VRIJE UNIVERSITEIT

Motion-based Equilibrium Reprocessing Therapy Fundamental and Clinical aspects

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus prof.dr. L.M. Bouter,
in het openbaar te verdedigen ten overstaan van de
promotiecommissie van de faculteit der Geneeskunde op
vrijdag 25 november 2011 om 11.45 uur
in de aula van de universiteit, De Boelelaan 1105

door

Agali Mert

geboren te Eindhoven

promotor : prof.dr. C.R. Leemans

copromotoren : dr. W. Bles
prof.dr. J.E. Bos

Opgedragen aan:

Mijn vrouwen

Yurtta sulh, cihanda sulh
(Peace at home, peace in the world)

Mustafa Kemal Atatürk

List of abbreviations

A

a	standard unit for acceleration ($m.s^{-2}$)
AMST	AMST SystemTechnik GmbH
ANOVA	ANalysis Of VAriance

C

CAREN	Computer Assisted Rehabilitation ENvironment
CML	Centrum voor Mens en Luchtvaart/Center for Man in Aviation (RNLAF)
CNS	Central Nervous System
CO_2	Carbon Dioxide

D

DESDEMONA	DESorientation DEMONstrator Amst
Df	Degrees of freedom (statistics)
Dof	Degrees of freedom (motion)
DPMv	Dorsal PreMotor cortex

E

ENT	Ear Nose & Throat
ESA	European Space Agency

F

F-test	any statistical test that has an F-distribution

G

g	Gravitational acceleration
GIF	Gravito-Inertial Force
GIK	Gravito-Inertiële Kracht

H

HR	Heart Rate
Hz	Hertz

L

LEETR	Lowest Expected End-tidal CO_2 To be Reached
LGN	Lateral Geniculate Nucleus

M

MERT	Motion-based Equilibrium Reprocessing Therapy
MISC	MIsery SCore
mmHg	millimeter of mercury (measure of pressure; 1 mmHg= 0.133kPa)
MANOVA	Multivariate ANalysis Of VAriance
MRC	Military Rehabilitation Center, also a measure for muscle generated force
MSI	Motion Sickness Incidence
MSQ	Motion Sickness Questionnaire
$m.s^{-2}$	meter per second squared; standard unit for acceleration
MSSQ	Motion Sickness Susceptibility Questionnaire
MST	Medial Superior Temporal cortex

P

$PACO_2$	Partial pressure of CO_2 in alveolar air
$PaCO_2$	Partial pressure of arterial CO_2
$PetCO_2$	Partial pressure of end-tidal CO_2
PM&R	Physical Medicine and Rehabilitation
PIVC	Parieto Insular Vestibular Cortex
PVC	Primary Visual Cortex

R

RF	Respiratory Frequency
RNLA	Royal Netherlands Army
RNLAF	Royal Netherlands Air Force

S

SD	Standard Deviation or Spatial Disorientation (depending on context)
SEM	Standard Error of the Mean
SV	Subjective Vertical
SV-model	Subjective vertical conflict motion sickness model
s.w.	Specific weight

T

TV	Tidal Volume

V

VIP	Ventral IntraParietal cortex

Index

1. Introduction **9**
1.1 Homeostasis of man 10
1.2 The visual system 13
1.3 The vestibular system 17
1.3.1 The semicircular canals 18
1.3.2 The otolith system 19
1.3.3 The vestibular nuclei and their projections 21
1.4 Basic aspects of motion sickness 23
1.5 Respiratory control and the vestibular system 24
1.6 Experimental techniques 26

2. Respiratory consequences due to forward bowing of the body during cross-coupled angular motion stimuli **27**
2.1 Introduction 28
2.2 Method 31
2.2.1 Subjects 31
2.2.2 Experimental measurements and questionnaires 31
2.2.3 Design and procedures 32
2.2.4 Statistical analysis 33
2.3 Results 33
2.3.1 Inter-individual differences and post-rotation condition 35
2.4 Discussion 36

3. The influence of body orientation with respect to the gravito-inertial force on the incidence of motion sickness during linear oscillation **41**
3.1 Introduction 42
3.2 Method 44
3.2.1 Subjects 44
3.2.2 Equipment 45
3.2.3 Procedures 45
3.2.4 Design 46
3.2.5 Statistical analysis 46
3.3 Results 47
3.4 Discussion 50

4. Oscillatory linear motion and respiration: effect of frequency on the provocation of motion sickness 55
4.1 Introduction 56
4.2 Method 58
4.2.1 Subjects 58
4.2.2 Experimental measurements and Questionnaires 58
4.2.3 Stimulus 59
4.2.4 Study design 64
4.2.5 Statistical analysis 64
4.3 Results 64
4.3.1 MSSQ scores 64
4.3.2 Occurrence of MISC 5 65
4.3.3 Analysis per frequency 65
4.3.4 Respiration parameters 70
4.3.5 Perceived linear displacement and tilt angle scores 72
4.4 Discussion 72

5. Motion-based Equilibrium Reprocessing Therapy: A novel treatment method for chronic peripheral vestibulopathies 77
5.1 Introduction 78
5.2 Method 79
5.2.1 Questionnaire 79
5.2.2 Subjects 80
5.2.3 Procedure 81
5.3 Results 81
5.4 Discussion 82

6. Influence of moving visual surroundings on walking stability 85
6.1 Introduction 86
6.2 Method 88
6.2.1 Subjects 88
6.2.2 Hardware 89
6.2.3 Software 90
6.2.4 Experimental Measurements 90
6.2.5 Study Design 91
6.2.6 Statistical analysis 91
6.3 Results 91
6.3.1 Qualitative aspects of gait 91
6.3.2 Quantitative aspects of gait 92
6.4 Discussion 93

7. General discussion and future prospects **95**

8. References **102**

9. Summary **111**
9.1 Samenvatting 114
9.2 Özet 117

Dankwoord **119**

Curriculum Vitae **122**

1. Introduction

1.1 Homeostasis of man

It's a miracle that we can find our way home, if we realize that our brain has to process numerous stimuli and that those stimuli do not enter the brain simultaneously. For example, we perceive visual and auditory information as simultaneously, although the visual information before 'hitting' the retina is travelling at the speed of light, and the auditory information before being processed in the ears with the speed of sound. A truly remarkable achievement, moreover the brain also integrates sensory information from other afferent signals, like proprioceptive or vestibular. The resulting percept is coherent, it all happened at the "same time".

Numerous case studies, most commonly known by the general public in books by Oliver Sachs (1985), but also Ramachandran (1998) and Damasio (1994) give us insight into the intricate and very delicate neurological homeostasis of the human brain.

For example visual information transferred from the retina to the brain is coded into electrical signals, and even at this lowest level of information processing, already visual information is modified because the 'rods' and 'cones' in the retina transferring this information do not have a one-on-one representation in the brain. Interestingly, before reaching the cortical regions of the brain, the already coded information is further processed by subcortical structures. And when finally this information reaches the occipital lobe located at the back of the head and there reaching the primary visual cortex (PVC), also known as Brodmann's area 17, striate cortex or V1, this coded information is further dissected and distributed to other cortical areas. All of these areas decode specific visual information like form, speed of motion and color (Blumenfeld 2002). To further add to the wonder, this decoded information has to be reintegrated with other sensory stimuli like auditory signals, and then we become aware that say a little daughter is approaching with arms wide open yelling "Daddy, daddy", but also maybe become aware that (being on a vacation in Africa) a rhinoceros is running towards us, angrily. Both situations have other implications, of course, but in general the information processing is the same.

If now, due to for instance a blood clot, a visual cortical area becomes ischemic and dies, a possible consequence could be that a person is still able to process images, but not movement (akinetopsia). In the case of the rhinoceros this could mean that one would see a rhinoceros quietly grazing and the next image that literally 'pops' up in the mind could be a bad tempered rhinoceros in front of the person.

Also, viral labyrinthitis, a self limiting disease of the vestibular system, can cause serious discomfort and incapacitation (Vibert et al. 1999). Persons having had the 'privilege' to experience this disease can vividly tell about the nausea, dizziness, vomiting and

problems with maintaining posture. These symptoms in themselves also point out the involvement of the autonomic system and the spinal muscles in vestibular disease. Luckily, most patients get well within a few weeks time, but there is a minority of patients that develop chronic symptoms of vertigo or dizziness. The adaptation process in those cases is apparently suboptimal and the residual symptoms can lower the patient's level of daily functioning significantly.

Not only in disease, also in health problems can arise. In my work as a RNLAF flight-surgeon, I was confronted with the phenomenon of Spatial Disorientation (SD) in pilots. Here we realize that the human vestibular system functions quite well in normal daily circumstances, but that it is not able to reconstruct the maneuvers of a military fighter aircraft: The pilot may perceive motion of the aircraft which doesn't correspond with the actual aircraft motion, which is very dangerous of course. Obviously, this is not a typical Dutch problem, but happens worldwide, causing many casualties, and requires therefore SD training in student pilots (Previc & Ercoline, 2004). This training is also provided by the CML (Centrum voor Mens en Luchtvaart/ Center for Man and Aviation) and the neighboring TNO Human Factors in Soesterberg, where I got acquainted with the many visual and vestibular illusions pilots have to deal with in flight. The flexibility of the brain is amazing if one realizes how the brain integrates the visual out-the-window view in a flight simulator with the motion cues from the motion platform mostly without any obvious problems.

Nevertheless, some student pilots have problems in the integration of the sensory signals in flight, and develop air sickness, just another form of motion sickness. Motion sickness, however, is not limited to pilots. Most people know from their youth that while sitting in the back of the car one starts to feel nauseated or maybe even start to vomit. Sea sickness, air sickness, space sickness and simulator sickness are all forms of motion sickness. In general, habituation takes place sooner or later in about 90% of the motion sick passengers.

Although motion sickness occurs with normal functioning sensory organs and is in fact a normal response to an unusual motion environment, in military aviation the occurrence of motion sickness can seriously compromise performance, is therefore unwanted and in many Air Forces susceptibility to motion sickness is an exclusion criterion for admittance to initial pilot training. Nevertheless, still quite some student pilots are confronted with motion sickness during their flight training, and it is therefore important for Air Forces worldwide to have a thorough understanding of motion sickness, of the effects it has on the human body, and to have highly successful motion sickness desensitization programs. These programs aim to diminish the motion sickness susceptibility and to let the student pilots resume pilot training. Not being able to fly anymore is for pilots a serious disabling occupational condition. The flight-surgeon

grounding these pilots is usually not the most popular officer in a squadron. With the desensitization program at the CML and TNO about 90% of the pilots could be successfully desensitized and return to their pilot training.

In this desensitization program emphasis was also laid on the beneficiary effects of a good respiration, which helped the students quite a lot (see also Lucertini and Lugli, 2004). But the physiological mechanism responsible for this beneficiary effect was still unclear. The first part of my thesis (Chapters 2-4) therefore explores the role of respiration in relation to the induction of motion sickness, in particular in the RNLAF and TNO motion sickness desensitization program.

After finishing my training as a resident in Physical Medicine & Rehabilitation (PM &R), I started to work at the Military Rehabilitation Center Aardenburg (Doorn, The Netherlands), being responsible for the training and medical research with the CAREN motion platform. Here, working with patients with deficient sensory information because of missing limbs, or with other diseases, the importance of congruent sensory information is demonstrated again, especially the ability of the system to compensate for missing sensory information. Just as healthy people may get used to conditions that provoke motion sickness, patients compensate for a unilateral vestibular loss, and training on CAREN improves the patients' compensation process. Some of these issues could be demonstrated scientifically, and are integrated in this thesis as well in Chapters 5 and 6.

Interestingly, having worked as a flight-surgeon and now as a PM&R specialist I realized a striking but not very obvious similarity between these healthy student pilots and patients with vestibular disease in the *chronic* phase: their sensory end-organs, the vestibular system, are in both situations functioning within their own normal parameters. It is homeostasis, albeit dysfunctional. The adaptation process to nauseating stimuli in student pilots, as their vestibular organ is healthy, takes place above the level of the vestibular organs at subcortical and maybe also cortical levels. This offers potential possibilities for patients with peripheral vestibular disease in the chronic phase as the subcortical and cortical structures are intact. One wonders whether it is possible to "reprocess their equilibrium"[1] with principles used in the military motion sickness desensitization programs. In Chapter 6 a novel type of therapy for vestibular patients, Motion-based Equilibirium Reprocessing Therapy, is introduced and the first results presented.

---

[1] The term "Equilibrium" is preferred instead of a more somatic term like "Balance" as the experienced problems by patients extend beyond the scope of the somatic disease and include amongst others impaired level of functioning and emotional distress.

This thesis, in a sense follows my career in the Dutch Armed Forces. Fundamental aspects of vestibular functioning were investigated during my work as a flight-surgeon. Clinical aspects of vestibular functioning were investigated after having finished my residency. This enabled me to directly use the data from fundamental research and transfer them into clinical practice. The primary aim of this thesis was therefore to broaden the understanding of a possible respiratory contribution to motion sickness, with the possible consequence to enhance the efficacy of pilot selection, and to design a therapeutic regime for vestibular patients in the chronic phase of their illness (with the same success rates as the military desensitization programs) and just maybe to increase mutual understanding between pilots and flight-surgeons.

The experiments on topics concerning the fundamental aspects of vestibular functioning could be incorporated in the projects under investigation at TNO, and they have been described in chronological order in chapters 2, 3 and 4. The clinical aspects are described in chapters 5 and 6.

For a better understanding of motion sickness it is important to have a basic knowledge of the principal actors in motion sickness: the visual and vestibular system. These will be dealt with in the next paragraphs. The relevant information will be dealt with in the experimental chapters as well, which means that these chapters can be read independently from the other chapters.

1.2 The Visual System

The eye is more or less a ball shaped structure. Apart from the lens, the iris and the optic nerve, the retina comprises the entire inner lining of the eye (Fig. 1.1). Therefore any straight object is projected in a curved fashion on the retina. Furthermore, because of its shape the lens projects an inverted and reversed image on the retina. The retina projects visual information through the optic nerve towards the brain. The optic nerve leaving the eye towards the brain is not covered by a retinal layer. This means there is blind spot in each eye (Moore 1999). Because these spots do not project the corresponding visual area the brain 'fills' in these areas and we are not aware of a blind spot. Interestingly, this filling in also happens with persons having only one functioning eye. For an accessible and very interesting overview of how our brain magically creates vision the book of Hoffman (1998) is worth reading.

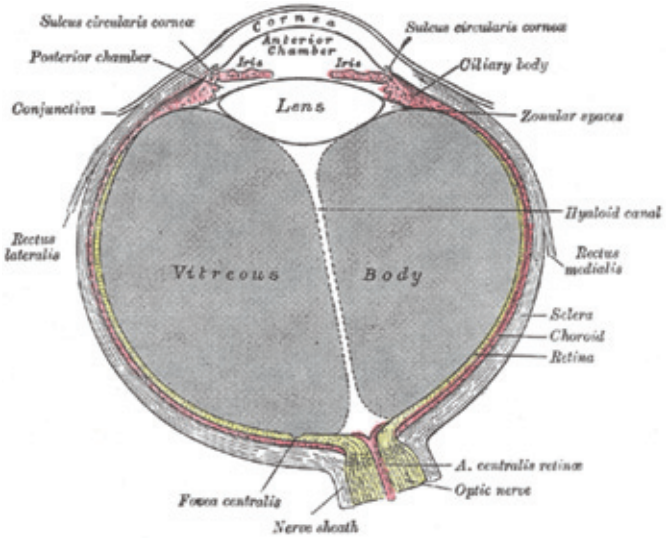


Fig 1.1 Horizontal section of the eyeball (Gray 1918)

The retina contains two types of photoreceptive cells: rods and cones. Cones are found only in the central fixation points of each eye, the fovea and in the small circular area surrounding the fovea, the macula. The cones are appropriate for detecting details and color. Rods, which are 20 times more numerous in number than cones, don't detect color, but have an important function in vision during dim lighting conditions (Blumenfeld 2002). Knowing this it is interesting to realize that the fovea and macula comprise about 6% of the visual field, and yet, we perceive the world sharp and in full color. The fovea comprising 2% of the visual area is responsible for 50% of the nerve fibers of the optic nerve and the same amount of cells in the primary visual cortex (Blumenfeld 2002; Moore 1999). This is a truly disproportionate cortical representation indeed, but understandable because of the very high visual acuity of the fovea.

Modulation of visual information takes place within the retinal layer. The retina consists of several layers: the photoreceptor, bipolar and ganglion cell layer. The outer and inner plexiform layer form a junction layer between the aforementioned cell layers and contain interneurons (amacrine and horizontal cells) that either have inhibitory or excitatory connections with the adjacent bipolar or ganglion cells. Ganglion cells transfer information via synaptic transmission and can actually be divided in two types of cells: P and M cells. P cells are more numerous and respond to detail and colour. M cells respond best to gross stimulus features and motion (Filliard 2009; Blumenfeld 2002).

The axons of the retinal ganglion cells are sent into the optic nerve and partially cross in the optic chiasm. The result of this is that for example the right hemiretina of each eye passes into the right optic tract. The optic tracts are a continuation of the optic nerves, but by nomenclature the part posterior to the optic chiasm is called optic tract. Continuing its way most of the optic tract enter the thalamus into the lateral geniculate nucleus (LGN), while a minority of the axons remain outside the thalamus and enter the superior colliculus and the pretectal area (Fig. 1.2). This extrageniculate pathway is important in visual attention and orientation, while the lateral geniculate pathway is important in visual discrimination and perception. The M cells (transferring information about movement, gross spatial features) in the retina relay their information to the magnocellular layers of the LGN and the P cells (information about detail, form and color) to the parvocellular layers.

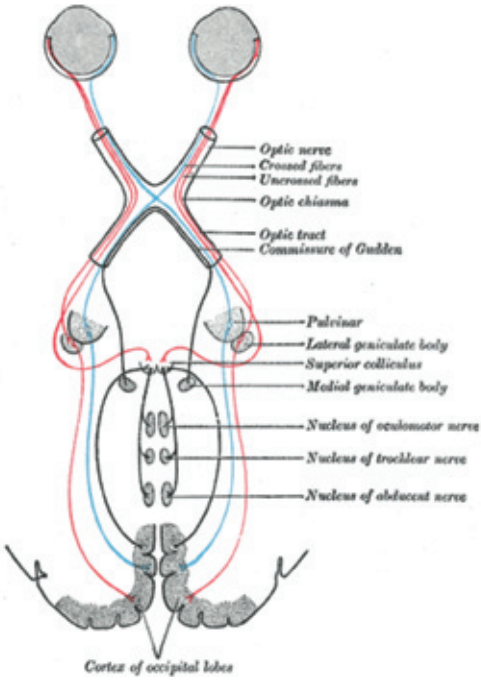


Fig 1.2 Central connections of the optic nerves and tracts (Gray 1918)

The axons leaving the LGN fan out into the optic radiations and enter the primary visual cortex. The information relayed by the fovea (occupying as indicated previously only 2% of the visual field) occupies half of the primary visual cortex. From here neurons project to the visual association cortex. It is important to distinguish two pathways here. The dorsal pathways and the ventral pathways. The dorsal pathways project to the parieto-occipital association cortex and are also called the "Where?"

pathway as it analyzes motion and spatial relationships. The ventral pathway relays information to temporo-occipital association cortex and is also called the "What?" pathway as it analyzes form (e.g. faces, letters etc) and color (Blumenfeld 2002). Consequently, lesions in the "What?" or Where?" pathway give rise to different types of symptomatology (Fig. 1.3).

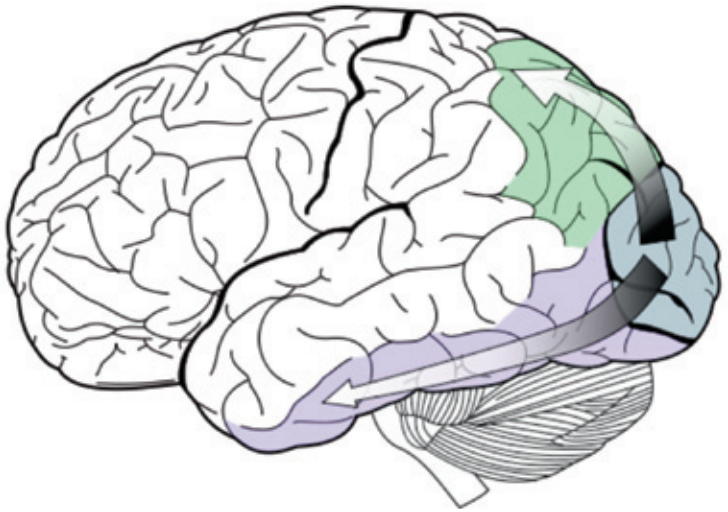


Fig 1.3 The "What" (purple) and "Where" (green) pathways of the visual association cortex (picture from http://en.wikipedia.org/wiki/File:Ventral-dorsal_streams.svg).

One might ask oneself, how much do we actually rely on visual information during daily living conditions. The answer is quite complex, as most research is done in standing subjects: In a well-lit environment with a firm base of support, healthy persons rely on somatosensory (70%), vision (10%) and vestibular (20%) information. However, depending on circumstances subjects are able to re-weigh their sensory information (Peterka 2002).

In conclusion, visual information is even at the retinal layer amongst others coded and segregated in terms of form and color. The fovea has a very high visual acuity and despite the small visual field of 2% is disproportionally represented at the primary visual cortex comprising 50% of the primary visual cortex. Higher-order visual processing is done in the association cortices, popularly called the "What?" and "Where? pathways. Therefore, there is asynchronous activation of brain areas during "seeing" and seeing is not limited to one single area of the brain. One might even hypothesize that the entire brain sees.

1.3 The Vestibular System

Describing the phylogenesis of the vestibular system, Gray (1955) colorfully reports the presence of vestibular systems throughout the animal kingdom. Jelly-fish being the most primitive life forms to possess a vestibular system, have theirs usually lying between the tentacles and the system is composed of statocysts (ear stones). It is safe to say the vestibular system is evolutionary a very old system. Because of the absence of tentacles in human, the location of the vestibular system is somewhere else, namely in each internal ear and located behind the petrous part of the temporal bone (Moore 1999).

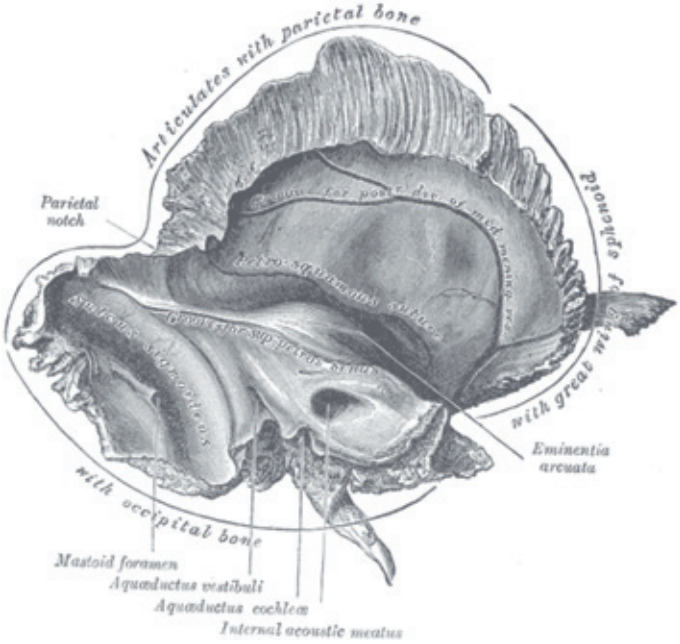


Fig 1.4 Left temporal bone. Inner surface (Gray 1918)

The visual system can be turned on and off by merely closing the eyes: this is not possible for the vestibular system. There is a constant electrical current going to higher order brain structures.

The vestibular system consists of two types of sensory organs. The utricules and saccules are the sensory organs for perception of linear accelerations of the head in the vertical and horizontal plane respectively. The semicircular canals are responsible for the detection of angular accelerations. The utricule and saccule are contained by a small oval chamber of 5 mm in length, the vestibule. The vestibule is also continuous with the semicircular canals posteriorly (Blumenfeld 2002).

The vestibular system is very important in gaze stabilization, maintaining posture and orientation. Projections to cortical and subcortical areas are consequently numerous and amongst other vestibulo-ocular , vestibulospinal, vestibulo-cerebellar and vestibulo-cerebral projections are present (Filliard 2009).

In the next two paragraphs two distinct organs of the vestibular system will be discussed: the semicircular canals and the otolith system.

1.3.1 The semicircular canals

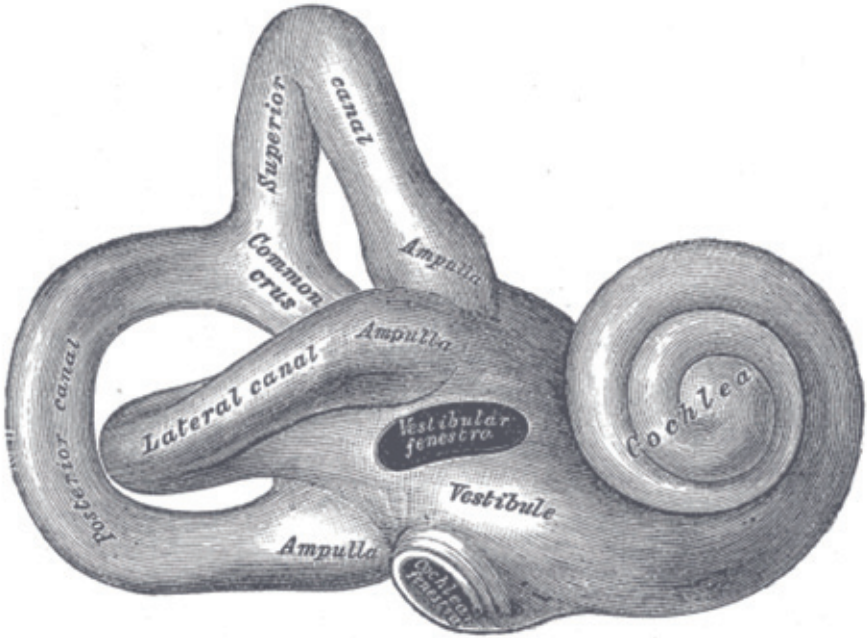


Fig 1.5 Right osseous labyrinth. Lateral view. (Gray 1918)

Each vestibular organ comprises three semicircular canals, namely the anterior (or superior), posterior and lateral canals (Fig.1.5). The canals are orthogonal to each other and occupy three planes in space. Interestingly the anterior and posterior canals are inclined 45 deg. to the sagittal plane. This orientation means that pure roll or pitch motion results in activation of these two canals. The semicircular canals are 'tubes' housing a viscous liquid, the endolymph. At one end of a canal there is a swelling, the ampulla. At the base of the ampulla there is a crest, the crista, on which the sensory hair cells are present. Within the canal in the ampulla is a gelatinous mass, the cupula, in which the hair cells project. The cupula prohibits flow from the endolymph through

the ampulla. Because of the inertia of the endolymph any angular acceleration in the corresponding plane of the semicircular canal will result in an applied force on the cupula, which will result in a slight bending of the hair cells. Thus the hair cells of each canal register movement of the endolymph in the corresponding plane resulting in stimulation of the bipolar neurons of the vestibular ganglion of Scarpa. Since the specific weight (s.w.) of the cupula is the same as that of the endolymph, the semicircular canals are not sensitive to linear accelerations.

