performance changes that occur in spaceflight. Must these factors be studied in orbital flight? In parabolic flight, brief periods of free fall and high gravitoinertial force level alternate and many individuals become motion sick as a consequence of these periodic variations. This makes it necessary to measure baseline susceptibility to the parabolic maneuvers per se or it would not be possible to evaluate the relative provocativeness of different forms of superimposed stimuli. The brief periods of free fall and high force available also limit the measurements that can be made to those compatible with multiple 20–30 s intervals. With prolonged exposure to free fall in orbital flight, a variety of adaptive changes occurs as sensory-motor control and orientation mechanisms accommodate to weightless conditions (see Fig. 4). Those changes with relatively long time constants will be missed in parabolic flight experiments. By contrast, those with short time constants, e.g. seconds or minutes, may first be identified in the course of parabolic flight experiments.

The great advantage of spaceflight for studying physiological changes is the long time periods available for making observations. However, it takes about 8 min to achieve orbital flight after launch and a much longer period before systematic experimental observations can be made. In ground-based studies of sensory-motor performance, adaptation can often be generated in brief periods of time. Exposure periods are often as brief as several minutes and rarely much longer than 30–60 min because adaptation occurs so rapidly. Some sensory-motor accommodations to weightlessness may involve virtually instantaneous adaptation or resetting. For example, during initial exposure to weightlessness in parabolic flight, individuals generally within a try or two are able to catch objects that are thrown to them. It is as if there is a parameter resetting for certain sensory-motor abilities that is extremely rapid (Lackner and DiZio 2000a, b). In orbital flight, the set-up of experimental apparatus involves unstowing and putting together the test rig and instrumentation and often involves considerable head and body movements which can be quite provocative. In the Spacelab 1 mission, astronauts found setting up the apparatus for experiments on vestibular function to be more stressful than the actual experiments (von Baumgarten 1986). In some cases, setting up the apparatus may be generating the sensory-motor adaptation that the experiment was designed to test. The ability to contrast the effects of high and low force levels within a short time span in parabolic flight is thus extremely advantageous and can reveal effects that otherwise might go unnoticed or would be much harder to identify in spaceflight. At present, parabolic flight constitutes the best available terrestrial technique for studying etiological factors in space motion sickness. The aftereffects of prolonged exposure to $+g_x$ centrifugation (Bles et al. 1997) are an intriguing phenomenon which deserves further exploration despite the lack of a clear link to space motion sickness.

Prediction of susceptibility to space motion sickness

In the space shuttle missions, about 70% of the astronauts experience space motion sickness symptoms during the first 3 days. Because the shuttle missions are of relatively brief duration, generally 7–14 days, 3 days of impaired performance represent a severe mission

impact. In long duration missions lasting months such as on the International Space Station or years such as on a projected manned mission to Mars, 3 days are less important. Consequently, the ability to adapt fully to the space environment can be as important or even more important than initial susceptibility in long duration missions. This raises the issue whether it is possible to predict how astronauts will adapt to the space environment and whether it is possible to pre-adapt astronauts to the types of provocative stimulation they will encounter in spaceflight.

Attempts to develop predictors of motion sickness have included (1) trying to identify psychological or personality characteristics linked to motion sickness susceptibility, (2) motion sickness questionnaires, and (3) assessments of motion sickness susceptibility with different forms of provocative stimulation. Excellent reviews of the early literature are provided by Money (1970), Reason and Brand (1975), Reschke (1990), and Tyler and Bard (1949). Despite numerous reports of psychological correlates of motion sickness susceptibility, the correlations have little practical value for predicting susceptibility. The studies show that among highly susceptible individuals some have specific personality traits; however, no information is available about the motion sickness susceptibility of individuals with these traits in general (Wendt 1948; Tyler and Bard 1949). Many investigators have suggested relationships between fear, anxiety, and apprehension and motion sickness, but Dobie (1974) has made the important observation that some instances of sickness are not true motion sickness but fear reactions.

Spacelab 1 prediction tests

Prior to spaceflight, the four Spacelab 1 payload crew members were exposed to a broad range of provocative tests of motion sickness in the laboratory and in parabolic flight (Money et al. 1984). The ground tests included (1) sinusoidal horizontal oscillation at 0.2 Hz along the head *y* axis, (2) head-over-heels rotation about the head *y* axis at 20 rpm, (3) ingestion of deuterium oxide, "heavy water", to render the horizontal semicircular canals gravity sensitive, and (4) wearing prism spectacles to reverse the visual field. The parabolic flight test involved touching the head to the knees then to the head rest on the seat back. One cycle was completed each 3 s during the approximately 25 s periods of weightlessness in each parabola.

The susceptibility to space motion sickness of these four payload specialists and the time course of their symptom development and abatement were carefully monitored during the Spacelab 1 mission. Post-flight it was only possible to repeat the parabolic flight susceptibility tests.

Three of the four astronauts vomited repeatedly during spaceflight, only one did not, and he like one of the others had taken an antimotion sickness medication (scopolamine and dexedrine) before launch. The other two were medicated after symptoms developed. Performance on the pre-flight susceptibility tests did not predict in-flight susceptibility. The least susceptible astronaut during spaceflight was the most susceptible in the pre-flight tests. The other three were basically similar in their in-flight performance and susceptibility but varied in their pre-flight susceptibilities to the different test protocols. Importantly, however, in their post-flight tests in parabolic flight, all of the astronauts were insusceptible to motion sickness when making pitch head and trunk movements during weightlessness. This pattern suggests a carry over of adaptation acquired in spaceflight.

The failure to find a relationship between ground-based assessment tests and in-flight susceptibility is perhaps not surprising. The test population was small, only four subjects, and the ground-based tests were not developed to specifically mimic aspects of the factors that would be altered in spaceflight, but were ongoing laboratory procedures.

Susceptibility questionnaires

Motion sickness questionnaires have been developed by the military to predict susceptibility in operational conditions (e.g. Alexander et al. 1955; Hardacre and Kennedy 1965; Miller and Graybiel 1970: Reason and Brand 1975; Lentz and Collins 1977). Subjects reporting a past history of motion sickness generally show greater susceptibility when tested in experimental devices than those who do not (Alexander et al. 1955; Miller and Graybiel 1970). Subjects who are classified as highly susceptible on the basis of their questionnaire answers are also more likely to report having highly susceptible parents or siblings. Lentz and Collins (1977) point out that this may be in part attributable to similar exposure histories. Bakwin (1971) and Abe et al. (1970), however, believe that motion sickness susceptibility may be in part genetically determined. Asians have also been found to be more susceptible than Caucasians (Stern et al. 1996).

Lentz (1976) found there was no correlation between a subject's susceptibility score on a questionnaire and the duration of vestibular nystagmus and sensations of turning during and following exposure to angular acceleration despite earlier reports of a direct relationship between sensation and nystagmus cupulograms

(plots of duration of aftersensation of rotation and nystagmus versus log of angular velocity impulse) and susceptibility to motion sickness (de Wit 1953; Groen 1957). Bles et al. (1984) and Dobie (1974) have also failed to confirm a relationship between aftereffect duration and susceptibility after sudden deceleration from constant velocity rotation. However, DiZio and Lackner (1991) found a strong correlation between susceptibility to motion sickness in parabolic flight and the extent to which post-rotary head movements decrease the duration of the post-rotation nystagmus under 1 g conditions. This pattern points to a link between velocity storage and space motion sickness. Cohen et al. (2003) and Dai et al. (2003) recently provided strong evidence that velocity storage activity is implicated in the evocation of motion sickness elicited by Coriolis cross-coupled stimulation in 1 g.

Disadvantages of the questionnaire approach include that it is not possible to determine accurately the nature and intensity of a subject's prior exposure to provocative stimulation and that subjects differ in their knowledge of motion sickness symptomotology with most simply equating motion sickness with nausea and vomiting. Two other factors are of concern: (a) questionnaires provide information about past episodes of motion sickness and not about a subject's ability to adapt to provocative motion nor about the rate of recovery from acute motion sickness, and (b) when a motion sickness questionnaire is being used as a screening device, candidates are reluctant to reveal their full range of motion sickness experiences. Motion sickness questionnaire evaluations also typically show greater sickness susceptibility for women than men (Reason 1968; Reason and Brand 1975; Lentz and Collins 1977). However, some experimental studies contrasting male and female susceptibility have not found any significant differences (Cheung and Hofer 1998; Woodman and Griffin 1997). Cheung et al. (2001) also failed to find susceptibility variations related to the female's menstrual cycle. However, others have reported females to be more susceptible than men and to also vary in their susceptibility during the menstrual cycle (Clemes and Howarth 2005; Golding et al. 2005; Grunfeld and Gresty 1998; Turner and Griffin 1995). The issue remains unresolved but any differences may be relatively minor.

Reschke (1990) has provided an excellent analysis of how test and performance measures might be used to predict the performance of subjects in different provocative operational environments. The important message from his large-scale study was that no ground-based test yet developed constituted an accurate predictor of susceptibility and severity in parabolic flight or in spaceflight. Harm and Schlegel (2002) since have found, however, that the severity of motion sickness in parabolic flight may correlate with higher pre-flight baseline levels of salivary amylase. Elevated baselines would be consistent with a higher base level of sympathetic nervous system activity in these individuals. Cardiac *R–R* interval variations and the sympathovagal index were also measured for the subject population and higher values tended to be associated with moderate to severe susceptibility to motion sickness during parabolic flight.

Experimental procedures for assessing susceptibility to motion sickness

Many techniques have been used to elicit motion sickness under partially or fully controlled conditions including (a) ships, (b) ship motion simulators, (c) elevators or vertical oscillators, (d) four-pole swings, (e) caloric irrigation, (f) "roll-pitch rockers", (g) visual inversion or reversal, (h) off-vertical axis, body rotation, (i) optokinetic stimulation, (j) varying angular accelerations, (k) Coriolis and cross-coupling accelerations generated by active or passive head movements while in a rotating chair or centrifuge, (l) parabolic flight, (m) galvanic stimulation, (n) virtual environments, and (o) sudden-stop stimulation. These procedures can elicit motion sickness symptoms in most people, with the exception of labyrinthine-defective individuals most of whom remain largely immune regardless of the nature or level of the stressor environment (see Physiology of motion sickness).