Goldberg and Fernandez (1975) have calculated the relationship between the angular acceleration in a plane and the endolymphatic displacement. The time constant is very dependent on the viscosity of the endolymph and is about 5 seconds. LaPlace calculations for the semicircular canals show that these canals are sensitive to high frequency movements of the head (as is the case for normal head movements), but not so for low-frequency movements. This is called high-pass filtering. In our perception however, changes in angular acceleration are not perceived as such, but as a change in speed.

Hair cells have a 'resting' charge rate. If now a person turns his head to the right, the hair cells of the right semicircular canal in the horizontal plane increase their firing rate and the ones in the left vestibular organ decrease their firing rate. This is caused by increase in depolarization of the right and hyperpolarization of the left anterior semicircular canal. This means that the hair cells in each ampulla can increase/decrease their firing rate in one unique direction only, but also that the corresponding semicircular canals act as a couple. The resting firing frequency and the difference in resting firing frequency between the corresponding canals determines whether the head is still in space (or moving at constant velocity) or that we are accelerating (Filliard 2009). In a disease like labyrinthitis, in which for example one canal can be functionally destroyed, a large difference between the firing rate between the corresponding canals and hence vertigo ensues. Luckily, in several weeks time the brain adapts to the new situation and this difference in firing rate becomes the new norm and symptoms subside. This latter signifies the power of modulation of signals from the vestibular organs by the brain (habituation). A power that is also used in motion sickness desensitization programs.

1.3.2 The otolith system

The otolith system captures linear acceleration and is composed of the utricule and saccule. The cells in the utricule are oriented horizontally (because of their orientation this happens with the head inclined about 15 deg.) and those in the saccule vertically. Hence they respond to linear acceleration in the horizontal and vertical plane respectively.

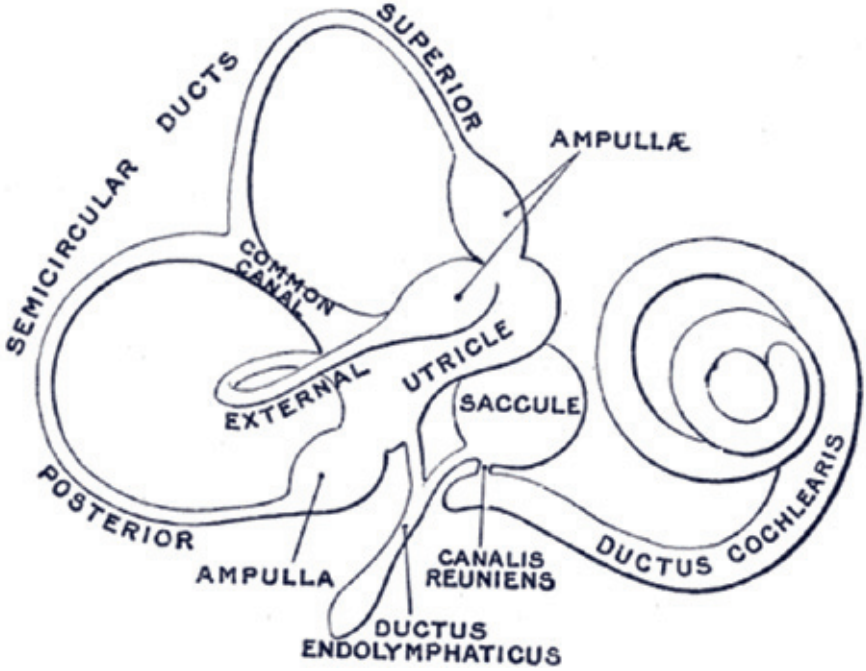


Fig 1.6 The membranous labyrinth (osseous enclosure removed). Location of utricule and saccule relative to the semicircular canals and cochlea. (Gray 1918)

The principle of neural transmission is comparable to the semicircular canals, because the otolith system also has hair cells. The hair cells are located on sensory epithelium, the macula. The ciliae of the hair cells protrude a gelatinous mass composed of calcium carbonate crystals, the otoconia. The s.w. of these calcium carbonate crystals is higher than the s.w. of the endolymph in the vestibule, which means that an acceleration results in a shifting of the otoconia over the macula, and hence in bending of the hair cells. Just as in the semicircular canal system, bending of the ciliae generates a neural signal. But contrary to the semicircular canal system the orientation of the hair cells is not uniform. This means that a typical linear acceleration will cause a neural response of only those hair cells oriented in the direction of the acceleration. A consequence of the difference in s.w. between macula and otoconia is that the system on Earth is continuously stimulated by gravity. So the resulting otolith stimulation by bending the head forward is practically identical with the otolith stimulation caused by a linear acceleration. In that sense bending of the ciliary organs is merely just bending of the ciliary organs causing a neural response, and other sensory input (e.g. visual, semicircular canals, neck) is necessary for the brain to make an appropriate analysis and this involves central nervous system (CNS) filtering too (Mayne 1974).

Also, on Earth the gravitational pull is constant, while inertial movements are transient. The concept of where the gravity vector is, and hence what upright is according to the brain, should in daily life not be challenged by simple head movements. Angelaki & Yakusheva (2009) have stressed out the importance of subcortical pathways in solving this tilt-translation ambiguity. In computational models this ambiguity is solved by acknowledging that in CNS processing the afferents of the otolith system show low-pass characteristics, and from mathematical analysis it is known that the time constant is 5-10 sec (Mayne 1974; Grant & Best 1987; Bos & Bles 2002). This means for example that during a sustained horizontal acceleration without visual information, the perceived vertical shifts within seconds and induces a sense of backward-tilt. This is called the somatogravic illusion. In military aviation the somatogravic illusion has been known to cause loss of aircraft and lives from even the most experienced fighter pilots (Mayne 1974; Cheung et al. 1995).

In summary, the otolith system measures the sum of all linear accelerations, be it by gravity or inertia as a result of true acceleration. This combined measured force is called the gravito-inertial force. As the utricule and saccule are almost perpendicular to each other, and as hair cells have a non-uniform distribution they code for both direction and amplitude of the gravito-interial force in space.

1.3.3 The vestibular nuclei and their projections

Contrary to the primary visual cortex, there is no such thing as a primary vestibular cortex. There are however at least nine cortical regions spread out throughout the brain involved with vestibular functioning. Apart from the cerebral cortex and the vestibular system, subcortical structures are involved: four vestibular nuclei (medial, lateral, superior, inferior), the thalamus and the cerebellum.

The vestibular nuclei are located in the brain stem, canine tooth shaped and together they are called the vestibular nuclear complex (Gray 1955). The vestibular nuclear complex projects to the cerebellum and thalamus. Within the cerebellum the fastigial nucleus has very strong connections with the vestibular nuclei but the cerebellum also receives direct input from the ganglion of Scarpa (Kornhuber 1974).

Vestibular information is combined with other sensory modalities, visual e.g., to determine whether the body or the surroundings are moving. This information processing is not always fail-safe as most train travelers will know. When two trains are parallel to each other and one starts to move, people in the non-moving train are actually misled by their spatial awareness into thinking that their train is moving. This form of perceived self motion is called linear vection and is caused by retinal flux (Dichgans & Brandt 1978; Kawakita et al. 2000).

Much and little is known about the cortical processing of vestibular inputs. Searching through medical search engines a tremendous amount of information can be found, but it should be kept in mind that most research is done with whole body passive movement, which of course in daily circumstances is only happening with passengers. Also most data from vestibulo-cerebello-thalamo-cortical projections come from animal studies.

Being aware of these limitations and that the cortical areas are highly connected, the vestibular cortical areas can be grouped in three functional areas (Shinder & Taube 2010) that represent the following higher cortical functions:

1) Sensory based representation by the medial superior temporal cortex (MST), the ventral intraparietal cortex (VIP), and the parietal area 7a. These areas contain primarily sensory based representations, where also visual information is processed (VIP). These areas are used for accurately determining spatial relationships during self motion and determine whether the perceived movement is the result of self movement or movement of objects, but also in determining the nature of combined perceived movement (object and self).
2 Motor based spatial representations by the dorsal premotor cortex (DPMv) and the vestibular cingulated cortex (also called area 23cv). There are dense vestibulo-thalamo-cortical projections, but also projections from the cortices to the vestibular nuclei: A complicated feedback loop indeed. These areas are amongst others used for smooth target pursuit, the cells (23cv) respond to and stay aligned with prominent objects and are connected to limb areas of the spinal cord (Hutchins 1988; He et al. 1995; Schinder & Taube 2010). One might hypothesize that these areas are evolutionary essential for hunting.
3) Postural awareness and control by the somatosensory area 3av and the parieto-insular vestibular cortex (PIVC). These areas have close relationships with the vestibular nuclei, the spinal cord and hence with the limbs, back and neck. This allows for a coordinated and dynamic representation for postural motion.

Two other vestibularly related cortical areas are known: area 2v and the temporoparietal polysensory cortex (TPv) but not much is known about their roles in head motion. Area 2v receives also visual input and TPv auditory.

In conclusion, spatial awareness through the vestibular complex and its projections to higher subcortical and cortical areas, is a highly complex phenomenon that is only partly understood, but nine vestibular cortical areas have been identified and they are involved in postural awareness/control, sensory and motor based spatial representations.

1.4 Basic aspects of motion sickness

Several theories on motion sickness exist and no one is truly satisfactory in predicting and explaining motion sickness in every situation, although significant progress has been made in the last decade.

A recent proposal by Bowins (2010) suggests to view motion sickness as a form of negative reinforcement designed to terminate conflicting motion stimuli and postural instability. A motion sick animal for obvious reasons is more prone to be eaten by predators.

The most known theory is the sensory rearrangement theory by Reason & Brand (1975). In this theory motion sickness is explained by a variance of motion signals (visual, vestibular and proprioceptive signals) with each other and/or with what is expected from previous experience.

The sensory rearrangement theory has made great contributions in the field of motion sickness, but is not able to explain why for example during optokinetic circular vection, experienced while being immersed in an optokinetic drum, almost no motion sickness occurs. Based on the sensory rearrangement theory, there is a conflict between the vestibularly and visually sensed motion information (no motion and motion respectively). Hence motion sickness should ensue.

Based on experimental data (Bles et al. 1995) and the mathematical motion sickness theory by Oman (1982), Bles et al. (1998) have proposed the following:

"All situations which provoke motion sickness are characterized by a condition in which the sensed vertical as determined on the basis of integrated information from the eyes, the vestibular system and the nonvestibular proprioceptors are at variance with the subjective vertical as predicted on the basis of previous experience".

This is called the 'subjective vertical conflict motion sickness model' or SV-model, and this model is good in predicting those circumstances that will lead to motion sickness like experienced during coriolis effects, sea sickness, the effects of micro- and hypergravity, air and car sickness, simulator sickness and even clinical vertigo.

In the case of the above mentioned optokinetic circular vection, the SV-model predicts the absence of motion sickness, because the stimuli are neutral with respect to gravity (Bles et al. 1998).

The symptom complex of motion sickness comprises amongst others: nausea, fullness of the head, stomach awareness, burping and vomiting (Kennedy & Lane 1999). Dahlman et al. (2009) investigated (short-memory) performance during increasing levels of motion sickness. They conclude that performance declines as perceived motion sickness progresses. The importance of coping with motion sickness, the role of the vestibular system and its deleterious effects on performance were already known during WWII, and during the transport to the shores of Normandy in WWII, the soldiers were allocated drugs against motion sickness (Nobile 1955). In a recent study during a NATO exercise, it was found that (subjective) performance decreases already significantly at MISC levels of 2 (Bos et al. 2002; Bos 2004). And, as said before, in the RNLAF motion sickness is considered to negatively affect the pilot's functioning since it is a reason to exclude students from the initial pilot training. This might happen if during the selection phase they have to handover the control of the aircraft to the instructor because of motion sickness.

In conclusion, there are several theories on motion sickness. The sensory rearrangement theory by Reason and Brand being the most well known. The 'subjective vertical conflict motion sickness model' by Bles et al. (1998) has proven to be able to predict and explain motion sickness, also in those cases the sensory rearrangement theory could not. Motion sickness influences performance and is in (military) aviation irreconcilable with pilot functioning.

1.5 Respiratory control and the vestibular system

The importance of the respiratory system is well known in major trauma. In Advanced Trauma Life Support protocols ensuring a patient's airway and adequate breathing (ventilation) is considered hierarchically more important than controlling circulation. Also while running, when the body might need more than 20 times the oxygen consumption compared to resting conditions and hence also produces large amounts of CO_2, there is an almost effortless increase in ventilation. The lungs play a crucial role in maintaining tissue oxygenation and ensuring life.

The delicate balance of inspiration where the lungs never overinflate during inspiration is a nice example of how our lungs (through stretch receptors in the lungs) act in concert with subcortical structures (Kubin et al. 2006) making sure that during the almost 13.000 breaths per day nothing goes wrong. Although intuitively one might suspect that in normal circumstances the respiratory drive is mediated through oxygen levels, this is actually not the case. In normal circumstances CO_2 drives respiration (Guyton 1991).

Cell-metabolism requires oxygen and this is transported in red blood cells by hemoglobin. A product of metabolism is CO_2. As high levels of CO_2 are toxic to the body, CO_2-levels need to be regulated meticulously. At the level of the lungs and specifically at the level of the alveoli, gaseous exchange between the lung capillaries and alveoli takes place: oxygen in the alveolar air is taken up in the red blood cells, and CO_2 given off from the blood and exhaled. The last portion of exhaled gas very closely equals the partial pressure of alveolar air ($PACO_2$). In lungs of healthy persons the partial pressure of arterial CO_2 ($PaCO_2$) equals the $PACO_2$. The partial pressure of end-tidal CO_2-levels ($PetCO_2$) in exhaled air very closely resembles the $PACO_2$ in normal functioning lungs the $PaCO_2$, when physiological dead space ventilation due to the conducting airways is considered negligible. (F. Hermens, pulmonologist, personal communication, March 10 2011; Guyton 1991). In hyperventilation situations CO_2 is washed out from the body, leading to low levels of $PaCO_2$ and hence low levels of $PetCO_2$. This is called hypocapnia.

The brain regulates breathing through subcortical structures in pontine and brain stem regions (medulla oblongata). The neural respiratory center is composed of 1) a dorsal respiratory group, located in the nucleus of the solitary tract, that mainly causes inspiration, 2) the ventral respiratory group, located in the nucleus ambiguous and retroambiguous, causes either inspiration or expiration, depending on which neurons are stimulated and 3) the pneumotaxic center, located in the pons, which controls rate and pattern of breathing (Guyton, 1991). There is anatomical evidence but also experimental evidence that electrical stimulation of the medial and inferior vestibular nuclei stimulate the ventral respiratory but not the dorsal respiratory group (Yates & Miller 1998; Hernandez et al. 2004). Also Hernandez et al. (2004) have shown that in rats electrical stimulation of the cerebellar fastigial nucleus in general results in strong hyperventilation. This region is recognized as one of the major regions responding to hypercapnia (Gozal et al. 1994).

Hernandez et al. (2004) have also shown that hypercapnia results in an increased ventilatory drive which is attenuated by lesions of the medial vestibular nucleus. These vestibulo-cerebello-respiratory interconnections can be seen as an anatomical rationale for the use of breathing exercises to alleviate motion sickness, as is commonplace during the motion sickness desensitization program of the RNLAF and also of the Italian Air Force (Lucertini & Lugli 2004). Yen Pik Sang (2003) has shown the effectiveness of controlled breathing in preventing motion sickness during mildly nauseogenic motion.

In conclusion, respiration is an autonomous process, which at the level of the brain in normal circumstances is mediated through CO_2 levels. Anatomical connections between the vestibular nuclei and the respiratory neurons are present and vestibular symptoms like nausea can possibly be modified through breathing techniques.

The presence of these anatomical connections makes it worthwhile to investigate how pulmonary parameters like respiratory frequency and CO_2 relate to the development of motion sickness. This will be dealt with in the next chapters.

1.6 Experimental techniques

There are many ways to investigate the vestibular system. Routine testing in clinical practice by ENT specialists includes amongst others caloric testing. However, in clinical practice the most commonly used investigation is the Hallpike maneuver: the upper body of a patient is tilted backwards, the neck hyperextended and the head rotated in one direction. Gaze fixation is prevented by using Frenzel glasses. In research, interests for the vestibular system literally reach space (Nooij 2009). This thesis is however Earthbound.

In our experiments we have used four experimental set-ups to provide motion stimuli. They were in chronological order at TNO Soesterberg a Barany chair, the ESA-sled, and the DESDEMONA motion facility, and at the MRC Doorn the CAREN virtual reality system. These facilities will be described in more detail in the consecutive chapters.

2. Respiratory consequences due to forward bowing of the body during cross-coupled angular motion stimuli

Summary

Introduction: *In motion sickness desensitization programs the motion sickness provocative stimulus is often a forward bending of the trunk on a rotating chair, inducing Coriolis effects. Since respiratory relaxation techniques are applied successfully in these courses, we investigated whether these repetitive trunk movements by themselves may induce hyperventilation and consequently add to the motion sickness.*

Methods: *Twelve healthy subjects participated. In the BASELINE condition subjects sat relaxed on the stationary chair. In condition HYPERVENT subjects performed voluntary hyperventilation (the level was prescribed). In two other conditions subjects rhythmically bended their trunk on a stationary chair (condition TILT-STAT) and on a rotating chair (condition TILT-ROT). In all conditions we measured respiratory and cardiovascular activity (heart frequency, tidal volume, end-tidal CO_2 and respiration frequency).*

Results: *Nine out of the 12 subjects had to stop prematurely in the TILT-ROT condition because of moderate nausea. Except for heart rate in condition TILT-ROT, the measured physiological parameters in these subjects in conditions TILT-STAT and TILT-ROT were not statistically different from the BASELINE condition. Only in condition HYPERVENT significant differences were observed, but no nausea.*

Discussion: *The findings show that hyperventilation is not the main cause of nausea during the Coriolis effects. We conclude that during the pilot desensitization program with Coriolis stimuli measurement of cardiovascular and respiratory parameters is not necessary, but in those cases that do not respond to the intervention we recommend paying attention to respiratory parameters as hyperventilation does occur on an individual basis.*

Acknowledgments
I wish to thank Lt.Col. F. van Hootegem MD RNLAF for his operational and stimulating support, Ineke Klöpping MD for assistance with medical-ethical issues, Arno Krul, statistician, for his help in the data-analysis, and the test subjects for supplying such interesting data.

The original version has been published as:
Mert A, Bles W & Nooij SAE: Hyperventilation in a motion sickness desensitization program. Aviat Space Environ Med 2007; 78: 505-509.

2.1 Introduction

The joy of traveling by car, train, bus or plane is not necessarily shared by those who suffer from motion sickness. The symptom complex of motion sickness comprises amongst others: general discomfort, fatigue, boredom, drowsiness, headache, eyestrain, difficulty focusing, increased/decreased salivation, sweating, nausea,

difficulty concentrating, depression, fullness of head, blurred vision, dizziness (eyes open/closed), vertigo, visual flashbacks, faintness, awareness of breathing, stomach awareness, increased/decreased appetite, desire to move bowels, confusion, burping and vomiting. All of these symptoms reduce travel comfort (Kennedy et al. 1993). To combat this problem human ingenuity has come up with several solutions, one more successful than the other, from pharmacological drugs like cyclizine to Korean hand acupressure and wrist-bands (Bertalanffy et al. 2004; Miller & Muth 2004). For those who travel only during their holidays these solutions may be effective. For those who suffer from motion sickness during the exercise of their duties, for example pilots, the problem needs a different solution, because anti-motion sickness drugs often induce sleepiness, which affects the task performance. One solution is to expel student pilots suffering from motion sickness during the selection procedure (Bles et al. 1995). When, on the other hand, motion sickness susceptibility becomes evident after the selection procedures, motion sickness desensitization programs may offer a solution (Dobie 1974; Stott 1992). Such programs aim at decreasing the pilots' motion sickness susceptibility by means of repetitive exposure to provocative stimuli. In the desensitization program of the RNLAF the provocative maneuvers primarily consist of pitching head and trunk movements (0.25 Hz) during constant velocity rotation on a Barany chair, similar to the Coriolis Stress Test (Bles et al. 1995). During the 2-week course, the pilots' susceptibility gradually decreased as shown by the endurance of head movements at increased angular velocities. After participation in such a desensitization program 80 to 90% of the student-pilots can continue their training without problems (Dobie 1974; Stott 1992; Bles et al. 1995; Lucertini & Lugli 2004). The success rate of the desensitizations performed by TNO and CML until December 2010 is in the same order of magnitude.

Recent studies have shown that during motion slow-deep breathing (Jokerst et al. 1999) and controlled breathing (Yen Pik Sang et al. 2003) also suppress the symptoms of motion sickness. Similarly, relaxation breathing techniques are applied successfully in the desensitization program of several air forces to counter the irregular breathing of the subject during the pitching head movements (Bos et al. 2001). However, fast-deep breathing may *enhance* the motion sickness process, comparable to how, for instance, the Valsalva (forcible expiration against a closed glottis) and Mueller maneuver (forcible inspiration against a closed glottis) can cause nausea and vomiting (Lipana et al. 1969). Hyperventilation also induces symptoms similar to those of motion sickness: Table 2.I presents a subset of symptoms that are included in questionnaires for monitoring motion sickness (Simulator Sickness Questionnaire, see Kennedy & Lane 1993; Motion Sickness Susceptibility Questionnaire, see Golding 1998) and hyperventilation (Nijmegen Questionnaire for Hyperventilation, see Van Dixhoorn & Duivenvoorden 1985). It is striking to see the large overlap. Although nausea is not listed in the Nijmegen questionnaire (see also Method section), it has been observed as a symptom of hyperventilation in several cases (Lum 1975; Perkin & Joseph 1986; Han et al.

1998; Han et al. 2000). The relation between motion sickness and hyperventilation is illustrated further by Humphriss et al. (2004), who found that of a group of patients seen for vestibular assessment 23% were diagnosed for the Hyperventilation Syndrome.

Table 2.I. Comparable symptoms in Nijmegen questionnaire and Motion Sickness Questionnaires (MSQ).

Nijmegen questionnaire	**MSQ**
Bloated abdominal sensation	Stomach awareness Desire to move bowels
Shortness of breath Accelerated or deepened breathing Unable to breathe deeply	Awareness of breathing
Dizzy spells	Dizziness Vertigo
Blurred vision	Blurred vision Difficulty focusing
To be confused, losing touch with reality	Confusion

Bles and Wientjes (1988) found hyperventilation in subjects suffering from seasickness during a sea voyage. Unanswered in that study was whether the hyperventilation was due to the enforced breathing pattern induced by the ship motion. That body motion has an effect on breathing patterns was pointed out in an earlier study by Bles (1976), who observed strong breathing rhythm synchronization with sinusoidal vertical motion stimulus pattern at frequencies that were close to the frequency where vertical stimulation is maximally motion sickness provocative. The question whether hyperventilation was involved could not be answered at that time, because only the breathing rhythm was recorded and not the end-tidal CO_2.

Consequently, the effect of breathing pattern on motion sickness symptoms could contaminate the results of the Coriolis Stress Test: It is possible that forward bowing of the trunk by itself alters the breathing pattern. This might then induce hyperventilation, which in turn results in symptoms similar to motion sickness.

The present study aims at investigating whether hyperventilation occurs during the standard RNLAF desensitization protocol as described above, and how this relates

to the commonly used motion-sickness end-point of moderate nausea. To that end, respiratory and cardiovascular parameters were compared to the evoked nausea level in conditions where subjects bowed their trunk and head forward when the chair was stationary and when the chair was rotating. We also investigated whether voluntary hyperventilation alone (on a stationary chair) induced symptoms similar to motion sickness.

2.2 Method

2.2.1 Subjects

The twelve subjects were four healthy male and eight healthy female volunteers with a mean age of 23.6 years, SD 6.7. They were not receiving any current medication, except for the female subjects who had to be on oral contraceptives (to eliminate menstrual cycle susceptibility to motion sickness) to enter the study (Golding et al. 2004).

Subjects gave informed consent and were free to withdraw at any time. The experiment was carried out under the constraints of a protocol relating to experimentally induced motion sickness, which had Ethical Committee approval.

2.2.2 Experimental measurements and questionnaires

Breathing parameters and the heart frequency were collected using the K4B2 portable breath-by-breath analyzer by Cosmed (Rome, Italy). The parameters analyzed were breathing frequency (/min), tidal volume (l), end-tidal CO_2 (mmHg) and heart frequency (beats/min). Heart frequency was measured simultaneously with the K4B2 using a *thorax belt*, which was linked to the K4B2.

The level of motion sickness during the experiment was rated on a 6 point rating scale (denoted by the Misery Scale or MISC), where 1='No problems'; 2='Initial symptoms, but no nausea' 3='Mild nausea'; 4='Moderate nausea'; 5='Severe nausea and/or retching; and 6='Vomiting'.

A motion sickness susceptibility score was obtained using the Motion Sickness Susceptibility Questionnaire (MSSQ, see Golding 1998). The score ranged from 0 (not susceptible) to 200 (very susceptible), based on the subject's previous experiences with motion sickness. The Nijmegen Questionnaire for Hyperventilation (NQH) was used as a diagnostic assessment tool for the hyperventilation syndrome. It consists of a list of 16 symptoms of which the experienced frequency is rated on a 0 to 4 point scale. The NQH has a specificity and sensitivity of more than 92% and a summed score of

more than 23 out of 64 is considered as positive for the hyperventilation syndrome (Van Dixhoorn & Duivenvoorden 1985). A person has to rate the following components of the NQH: Chest pain, feeling tense, blurred vision, dizzy spells, feeling confused, faster or deeper breathing, shortness of breath, tight feelings in chest, bloated feeling in stomach, tingling fingers, inability to breathe deeply, stiff fingers or arms, tight feelings round mouth, cold hands or feet, palpitations and feelings of anxiety.

2.2.3 Design and procedures

Prior to the start of the experiment subjects completed the MSSQ and the NQH. The K4B2 was calibrated according to the instructions provided by the instruction manual of the manufacturer. During all conditions, the subject was seated on a Barany chair (Figs. 2.1 and 2.2). This chair is the same chair that is used for all the desensitizations performed so far by TNO and CML. There were three control conditions: The experiment started with a 3 minute baseline measurement (BASELINE) where the subject sat quietly on a stationary chair. In condition TILT-STAT we investigated the possible effect of body movements on motion sickness and respiration: during one minute the subject made pitching head and trunk movements with an amplitude of about 60° at a frequency of 0.25 Hz (chair stationary).

Fig. 2.1 The hand-driven Barany chair was part of the SD training as provided by the RNLAF in the last century at Kampweg 2, Soesterberg. In 1988 the Barany chair was saved from the garbage dump and given to TNO. The chair got motorized and was for years active in SD demonstrations and in the desensitization protocol. In this form the chair was used in the present experiment.

The movements were paced by an auditory signal. The HYPERVENT condition investigated the effect of voluntary hyperventilation on motion sickness. With this we could determine the Lowest Expected End-Tidal CO_2 (mmHg) to be Reached (LEETR), which gives insight into the normal physiological end-tidal CO_2 boundaries of the subject. During a period of one minute the subjects, sitting on a stationary chair, were to breathe fast and deep. Subjects could stop doing this, if they felt they needed to. After each of the three conditions mentioned above, subjects rated their experienced nausea-level on the MISC. In the actual experimental condition (TILT-ROT) the subjects made the same pitching movements as in the TILT-STAT condition, but now the chair was rotating at constant velocity. Starting at 60°/s, the velocity of the chair was increased each minute in steps of 5°/s to a maximum of 120°/s. The experienced nausea level was rated at the end of each minute, before increasing the chair velocity. The chair was brought to a stop when MISC scores were 4 or higher, or when a velocity of 120°/s was reached (15 min.). Measurements continued until the parameter-values were back to baseline, with a maximum of 15 minutes.

2.2.4 Statistical analysis

For statistical analysis median values of breathing frequency, tidal volume, end-tidal CO_2 and heart frequency were used, taken over the one-minute measurement period. For the TILT-ROT condition the last minute before stopping the chair motion was used. In the analysis, hyperventilation was defined as a $PetCO_2$ below 31 mmHg (Gardner et al. 1986)

The data was submitted to a repeated measures ANOVA to investigate differences between conditions. A Tukey HSD test was used for post-hoc analyses. Results were considered significant at the $p<0.05$ level and highly significant at the $p<0.01$ level.

2.3 Results

In the BASELINE and TILT-STAT conditions no nausea was present. All subjects scored a MISC of 1. After the HYPERVENT condition three subjects had a MISC level of 2. In the TILT-ROT condition the nine subjects who reached a MISC-score of 4, were included for statistical analysis. The other three subjects –all of whom were male- were excluded from statistical analysis as their MISC scores after reaching 120°/s were 1, 2 and 2 respectively and none of them hyperventilated during the run. Their mean Nijmegen questionnaire scores (9.3, SD 2.9) and age (31.0, SD 10.5) were not statistically different from the group included for analysis (11.4, SD 5.9 and 21.1, SD 2.7): none of the 12 test subjects was suffering from the hyperventilation syndrome.

The subjects included for analysis had a mean MSSQ of 64.1 (SD 28.7, population mean 45.5, see Golding 1998). Those who were not included in the final analysis had a mean MSSQ score of 29.9 (SD 9.9).

The mean rotational speed before reaching MISC 4 was 90°/s (SD 18.9).

In Table 2.II the physiological data is summarized for all measurement conditions.

*Table 2.II. Means of medians (n=9) of respiratory frequency (RF), tidal volume (TV), heart rate (HR) and end-tidal CO_2 ($PetCO_2$) in the four experimental conditions. The standard deviation is given between brackets. The asterix * indicates a highly significant difference from BASELINE, p<0.001. The cross † indicates a significant difference from TILT-STAT, p=0.048.*

	BASELINE	**TILT-STAT**	**HYPERVENT**	**TILT-ROT**
RF (/min)	15.3 (2.7)	17.0 (3.0)	31.8 (8.8)*	17.8 (4.8)
TV (l)	0.7 (0.5)	0.8 (0,4)	1.4 (0.7)*	0.9 (0.5)
HR (bpm)	77.1 (15.3)	78.9 (14.1)	85.3 (15.8)*	87.8 (16.3)*†
$PetCO_2$ (mmHg)	33.6 (1.4)	33.5 (1.4)	21.7 (2.2)*	32.5 (3.6)
MISC (1-4)	1	1	1.3 (0.5)	4*

Only in the TILT-ROT, the heart rate, and in the HYPERVENT condition, the respiratory frequency, tidal volume, heart rate and $PetCO_2$, were significantly different from baseline values.

The $PetCO_2$ reached in the HYPERVENT condition was 21.7 mmHg: a decrease of 11.9 mmHg as compared to the baseline value and the maximum decrease to be expected and reached in this experiment (LEETR). Compared to the baseline value this meant a maximum expected decrease of 35.4%.

Although the heart rate of the TILT-STAT did not differ significantly from baseline conditions, it was however marginally significantly different from the TILT-ROT (p=0.048), but not from the hyperventilation condition (p=0.43).

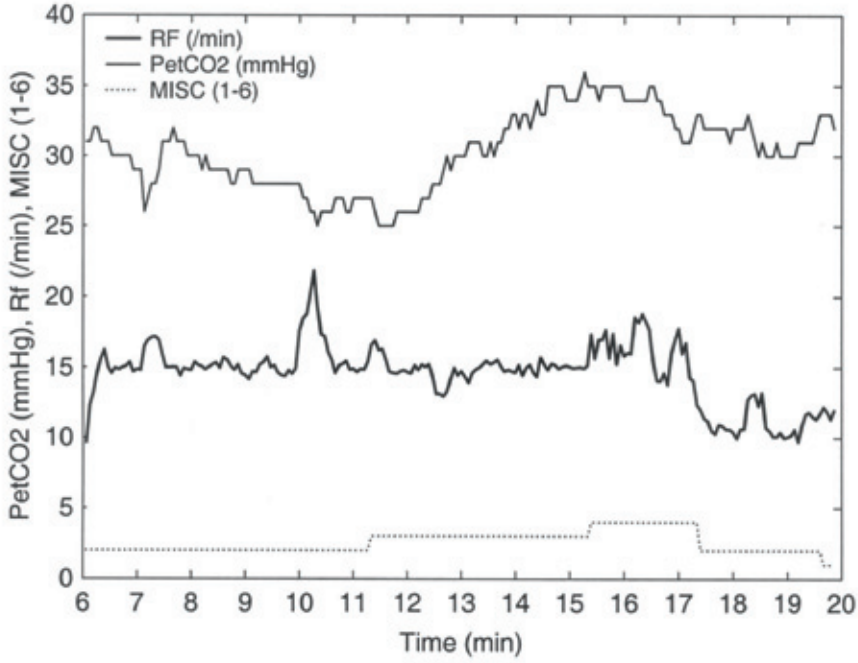


Fig. 2.2. End-tidal CO_2 levels ($PetCO_2$ mmHg), Respiratory frequency (RF/min) and MISC (1-6) of a subject from start of per-rotation condition (06:00-16:14 min) until discontinuation of measurements (20:00 min).

2.3.1 Inter-individual differences and post-rotation condition

It should be noted that there are marked inter-individual differences between test-subjects during the test condition: as in one individual (Fig. 2.2), during the per-rotation condition a slow decrease of 6 mmHg from 31 to 25 mmHg of $PetCO_2$ levels is seen, followed by an increase to 34 mmHg. The test was halted after 105°/s at 16.10 min. In the post-rotation condition a slow decrease to a $PetCO_2$ of 30 mmHg is seen. Per-rotationally a marked rise in the respiratory frequency to 22/min is seen (large spike in the graph). This corresponds to a further decrease in $PetCO_2$ levels. Although there is a decrease of respiratory frequency post-rotation the decrease of the corresponding $PetCO_2$ levels can be explained by an increase of tidal volume (from 0.5 liter to a maximum of about 0.9 liter, data not shown). In this subject the lowest $PetCO_2$ value during the hyperventilation condition (LEETR) is 18 mmHg. The decrease in $PetCO_2$ levels relative to the LEETR values is therefore 6/(31-18) = 46%.

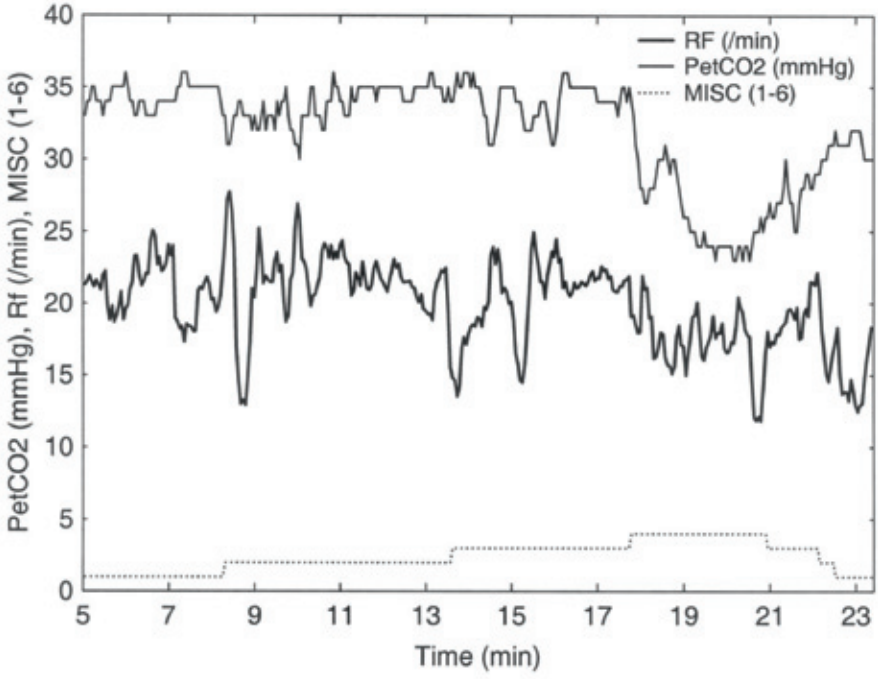


Fig. 2.3 End-tidal CO_2 levels ($PetCO_2$ mmHg), Respiratory frequency (RF/min) and MISC (1-6) of a subject from start of per-rotation condition (05:00-18:09 min) until discontinuation of measurements (23:34 min).

In another subject (Fig 2.3) $PetCO_2$ levels (mmHg) remained roughly constant until the last minute of rotation and after discontinuation of the experiment $PetCO_2$ levels dropped from 34 to 24 mmHg, which is a 100% drop relative to the LEETR value. Also can be seen that the mean respiratory frequency in this subject is above 20/min during the major part of the experiment and drops to about 17 after discontinuation of the experiment. This indicates that respiratory frequency alone cannot depict a hyperventilatory response.

2.4 Discussion

We started out to investigate the occurrence of hyperventilation in motion sickness desensitization protocols. Prior to the experiment subjects had to fill out the Nijmegen Questionnaire for Hyperventilation and the MSSQ for motion sickness. Breathing and cardiovascular parameters were measured during the experiment.

The three subjects that did not reach MISC levels of 4 were all male and were omitted from analysis as the absence of both moderate nausea and hyperventilation during the run would not contribute to understanding the relationship between hyperventilation and experienced nausea during the Coriolis stress test. There was no statistical difference in Nijmegen score and age between the groups in- and excluded for final statistical analysis. Because it has been described by Golding et al. (2004) that women are more susceptible for motion sickness because of hormonal influences, in this experiment all female subjects were on oral contraceptives, which would rule out menstrual cycle factors.

The MSSQ levels of the subjects who reached MISC 4 indicate that they were slightly higher than the general population (Golding 1998), which is preferable as we wanted to investigate the relationship between motion sickness and hyperventilation.

End-tidal PCO_2 ($PetCO_2$) recorded from expired air is regarded as equivalent to arterial PCO_2 ($PaCO_2$) in resting subjects with normal lungs. The range of normal $PaCO_2$ in normal subjects is 35-45 mmHg. Based solely on the lower end of this range, hyperventilation was therefore commonplace in our study. However, the normal range has been determined from measurements recorded under conditions at rest in the laboratory and should therefore only be used as a reference for these situations (Osborne 2000). It has been reported that the lower limit of the normal range in the laboratory therefore should be 31-32 mmHg (Gardner et al. 1986). The reported mean of this experiment is therefore well within the normal range.

During the TILT-STAT condition no significant change in $PetCO_2$ levels or breathing frequency was seen. Consequently, tilting the upper body per se does not invoke hyperventilation or a change in breathing frequency. We could only determine a significant change in respiratory frequency during the HYPERVENT condition. This might indicate that making fore and aft movements with the upper body, even on a rotating Barany chair, did not change the breathing frequency. However, baseline respiratory frequency is 15.3/min, tilting the body was done at a frequency of 0.25 Hz, which could represent a breathing frequency of 15/min. Breathing with a fixed frequency of 0.25 Hz would imply no deviations from a breathing frequency of 15/min and be seen as a fairly straight line in a graph. This was seen only in one subject, which implies that a forced breathing pattern is not commonplace during the Coriolis stress test. This latter observation also means that measuring respiratory frequency can give useful information about the quality of breathing which can be used for intervention during a desensitization program, for example advising to focus on quiet relaxed breathing.

During the HYPERVENT condition, during which the subjects had to breathe fast and deep, a significant increase in respiratory frequency and tidal volume and a significant

drop in $PetCO_2$ levels were seen. This means that the subjects carried out the task accordingly. Hyperventilation alone caused a small increase in MISC levels in three female subjects, even though there was no vestibular stimulus.

For ethical reasons we were forced to limit the hyperventilation condition to one minute. The hyperventilation provocation test used in a clinical setting during which patients have to breathe deep and fast lasts three minutes, a further decrease of approximately 3 mmHg in $PetCO_2$ levels might occur compared to one minute of hyperventilating (Hermens F. Personal communication; Aug. 17, 2006). According to Rafferty et al. (1992) one can on theoretical grounds alone expect that the longer a hyperventilation condition prevails the more prominent the symptoms will be and hence the more frequent a rise in MISC values might be seen. Therefore, subjects who keep their Pet CO_2 levels below 29 mmHg during prolonged periods of time might therefore be prone to hypocapnic symptoms (Rafferty et al. 1992), especially subjects who are experiencing symptoms before referral (Han et al. 1998; Han et al. 2000).

The use of LEETR values has proven to be useful. In one subject the ultimate $PetCO_2$ levels reached during and after the TILT-ROT condition are the same as during the HYPERVENT condition. A decrease to 24 mmHg $PetCO_2$, a decrease of 10 mmHg $PetCO_2$, which is a 100% decrease compared to the LEETR value of this subject but "only" a 30% decrease compared to baseline. We recommend using LEETR values in further experiments for the above mentioned reason.

On a group level we conclude that hyperventilation did not take place in the TILT-ROT condition. It has been described by Bles et al. (1988) that paced roll-pitch movements do influence the occurrence of hyperventilation. The drop in CO_2 levels is small in their experiment, but they did not determine LEETR levels and hence were not able to put the observed decrease in perspective. Dixon et al. (1961) have shown that vertical body movements can influence diaphragmatic movements and cause mandatory breathing at that frequency. If this results in fast and/or deep breathing, this can result in a drop of $PetCO_2$ levels and hence hyperventilation. In the TILT-ROT and TILT-STAT conditions the mechanical effect of pitching the trunk was not sufficient to induce hyperventilation. The rise in MISC-scores in condition TILT-ROT is therefore primarily due to vestibular Coriolis effects.

Heart rate changed significantly during the HYPERVENT and TILT-ROT condition compared to BASELINE. Since in the TILT-STAT condition no significant change in heart rate is seen, and since hyperventilation and motion sickness did not occur in the TILT-STAT condition, and since hyperventilation did not occur in the TILT-ROT condition, the increase in heart rate during TILT-ROT seems to be related to motion sickness. Other studies showed that with increasing nausea these cardiac changes seem

related to a decrease in parasympathic activity (Doweck et al 1997; Gianaros et al. 2003, Yokota et al. 2005).

Subjects were allowed to go home when MISC, respiratory and cardiovascular parameters returned to baseline values. It should be noted, however, that even after these parameters were back to baseline values, some of the test-subjects told afterwards that they were still feeling "a bit weird" or having "a strange sensation in the stomach" after having left the institute. One test-subject told that this feeling lasted the entire day. It seems that longer lasting changes take place in the human body that cannot be linked to the parameters we measured.

Interestingly, one subject who was excluded from statistical analysis because of MISC level of 2 at the end of the TILT-ROT condition, showed a steady increase in MISC level after 1 minute of stopping the rotation of the chair, which after two more minutes resulted in vomiting (Fig. 2.4). Two and a half minutes prior to vomiting a drop in $PetCO_2$ levels from 38 to 34 mmHg was seen. This was a 27% drop compared to LEETR value. For obvious reasons data collection was discontinued after vomiting.

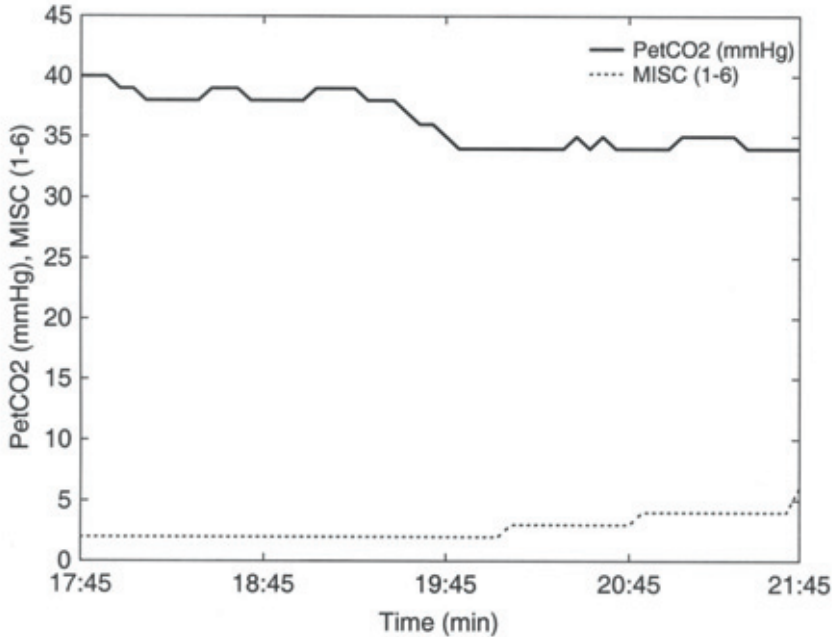


Fig. 2.4. End-tidal CO_2 levels ($PetCO_2$ mmHg) and MISC (1-6) of a subject who was excluded from statistical analysis. Timeframe is from the last minute of the per-rotation condition (17:45-18:45 min) until the moment of vomiting (21:45 min) in the post-rotation condition.

Although it cannot be deduced from these data, there is evidence that a hyperventilatory response can suppress the symptoms of mild nausea. In this subject the occurrence of a mild hyperventilatory response prior to vomiting might indicate that a compensatory and regulatory hyperventilatory mechanism takes place, trying to compensate for increasing nausea. This is in accordance with the finding that inducing hyperventilation and thereby activating thoracic receptors can decrease mild nausea and increase tolerance time for nauseating stimuli (Lipana et al. 1969; Zabara et al. 1972; Lang 1999). It seems unlikely that hyperventilation alone did increase the nausea, as the data from the HYPERVENT condition showed no increase in MISC scores.

The results suggest that during the pilot desensitization program measurement of cardiovascular and respiratory parameters is not necessary, but in those cases that do not respond to the intervention we recommend paying attention to respiratory parameters as hyperventilation does occur on an individual basis.

One could even suggest implementing the NQH in desensitization protocols, because it gives insight into the origin of the problem: vestibular or respiratory.

Lucertini et al. (personal communication; June 16, 2005) have used the Nijmegen questionnaire and have found that Nijmegen scores drop after having successfully completed the desensitization course.

In conclusion, forward bowing of the trunk did not cause hyperventilation and symptoms produced during the Coriolis stress test were not due to hyperventilation. The experienced nausea by the test subjects during our experiment must be for the largest part attributed to the complex vestibular stimulation.

3. The influence of body orientation with respect to the gravito-inertial force on the incidence of motion sickness during linear oscillation

Summary

Introduction: *In tilting trains partial alignment to the gravito-inertial force (GIF) in the curves seems to be the best tilt compensation to reduce the incidence of motion sickness. We investigated the effect of type of alignment to the GIF on the development of motion sickness during low-frequency horizontal motion.*

Methods: *twelve healthy subjects participated. The design was a three period, single blind, crossover, counterbalanced for order trial. Cardiopulmonary measurements, MIsery SCores (MISC) and questionnaire data (Motion Sickness Susceptibility Questionnnaire, Nijmegen Questionnaire for Hyperventilation) were obtained. The stimulus was a sinusoidal movement (0.176 Hz, 0.2 g peak acceleration) on the ESA-sled. The cabin was compensated for 0% (A-0), 50% (A-50) and 100% (A-100) to the GIF. Runs were 1 week apart.*

Results: *There is a tendency for the A-50 condition to delay the development of motion sickness. Based on the survival curves the possible effect seems temporary. However, MISC 2 early in the runs results in high positive and negative predictive values for dropout and survival during the runs. No synchronization of the respiratory frequency with the sled motion was observed. There is a significant ($p=0.002$) drop in relative end-tidal CO_2 levels.*

Discussion: *There seems to be a rationale for partially compensating to the GIF while trying to prevent motion sickness in tilting trains: Sitting comfort is just better than without compensation at all, and Coriolis effects are just not as nauseating as with complete tilt compensation. Also, a drop in end-tidal CO_2 levels might be a sign of pulmonary compensation for the nauseating stimulus.*

Acknowledgments
We wish to thank Mr. Arno Krul for his valuable statistical insight. Also we thank the test-subjects who actually were the last test-subjects on the ESA-sled before it was dismantled at TNO in Soesterberg. Also we wish to thank Dr. Suzanne Nooij for her invaluable assistance.

The original version has been published as:
Mert A & Bles W. Impact of alignment to gravito-inertial force on motion sickness and cardiopulmonary variables. Aviat Space Environ Med 2011; 82: 694-8.

3.1 Introduction

Motion sickness is a problem, which manifests itself in various transport means and is known as car sickness, sea sickness, air sickness, space sickness, or simulator sickness (Reason & Brand 1976). Because motion sickness may affect performance, motion sickness is of special importance in the military where the operational motion envelopes

are largely extended compared to those in public transport. The importance of coping with motion sickness, the role of the vestibular system and its deleterious effects on performance were already known during WWII (Nobile 1955). During the transport to the shores of Normandy in WWII, the soldiers got drugs against motion sickness (Nobile 1955; Reason & Brand 1976) Even now motion sickness is still of operational importance. In bomber crews it has been reported that motion sickness can lead to incapacitation (Strongin & Charlton 1991). Also, about 5% of the gunners of tank-crew in the Royal Netherlands Army (RNLA) reported motion sickness (Droppert 2006). Typically, motion sickness is provoked at critical moments as provoking stimuli will mostly be the strongest then. For obvious reasons suffering from motion sickness, albeit a normal physiological response to certain motion stimuli, is incompatible with duties as a fighter-pilot. Because of the negative side effects of many anti-motion sickness drugs, military personnel is not allowed to take these drugs on a regular basis. In the Royal Netherlands Air Force (RNLAF) motion sickness is therefore an exclusion criterion for admittance to initial pilot-training. Luckily, the success rate of most motion sickness desensitization programs is very high (Dobie 1974; Stott 1992; Bles et al. 1995; Lucertini & Lugli 2004; Yen Pik Sang et al. 2005) and after completing the desensitization course between 80-90% of military personnel can continue performing their duties.

Motion sickness is often described as the result of an intra- or intersensory conflict between perceived self-motion / attitude and the expected self-motion / attitude (Reason & Brand 1976). Bles et al. (1998) explained motion sickness to be the result of only one typical conflict, i.e. the conflict between the sensed and the expected magnitude and direction of gravity. This may explain the motion sickness observed in car driving, since accelerating, braking, cornering and low frequency linear oscillation during lane changes produce horizontal forces, which make the gravito-inertial force (GIF), and consequently also the Subjective Vertical, deviate from gravity. For similar reasons people may get sick in trains running fast at curved trajectories (Förstberg et al. 1998), in buses (Turner & Griffin 1999; Golding et al. 2001) or on ships (Lawther & Griffin 1988). Especially if people cannot anticipate to the GIF by a postural response (Fukuda 1975, Rolnick & Lubrow 1991; Yates & Miller 1998; Yates et al. 1998), this may result in motion sickness and affect motion perception (Bles et al. 1998; Bos & Bles 2002; Golding et al. 2003).