Miller and Graybiel (1970b, 1972) tested subjects on an extensive set of provocative procedures to determine whether susceptibility to one type of provocative stimulation (e.g. off-vertical axis rotation) would predict susceptibility to another (e.g. Coriolis cross-coupling stimulation). They found that subjects who are extraordinarily sensitive to one form of motion tend to be strongly susceptible to others as well. By contrast, for most individuals, susceptibility to one form of stimulation had little relation to susceptibility to another. Even more troubling, there was not comparable motion sickness susceptibility for provocative conditions that otherwise seemed closely related, e.g. executing head movements during rotation in a slow rotation room versus in a rotating chair.

It is important to recognize that a given sign or symptom of motion sickness may not have the same functional significance for different individuals. For example, some people when they experience nausea and vomiting are basically incapacitated and unable to perform essential activities, and it may take hours after

removal from the provocative situation for them to recover. By contrast, and more rarely, some subjects may vomit after a minute or two of exposure to provocative stimulation, and then several minutes later may have recovered sufficiently to continue exposure. Such individual differences in the relative significance of motion sickness have not been taken into account in the design and interpretation of questionnaires and predictive tests of motion sickness.

Conclusions

Space motion sickness affects nearly 70% of all astronauts and cosmonauts. It can develop within an hour after launch and usually abates within 3 or 4 days. It is most severe when the body is actively adjusting to weightlessness and sickness may reoccur upon landing during readaptation to earth gravity. The physiological characteristics of space motion sickness parallel those of motion sickness on earth, except that pallor is not present. The engorgement of the venous return in the absence of hydrostatic pressure in the circulatory system explains the absence of pallor in spaceflight.

The fluid shift hypothesis has been a popular explanation of space motion sickness. However, neither ground-based experimental studies nor in-flight observations have provided support for it. Bed rest studies also do not evoke the motion sickness and disorientation expected from a labyrinthine hydrops origin. Notions of increased cranial pressure are not convincingly supported by available evidence, as well. The otolith asymmetry hypothesis, although intriguing, also has little experimental support. It potentially is a contributing factor but the other effects one would expect from a central compensation for a vestibular imbalance that is unmasked in weightlessness are absent, e.g. persisting sense of body tilt or displacement.

The key factor in eliciting space motion sickness appears to be head movements, especially head movements in pitch and roll. Both spaceflight and parabolic flight experiments strongly support this conclusion. The head movement contribution likely reflects not only just an influence of abnormal patterns of vestibular input but also altered sensorymotor control of the head and body in a weightless environment. Head loading during head movements on earth can evoke motion sickness in the presence of normal vestibular inputs. Head movements made during exposure to greater as well as less than 1 g background force levels elicit motion sickness. This pattern suggests that space motion sickness is not a unique disease entity.

Velocity storage of semicircular canal signals is affected by exposure to weightlessness with storage being attenuated, at least initially, for both vestibulooocular reflexes as well as for generating a sense of body spatial displacement. Attenuation of velocity storage in weightless conditions explains why after initial adaptation to the space environment Coriolis cross-coupling stimulation of the semicircular canals is so much less nauseating and disorienting. It also explains why astronauts and cosmonauts in spaceflight become so visually dependent and subject to visual reorientation illusions.

Autogenic feedback training has been proposed as a way of preventing and treating space motion sickness. The ground-based studies supporting this claim are seriously flawed and carefully controlled studies fail to show any beneficial effect. Treating advanced space motion sickness with injections of promethazine seems the best approach until better therapies can be developed. In operational conditions, promethazine does not have as sedating an effect as it does in laboratory experiments.

Many theories have been proposed to explain space motion sickness. The most adequate is the sensory conflict hypothesis. However, it is not a causal or mechanistic theory in the sense that one cannot specify input variables and predict a quantitative outcome. Nevertheless, it is useful as a classification scheme and for designing experiments until a more causal theory or mechanism can be developed or identified.

Ground-based models have been based on the assumption that situations that evoke symptoms characteristic of space motion sickness are potential tools for studying its etiology. Such analogies have little scientific merit. Parabolic flight maneuvers to generate periods of weightlessness are the only adequate analogue of spaceflight conditions. Periods of weightlessness are brief however and alternate with periods of high force. Consequently, systematic control conditions are essential in order to generate meaningful results. Any space-related events with long time constants will necessarily be missed.

At present, there are no adequate predictors of susceptibility and severity of space motion sickness. Questionnaires can identify those with a history of motion sickness under terrestrial conditions if the respondents answer honestly, but such protocols do not provide insight into the individual's ability to adapt to provocative motion environments which may be more important than susceptibility given that 70% of astronauts and cosmonauts experience some degree of space motion sickness. This issue is particularly important for very long duration space missions where a failure to adapt would be a major operational problem.

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