In tilting trains partial alignment with the GIF vector in curves of about 50% proved to have a maximal effect on reducing motion sickness and increasing travelling comfort (Förstberg et al. 1998). In this respect the study from Sagawa et al. (1997) is of interest, who described a suspension system to compensate for the fore-aft accelerations in ambulances by aligning the subject to the changing GIF direction during accelerating and braking (100% compensation). This system protected critically ill patients against

blood pressure variations that can compromise the condition of the patient (Waddell et al. 1975). This is the more interesting since linear low-frequency vertical motion makes people sick and affects breathing and cardiovascular output as well (Bles 1976). Relevant may be that in oscillating vertical motion the most provocative frequency to produce motion sickness (O'Hanlon & McCauley 1974) is pretty close to the normal breathing frequency of 0.25 Hz. Other studies found a similar tendency for maximum motion sickness incidence to be in the lower frequency range of about 0.2 Hz (Joseph & Griffin 1988; Golding & Markey 1996; Golding et al. 1997; Förstberg et al. 1998; Golding et al. 2001; Donohew & Griffin 2009; Mert et al. 2009).

Also noteworthy is that, with vertical or horizontal linear oscillating motion during one minute, there's a tendency of the breathing frequency to synchronise with the higher oscillating frequencies (0.4 and 0.8 Hz) (Mert et al. 2009). It was also observed that Coriolis cross-coupled stimulation provokes motion sickness easily (Bles 1998; Mert et al. 2007), and also elicits changes in circulation and respiration (Yates & Miller 1998).

The primary objective of this study was to assess the effect of 0% alignment, 50% alignment and 100% alignment of the body to the GIF-vector during low-frequency sinusoidal horizontal motion on the development of motion sickness, respiratory parameters and heart rate, especially at acceleration levels close to those encountered in public transport. A sinusoidally varying linear motion while varying the body's z-axis with respect to the GIF has the advantage, that there is a slow increase of nausea over a pre-determined time interval, while the frequency of the motion is the same in every condition.

The practical question was whether compensatory tilting of a person susceptible to motion sickness would delay the development of motion sickness. If so, how much alignment is optimal for prolonging tolerance time?

3.2 Method

3.2.1 Subjects

In this study, which had Ethical Committee approval (METOPP, Tilburg, The Netherlands), twelve healthy volunteers were included, four male and eight female in the age between 18 and 45 years (mean age 24 years, SEM 2.0). To rule out menstrual cycle influences all female subjects had to be on oral contraceptives (Golding et al. 2004).

Subjects gave informed consent and were free to withdraw from the study at any time.

3.2.2 Equipment

Horizontal motion (fore-aft motion) was produced by moving a cab with seat with back- and headrest along a straight horizontal track (ESA-sled facility at TNO Soesterberg, The Netherlands, see figure 3.1). The stimulus was a sinusoidal oscillation (1.96 $m.s^{-2}$ (=0.2 g) peak acceleration, 0.176 Hz frequency). We used fore-aft motion because this is found to be more nauseogenic than lateral motion (Mills & Griffin 2000). The maximum acceleration of 0.2 g is the maximum acceleration the sled was able to deliver. The choice of the frequency was not free: one could make a choice out of pre-programmed sinusoidal stimuli with a selection of frequencies and acceleration levels, but the combination was determined by the limited length of the track and the maximum acceleration of 0.2 g. The chosen stimulus came closest to our desired acceleration level and desired frequency (O'Hanlon & McCauley 1974).

During the A-50 and A-100 condition the seat was tilted by cab suspension machinery built by TNO around the y-axis through the subject's ears so that the cab followed the tilting angle of the GIF-vector for 50% and 100% respectively. Sled and seat motions were servo-controlled.

Breathing parameters and the heart frequency were collected using the K4B2 portable breath-by-breath analyzer by Cosmed (Rome, Italy).

3.2.3 Procedure

A motion sickness susceptibility score was obtained using the Motion Sickness Susceptibility Questionnaire (MSSQ, see Golding 1998). The score ranged from 0 (not susceptible) to 200 (very susceptible), based on the subject's previous experiences with motion sickness. The Nijmegen Questionnaire for Hyperventilation (NQH) was used as a diagnostic assessment tool for the hyperventilation syndrome. The questionnaire has a specificity and sensitivity of more than 90% and consists of a list of 16 symptoms of which the experienced frequency is rated on a 0 to 4 point scale. A summed score of more than 23 out of 64 is considered as positive for hyperventilation (Van Dixhoorn & Duivenvoorden 1985)

Prior to the start of the experiment subjects completed the MSSQ and the NQH, and a hyperventilation provocation test during one minute was performed.

Test sessions employed were no alignment (A-0), 50% alignment (A-50) and 100% alignment (A-100) to the GIF. During the A-50 and A-100 condition the seat was tilted by cab suspension machinery around the y-axis through the subject's ears so that the cab followed the tilting angle of the GIF-vector for 50% and 100% respectively.

During each experiment data sampling for statistical analysis occurred 3 minutes prior to start of the sled-movement (STILL), during the first minute of sled-movement (PRE) and the last minute before discontinuing the experiment (TEST). The experiment was discontinued after reaching MISC 4 or after 30 minutes. Subjects not reaching MISC 4 were excluded from statistical analysis for the cardio-respiratory parameters.

The physiological parameters collected were breathing frequency (/min), tidal volume (l), end-tidal CO_2 (mmHg) and heart frequency (beats/min). The level of motion sickness during each experiment was rated on a 6 point Misery Scale (MISC), where 1='No problems'; 2='Initial symptoms, but no nausea' 3='Mild nausea'; 4='Moderate nausea'; 5='Severe nausea and/or retching; and 6='Vomiting'.

During the runs, as a distraction task, subjects had to pull a retractable cord and turn a lever. Subjects had their eyes open, but the cab was light tight and completely dark inside.

3.2.4 Design

The study was designed as a three period, single-blind, crossover, counterbalanced for order trial. Test sessions were 1 week apart and occurred at the same time of the day.

3.2.5 Statistical analysis

Since this is a crossover design, each subject acted as his/her own control so that no evaluation of treatment group comparability was required with respect to the distribution of the demographic variables. Descriptive statistics were given for the continuous demographic variables. Unless specified otherwise data is presented as mean ± standard error of the mean.

Heart rate (HF), respiration rate (RF), tidal volume (TV) and end-tidal carbon dioxide ($PetCO_2$) were analyzed according to a MANOVA design using the Wilk's lambda statistic. Means of the individual median values were used for statistical analysis. This was done to reduce the impact of outliers. Post-hoc analysis was done with Tukey HSD test.

Furthermore, a relative drop in $PetCO_2$ was calculated by dividing the observed drop in $PetCO_2$ through the maximal drop in $PetCO_2$ levels as measured by the hyperventilation provocation test.

A survival curve (representing in time the proportion of subjects not having reached the end-point MISC 4) was calculated for each corresponding condition, also a Kaplan-

Meier analysis with log-rank testing for group comparisons and 95% confidence intervals for survival times for conditions A-0, A-50 and A-100. Furthermore, a positive and negative predictive value curve for assessing the predictive value of a MISC 2 in time for reaching MISC 4 was determined.
Results were considered significant at $p<0.05$ and highly significant at $p<0.01$

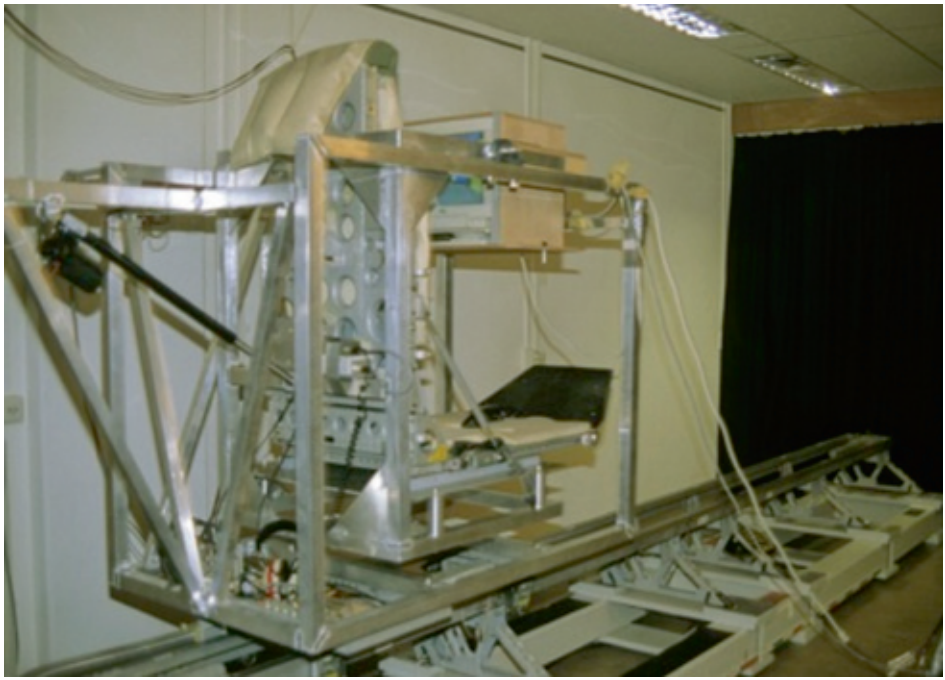


Fig. 3.1 The cab with the tilting chair on top of the ESA sled at TNO. The monitor was not in place during the experiment. The cabin was closed during the experiment, but opened because of the picture. This ESA sled – without tilting cabin - was in space with the German D1 Shuttle Mission, but made available by ESA for ground based research to a Dutch consortium (TNO Human Factors, TU Delft, AMC and VU Amsterdam) because the sled was not supposed to fly anymore after the disaster with the Challenger space shuttle.

3.3 Results

Subjects not reaching MISC 4 during an experimental condition were excluded from statistical analysis for the cardio-respiratory parameters for the corresponding condition. In condition A-0 and A-50 four subjects did not reach MISC 4 and in condition A-100 two subjects. The subjects who did not reach MISC 4 were the same for the different conditions. Only the two subjects who had a MISC 1 at the end of the 30 min run during condition A-0, survived condition A-100 with MISC 3 and 2

respectively and had MSSQ scores below 30 (28.7 and 19.8). The other two subjects not reaching MISC 4 in condition A-0 and A-50 had a MSSQ score of 39.6 and 89.8 respectively. None of the subjects who participated in the experiment were suffering from the hyperventilation syndrome.

The subjects included for analysis had a mean MSSQ of 61.7 ± 19.5 (population mean 45.5, see Golding 1998).

Multivariate analysis for the cardio-respiratory parameters and MISC-scores between the different conditions revealed no significant results; $F(10, 130)=1.17$, $p=0.32$. Intra-experimentally however a significant effect was seen; $F(10, 130)=39.5$, $p<0.001$) and this was due to the change in MISC scores ($p<0.001$). There were no significant interaction effects; $F(20, 216)=0.48$, $p=0.97$.

As respiratory frequency, tidal volume, heart rate and end-tidal CO_2 did not differ significantly from each other, pooling of the data (n=26) of the different conditions was possible and acceptable for the STILL, PRE and TEST runs. Table 3.I represents mean ± standard error for the pooled data for the corresponding physiological parameters. Synchronization of respiratory frequency with the stimulus frequency was not present.

The pooled data showed that the relative drop of end-tidal CO_2, as defined by the absolute drop in end-tidal CO_2 divided by the possible maximal drop in end-tidal CO_2 levels during one minute of hyperventilation, was 0.21% ± 1.96 for PRE and 9.4% ± 0.49 for TEST. A two-tailed Student's t-test was performed and considered statistically significant ($p=0.002$).

A survival curve (Fig. 3.2) of subjects not having reached MISC 4 at a specific moment shows that at 16 minutes conditions A-0, A-50 and A-100 have survival rates of 58%, 75% and 42% respectively. Their mean survival times (n=12) however were not statistically different from each other ($x^2=1.7$, $p=0.43$). The mean survival times (95% CI lower bound-upper bound) for conditions A-0, A-50 and A-100 were 19 (13.6-24.4), 20.8 (15.6-26.1) and 15.4 (9.9-20.9) minutes respectively.

Furthermore, a positive and negative predictive value curve (Fig. 3.3) for reaching MISC 2 (all conditions combined) and respectively predicting dropout or survival during the run shows that already after 2 minutes 93% and after 4 minutes 96% of the subjects that will NOT complete the run are identified. After six minutes 90% of the subjects that will complete the run are identified and after 8 minutes 100%.

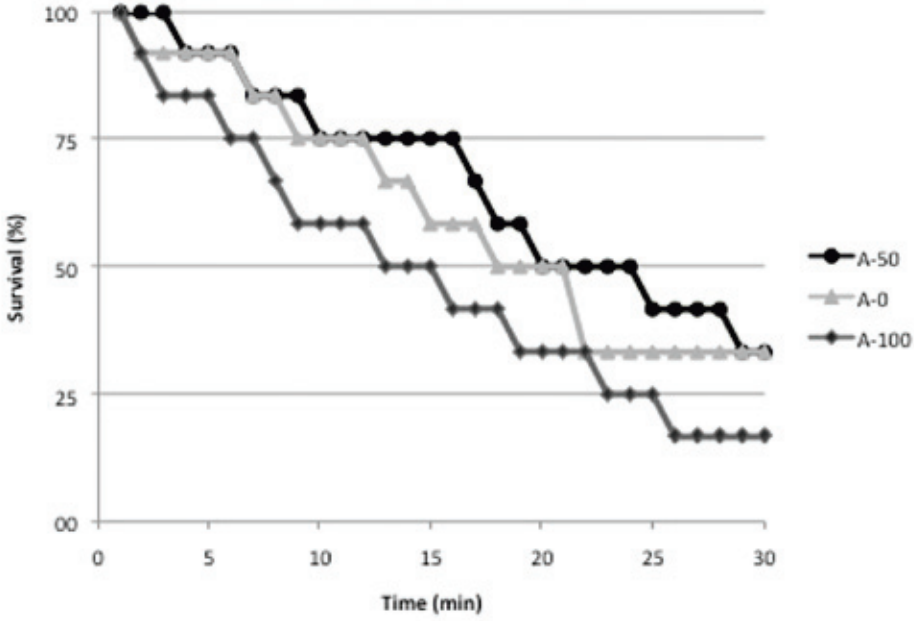


Fig 3.2. Survival curve (%) of subjects (n=12) during runs A-0, A-50 and A-100 within the experimental time frame of 30 minutes.

Table 3.I: respiratory frequency (RF, /min), tidal volume (VT, l), heart rate (HR, /min), end-tidal CO_2 ($PetCO_2$, mmHg) and MISC from pooled data from conditions A-0, A-50, A-100, selected on subjects reaching MISC 4, n=26.

	Still	**Pre**	**Test**	**P-value**
RF	17.4 ± 0.56	18.1 ± 0.77	16.6 ± 0.58	0.27
VT	0.6 ± 0.03	0.6 ± 0.03	0.6 ± 0.04	0.96
HR	78.5 ± 3.15	78.2 ± 3.60	80.2 ± 2.74	0.89
$PetCO_2$	34.7 ± 0.55	34.6 ± 0.51	33.5 ± 0.54	0.25
MISC	1	1.4 ± 0.06	4	0.000 (*)

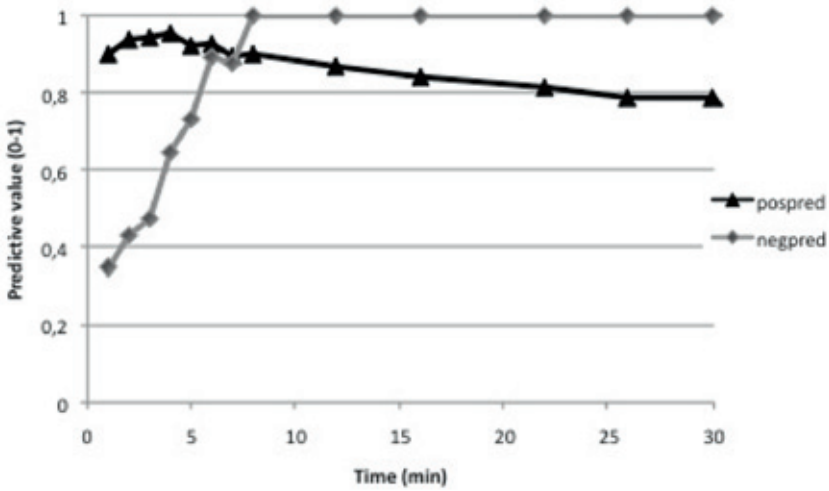


Fig. 3.3 Positive (pospred) and negative (negpred) predictive value for reaching MISC 4 of subjects having reached MISC 2.

3.4 Discussion

In investigating the role of compensating for the GIF during linear oscillation in the fore-aft plane while measuring experienced nausea, there seems to be a tendency that reaching the MISC 4 level takes longer in the A-50 condition compared to the A-0 and A-100 conditions.

Nevertheless, the difference seems to be smaller than the difference observed in tilting trains (Förstberg et al. 1998). An explanation might be that in the tilting trains subjects were free to move their head and look outside, whereas in our experiment subjects did not make head movements. With yaw, head movements in the curves without tilt compensation (0%), the Coriolis effect does not exist, but with increasing tilt compensation angle (50 and 100%) the Coriolis effect becomes above threshold (at about 7 deg/s; W. Bles personal communication; March 20, 2009) and more nauseating. In tilting trains vision is not compensating for this vestibular effect. Sitting itself is more comfortable with increasing tilt compensation, so it might be that at 50% there is an optimum for the combination of comfort and nausea. Detailed analysis about nausea development and head movements in tilting trains is necessary to substantiate this claim.

Also, while subjects got nauseated, at the used acceleration levels we could not observe a cardiovascular or pulmonary compromise. Because of this and that this is in fact a constant finding in our other experiments (Mert et al. 2007; Mert et al. 2009), one might even speculate that measuring and analysing heart rate, respiratory frequency and tidal volume are of little value in these experiments with rather low g-levels. Yet, there seems to be a role for measuring end-tidal CO_2 levels, as hyperventilation occurs on an individual basis (Mert et al. 2007; Mert et al. 2009) and measuring this will have a discriminatory function because of the overlap of symptoms between motion sickness and hyperventilation (Mert et al. 2007). In another study by Jáuregui-Renaud et al. (2000) the importance of the respiratory system in vestibular stimulation is exemplified by the fact that changes in heart rate variability and blood pressure variability through caloric stimulation of the vestibular system were explained by modifications of the respiratory pattern.

An interesting observation in our study is that the mean baseline respiratory frequency is 17.4/min. This higher than normal resting respiratory frequency is a phenomenon we have seen in our other experiments as well (Mert et al. 2007; Mert et al. 2009). We conclude that in laboratory conditions in which nauseating stimuli will be presented the 'resting' respiratory frequency tends to be higher, most probably because subjects are not really at ease at the beginning of an experiment.

We hypothesize that a MSSQ value <30 might be a good prognostic indicator for the identification of subjects that will not get ill during motion sickness provoking stimuli. If this holds true in prognostic research this can be used as a screening tool during for example pilot selection. Also, subjects reaching MISC 4 in one experimental condition have a higher probability to reach MISC 4 in the other two experimental conditions. Nausea in one condition seems to predict nausea in another and therefore can be seen as an extrinsic risk factor for experiencing motion sickness.

No significant drop in absolute end-tidal CO_2 levels is seen. In previous studies (Mert et al. 2007; Mert et al. 2009) we have argued that the relative drop in end-tidal CO_2 levels is a more useful measure than the absolute drop. This study again confirmed this as the statistically significant relative drop ($p=0.002$) at 0.176 Hz is about 9 % and this finding is in accordance and in the same order of magnitude compared to our other experiment (Mert et al. 2009). We therefore advocate the use of the relative maximal drop in end-tidal CO_2, and not the absolute end-tidal CO_2, for similar experiments. A mild hyperventilatory response accompanied by *mild* nausea, and controlled deep breathing are probably compensatory mechanisms to cope with the nausea and hence prolonging tolerance time to nauseating stimuli (Zabara et al. 1972; Jokerst et al. 1999; Lang 1999; Yen Pik Sang et al. 2003; Yen Pik Sang et al. 2005; Mert et al. 2007; Mert et al. 2009). On the contrary, Baranov et al. (1991) have shown that subjects

susceptible to motion sickness rocked on a parallel swing in head-down position develop a hyperventilatory response together with vestibular symptoms, both of which were alleviated in a majority of test subjects by adding a hypercapnic gas-mixture. Clinically, on experienced disability patients with chronic peripheral vestibular disease who were receiving Cawthorne and Cooksey exercises, Jáuregui-Renaud et al. (2007) have shown a significant and positive effect of regulating the breathing rhythm compared to proprioceptive exercises. In another study Jáuregui-Renaud et al. (2007) concluded that the vestibular system modulates the respiratory response and is dependent on the position of the head and trunk relative to gravity. This modulation was decreased with acute vestibular disease. A comparable result was seen in patients with bilateral vestibular loss, who showed almost no respiratory response to whole body oscillation in the yaw plane compared to healthy controls (Thurell et al. 2003). Although the exact role of respiration, respiratory alkalosis and of CO_2 in motion sickness and vestibular disease is not completely elucidated yet, from the above it is very likely that they play an important role. Moreover, in motion sickness desensitization programs breathing techniques are successfully applied for alleviating motion sickness symptoms (Dobie 1974; Stott 1992; Bles et al. 1995; Lucertini & Lugli 2004; Yen Pik Sang 2005).

In this study, no synchronisation of the respiratory frequency with the sled motion frequency was observed (Table 3.I). So the findings of Bles (1976) could not be reproduced. This may be due to the lower maximum acceleration of 0.2 g in the present study compared to the 0.5 g in the Bles study. However, for the provocation of motion sickness a higher acceleration level was not necessary in the present study. It is also possible that due to the position of the lungs in the chest the physical effect of body motion on the respiration in the fore-aft direction as used in the present study is more restricted than in the vertical direction as used in the Bles study (see also chapter 4). The incidence of motion sickness is irrespective whether the motion is horizontal, lateral or vertical, and the most nauseating frequency is in the 0.2 Hz range. Also the nauseogenity of stimuli decreases toward the higher frequencies (O'Hanlon & McCauley 1974; Golding & Markey 1996; Golding et al. 1997; Förstberg et al. 1998; Golding et al. 2001; Joseph & Griffin 2008; Donohew & Griffin 2009; Mert et al. 2009). Interestingly, the subjective vertical mismatch theory of motion sickness (Bles et al. 1998; Bos & Bles 2002), which takes into account in this case only vestibular parameters, predicts the 0.2 Hz maximum for motion sickness for sinusoidal vertical oscillation. Of course, not only motion frequency or motion type is a factor to be taken into account in motion sickness but also personal factors (Golding 2006), the availability of a back rest (Mills & Griffin 2000) and vision (Turner & Griffin 1999) for example. That seasick passengers prefer to stay in bed when they are motion sick is also due to the fact that they in that case only have to deal with the ship motion and not with the superposition of their own movements on the ship motion.

This is the first study analyzing positive and negative predictive value for dropout or survival to a nauseating stimulus after reaching MISC 2, defined by "initial symptoms, but no nausea". The high values of both after only a few minutes of exposure could make a Misery Score of 2 potentially useful for pilot selection. A prospective cohort study is an appropriate study design to investigate this. A patient-control study will result in quicker results, but however would also increase the risk of bias.

From other studies (Förstberg et al. 1998; Joseph & Griffin 2008) it is known that partial alignment to the GIF might prolong survival time for nauseating stimuli. Our data, although not significant, seem to be accord with these studies. Full alignment on the other hand might decrease tolerance time to these stimuli. Furthermore, the use of a survival curve gives potentially useful information in the development of nausea in time and, in our opinion, should be used more regularly in these types of experiments.

It is of course tempting to investigate whether at higher g-levels synchronization of the motion stimulus and the respiration is seen, but studying a possible relationship between motion sickness and respiration, as well as a possible beneficiary effect of 50% tilt compensation however is rather difficult, since subjects get sick much faster at higher acceleration levels.

After this study the motion simulator Desdemona became available at TNO, allowing more degrees of freedom and a much broader stimulus range, as well as higher acceleration levels. The study on this device is the subject of chapter 4.

4. Oscillatory linear motion and respiration: effect of frequency on the provocation of motion sickness

Summary

Introduction: *Motion Sickness Incidence (MSI) for vertical sinusoidal motion reaches a maximum at 0.167 Hz. Normal breathing frequency is close to this frequency. There is some evidence for synchronization of breathing with this stimulus frequency. We investigated if this enforced breathing takes place over a larger frequency range (0.05-0.8 Hz) and whether this contributes to the high MSI at 0.167 Hz.*

Methods: *Sinusoidal motion (amplitude. 0.3g, frequencies 0.05, 0.1, 0.2, 0.4 and 0.8 Hz) was applied. We measured nausea with the MISC-scores and respiratory parameters like tidal volume, respiratory frequency, end-tidal CO_2 and respiratory minute volume. Control conditions included rest and the hyperventilation provocation test.*

Results: *The nausea scores were highest at 0.2 Hz. With increasing frequencies the respiratory minute volume increased and the end-tidal CO_2 values decreased. The hyperventilation provocation test did not cause nausea.*

Discussion: *The main conclusion is that the high MSI at 0.167 Hz is not due to enforced breathing, since enforced breathing still increases with higher stimulus frequencies.*

Acknowledgments
We want to thank Mr. Arno Krul for his kind help in statistics, also the test subjects for wanting to be the first test subjects on DESDEMONA. Furthermore ing. Paul Bakker for operating the DESDEMONA facility.

The original version of this chapter was published as:
Mert A, Klopping-Ketelaars I & Bles W. Respiratory impact on motion sickness induced by linear motion. Basic and Clinical Aspects of Vertigo and Dizziness. Ann NY Acad Sci 2009; 1164: 173-179.

4.1 Introduction

O'Hanlon & McCauley (1974) found that the Motion Sickness Incidence (MSI) for vertical sinusoidal motion in the frequency range of 0.05–0.8 Hz reached a maximum around 0.167 Hz. (Fig. 4.1). Motion sickness incidence was determined as the percentage of subjects vomiting within 2 hours when exposed to the motion pattern of each particular data collection point. With 20 test subjects per data point, this required all together more than 500 test subjects. The rather asymmetric choice of data collection points is due to the constraints of the vertical motion simulator (e.g., a 6m stroke).

The cause for the peak in MSI at 0.167 Hz has long been debated, and although significant progress has been made recently (Bos & Bles 1998; Bos & Bles 2002)

a conclusive reason has not been found yet. Interestingly, the normal breathing rhythm of 10-15 breaths/minute, corresponding with 0.167-0.25 Hz, is in the same "nauseating" frequency range. This could be a coincidence, but perhaps breathing is enforced by the motion, inhaling during upward acceleration and exhaling during downward acceleration as a result of inertia of the internal organs, which may result in hyperventilation and consequently contribute to motion sickness. Such enforced breathing was observed by Bles (1976) when he exposed subjects to a vertical motion stimulus of 0.25 Hz with a maximum acceleration of 0.5 g: This caused in several test subjects enforced breathing synchronous to the stimulation. Dixon et al. (1961) have also shown that vertical body movements can influence diaphragmatic movements and cause mandatory breathing at that frequency. In experiments at sea, where the vertical motion is very provocative, hyperventilation was observed in seasick sailors as well (Bles et al. 1988). In the study described in chapter 3 motion sickness was present, but we could not find a synchronization of respiration with the motion stimulus. This may be due to the rather low value of the maximum acceleration of 0.2 g, which was the maximum acceleration that could be applied at that time. With the presence of the advanced motion platform Desdemona the maximum acceleration could be increased as well as the frequency range of the stimuli. So several questions arise: What is the impact of enforced respiration on motion sickness? Is enforced breathing present over the whole frequency range? Is enforced respiration responsible for the high MSI around 0.167 Hz?

To answer these questions we recorded respiratory parameters during sinusoidal motion stimuli at frequencies of 0.05, 0.1, 0.2, 0.4 and 0.8 Hz with a maximum acceleration of 0.3 g (see Fig. 4.1), while subjects rated their motion sickness severity.

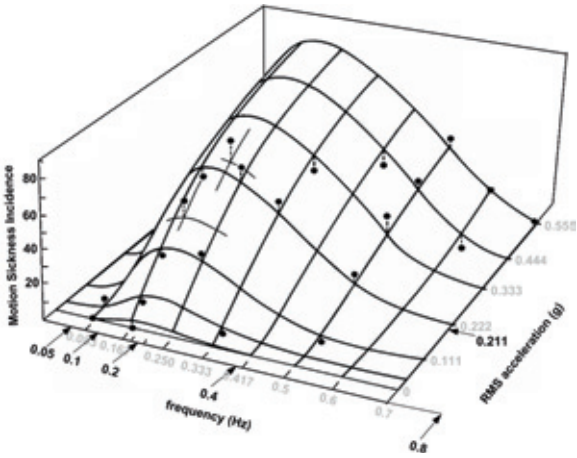


Fig. 4.1. The relationship between the stimuli of the present experiment (black arrows) with the data collection points of the O'Hanlon & McCauley study.

4.2 Methods

4.2.1 Subjects

25 healthy volunteers (13 men and 12 women), with a mean age, weight and height of respectively 22.8 ± 2.6 (SD) years, 71.2 ± 8.8 kg and 178.7 ± 9.2 cm participated in this study. No subject was on medication, except for the female subjects who had to be on oral contraceptives to rule out menstrual cycle susceptibility for motion sickness (Golding et al. 2004). Written informed consent was obtained from all subjects. The experimental protocol had Medical Ethical Committee approval. Subjects were free to withdraw from the study at any time.

4.2.2 Experimental measurements and Questionnaires

Respiratory parameters were collected using the K4B2 portable breath-by-breath analyzer (Cosmed, Rome, Italy). The parameters analyzed were respiratory frequency (/min), tidal volume (l), respiratory minute volume (l/min), end-tidal CO_2 (mmHg). From the respiratory frequency the average breathing period (s) was calculated. Heart rate was monitored using a heart rate monitor, which was linked to the K4B2.

The level of motion sickness was rated by the test subjects on a 6 point rating scale (denoted by the MIsery SCale or MISC), where 1='No problems'; 2='Initial symptoms, but no nausea'; 3='Mild nausea'; 4='Moderate nausea'; 5='Severe nausea and/or retching; and 6='Vomiting' (Mert et al. 2007). On request of the operator, shortly before the end of the run, subjects indicated their MISC score by showing for the monitoring camera the corresponding number of fingers.

To distract the subjects from the motion sickness, they also estimated the displacement of the cabin motion in the x-direction (fore-aft motion) or the z-direction (along their body axis) in meters. They also estimated any experienced tilt of the upper body in degrees. These estimates were verbally communicated to the operator after each test run.

The subjects' motion sickness susceptibility was obtained using the Motion Sickness Susceptibility Questionnaire (MSSQ). The score ranges from 0 (not susceptible) to 200 (very susceptible), based on the subjects' previous experiences with motion sickness (Golding 1988). The Nijmegen Questionnaire for Hyperventilation (NQH) was used as a diagnostic assessment tool for the hyperventilation syndrome (see also Chapter 2). It consists of a list of 16 symptoms of which the experienced frequency is rated on a 0 to 4 point scale. A summed score of ≥24 out of 64 is considered positive for hyperventilation (Van Dixhoorn & Duivenvoorden 1985).

4.2.3 Stimulus

For sinusoidal rectilinear motion stimuli with peak acceleration levels of 0.3 g over the frequency range from 0.05 to 0.8 Hz, a track length of about 60 m is required. Such a track for this sort of research, vertical or horizontal, was not available at TNO or CML. With the by AMST Systemtechnik (Austria) engineered and manufactured 6DoF motion platform Desdemona, however, an approximation of these conditions is possible (Fig. 4.2). Desdemona has a vertical displacement of 2 m and a horizontal displacement of only 8 m over the main arm, but she allows for counter-rotation by rotating the main arm with the counter-rotating cabin in an eccentric position (see insert in Fig. 4.3). By choosing appropriate eccentric positions the resulting constant angular velocity of the subject was zero, and at 0.05 Hz about 30°/s. Because of the complexity of the stimulus, this will be discussed in more detail.

The trunk and head of the subject in the cabin were either in a vertical attitude (cabin pitched forward over 25°, i.e. in line with gravity) or in a horizontal attitude (cabin pitched backward over 65°, i.e. perpendicular to gravity), allowing for stimulation along the subject's x- and z-axis . This pitching was necessary since the back- and headrest of the chair were tilted backwards over 25°. These two attitudes do not affect the Heave (H), Radius (R) or Counter-Rotation (CR) motion.

Vertical motion, generated with the Heave system (H): The motion is along the gravity vector. Because the frequencies of 0.05, 0.1 and 0.2 Hz require a track length which exceeds the length of the heave system (2 m), only the motion stimuli H-0.4 and H-0.8 can be used in the experiment (see Table 4.I)

Table 4.I Required displacement on the heave system to generate 0.3 g sinusoidal motion at the test frequencies, showing that only H-0.4 and H-0.8 are possible.

Condition	**Frequency (Hz)**	**Max. Accel. (G)**	**Max. Ampl (m)**	**Max. Displ (m)**	**Possible √ or not** X
H-0.8	0.80	0.3	0.12	0.23	√
H-0.4	0.40	0.3	0.46	0.93	√
H-0.2	0.20	0.3	1.86	3.71	X
H-0.1	0.10	0.3	7.42	14.85	X
H-0.05	0.05	0.3	29.70	59.39	X

Horizontal motion, generated with the track on the main arm (Radius, R): The motion is perpendicular to the gravity vector. Because the frequencies of 0.05 and 0.1 Hz require a track length which exceeds the length of the main arm (8 m), only the motion stimuli R-0.2, R-0.4 and R-0.8 can be used in the experiment (see Table 4.II).

Table 4.II Required displacement on the main arm to generate 0.3 g sinusoidal motion at the test frequencies, showing that only R-0.2, R-0.4 and R-0.8 are possible.

Condition	**Frequency (Hz)**	**Max. Accel. (G)**	**Max. Ampl (m)**	**Max. Displ (m)**	**Possible √ or not** X
R-0.8	0.80	0.3	0.12	0.23	√
R-0.4	0.40	0.3	0.46	0.93	√
R-0.2	0.20	0.3	1.86	3.71	√
R-0.1	0.10	0.3	7.42	14.85	X
R-0.05	0.05	0.3	29.70	59.39	X

Counter-Rotation, by combining yaw rotation of the main arm with yaw rotation of the cabin on the arm in an eccentric position (CR). To illustrate the final choice of these parameters the different options to generate the appropriate stimuli will be described first:

a. Cabin at fixed eccentric position (Radius 4 m): With the cabin at an eccentric position of 4 m, the main arm has to rotate with a velocity of 49.3°/s in order to generate a centripetal acceleration of 0.3 g according to the relationship $a=R.\omega^2$. By rotation of the cabin with respect to the main arm with the test frequencies, the subject will be exposed to a rotating acceleration vector of 0.3 g, which can be factorized in two sinusoidally varying acceleration vectors with a phase lag of 90° along his body's x- and y-axis when he is sitting upright, or along his z- and y-axis when he is in a supine position. These vectors are perpendicular to gravity. In Table 4.III the resulting motion stimuli are shown. Because the angular velocities at 0.8 Hz exceed the maximum speed of the cabin, this condition cannot be generated. Moreover, although condition CR-0.4 can be generated and the angular velocity can be applied such that it will not be perceived by the test subject, involuntary and voluntary head movements at 90°/s most probably provoke Coriolis effects which will influence the MISC scores.

Table 4.III. Rotation of the cabin at a fixed eccentric position of the arm during centrifugation.

Condition	**Frequency (Hz)**	**Cabin yaw wrt main arm (°/s)**	**Main arm yaw wrt Earth (°/s)**	**Cabin wrt Earth (°/s)**	**Eccentric position of cabin (ma)**	**Possible √ or not** X
CR-0.8	0.8	-288	+49.2	-238.7	4	X
CR-0.4	0.4	-144	+49.2	- 94.7	4	√
CR-0.2	0.2	-72	+49.2	- 22.7	4	√
CR-0.1	0.1	-36	+49.2	+ 13.3	4	√
CR-0.05	0.05	-18	+49.2	+ 31.3	4	√

b. Pure counter rotation: Here cabin and main arm rotate with equal but opposite angular velocity. The eccentric position of the cabin is chosen such that a centripetal acceleration vector of 0.3 g is generated in the cabin. This is shown in Table 4.IV. Now condition CR-0.8 is again not possible because of the high angular velocities, and conditions CR-0.1 and CR 0.05 are not possible because they require a larger radius than available on Desdemona.

Table 4.IV. Complete Counter Rotation of the cabin with respect to the main arm requiring different eccentric positions of the cabin to generate 0.3 g.

Condition	**Frequency (Hz)**	**Cabin yaw wrt main arm (°/s)**	**Main arm yaw wrt Earth (°/s)**	**Cabin wrt Earth (°/s)**	**Eccentric position of cabin (ma)**	**Possible √ or not** X
CR-0.8	0.8	-288	+288	0	0.12	X
CR-0.4	0.4	-144	+144	0	0.46	√
CR-0.2	0.2	-72	+72	0	1.86	√
CR-0.1	0.1	-36	+36	0	7.45	X
CR-0.05	0.05	-18	+18	0	29.79	X

c. Mixed choice: Inspection of Tables 4.III and 4.IV makes it clear that it is impossible to generate condition CR-0.8. It also suggests that a mix of the two Tables would be the best choice for the CR motion stimuli as shown in Table 4.V. With 30°/s it is unlikely that involuntary head movements due to the presence of the linear acceleration vectors provoke Coriolis effects.

Table 4.V. Final CR motion stimuli.

Condition	**Frequency (Hz)**	**Cabin yaw wrt main arm (°/s)**	**Main arm yaw wrt Earth (°/s)**	**Cabin wrt Earth (°/s)**	**Eccentric position of cabin (ma)**	**Possible √ or not X**
CR-0.4	0.4	-144	+144	0	0.46	√
CR-0.2	0.2	-72	+72	0	1.86	√
CR-0.1	0.1	-36	+49.2	+ 13.3	4	√
CR-0.05	0.05	-18	+49.2	+ 31.3	4	√

Table 4.VI: The nine possible runs for the frequency range of 0.05-0.8 Hz (corresponding with a displacement from 59.4 to 0.23 m) distributed over the Heave, Radius and Counter-Rotation motion. Subjects are either positioned such that they are stimulated in the subject's z-direction or in the subject's x-direction (fore-aft). The frequency of 0.4 Hz is special, since it is common for H, R and CR stimulation.

Test Frequencies Displacement	0.05 Hz 59.4 m	0.1 Hz 14.8 m	0.2 Hz 3.71 m	0.4 Hz 0.93 m	0.8 Hz 0.23 m
Heave (H)				+	+
Radius (R)			+	+	+
Counter-Rotation (CR)	+	+	+	+	

Altogether, the possible motion stimuli with Desdemona to generate a sinusoidally varying linear acceleration with an amplitude of 0.3 g are shown in Table 4.VI.

The choice of test runs shown in Table 4.VI allows us to extend the R conditions with the low frequency conditions by using CR if it can be shown that R and CR

conditions at 0.4 Hz do not reveal significant differences. If it can be shown that the H condition at 0.4 Hz is also not different from the R and CR conditions, and that the attitude does not influence the measurements, the implications of the present findings may be extended to vertical motions as well. This is necessary since there are principal differences between these three conditions: With H motion the stimulus is parallel to gravity, with R motion the stimulus is perpendicular to gravity, and with CR motion the stimulus is also perpendicular to gravity, but there is additional y-axis stimulation of the subject with a phase lag of 90°. Subjects were subjected to nine runs in either upright or supine position, but the 0.4 Hz runs were administered in both attitudes. This brings the total number of test runs per subject to 12. They were applied at random order.

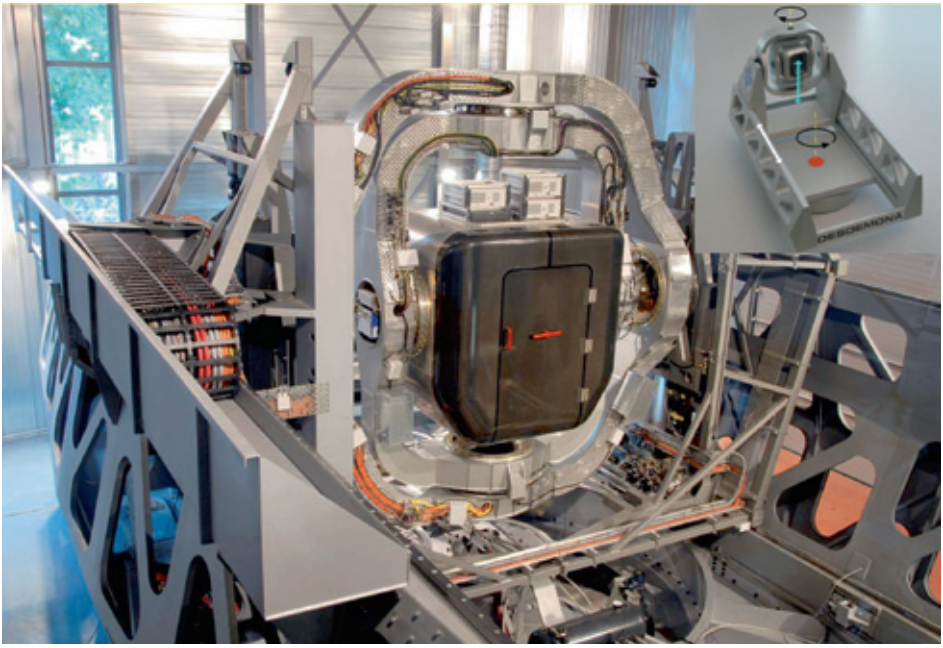


Fig. 4.3. The Desdemona motion platform at TNO Human Factors, Soesterberg, which was engineered and manufactured by AMST Systemtechnik, Austria. The insert shows the motion stimuli as generated with Desdemona. The magenta colored arrow indicates the Heave (H) motion: The cabin and the gimbals move vertically along the gravity vector. The white arrow indicates the Radius (R) motion: The heave carriage moves horizontally over the main arm, perpendicular to the gravity vector. The black arrows indicate Counter-Rotation (CR) motion: with the heave carriage in an eccentric position, the Cabin (yaw) and the Main Arm rotate at equal but opposite angular velocities. Velocity and eccentricity determine the G load and the frequency. The trunk and head of the subject in the cabin are either in a vertical attitude (cabin pitched forward over 25°, i.e. in line with gravity) or in a horizontal attitude (cabin pitched backward over 65°, i.e. perpendicular to gravity). These two attitudes do not affect the H, R or CR motion.

4.2.4 Study design

Prior to the actual experiment subjects had to fill out the MSSQ and the NQH. Prior to the start of the experiment a physician took a physical exam to ensure the physical health of the subjects. While subjects were seated on a chair cardio-respiratory baseline (Rest) values were collected for three minutes. After this subjects performed a voluntary hyperventilation provocation test (Hyperventilation), during which they had to breathe fast and deep for one minute. This enabled us to express the drop in $PetCO_2$ in each run as the percentage of the $PetCO_2$ drop in the hyperventilation provocation test compared to the baseline measurement.

Subsequently subjects were seated in the cabin and secured with a 5-point safety belt. There was light in the cabin, but subjects could neither look outside the cabin, nor look at any visual displays indicating the cabin motion.

Subjects underwent a maximum of 12 runs, each of which lasted 1 minute (see Table 4.VI). These twelve runs were either all nine runs in supine or in upright position, plus the three runs at 0.4 Hz in the complementary position. The order of these twelve runs was randomized. To distract the subject from the real goal of the study, they estimated during the run the maximum peak to peak displacement of the sinusoidal motion in x- or z-direction, which was communicated after each run.

After each stimulus the cabin was positioned for the next stimulus and the run only started after the subjects had returned to MISC 2 or less. The experiment was aborted as soon as the subject reached MISC 5.

4.2.5 Statistical analysis

Unless specified otherwise, data are presented as average ± standard deviation. Between group effects were analyzed with ANOVA procedures using the software program Statistica. Post-hoc analysis was carried out using a Tukey HS test. A difference is considered significant at $p<0.05$, and highly significant at $p<0.01$.

4.3 Results

4.3.1 MSSQ scores

The mean MSSQ score for the subjects was 63.5 ± 40.8 with a median of 59, which means that our subject group is more susceptible than on average (Golding 1998). The mean NQH score was 12.1 ± 6.7 with a median of 11.5. Three subjects were in the 'grey zone' with scores of 23, 24 and 24 concerning their NQH-scores.

4.3.2 Occurrence of MISC 5

Eleven subjects had to quit before they finished all conditions because they reached MISC level 5. This happened only at the frequencies 0.1, 0.2 and 0.4 Hz. From the subjects that finished the test conditions, six times the highest MISC score was a 4, four times a 3 and four times a 2, indicating that nausea was an issue for the majority of subjects.

4.3.3 Analysis per frequency

A systematic statistical analysis of the whole dataset is rather difficult because there were quite some missing data due to unfinished test runs as shown in table 4.VII.

Table 4.VII: The number of data points per run. H, R and CR stand for Heave, Radius and Counter-Rotation respectively. The numbers in the first row correspond with the motion frequency (Hz). Z and X in the first column represent the stimulus through the Z and X-axis of the body respectively. The baseline parameters Rest and Hyper-ventilation (n=25) are not shown in the table, none of the baseline parameters have missing values.

	H 0.8	H 0.4	R 0.8	R 0.4	R 0.2	CR 0.4	CR 0.2	CR 0.1	CR 0.05
Z	9	19	10	15	11	14	11	11	11
X	14	17	13	22	13	20	13	13	12

In a first analysis no significant differences between the different runs were seen for the respiratory minute volume, $PetCO_2$ and MISC scores. For the respiratory period only the H 0.8 X run is significantly lowered from baseline: 3.3 ± 0.14 (SEM) vs. 2.3 ± 0.18 sec.

As the 0.4 Hz runs were present for the Heave, Radius and Counter-Rotation conditions and also because these resulted in the largest amount of data points, an ANOVA-analysis on the data set of the 14 subjects who had completed all six 0.4 Hz conditions revealed no statistically significant differences between the Heave, Radius and Counter-Rotation conditions for the MISC scores and for the respiratory parameters like respiratory minute volume, average breathing period, and $PetCO_2$ levels (Fig. 4.4 a-d).

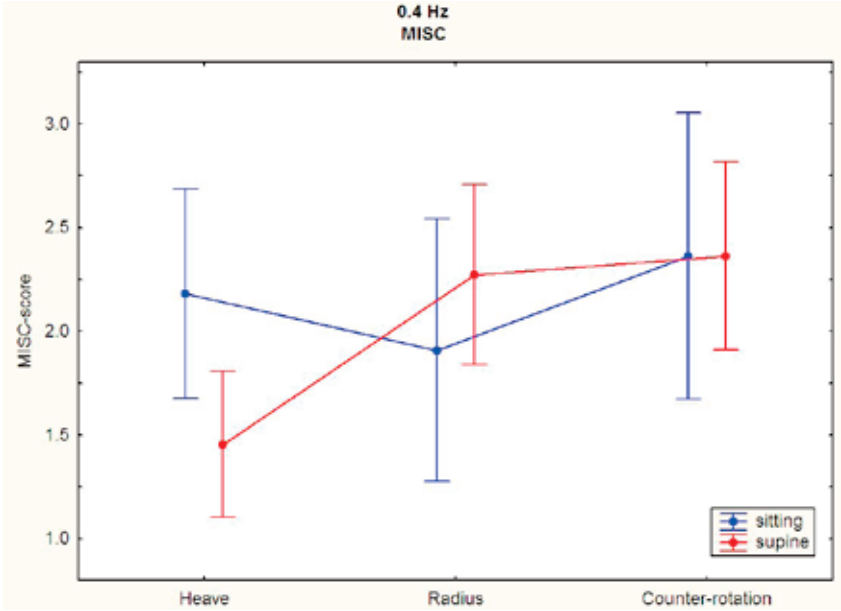


Fig. 4.4a MISC scores at 0.4 Hz

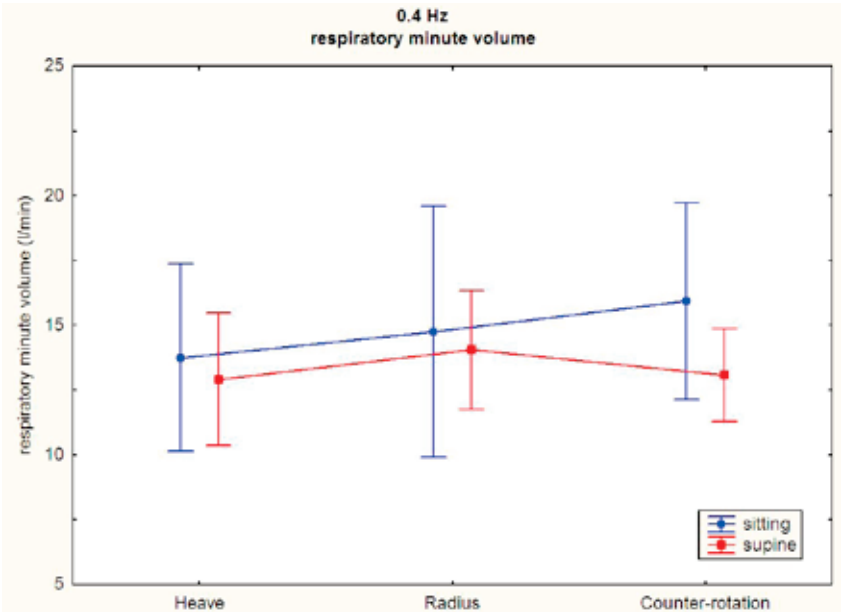


Fig. 4.4b Respiratory Minute Volume at 0.4 Hz

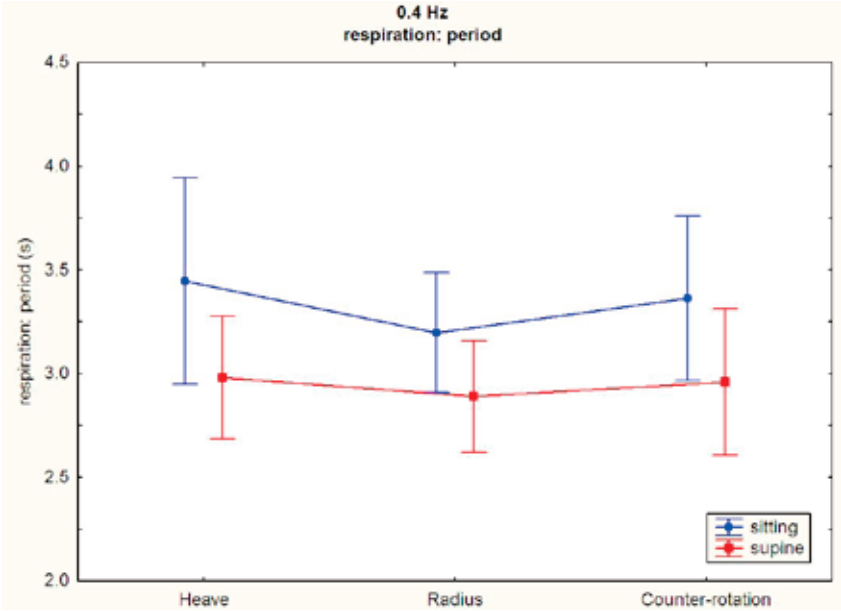


Fig. 4.4c Respiration period at 0.4 Hz

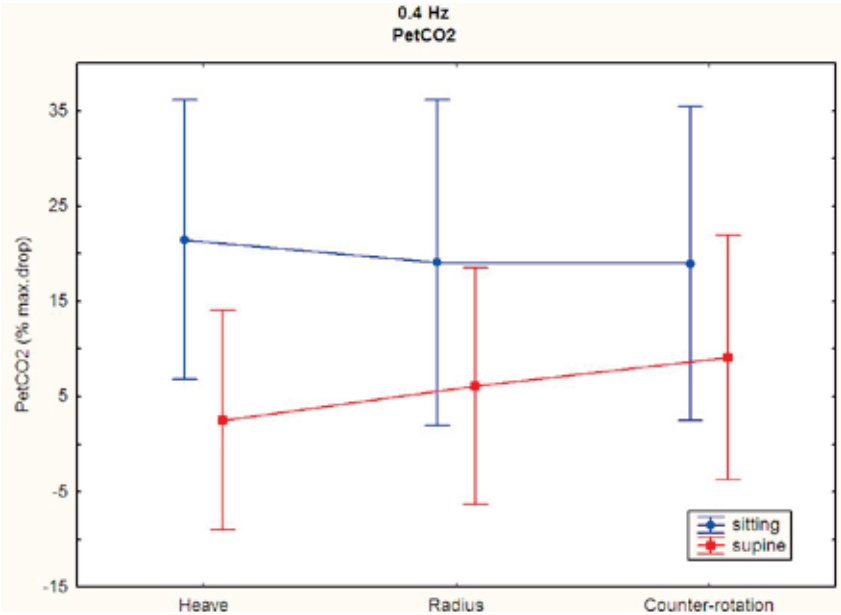


Fig. 4.4d $PetCO_2$ at 0.4 Hz

Although not significantly raised, in the upright sitting conditions the respiratory minute volume was systematically higher (and the respiratory period longer, so the respiratory frequency lower) than in the supine posture conditions, but this was seen in all three motion conditions. This is understandable because in sitting subjects, gravity ensures that bowels are not in the way, and hence breathing is facilitated.

To increase the number of data points the possibility of pooling the data per frequency was investigated. Post-Hoc analysis of the data set revealed no significant differences for the investigated parameters between the conditions shown in Table 4.VIII.

Table 4.VIII: Pooling of corresponding conditions per frequency. An ANOVA post-hoc analysis (Tukey HSD) revealed no significant differences ($p>0.05$) between the conditions presented in the rows. N corresponds with the number of data-points per frequency.

Frequency (Hz)	**Pooling of conditions**	**n**
0.8	H 0.8 Z, H 0.8 X, R 0.8 Z and R0.8 X	46
0.4	H 0.4 Z, H 0.4 X, R 0.4 Z, R 0.4 X, CR 0.4 Z and CR 0.4 X	107
0.2	R 0.2 Z, R0.2 X, CR 0.2 Z and CR 0.2 X	48
0.1	CR 0.1 Z and CR 0.1 X	24
0.05	CR 0.05 Z and CR 0.05 X	23

From this pooled dataset, analysis per frequency of motion was performed and the results are presented in table 4.IX. This table shows that for the respiratory parameters (respiratory minute volume, respiratory period and Pet CO_2) only the Hyperventilation and 0.8 Hz condition differ significantly ($p<0.05$) from the Rest condition. Concerning the MISC-scores, the runs and the Hyperventilation condition differ significantly from the Rest condition ($p<0.05$). From the table it can be seen that with increasing motion frequency, although not significant, the respiratory minute volume seems to increase and the respiratory period and $PetCO_2$ decrease. At 0.8 Hz the decrease in $PetCO_2$ is close to significance ($p=0.10$): 35.2 ± 0.73 vs. 38.2 ± 0.55 mmHg.

As it is known from the study from of McCauley and O'Hanlon (1974) that in (vertical) oscillating motion the maximum nausea incidence occurs close to 0.2 Hz, MISC values were also compared against the 0.2 Hz condition. The MISC values of the baseline measurements (hyperventilation and Rest) and 0.8 Hz condition are significantly

lower as compared to the 0.2 Hz motion stimulus. Also the 0.05 Hz stimulus is close to significance (p=0.09). In Fig. 4.6 the average MISC scores are shown for the Rest period, the Hyperventilation provocation test, and for the five stimulus frequencies. In the rest period everybody had a MISC score of 1. At the end of the hyperventilation provocation test only MISC scores of 1 and 2 were obtained: nobody scored nausea (MISC 3 or more). Fig.4.5 is in line with the expectation based on Fig 4.1.

Table 4.IX: The respiratory parameters (respiratory minute volume, respiratory period and Pet CO_2) and MISC values per motion frequency. Statistical significance is tested against $\alpha<0.05$ and compared with the Rest condition. For the MISC condition also comparison of the conditions with 0.2 Hz is performed as from the McCauley & Hanlon (1974) study the 0.2 Hz motion frequency results in the highest motion sickness incidence.

Condition	**Respiratory minute volume (l/min)**	**Respiratory period (s)**	**$PetCO_2$ (mmHg)**	**MISC**
0.05 Hz	10.4 ± 0.41	3.5 ± 0.19	37.8 ± 0.81	1.9 ± 0.14 *§
0.1 Hz	11.2 ± 0.50	3.5 ± 0.14	37.0 ± 0.87	2.2 ± 0.28 *
0.2 Hz	12.2 ± 0.37	3.5 ± 0.10	36.4 ± 0.59	2.6 ± 0.18 *
0.4 Hz	14.1 ± 0.47	3.1 ± 0.06	35.6 ± 0.50	2.3 ± 0.10 *
0.8 Hz	13.8 ± 0.91	2.8 ± 0.09 *	35.2 ± 0.73 §	1.8 ±0.12 *¶
Hyperventilation	83.5 ± 5.74 *	1.4 ± 0.05 *	18.6 ± 0.53 *	1.6 ± 0.10 *¶
Rest	11.7 ± 2.19	3.3 ± 0.14	38.2 ± 0.55	1 ± 0.0¶
p-value	*: $p<0.05$	*: $p<0.05$	*: $p<0.05$ §: $p=0.10$	*: $p<0.05$ ¶, §: compared to 0.2 Hz, $p<0.05$ and 0.09 respectively

MISC values in this study ranged from 1-5. As it is commonplace to speak of nausea incidence in motion sickness research literature, it is of interest to also investigate the results in terms of "no nausea" and "nausea". By dichotomous transformation of the MISC-scores into 'no nausea' (MISC ≤2) and 'nausea' (MISC ≥ 3) binomial testing of the entire data set was performed. As 0.2 Hz has the highest nausea incidence in

our dataset and this is also seen from the study by McCauley and O'Hanlon (1974) hypothesis testing was against this frequency and our observed nausea incidence of 0.46. Table 4.X represents the results of the binomial testing.

*Table 4.X: Binomial testing of pooled data of subjects not getting nauseated (MISC 1-2=0) and subjects that got nauseated (MISC 3-5=1). The asterix * indicates a significant difference between the 0.2 Hz condition and the corresponding condition at an* $\alpha<0.05$.

Frequency (Hz)	**N**	**Mean ± SD**	**p-value**
0.05	23	0.17 ± 0.39	0.004*
0.1	24	0.29 ± 0.46	0.072
0.2	46	0.46 ± 0.50	0.542
0.4	107	0.36 ± 0.48	0.029*
0.8	46	0.20 ± 0.40	0.001*

* Statistical significance at an $\alpha<0.05$.

From table 4.X it is seen that the nausea incidence in the 0.05, 0.4 and 0.8 Hz condition are significantly lower than in the 0.2 Hz condition. The 0.1 Hz is not significantly different from 0.2 Hz condition although the p-value is very close to significance.

4.3.4 Respiratory parameters

With increasing frequency of movement (0.05-0.8 Hz) there is a relatively mild but steady increase of the average respiratory minute volume and a decrease in the respiratory period. Consequently there was a drop in $PetCO_2$ with increasing frequency. In Fig. 4.6 the drop in $PetCO_2$ is shown as a percentage of the drop in $PetCO_2$ between the baseline measurement and the hyperventilation provocation test. Note the peak in MISC score at 0.2 Hz in Fig. 4.5, and the steady drop in $PetCO_2$ over the whole investigated frequency range in Fig. 4.6.

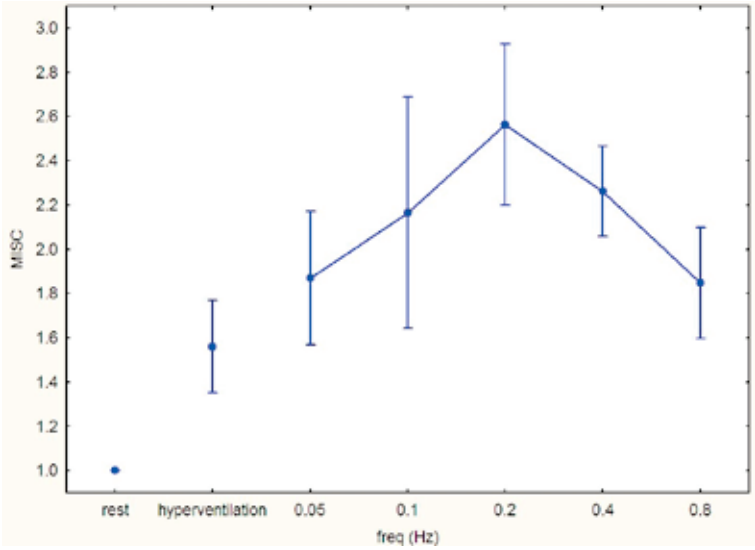


Fig. 4.5. Average MISC scores with 95% confidence intervals, where 1='No problems'; 2='Initial symptoms, but no nausea'; 3='Mild nausea'; 4='Moderate nausea'; 5='Severe nausea and/or retching; and 6='Vomiting'. Data is shown for the Rest period (baseline), the hyperventilation provocation test, and for each stimulus frequency (pooled data).

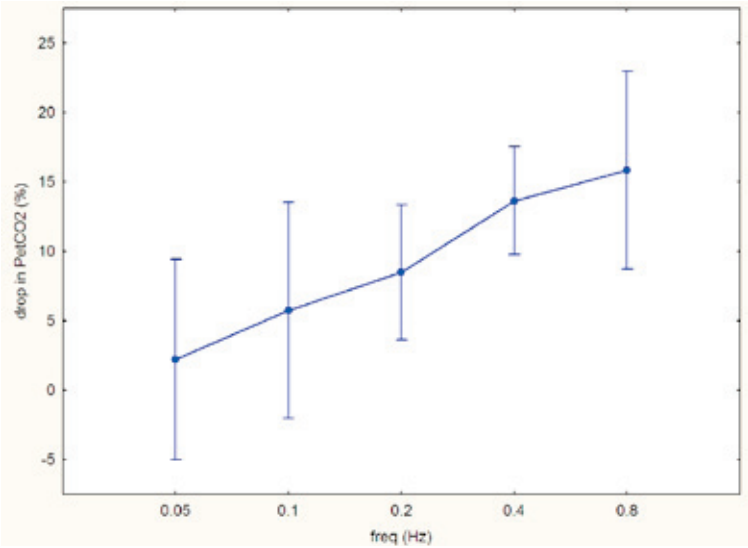


Fig. 4.6. Average drop in $PetCO_2$ with 95% confidence intervals for the pooled data at each stimulus frequency. The drop is expressed as the percentage of the $PetCO_2$ drop in the hyperventilation provocation test compared to the baseline measurement (rest).

There is a tendency of the respiratory frequency to synchronize with the sinusoidal movement of the cabin. In several cases, particularly during the 0.4 and 0.8 Hz movements, synchronization of the respiratory frequency took place, which meant a decrease of the average breathing period from 3.5 s at 0.05, 0.1 and 0.2 Hz to 3.1 and 2.8 s at 0.4 and 0.8 Hz respectively (with stimulus periods of 2.5 and 1.25 s). That these average values do not coincide with the stimulus frequency is due to the fact that the effect of synchronization is seen in about 40% of the subjects at the 0.4 Hz stimuli, and in about 20% of the subjects at the 0.8 Hz stimuli. In one subject at 0.8 Hz vertical motion the respiration minute volume increased even to 40.9 l/min with a MISC score of 4 (cf. 12.2 l/min at rest and 58.9 l/min in the hyperventilation provocation test with a MISC score of 1).

4.3.5 Perceived linear displacement and tilt angle scores

Although not the primary objective of this study, the estimates about the perceived displacements were quite interesting: at 0.8 Hz the real displacement was only 0.23 m, but the average estimated displacement was 1.5 m (median value 1 m). At 0.01 Hz the real displacement was 59.4 m, but the average estimate was 11.6 m (median value 8 m). So there is a huge overestimation at the higher frequencies, and considerable underestimation at the lower frequencies.

During the Heave motion tilt of the body was perceived only once by a subject in line with gravity with an estimated peak-to-peak tilt angle of 4°. At the lower frequencies of the Radius and Counter-Rotation stimuli body tilt was reported especially at 0.05 Hz in about 25% of the test runs (hill-top illusion). From these cases the median peak-to-peak tilt angle was 33°. With increasing frequencies tilt was reported less frequently, whereas the amplitude got less as well, until at 0.8 Hz on the radius body tilt was reported only in 9% of the test runs (average value 7°).

4.4 Discussion

We started out to investigate the role of passive linear oscillation on respiratory parameters and motion sickness, with special attention to the possible contribution of respiration on the high motion sickness incidence around 0.167 Hz.

Our findings of a highest MISC score and nausea incidence at 0.2 Hz (Fig. 4.5) are in line with data from literature (O'Hanlon & McCauley 1974; Golding & Markey 1996). As indicated before in the introduction of this chapter, the endpoint used in the O'Hanlon and McCauley study was vomiting within the two hours of the test run. So the result of a test run was quite simple: vomiting / no vomiting. They needed >400 (!) subjects: For each data point they used 20 subjects and every subject was used only

once. The subjects were examined one by one, and remained in the cabin for two hours unless they vomited earlier. Such an experiment allows statistics, but is hard to replicate nowadays[2].

The endpoint used in our study was set lower, just ''very nauseated'', which was preferred by the medical ethical committee, as well as enjoyed by the altogether 26 test subjects. Moreover, the total motion stimulus time in our study was only about ten minutes, exploring different frequencies, different stimulus modes and different attitudes, each stimulus run lasting only one minute. The advantage of the differentiation in the MISC scores is that – even if they did not reach a MISC level of 5, the lower MISC scores were still taken into account, which helps to shape the general picture, i.e. the peak in Fig. 4.5. It is allowed to use the MISC scores, since Wertheim validated these MISC scores against real motion sickness incidence (Wertheim et al. 1992). True, we investigated only one acceleration value of 0.3 g, but for the purpose of the study – the relationship between respiration and motion sickness – this was sufficient. This way the duration of the experiment took only five working days.

$PetCO_2$ levels decrease with increasing frequency (Table 4.IX; Fig. 4.6), in fact, a possible peak has not been reached with the frequencies used. Comparison of this drop in $PetCO_2$ with the respiratory minute volume, respiration period and stimulus frequency, shows in a number of subjects enforced respiration due to synchronization with the stimulus frequency. This synchronization, however, is most prominent with the stimulus frequencies 0.4 and 0.8 Hz.

From the observations of Bles (1976) with the vertical motion platform ''Hotsklots'' synchronization of breathing was often observed with the vertical linear oscillation with a 0.5 g stimulus. So the stimulus in the present study, although too strong for all subjects to complete all test runs because of motion sickness, was probably not strong enough to evoke the mechanical effect of enforced breathing in all subjects.

Nevertheless, the data of our present study strongly suggest that the peak in MSI at 0.167 Hz for linear oscillation is not due to enforced breathing. A primarily vestibular cause is therefore more likely (Bos & Bles 1998).

---

[2] *Such a complete experiment would be hard to perform nowadays: One subjects requires about 2.5 hrs to perform the experiment. So each day three subjects could be dealt with, i.e. 15 subjects per week. Thus at least 400 / 15 = 27 weeks, plus one week preparation and piloting, resulting in 28 weeks, are necessary. Even with a moderate price for using the simulator a total amount of about € 1.000.000,- would be required to run the simulator for such an experiment, not taking into account the personnel costs to operate the simulator.*

The hyperventilation provocation test showed a very mild increase in MISC values, but no nausea. In this respect one subject is quite exemplary. This subject who met our inclusion criteria for the study and who had a history of hyperventilation syndrome during his childhood, showed during several runs a drop in $PetCO_2$ levels of more than 50% relative to his maximum drop, with a MISC 2. The subject recognized these symptoms as identical to hyperventilation. This drop resulted in symptoms of tingling, lightness in the head, dizziness. The physiologic state he considered as highly uncomfortable and for a short while considered to withdraw from the experiment. During another run he reached MISC 4 and a 60% drop in $PetCO_2$ levels relative to his maximum drop. After the run the drop continued and reached approximately 90% of his maximum drop with a MISC 2.

This subject showed that sickness during motion, even though highly uncomfortable, is not the same as motion sickness and that for motion sickness to occur, nausea is imperative. Literature concerning the role of hyperventilation during motion and especially motion sickness is sparse. Breathing techniques are applied successfully during desensitization programs of motion sickness, even though enforced respiration is present in only a minority of cases (Bles et al. 1976; Mert et al. 2007). It has also been shown that during motion slow-deep breathing (Jokerst et al. 1999) and controlled breathing (Yen Pik Sang et al. 2003), symptoms of motion sickness are suppressed. From animal studies we know that hyperventilation can decrease *mild* nausea and increase tolerance time for nauseating stimuli (Zabara et al. 1972; Lang 1999). Although conclusive evidence is difficult to provide, our data support this finding: several subjects, showing strong enforced breathing and a large drop in $PetCO_2$ with moderate nausea scores of MISC 3 and 4. Not only physiological phenomena as changes in respiratory minute volume or end-tidal CO_2 seem important. For example a subject showed in the vertical displacement runs breathing synchronization with the movement. This also resulted in a hyperventilatory response. Afterwards she said that breathing synchronization helped her in gaining a feeling of control over the movement. Several other subjects, who reached a MISC of 4 or more, were asked what they thought could have helped them prolonging their run-time. Virtually all responded that a feeling of control, for example with an artificial horizon could have been helpful.

We have shown that linear *low frequency* oscillation (0.05-0.2 Hz), as compared to the higher frequency range (0.4-0.8 Hz), has almost no impact on respiratory frequency. In applying linear oscillation in motion sickness studies, it is therefore preferable to use lower frequency stimulation in order to avoid respiratory influences.

As for motion perception, the outcome of the displacement and tilt estimates are quite surprising. As expected, the tilt estimates prevail at the lower frequencies. However, one would expect that subjects perceive large displacements if no or small tilt angles

are reported, and vice versa, a large tilt angle percept suggests a small displacement percept. After all, the percept of a tilt angle is due to the vector sum of the gravitational acceleration vector and the horizontal linear acceleration vector. Indeed, at 0.05 Hz twelve subjects reported large displacements ranging from 8-50 m without a tilt percept. In the other eleven subjects with estimates ranging from 2-7 m, tilt was reported by six subjects, with peak-to-peak estimates ranging from 10 up to 120 degrees, but five subjects with small displacement estimates between 3.5 and 5 m did not report any tilt at all, which is quite surprising. May be that one minute is not sufficient to get a clear picture of the stimulus, or that the subjects were confused – after all they were quite naïve with respect to the stimuli possible with Desdemona – because they could reject the percept as impossible in the Desdemona hall with a length of only 14 m.

As in many experiments on motion perception, it is helpful to use subjects who have some experience in this sort of experiments and who have practised in distance estimation. In the present experiment this was not necessary, since the emphasis was laid on the respiratory parameters and the motion sickness scores, the results of the displacement task should be seen as an interesting pilot experiment.

5. Motion-based Equilibrium Reprocessing Therapy: A novel treatment method for chronic peripheral vestibulopathies

Summary

Introduction: *Vestibular disease can handicap people physically, emotionally and socially. Vestibular rehabilitation has proven to be a safe method to partially alleviate symptoms. It was hypothesized that principles of military aviation vestibular desensitization procedures that have a success rate of more than 80% can be extrapolated to chronic vestibular disease. A specific treatment protocol was devised and preliminary experiences are discussed.*

Methods: *The 6DoF virtual reality motion base CAREN, located at the Military Rehabilitation Center Aardenburg in Doorn, the Netherlands was used. Five patients were exposed to sinusoidal vertical passive whole body motion in increasing intensity for a maximum of 10 sessions. Sessions were either 3 or 5 times a week. This was done to gain insight in possible successful therapy frequencies. Changes in symptoms and Dizziness Handicap Inventory scores (after 1 month) were gathered.*

Results: *All subjects experienced significant positive symptom change and a decrease in DHI scores.*

Discussion: *Motion-based Equilibrium Reprocessing Therapy seems to be a successful, in its origin a simple, quick and well tolerated form of therapy. Larger series, follow up and randomized trials are needed to further substantiate these preliminary results.*

Acknowledgment
We wish to thank Tessa Frunt for programming the application and for keeping up with the monotonous sound of the platform during a 30-minute session.

5.1 Introduction

Diseases of the vestibular system, vestibulopathies, in the acute phase can cause nystagmus, dizziness and vertigo (Dieterich & Brandt 2008). These symptoms are often debilitating, but usually temporary. In case symptoms persist they are less severe, but nonetheless can cause suffering and reduce the level of daily activities and participation. Vestibular rehabilitation programs, comprising amongst others improving balance in stance and the application of Cawthorne & Cooksey head movement exercises have varying success rates (Boyer et al. 2008; Hall & Cox 2009). Medical treatment of vestibular dysfunction with betahistine, oral corticosteroids, carbamazepine to name a few, is limited in indication and often also in response (Brandt et al. 2009). When talking with these patients in clinical practice frustration and disappointment is often present.

In military aviation motion sickness, an occupational dysfunction of the vestibular system is treated with desensitization programs, because medication often has operational restrictions. The similarities between these different programs are the psycho-education on the vestibular system and a gradually increasing exposure to

sickness inducing stimuli (Banks et al. 1992; Lucertini & Lugli 2004; Mert et al. 2007). In the Dutch motion sickness desensitization program Coriolis cross-coupling on a rotating chair is "administered". Subjects start at 60°/sec or lower rotation rates of the chair, close their eyes and make fore-aft movements of the upper body. After two weeks subjects are able to perform these movements at a speed of sometimes up to 180°/sec (Bles et al. 1994; Bles & de Graaf 1995)

The Dutch motion sickness desensitization program started in the 1980s has a success rate of more than 80% and this is comparable with other Air Force desensitization programs (Lucertini & Lugli 2004; Banks et al. 1992).

Although differences of origin between motion sickness and vestibulopathies are apparent, there is also an intriguing similarity as physical symptoms arise because according to signals from the vestibular system there is an apparent motion conflict. One might wonder whether a similar desensitization program, but with a less provocative stimulus (because aircrew in general have a high tolerance to motion sickness), might be appropriate and successful for peripheral vestibulopathies in the chronic phase. Introducing motion conflict and hence induce (slowly increasing) motion sickness, analogous with military desensitization programs, could on theoretical grounds, prove to be a successful method of treatment.

At the Military Rehabilitation Center Aardenburg (Doorn, The Netherlands) a novel vestibular rehabilitation program based on military aviation desensitization principles has been designed and the case series presented here are the first results of this program.

5.2 Method

5.2.1 Questionnaire

Before and after the procedure subjects were asked to fill in the Dizziness Handicap Inventory (DHI), a valid and reliable instrument to rate signs and symptoms of vestibular disease on a functional (9 items), emotional (9 items) and physical (7 items) level. The DHI's score ranges from 0 (no disability) to 100 (severe disability). (Jacobson & Newman 1990). There are three possible answers: *yes* gives a score of 4 points, *sometimes* 2 and *no* 0 points.

It has been proposed by Whitney et al. (2004) that a total DHI score of 0-30 reflects *mild*, 31-60 *moderate* and 61-100 *severe* disability.

Also a change of least 10% in scores after an intervention can be considered a clinically significant result (Treleaven 2006).

5.2.2 Subjects

In the series so far five subjects participated.

Subject 1 (S1): S1 suffered from mal de débarquement syndrome for 3 years before he was presented at the rehabilitation clinic. He had a continuous fore-aft motion sensation that worsened when closing the eyes. The onset of the symptoms was after riding on a wobbly road for hours on end. He also had a workup by a specialist in internal medicine to rule out internal disease. Otoneurological analysis revealed an Optokinetic After-Nystagmus (OKAN) of more than 70 seconds, which is quite long as the time constant for OKAN is 10-20 sec (Tijssen et al. 1989). He received the stimulus every day (Monday through Friday). S1 did not fill out the questionnaire as he was the first patient to come to us with his problem and asked us if we could help him. It was for him that we designed this procedure and since it worked for him we continued with this procedure with other patients and went on to build a patient series.

Subject 2 (S2): S2 suffers from vestibulopathy eci with Menière-like symptoms. She was supervised by an ENT therapist for several years and had received vestibular rehabilitation by a physical therapist. She experienced disequilibrium together with a slight roll sensation and dared not to walk outside without holding on to her husband for support. There was also fear of falling in dim-lit situations. She received the protocol every other day (monday-wednesday-friday). Her DHI score prior to start of the desensitization procedure was 76.

Subject 3 (S3): S3, a 62-year-old woman, was diagnosed with severe Menière's disease 10 years ago. There was deafness of the left ear that had progressed together with the disease. Her last Menière episode was three months before the start of the desensitization procedure. Dizziness was commonplace during the day. She experienced severe limitations in almost all domains of her life. She had had 40(!) physical therapy sessions based on Cawthorne and Cooksey exercises. Her DHI score was 72 prior to the start of the sessions. Her session frequency was 5 times a week (Monday through Friday).

Subject 4 (S4): S4, a 42-year-old man with BPPD symptoms for more than 5 years of unknown etiology. Fast head movements resulted in nausea after 5-10 seconds. The subject had received the Epley procedure several years before, but this did not alleviate the symptoms at all. Sporting activities were impaired. Also turning in bed was highly provocative and sleeping quality was impaired. His DHI score prior to start of the therapy was 40. His session frequency on CAREN was three times a week (Monday-Wednesday-Friday).

Subject 5 (S5): S5, a 39 year old woman with longstanding Menière's disease who had received intratympanal gentamicin injections for 6 times. She experienced severe limitations in all domains of her life. Her dizziness score was 9/10 and nausea score 6/10. Also she experienced fatigue. She vomited once every day. Working capacity was not available. Playing with her daughter was possible for 15 minutes on end. Household chores were limited to one a day. Her DHI score prior to start of the therapy was 82. Her session frequency on CAREN was five times a week.

5.2.3 Procedure

The 6DoF motion base of the CAREN system (Motek Medical, Amsterdam) at the military rehabilitation center Aardenburg in Doorn, Netherlands was used. A wheelchair with head and back rest was put on the platform and people were seated.

At a frequency of 0.2 Hz a vertical sinusoidal stimulus was administered. This way we could make best use of largest possible displacement of the CAREN system without inducing extra passive body and head movements as would be the case in a fore-aft and side-to-side stimulus.

The following displacements were used: 10 cm, 20 cm, 30 cm, 35 cm, 40 cm and 45 cm. Every minute the Misery Score (MISC 1-6) was obtained: MISC 1=no nausea, MISC 2= initial symptoms, but no nausea, MISC 3=mild nausea, MISC 4=moderate nausea, MISC 5= severe nausea and MISC 6=vomiting. Discontinuation of the stimulus occurred when a MISC 4 (moderate nausea) was reached. Also subjects were asked to rate their dizziness on a 1-10 scale every minute (1=no dizziness, 10=extreme dizziness).

Maximum stimulus duration was 30 minutes. If a person did not reach MISC 4 for a specific stimulus within 30 minutes, the next stimulus day a larger displacement was used. Maximum duration of the desensitization protocol was 10 sessions.

5.3 Results

S1: after two sessions the experienced fore-aft sensation disappeared and the dizziness score fell from 7 to 4. He experienced less motion conflict, but as a residual symptom he experienced a very small roll sensation to the left. Probably this was already present prior to the desensitization but overseen because of the dominant fore-aft movement. Fatigue was less. Several months after the sessions he was reassessed in a vestibular clinic, the OKAN had not changed, his symptom change however persisted.

S2: Her DHI-score fell from 76 to 36. The feeling of fullness of the head disappeared, she was more confident in dim-lit conditions and for the first time in about two years

she walked outside without holding on to her husband. She was seen after three months at the clinic for follow-up and the therapeutic effect persisted.

S3: After 3 sessions there was less experienced dizziness throughout the day. After 6 sessions nausea levels at 0.40 m Heave did not rise above MISC 2. During daily activities head movements were less provocative for dizziness. After 8 sessions she reported she felt "normal", although she was not completely symptom free. Reading was not impaired anymore and also playing and lifting her grand-child was not provocative anymore. However, she experienced a mild Meniere's attack a few days after completing the program. Nonetheless, her DHI of 72 at the start of the therapy was at follow-up 12.

S4: After only one session head movements were less provocative and sleeping quality improved dramatically, as he did not wake up during the night anymore. Car travel as a passenger resulted in much less dizziness and nausea. After completion of the runs MISC and dizziness levels during sessions and the day did not rise above 2. At the end of the sessions he was not completely symptom free but head movements and nausea did not cause the amount of impairment compared to prior to start of the sessions. Also he said he was much better able to "control" his remainder of the symptoms. His DHI score of 40 fell to 10. For the first time in years he found himself able to do chores at home under the sink.

S5: She tolerated the sessions increasingly well. After the first week the daily vomiting ceased. Dizziness and nausea score were diminished to 6/10 and 2-3/10 respectively. The DHI score fell from 82 to 70. The reduction in symptoms resulted in the ability to perform more household tasks per day. Also playing with her child was possible for one hour on end. Vomiting was only present for 1-2 times/week. Also weeks with no vomiting were present. Working capacity however was still not present.

5.4 Discussion

This is the first study that uses passive whole body sinusoidal oscillations as a therapy for the symptoms of peripheral vestibular disease. The subjects used in this study completed the protocol and hence it is concluded that analogous to motion sickness desensitization programs it is possible to habituate subjects with peripheral vestibular disease to vestibular stimuli of increasing intensity.

We hypothesize that the effectiveness is possibly due to the fact that the vertical motion stimulus, elicits otolith stimulation without the (usually expected) concomitant stimulation of the semicircular canals. With continued stimulation this might influence the experienced pitch/roll amplitude and hence dizziness and nausea in a positive way.

In our opinion, the positive outcome as seen with a decrease in reported symptomatology, increase in activities and reduction in the DHI score together with the fact that the total therapy time in this set up is a maximum of ten sessions in two weeks time, makes it worthwhile to conduct a larger study. It is interesting to note here that our patients were in a chronic phase of their illness while having marginally responded to prior forms of vestibular therapy.

Furthermore, the Dutch motion sickness desensitization protocol focuses on daily sessions, habituation studies to simulator sickness (Kennedy et al. 1993) point towards a session frequency of 2-3 times a week for habituation to occur (habituation usually occurs in 6 sessions). Our results are in accord with these results and we think that a therapy frequency of three times a week should in general suffice.

In comparison, vestibular rehabilitation therapy takes much longer and focuses more on self-administration of head exercises for example (Hillier & McDonnel 2007). The therapy we designed and conducted with the CAREN system focuses on controlled administration of nauseating stimuli with slowly increasing intensity.

The concept of whole body movement has been used in a complete other fashion by the research group of Sugita-Kitajima (2010). They used the rolling-over maneuver for benign paroxysmal positioning vertigo and compared this to the canalith repositioning maneuver according to Epley and found similar results.

Pavlou et al. (2004) showed additive effect on a vestibular rehabilitation regime with the use of a roll dome, head-mounted display, optokinetic drum and a home video. However, all these elements were part of their additive therapeutic regime, and therefore from their study the effect of each of these elements is not clear. Furthermore, their subjects received therapy twice a week for eight weeks. On theoretical grounds, as described above this is probably a suboptimal frequency for quick desensitization. One might hypothesize that adding a roll dome and/or optokinetic drum through virtual reality to our procedure, might also have an additive effect.

There are however some critical points that need to be made. First of all S1 suffered from the mal de débarquement syndrome. In general a 'rocking' motion of a boat can cause this, although car or air travel are able to cause the condition as well. Furthermore, as the syndrome can last for years, symptoms tend to ameliorate in time. Nonetheless, the quick response S1 had to the therapy makes a natural cause for his symptom decrease unlikely. Also, the syndrome tends to occur in women, which might imply hormonal influences (Golding et al. 1998; Cha 2009), but the syndrome is not solely the realm of women. It seems likely that the same pathophysiological phenomena are at the base of the syndrome with an increased likelihood for the development of the

syndrome in women because of hormonal differences. The exact mechanism however is poorly understood (Cha 2009).

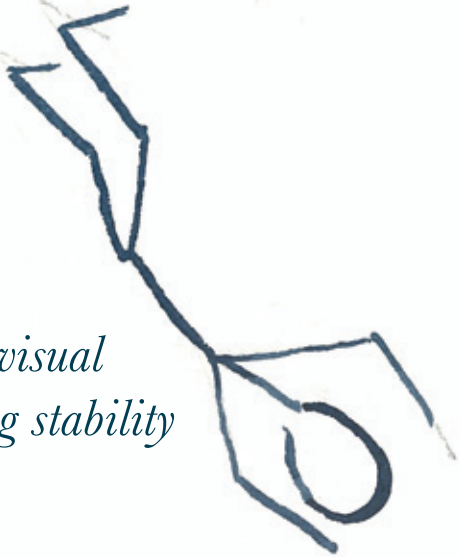
We focused on a central mechanism for the explanation of the therapy. However a peripheral mechanism is not ruled out at this stage. In Menière's disease for example, saccular endolymphatic hydrops is quite common (Lin et al. 2006). The vertical oscillation directly influences the saccule. However, a potential peripheral therapeutic effect of the saccular stimulation on the hydrops seems unlikely. On the other hand, it is possible that the contralateral (unaffected) saccule played an important role in the rehabilitation process. This however, analogous to the military vestibular desensitization protocols, means central involvement, as the contralateral saccule is unaffected in unilateral Menière's disease.

It could also be hypothesized that substitution with another sensory system took place, but as subjects were seated and had their eyes closed this explanatory mechanism seems unlikely. A central mechanism for the treatment of dizziness, would imply that other diagnoses would also benefit from this form of therapy. We have indeed applied this therapy for two post-stroke patients in their chronic phase with complaints of dizziness. Both patients benefitted from this therapy with significant reduction in DHI scores. Also, not only oscillatory movement might be of therapeutic benefit, but also visual stimuli as indicated by the study of Pavlou et al. (2004). Anecdotal benefit for the treatment of post-concussion dizziness with horizontal translations of the visual field in virtual reality might also be present (Wilken JM, personal communication, April 29 2011) and this is also our own anecdotal experience at the Military Rehabilitation Center. All of these examples imply central compensatory mechanisms.

We have used the CAREN system in this experimental set-up, and although our set-up with a 6DoF motion base offers considerable freedom in designing specific therapies, we have the impression that a chair with a possibility to perform vertical sinusoidal movements at a frequency with 0.2 Hz would have offered ample therapeutic modalities in these patients.

The theoretical concept seems viable, but should be compared to a form of vestibular rehabilitation for further assessment. In a recent Cochrane review by Hillier & McDonnel (2007) it was concluded that vestibular rehabilitation is a safe and potentially successful form of therapy for unilateral peripheral vestibular dysfunction.

As a final remark we postulate the following name for this kind of therapy: Motion-based Equilibrium Reprocessing Therapy (MERT).



6. Influence of moving visual surroundings on walking stability

Summary

Introduction: *Balance is negatively influenced by optokinetic stimuli. Fall research with these stimuli has been done with standing subjects. Virtually nothing is known of the influence these stimuli have on risk of falling while walking. The objective of this study was to investigate the influence of optokinetic roll stimuli on balance during walking.*

Methods: *The 6DoF CAREN virtual reality motion base located at Doorn, The Netherlands, was used. A roll dome with in the center a rectangular structure to promote gaze fixation was projected on a 180° field of view 6 m semi-circular wall. The roll dome rotated counterclockwise at 30°/s and the subject walked at a speed of 3.6 km/h. Qualitative and quantitative aspects of gait of 10 subjects was collected.*

Results: *Subjects experienced severe gait disturbances during walking. They could not compensate for the optokinetic stimulation and risk of falling was evident. The quantitative analysis showed decreased step time, step length. There seemed to be an increase in step width, but this could not reach significance ($p=0.13$). However, the mean standard deviation of the subjects increased significantly for all these parameters ($p<0.05$), indicating increased variability in the walking parameters.*

Discussion: *Optokinetic (roll) stimuli have a profound negative effect on walking stability and in subjects increase the risk of falling. These results illustrate the need to use well-calibrated virtual reality stimulation in the training applications, and the need of adequate visual daily environments for patients relying especially on the visual information.*

Acknowledgments
We wish to thank Tessa Frunt and Roos vd Lint for their enormous support with this experiment and who made this experiment possible.

The original version has been published and presented as part of the Rehab Week 2011:
Mert A, Hak L & Bles W. Influence of moving visual surroundings on walking. International Conference on Virtual Rehabilitation (ICVR), Rehab Week Zurich, ETH Zurich Science City, Switzerland, June 27-29 2011: 1-4. DOI:10.1109/ICVR.2011.5971845

6.1 Introduction

Aviation has enriched life with several types of illusions. Also it has given these types of illusions their sometimes illustrious name like graveyard spiral, black hole approach or the Giant Hand illusion (Davis et al. 2008). These illusions point towards an inadequacy of the sensory systems to adequately represent the physical movements. The brain tries to calculate a "best fit" from these complex non-representative data: In these situations trusting your instruments is life saving.

Modern travel over ground also can result in illusions, such as the "train illusion": When the train on an adjacent track departs, one can experience a strong (yet faulty) illusion of departure of the own train. This perceived self-motion is called vection and the phenomenon of vection was first described by the physicist Mach in 1875. Vection can have linear and/or angular components (Mast et al. 2001).

In activities of daily life, like driving, walking and cycling, but also when picking up toys from the ground because a child "forgot" to put them in the basket, normal functioning of the senses, (sub)cortical structures and the neuromuscular system is of importance for maintaining adequate balance and orientation as the gravitational pull is omnipresent on this planet. In healthy people this might be interpreted as an effortless achievement. In the aging human, however staying upright is challenged by (accumulations of) impairments and pathology (Horak et al. 1989; Horak et al. 2006; Volpato et al. 2010). According to Tinetti et al. (1988) the most important biomechanical constraint on balance is the size and quality of the feet: the base of support. Also joint mobility, muscle strength and adequate sensory input are of importance. All these factors influence stability and subjects with small limits of stability are prone to falls (Duncan et al. 1990). In clinical practice decreased joint mobility, sensory input and muscle strength can arise in critical illness neuropathy or diabetes for example. Other factors influencing postural performance are movement strategies (ankle or Center of Mass strategies), the sensory environment (dim-lit conditions e.g.), postural orientation (verticality), dynamics of control during gait and cognitive resources (dual tasking e.g.) (Karnath et al. 2000; Teasdale & Simoneau 2001; Horak et al. 2006). A general observation is that compensation for these impairments is often found in relying more on the visual information, which is helpful indeed as long as the visual information is reliable and provides information about the direction of gravity.

Furthermore, posturographic studies have given insight into the dynamic process that standing actually is. A recent systematic review on risk factors of falling in elderly by Piirtala & Era (2006) showed a potential role of various aspects of mediolateral displacement of the center of position, but the results are inconclusive. Interestingly though the base of support by feet mediolaterally is quite small. Bles (1979) has shown that visual stimuli, for example roll stimuli can cause a shift in the subjective vertical and cause falling. All these studies have in common that they have been performed on standing subjects. In general though people do not fall while standing still, although motion parallax, a depth cue that results from objects moving across our field of view, can positively or negatively influence stability while standing: On the edge of a cliff with a wide view and no objects nearby to induce sufficient parallax, stability is impaired (Bles 1979).

Yet, for an adequate understanding of why humans fall, it is necessary to perform research in walking subjects. In this pilot study we wanted to investigate the role of visual (roll) stimuli while walking, because as Bles (1979) has shown roll stimuli on their own can also cause a mediolateral displacement of the center of position. The perceived sense of self-motion (while standing) due to visual roll stimuli can be explained by acknowledging that both the vestibular and the visual afferents project onto the vestibular nuclei, thus giving rise to a sense of self motion (Bos et al. 2008).

Literature on this subject in walking subjects is sparse however. A literature search on Pubmed combining search terms "roll vection" and "walking" resulted in 2 studies: The study by Jahn et al. (2001) investigated the influence of wearing prism spectacles on gait deviation. Only the study by Schneider et al. (2008) investigated the effect a virtual roll dome, projected via a head mounted display, has on walking 6 meters. They found that only the first few meters resulted in "initial balance responses in the roll plane".

One might hypothesize that after the first few meters an adequate corrective response takes place, but nothing is known whether or not this response is substantiated in the next meters or even minutes of walking.

Our exploratory study on this subject aims to investigate the effect a continuing roll stimulus has on sustained walking during several minutes.

6.2 Method

6.2.1 Subjects

There were 10 healthy subjects with a mean age of 27.9 ± 7.0 years who volunteered for this study. They were not receiving any medication, except for female subjects who were allowed to be on oral contraceptives.

Written consent was obtained from all subjects. The experiment was carried out under the constraints of a protocol relating to experimentally-induced gait variability, which had Medical Ethical Committee approval. Subjects gave informed consent and were free to withdraw at any time.

A lower body V-GAIT marker set-up was used (see Fig. 6.1). This enabled quantitative measurements. From 6 of these 10 subjects quantitative data were suitable for further data-analysis.

6.2.2 Hardware

The CAREN (Motek Medical, Amsterdam) facility located at the Military Rehabilitation Center in Doorn, Netherlands is a 6DoF motion base on which a single belt (max 18 km/h) treadmill is integrated. Directly underneath the treadmill are four force plates. A 6 meter screen enables a 180˚ field of view. Three LCD projectors, several meters above the subject, can project a virtual environment on the screen. Nine Vicon 3D (infra-red) motion capture cameras are located at the level of the LCD projectors and 3 more at the level of the motion base. Figure 6.1 represents the CAREN setup at the Military Rehabilitation Center in Doorn.

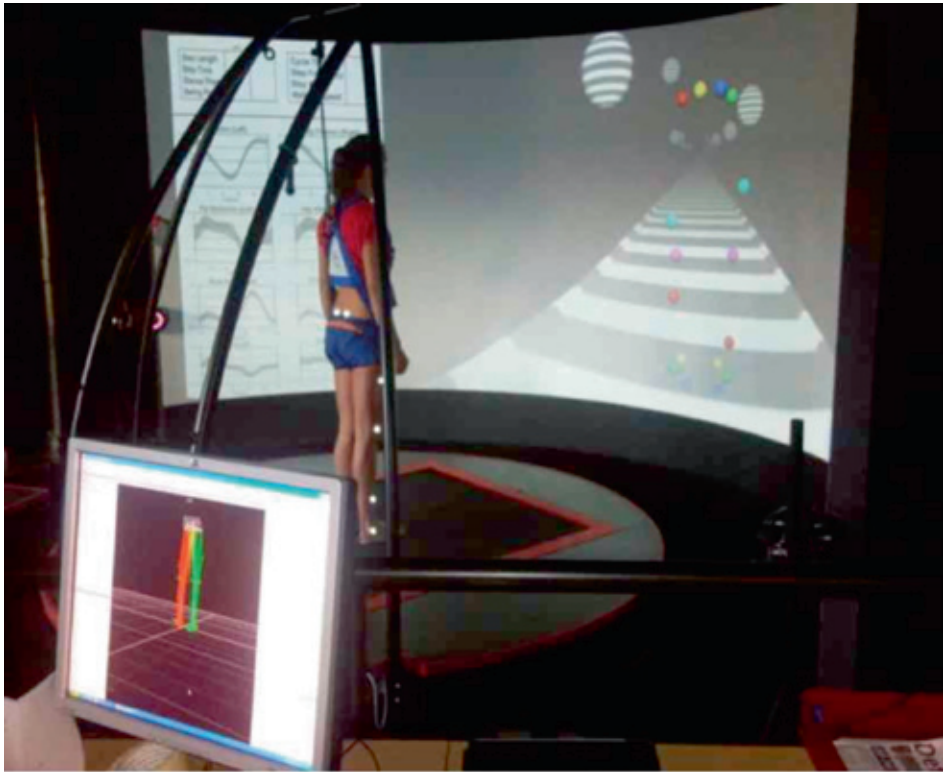


Fig 6.1 Experimental setup of the CAREN system at the Military Rehabilitation Center in Doorn, The Netherlands. The pictures presented here is the setup for gait analysis. Apart from analysis and research it is also used for training. The trainable modalities on the system are amongst others balance, gait, dual tasking, but it is e.g. used also for a special desensitization procedure (Motion-based Euqilibrium Reprocessing Therapy) for chronic peripheral vestibular disease.

6.2.3 Software

A virtual roll dome (Fig. 6.2) consisting of dots in different colors and sizes was constructed using 3D-max software. In the centre of the dome a rectangular shape was present, thus enabling a sense of verticality and promoting gaze fixation of central vision. The roll dome rotated counterclockwise at an angular speed of 30˚/s.

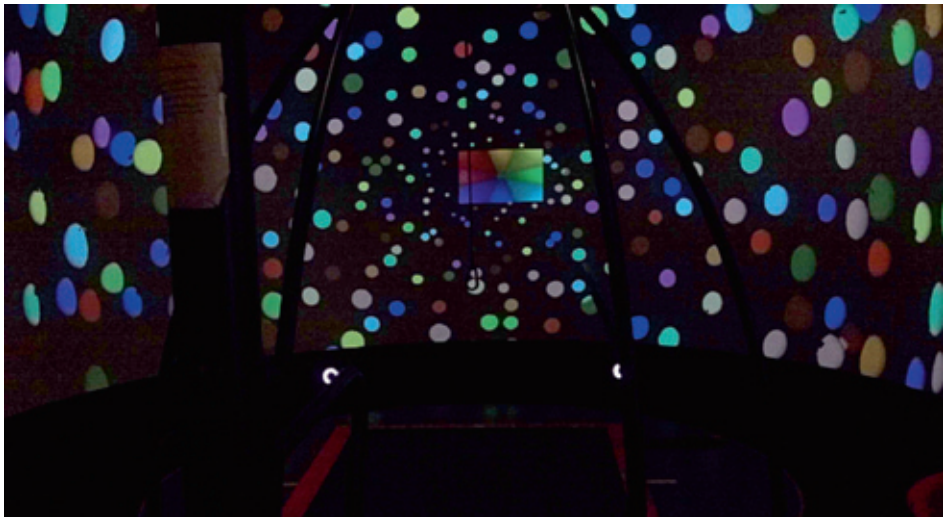


Fig 6.2 The roll dome is projected on the 6 m semicircular 180˚ field of view screen. Subjects walk on the treadmill and are secured in a harness. Directly underneath the treadmill are four force plates. In this experiment subjects were instructed to look at the rectangular shape. This shape did not move during the experiment, the roll dome rotated counterclockwise.

6.2.4 Experimental measurements

The following aspects of the potential influence the roll dome might have on gait were collected:

1. Shift of the subject to the left or right side of the treadmill (relative to the center of the treadmill) and the amount of time the subject stays on that side: The following distinction was made and was rated by the CAREN operator: 0-25%, 25-50%, 50-75%, 75-100%.
2. The direct influence of lateroflexion of the head on gait: After two minutes of walking subjects were instructed to lateroflex their head to the left and 5 seconds later to the right for 5 seconds.
3. Gait changes after stopping the roll stimulus: after 4 minutes of walking the roll dome was stopped but the treadmill continued at the same speed for 10 seconds

after which the treadmill gently came to a stop. During this period gait changes were examined.
4. The experienced tilt in degrees while walking: Experienced tilt was asked afterwards.

The following quantitative data were collected:
Mean step time, step length and step width were collected during the control and roll dome walking time. Also as a value of gait variability, the standard deviations (SD) of these conditions (SD of step time, SD of step length and SD of step width) were collected.

6.2.5 Study design

Prior to the start of the experiment, subjects had to familiarize themselves with treadmill walking for six minutes. According to Matsas et al. (2000) this is necessary to eliminate initial changes in gait variability. The control parameters were collected for two minutes after the familiarization period. During this entire period subjects were walking in a well-lit environment without the visual distorting stimulus.

In the experiment the visual roll dome was applied first and after 10 seconds the treadmill was started as well with a velocity of 3.6 km/h. After 4 minutes the application was stopped (see also 6.2.4) and 10 seconds later the treadmill. Data was collected during the whole period.

6.2.6 Statistical analysis

An ANOVA at an $\alpha<0.05$ for the quantitative parameters mentioned in 6.2.4 was performed using SPSS 13.0.

6.3 Results

6.3.1 Qualitative aspects of gait

The roll dome rotated counterclockwise and all subjects almost immediately shifted to the left side of the treadmill and they walked there for more than 75% of the time (>3 min). Gait was remarkably changed: There was widening of the gait and crossed-steps were observed. Also there was leaning of the torso concomitant to the roll stimulus. Subjects told us afterwards they felt an inability to correct for the perceived roll stimulus.

After stopping the roll dome, all subjects almost immediately shifted to the opposite side of the treadmill, so they overshoot the center position of the treadmill.

During the runs subjects were asked to lateroflex their head counterclockwise (left ear down) and then clockwise (right ear down). In some subjects counterclockwise and clockwise lateroflexion of the head increased gait instability. There was, however, one subject in which counterclockwise lateroflexion of the head resulted in normalization of gait width and clockwise lateroflexion resulted in widening of gait width.

Perceived tilt to the right while walking was reported by all subjects, ranging from10 to 45 degrees.

None of the subjects, but one experienced nausea (MISC>2). Discontinuation of the experiment after 1 minute was necessary for this subject. However despite the discontinuation of the stimulus, nausea increased and she finally vomited. Afterwards she told us she was prone to motion sickness.

Subjects told us they were glad they wore a safety harness; they believed they would have definitely fallen if they had not.

6.3.2 Quantitative aspects of gait

Compared to the control walking parameters, during the roll dome condition step length and step time decreased ($p<0.05$). Also there was an increase in the standard deviation of these parameters compared to the control walking parameters ($p<0.05$). There was no significant increase in step width ($p=0.13$). The mean standard deviation of step width, however, increased significantly compared to control values. The results are shown in Table 6.I.

Table 6.I: The investigated parameters of the six subjects (step length, SD of step length, step width, SD of step width, step time and SD of step time) are presented as mean ± standard deviation. Statistical significance (*) testing is performed at an $\alpha<0.05$.

	Control	Roll dome	p-value
Step length (m) SD of step length (m)	0.67 ± 0.07 0.02 ± 0.007	0.55 ± 0.09 0.07 ± 0.04	0.04* 0.01*
Step width (m) SD of step width (m)	0.23 ± 0.02 0.03 ± 0.007	0.28 ± 0.06 0.07 ± 0.004	0.13 0.001*
Step time (s) SD of step time (s)	0.5 ± 0.04 0.01 ± 0.002	0.43 ± 0.05 0.03 ± 0.01	0.001* 0.002*

6.4 Discussion

This is the first experiment that investigated the role visual roll stimuli have on gait during prolonged walking and perceived vection while walking. With the theory of the subjective vertical (Bles et al. 1998), vection can be explained. Vection shows low-pass behaviour with a time constant in the same order if magnitude of that of the semicircular canals. The addition of both visual and vestibular information results in a fair estimate of 'true' self-rotation (Bos et al. 2008).

We have shown that in walking subjects visual roll stimuli have a very strong influence on gait stability and this effect lasted the entire stimulus time. Our results are in contrast with results of Schneider et al. (2008), who only saw an influence of visual roll stimuli the first meters of walking, but they only measured for a distance of six meters walking. We observed that our test subjects walked on the left side of the treadmill for a prolonged period of time. Interestingly, Jahn et al. (2001), who used prism spectacles and therefore created a distortion of optic flow, observed a deviation of the gait towards the optic flow. The direction of visual stimuli seems to be important for the control of locomotion.

Interestingly though, after cessation of the stimulus when subjects kept on walking, all showed an "overshoot" to the right side of the treadmill. Tanahashi et al. (2007) who investigated the effect of visual simulated roll motion on vection and postural stabilization in *standing* subjects, observed an overshoot of the center of gravity towards the contralateral side of the roll stimulus after discontinuation of their stimulus. Also during their experiment inclination of the body and head was present and worsened when there was perceived vection. The results of our experiment that focused on *walking* subjects are in accord with that of Tanahashi et al. (2007). There seems to be a potential of generalization of "balance data" acquired from stance to walking.

The reason for the overshoot is not known (Tanahashi et al. 2007), but in our opinion there might be a sound explanation for the inclination of the bodies towards the direction of the roll stimulus. According to the theory of the subjective vertical by Bles et al. (1998) a shift in the perceived vertical through roll stimuli can take place and this is the case indeed in standing subjects (Bles 1979). The experienced tilt to the right during counterclockwise rotation of the roll dome results in a shift of the perceived vertical towards the left and hence the body inclines towards the left. A temporary shift in the perceived vertical in walking subjects is explained and actually predicted by this theory.

From the perspective of falling in elderly it is noteworthy to remark the inability of subjects to adequately correct for the roll stimulus. According to Peterka (2002)

depending on the circumstances "reweighing" of sensory information takes place, to retain upright stance. This means that for example in dimly lit conditions more weight is put on vestibular information. Optokinetic stimuli put elderly people, because of potential sensorimotor problems already discussed in the introduction, in a disadvantageous position as their ability to reweigh sensory information is impaired.

We conclude that optokinetic (roll) stimuli – as might be experienced through a startled flock of birds, walking in a crowd or an entering train while standing close to the edge of platform (to name a few examples) - have an (almost) immediate effect on walking and are a potential problem for the elderly and vertigo patients.

Reliable visual information in elderly subjects and vertigo patients is of utmost importance to maintain adequate balance. Therapeutic strategies for these subjects should be aimed at providing in our daily life visual surroundings that do not disturb balance. In view of the large influence of these stimuli it also illustrates the necessity to apply well-calibrated motion stimuli in a virtual reality system such as the CAREN system. Also, our healthy test subjects showed an increased risk of falling together with an inability to deal with the stimulus. This stresses out the importance of fall training in subjects with impaired sensorimotor functioning.

As a final remark projecting virtual scenery on a 180° field of view screen with a treadmill on a motion base seems to be a valuable experimental tool to investigate the relationship between visual (optokinetic) stimuli, walking and risk factors of falling. Our next experiments will implement extended 3D-kinematic data to further explore the role of visual stimuli, but also of motion base perturbations, on walking stability in healthy subjects and balance-impaired patients.

7. General discussion and future prospects

We should aim for the stars.

This thesis describes fundamental and clinical aspects of vestibular functioning, focusing on motion sickness and peripheral vestibular pathology.

In the experiment mimicking the stimuli used for the desensitization protocol no signs of hyperventilation were found. It means that the, at a fixed tempo, forward bowing of the trunk during chair rotation does not generate forces in the body that affect the breathing rhythm: no synchronization of the breathing rhythm and the forward bending of the trunk were observed. The practical meaning of this finding is that with the standard desensitization protocol one should not be afraid that hyperventilation will be induced. Nevertheless, student pilots with air sickness problems attending the desensitization course, are made aware that relaxed breathing is an important issue to control the motion sickness. Interestingly, student pilots are mostly grateful for this advice and confirm that it helps during the course. In motion sickness desensitization programs the Nijmegen Questionnaire for Hyperventilation (NQH) can be used as a screening instrument for the hyperventilation syndrome. In those cases that persons do not respond to the initiated desensitization program and test negative on the NQH other diagnoses should be considered. If necessary, measuring respiratory parameters can serve as an instrument to evaluate the quality of breathing during motion sickness desensitization programs.

From the ESA-sled experiment it is concluded that a linear sinusoidal fore-aft movement with low g-levels (max. 0.2 G) will result in a (generally slow and) steady increase in nausea scores over time. At these low g-levels and low frequency movement (0.167 Hz) again no synchronization of the respiratory frequency with the motion stimulus was observed. Moreover, despite the presence of serious nausea, the data did not show any response close to hyperventilation. This result indicates that at these low g-levels respiration is not involved in the development of motion sickness. When compensating for the gravito-inertial force (GIF) there is a tendency that partial alignment will result in less nausea, although this relationship is not significant in our experiment. From survival series it is seen that a possible protective role of partially compensating for the GIF is temporary.

With the DESDEMONA motion platform the maximum g-level of the sinusoidal motion stimuli was consequently increased to 0.3 g. It was found that respiratory alignment with the applied motion stimulus is (irrespective of motion type) more likely to occur at the higher motion frequencies. Also, instances of synchronization of the breathing rhythm were seen in quite some subjects with increasing motion frequency, and a few subjects showed a real hyperventilation response. The maximum incidence of nausea, however, was found in the 0.2 Hz range, which corresponds to findings in the literature. Therefore, the presence of this peak for the MISC scores and the increasing $PetCO_2$ with increasing frequencies means that this peak in the MISC is not due to enforced respiration. Since the

classical sensory mismatch theory is unable to explain this peak at 0,2 Hz, more attention should be paid to the Subjective Vertical mismatch concept, which enabled simulation of this peak at 0.2 Hz.

Consequently, the results of these three fundamental studies on motion stimuli and the possible effect of respiration on the occurrence of motion sickness showed that the motion sickness incidence was considerable and that respiration was not a provocative factor. Enforced respiration leading to hyperventilation was seen in some subjects at 0.3 g linear oscillation, and they all were motion sick as well. However, the hyperventilation provocation test provoked dizziness, but no nausea. One of the consequences of these experiments is that there is no need for the RNLAF and TNO to change the desensitization protocol.

Of course it is tempting to proceed the research on this subject with sinusoidal motion stimuli with amplitudes of 0.4 g or 0.5 g. In the TNO study with the ''Hotsklots'' (Fig. 7.1) during vertical sinusoidal motion with an amplitude of 0.5 g, enforced respiration was observed by measuring the breathing rhythm. Motion sickness and heart rate were recorded as well, but the end-tidal CO_2 was not measured. However, to accomplish such an experiment was unfortunately not possible. Since it may be expected that quite some test subjects would be required to obtain enough usable data, such a study would be a rather time consuming and therefore expensive venture. It is also true that the financial climate is rather cold. The third most decisive point is that my present position as head of the research and rehabilitation training on the CAREN system at the Military Rehabilitation Centre at Doorn, implicates that focus should be laid more on postural balance and rehabilitation training programs.

Fig. 7.1 The 'Hotsklots', a motion simulator located at TNO Soesterberg from 1973-1975. By moving the tower the vertical motion could be damped from 4 m to 1.5 m. Maximum acceleration was 0.5 g. This device was originally built to simulate the dropping of concrete blocks from a cableway (to build a dam in the Oosterschelde). Investigated was the effect of the motion on the crew in terms of motion sickness. The political decision to keep the Oosterschelde open, implicated unfortunately the untimely end of this research project.

Fig 7.2 The CAREN motion platform (MOTEK, Amsterdam, The Netherlands) is a hexapod system, with a treadmill and four force plates underneath it. The 6 m semicircular screen enables a 180° field of view. There are twelve motion sensitive true infrared cameras (VICON) located around the platform and they respond to reflective markers.

The first of the last two experimental chapters stresses another interesting feature: just as the motion sickness desensitization courses diminish the susceptibility to motion sickness, with CAREN we used certain motion stimuli to diminish the vertigo problems. The first results of the Motion-based Equilibrium Reprocessing Therapy seem to point towards the same success rates of military motion sickness desensitization programs. Moreover if these results hold up in larger patient series and randomized experiments, this could mean a dramatic change and simplification of principles of vestibular rehabilitation. Mere vertical sinusoidal whole-body oscillation at a frequency of 0.2 Hz could be sufficient. Also, from the motion sickness desensitization programs and the Motion-based Equilibrium Reprocessing Therapy, we feel that therapists should not worry of nausea in their patients during therapy. It seems that *slowly* increasing nausea (to moderate levels) might actually be very important for Equilibrium Reprocessing to occur.

The last experimental chapter utilized the advanced possibilities of the CAREN system to demonstrate the importance of synchronized sensory information on locomotion. We have shown, for the first time, that visual roll stimuli have a profound and sustained effect on walking stability and probably increase the risk of falling. Falling per se could not be demonstrated as subjects wore a security harness that prevented the actual falling, but from the reports of the subjects and what we saw during the experiment it

was evident that without the harness subjects would have fallen of the motion-platform. The experiment was carried out with healthy subjects. Patients and elderly with compromised sensory functioning through for example diabetic neuropathy, but also people with significant (degenerative of posttraumatic) arthritis and hence decreased flexibility of joints have most likely a considerable higher risk of falling as a result of these visual stimuli.

The CAREN system (Fig. 7.2) is a hexapod motion platform, with on the platform a treadmill, as well as a facility to project the corresponding virtual environment. Interestingly, with the CAREN system it is also clear that the synchronization in time and place between the motion and the virtual environment is crucial to ensure adequate training and absence of simulator sickness (also a form of motion sickness). If this synchronization is not the case this may result in negative transfer of training, which should be avoided of course, and motion sickness will be easily provoked. Happily enough, motion sickness is not a regular sign during the normal rehabilitation training. Actually, apart from the patients qualified for the Motion-based Equilibrium Reprocessing Therapy, it has only been seen in a handful of people of the approximately 1300 we have trained on the system the last 3 years.

The use of virtual reality applications and serious games has in the last years gained considerable momentum in the field of rehabilitation. Although therapists who use virtual reality and serious gaming are very motivated, they usually lack fundamental knowledge of virtual reality and serious gaming principles and hence are prone to make design flaws in their therapeutic set-up (Mert et al. 2009). The same goes for editors and reviewers actually (Mert et al. 2009). Therefore I think it is important to place a few remarks on this subject.

For adequate transfer of training to happen from the virtual to the real environment the aspect of presence is important. Presence can be defined as the willingness to suspend disbelief that one is actually in a mediated environment (Lombard & Ditton 1997; Schuemie et al. 2001; Sherman & Craig 2003). Complete presence is seldom necessary, but the competence or part skill trained should resemble as much as possible what is required from the subject. Action realism, but also the way the situation in the virtual environment and the task performed, are very important elements of presence (Lombard & Ditton 1997). Presence should not be confused with immersion (Slater 1999) and is much more than experiencing stimuli from displays (Edmans et al. 2007). The possibility to actually manipulate virtual objects enhances presence much more than the use of track balls or a mouse for example (Lombard & Ditton 1997).

Furthermore, when designing virtual reality one should always realise that not every situation is suitable for or best trained in a virtual environment (Heeter 1992).

In the military the use of virtual environments for the training of procedures, optimizing behavior and team performance in dangerous situations is commonplace. Simulators are cost-effective and they enable trainees to train the aforementioned elements, amongst others. The use of virtual reality simulators in military aviation has become commonplace in the last 40 years. Nausea and dizziness were important problems but from the knowledge that has become available from research during these decades, these problems can now be adequately controlled (Kennedy et al. 1987; Mert et al. 2007).

Therefore it is just as important to know how motion sickness emerges from vestibular stimuli and which physiological changes can take place, but also how and why enabling presence in virtual environments is important.

This thesis has offered a better understanding of how the vestibular system interacts with the respiratory system and has also given some insight into a possible protective role of the respiratory system in alleviating moderate nausea. It seems only natural to further investigate this relationship. To know how and when a simple respiratory intervention alleviates motion sickness has practical implications for pilots, crew members at sea but also for recreational travelers, especially those not being in control of the steering wheel. Also for pilot selection, designing appropriate tests with high predictive values concerning the occurrence of motion sickness during vestibular stimuli should have priority. Furthermore, in desensitization programs, which already have high success rates, emphasis should be laid on those cases that don't respond well on the intervention. Translation of knowledge of these programs, and in a broader sense in the field of vestibular research, to practical clinical applications that are able to alleviate the often debilitating symptoms of vestibular illness should be a responsibility of clinicians working in the field of vestibular research.

Yet, it would also be naïve and a gross distortion of reality to make the aforementioned research objectives main research themes in the field of vestibular research, because answering these relationships will possibly not be the great leap forward. Nor will fundamental research alone, the investigation into ergonomic and psychophysiological principles or how the vestibular system acts in space give us a final answer. Vestibular research has many types of specialist working: anatomists, medical doctors, physiologists, physicists, mathematicians, to name a few. It is easy to conclude that there must be a huge amount of data available, but also fragmented. The ignorance of the medical field into vestibular theories other than the sensory rearrangement theory is quite exemplary.

Combining knowledge other than during scientific congresses or reading different types of articles is necessary to create a leap forward. In my opinion vestibular research has

evolved such that it needs an international collaborative transdisciplinary approach. This would also do just to the challenges faced in this very dynamic era and such a collaborative approach would enable us to maximize scientific output with minimal costs for society. That such a collaborative approach works better than "doing it by yourself" is pretty obvious in the grandest of humanity's projects, namely The International Space Station and also the Hadron collider at CERN. Several years ago the researchers at CERN have gotten a 300 million euro research grant from the EU. This is an astronomical amount of course, but it costs only 1 euro per citizen of the EU: A small amount to pay indeed.

On a much smaller level, this thesis, a collaborative approach has worked quite well. People with backgrounds in health, movement, medical sciences and physics working together, have produced sound integrated scientific material much faster than would have been achieved working mono-disciplinarily.

In my opinion, scientists in this field should work on creating their own "Hadron collider", while combining fundamental and applied research. This will give this research field the best position for a thorough theoretical foundation of research, optimal quick results, diffusion of these results to the appropriate fields, no doubling of research and, this will please our benefactors, the best value for money.

As a final remark, the reader might think of this as "aiming for the stars", but even "reaching the sky" would be an incredible achievement and a proud step forward.

8. References

1. Angelaki DE and Yakusheva TA. How vestibular neurons solve the tilt/translation ambiguity. Basic and clinical aspects of vertigo and dizziness: Ann N Y Acad Sci 2009; 1164: 19-28.
2. Banks RD, Slaisbury DA and Ceresia PJ. The Canadian Forces Airsickness rehabilitation program, 1981-1991. Aviat Space Environ Med 1992; 63: 1098-101.
3. Baranov VM, Tikhonov MA, Matsnev EI, Volkov MIu, Markin AS and Khaïdakov KS. Role of external respiration in the formation of the autonomic component in motion sickness. Kosmol Biol Aviakosm Med 1991; 25: 20-24. (only abstract available, article in Russian)
4. Bertalanffy P, Hoerauf K, Fleischhackl R, Strasser H, Wicke F, Greher M, Gustorff B and Kober A. Korean hand acupressure for motion sickness in prehospital trauma care: a prospective, randomized, double-blinded trial in a geriatric population. Anest and Analg 2004; 98: 220-3.
5. Bles W. Coriolis effects and motion sickness modelling. Brain Res Bull 1998; 47: 543-549.
6. Bles W. Measurements on the effects of vertical sinusoidal movements on humans. TNO Human Factors Research Institute (in Dutch), Soesterberg, The Netherlands 1976; Report no.: 1976-C4.
7. Bles W. Thesis: Sensory interactions and human posture- an experimental study. Vrije Universiteit, Amsterdam, The Netherlands. April 5 1979.
8. Bles W, Boer LC, Keuning JA, Vermeij P and Wientjes CJE. Seasickness: Dose-effect registrations with HMS Makkum. TNO Human Factors Research Institute, Soesterberg, The Netherlands 1988; Report no.: IZF-1988-5.
9. Bles W, Bos JE, de Graaf B, Groen E and Wertheim AH. Motion sickness: only one provocative conflict? Brain Res Bull 1998; 47: 481-87.
10. Bles W and de Graaf B. Onderzoek naar en behandeling van lucht- en zeeziekte [Research on and treatment of air and sea sickness] 1995. In: W. Bles e.a (eds). Nederland in evenwicht? : uitgave ter gelegenheid van het tienjarig bestaan (1985-1995) van de Landelijke Vestibulaire Werkgroep. Utrecht, Tijdstroom.
11. Bles W, de Graaf B and Bos JE. Vestibular examination in pilots susceptible to motion sickness. AGARD Conference Proceedings 553. The Clinical Basis for Aeromedical Decision Making 1995; 15: 1-8.
12. Bles W, de Graaf B and Krol JR. Space adaptation and sickness induced by centrifugation: vestibular consequences of earth anomalous gravity. TNO Human Factors Research Institute, Soesterberg, The Netherlands 1995; Report no.: TNO-TM 1995 B-12.

13. Bles W, Hosman RJAW and de Graaf B. Desdemona: advanced disorientation trainer and (sustained-G) flight simulator. AIAA Modeling and Simulation Technologies Conference. Denver, Co. August 14-17 2000. AIAA 2000-4176.
14. Bles W, Wientjes CJE. Well-being, task performance and hyperventilation: influence of visual frame of reference and artificial horizon. TNO Human Factors Research Institute, Soesterberg, The Netherlands 1988; Report no.: IZF 1988-30.
15. Blumenfeld H. Neuroanatomy through Clinical Cases. Sinauer Associates Inc., Sunderland. 2002.
16. Bos JE. How motions make people sick such that they perform less: A model based approach. AVT106 Symposium, Prague, October 2004.
17. Bos JE and Bles W. Modelling motion sickness and subjective vertical mismatch detailed for vertical motions. Brain Res Bull 1998; 47: 537–542.
18. Bos JE and Bles W. Theoretical consideration on canal-otolith interaction and an observer model. Biol Cyber 2002; 86: 191-207.
19. Bos JE, Bles W and Groen EL. A theory on visually induced motion sickness. Displays 2008; 29: 47-57.
20. Bos JE, Colwell JL and Wertheim AH. A focus on motion sickness regarding the 1997 NATO performance assessment questionnaire (PAQ) data. TNO Human Factors Research Institute, Soesterberg, The Netherlands 2002; Report no.: TNO-TM-02-A017.
21. Bos JE, Kistemaker JA and Bles W. Desensitisation of sailors. TNO Human Factors Research Institute, Soesterberg, The Netherlands 2001; Report no.: TM-01-A027.
22. Bowins B. Motion sickness: A negative reinforcement model. Brain Res Bull 2010; 81: 7-11.
23. Boyer FC, Percebois-Macadré L, Regrain E, Léveque M, Taïar R, Seidermann L, Belassian G and Chays A. Vestibular rehabilitation therapy. Neurophysiol Clin 2008; 38: 479-87.
24. Brandt T, Zwergal A and Strupp M. Medical treatment of vestibular disorders. Expert Opin Pharmacother 2009; 10: 1537-48.
25. Cha Y-H. Mal de débarquement. Semin Neurol 2009; 29: 520-27.
26. Cheung B, Money K, Wright H and Bateman W. Spatial disorientation-implicated accidents in Canadian forces, 1982-92. Aviat Space Environ Med 1995; 66: 579-85.
27. Dahlman J, Sjörs A, Lindström J, Ledin T and Falkmer T. Performance and autonomic responses during motion sickness. Hum Factors 2009; 51: 56-66.
28. Damasio AR. Descartes' Error: Emotion, Reason and the Human Brain. Putnam Publishing, 1994.
29. Davis JR, Johnson R, Stepanek J and Fogarty JA. Fundamentals of Aerospace Medicine. 4th edition. Wolters Kluwer, New York. 2008.
30. Dichgans J and Brandt T. Visual-Vestibular Interaction: Effects on Self-motion Perception and Postural Control. In: Held R, Leibowitz, H and Teuber HL (Eds): Handbook of Sensory Physiology, volume VIII Perception. Springer, Berlin 1978.

31. Dieterich M and Brandt T. Functional brain imaging of peripheral and central disorders. Brain 2008; 131: 2538-52.
32. Dixon ME, Stewart PB, Mills FC, et al. Respiratory consequences of passive body movement. J Appl Physiol 1961; 16: 30-34.
33. Dobie TG. Airsickness in Aircrew. AGARDograph no. 177, 1974.
34. Donohew BE and Griffin MJ. Motion sickness with fully roll-compensated lateral oscillation: effect of oscillation frequency. Aviat Space Environ Med 2009; 80: 94-111.
35. Doweck J, Gordon CR, Schlitner A, Spitzer O, Gonen, Binah O, Melamed Y and Shupak A. Alterations in R-R variability associated with experimental motion sickness. J Autonom Nerv Syst 1997; 67: 31-7.
36. Droppert RM. Effecten van beweging van Leopard 2A5 en 2A6 op het welbevinden van de bemanning: Schutterziekte of motion sickness bij tankbemanningen? Onderzoeksscriptie i.h.k. van de opleiding tot bedrijfsarts. SGBO, Nijmegen, 2006.
37. Edmans JA, Gladman JRF, Cobb S, Sunderland A, Pridmore T, Hilton D and Walker MF. Validity of a virtual environment for stroke rehabilitation. Stroke 2006; 37: 2770-75.
38. Filliard MN. Thesis: Cohérence des stimuli visuels et vestibulaires sur simulateur de conduite et en réalité virtuelle. Université Pierre & Marie Curie, Paris, France. October 19 2009.
39. Förstberg J, Anderson E and Ledin T. Influence of different conditions for tilt compensation on symptoms of motion sickness in tilting trains. Brain Res Bul 1998; 47: 525-535.
40. Fukuda T. Postural behaviour and motion sickness. Acta Otolayngol 1975; suppl 330: 9-14.
41. Gardner WN, Meah MS and Bass C. Controlled study of respiratory responses during prolonged measurement in patients with chronic hyperventilation. Lancet 1986; 328: 826-830.
42. Gianaros PJ, Quigley KS and Muth ER. Relationship between temporal changes in cardiac parasympathetic activity and motion sickness severity. Psychophysiology 2003; 40: 39-44.
43. Gozal D, Hathout GM, Kirlew KA, Tang H, Woo MS, Zhang J, Lufkin RB and Harper RM. Localization of putative neural respiratory regions in the human in the human by functional magnetic resonance imaging. J Appl Physiol 1994; 76: 2076-83.
44. Goldberg JM and Fernandez C. Vestibular mechanisms. Annu Rev Physiol 1975; 37: 129-162.
45. Golding JF. Motion sickness susceptibility questionnaire revised and its relationship to other forms of sickness. Brain Res Bull 1998; 47: 507-516.
46. Golding JF. Motion sickness susceptibility. Auton Neurosci 2006; 129: 67-76

47. Golding JF, Bles W, Bos JE, Haynes T and Gresty MA. Motion sickness and tilts of the inertial force environment: active suspension system vs. active passengers. Aviat Space Environ Med 2003; 74: 220-7.
48. Golding JF, Finch MI and Stott JR. Frequency effect of 0.35-1.0 Hz horizontal translational oscillation on motion sickness and the somatogravic illusion. Aviat Space Environ Med 1997; 68: 396-402.
49. Golding JF, Kadzere P and Gresty M. Meeting Abstract: Motion sickness and the menstrual cycle. Aviat Space and Environ Med 2004; 75: 488.
50. Golding JF and Markey HM. Effect of frequency of horizontal linear oscillation on motion sickness and somatogravic illusion. Aviat Space Environ Med 1996; 67: 121-126.
51. Golding JF, Mueller AG and Gresty MA. A motion sickness maximum around the 0.2 Hz frequency range of horizontal translational oscillation. Aviat Space Environ Med 2001; 72: 188-92.
52. Grant W and Best W. Otolith-organ mechanics: lumped parameter model and dynamic response. Aviat Space Environ Med 1987; 58: 970-76.
53. Gray H. Anatomy of the Human Body. Lea and Febiger, Philadelphia. 1918.
54. Gray O. A brief survey of the phylogenesis of the labyrinth. J Laryngol and Otol 1955; 151-79.
55. Griffin MJ and Mills KL. Effect of frequency and direction of horizontal oscillation on motion sickness. Aviat Space Environ Med 2002; 73: 537-43.
56. Guyton AC. Regulation of Respiration. In: Textbook of Medical Physiology. WB Saunders Company, Philadelphia. 1991.
57. Hall CD and Cox LC. The role of vestibular rehabilitation in the balance disorder patient. Otolaryngol Clin North Am 2009; 42: 161-9.
58. Han JN, Schepers R, Stegen O, Van den Bergh O and Van de Woestijne KP. Psychosomatic symptoms and breathing pattern. J Psychosom Res 2000; 49: 319-33.
59. Han JN, Stegen K, Schepers O, Van den Bergh O and Van de Woestijne KP. Subjective symptoms and breathing pattern at rest and following hyperventilation in anxiety and somatoform disorders. J Pychosom Res 1998; 45: 519-32.
60. He SQ, Dum RP and Strick PL. Topographical organization of corticospinal projections from the frontal lobe: motor areas on the medial surface of the hemisphere. J Neurosci 1995; 15: 3284-306.
61. Heeter C. Being There: The Subjective Experience of Presence. Presence: Teleoperators and Virtual Environments 1992; 1: 262-271.
62. Hernandez JP, Fadi X and Frazier DT. Medial vestibular nucleus mediates the cardiorespiratory responses to fastigial nuclear activation and hypercapnia. J Appl Physiol 2004; 97: 835-42.
63. Hillier SL and McDonnell M. Vestibular rehabilitation for unilateral peripheral vestibular dysfunction. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005397. DOI: 10.1002/14651858.CD005397.pub2. Updated 2010.

64. Hoffman DD. Visual intelligence: how we create what we see. WW Norton & Company, New York. 1998.
65. Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls. Age and Ageing 2006; 35-S2: ii7-ii11.
66. Horak FB and Shupert CL. Components of postural dyscontrol in the elderly: a review. Neurobiol Ageing 1989; 10: 727–38.
67. Howarth HVC and Griffin MJ. Effect of roll oscillation frequency on motion sickness. Aviat Space Environ Med 2003; 74: 326-31.
68. Humphriss RL, Baguley DM, Andersson G and Wagstaff S. Hyperventilation in the vestibular clinic: use of the Nijmegen Questionnaire. Clin Otolaryngol 2004; 29: 232-7.
69. Hutchins KD, Martino AM and Strick PL. Corticospinal projections from the medial wall of the hemisphere. Exp Brain Res 1988; 71: 667-72.
70. Jacobson GP and Newman CW. The development of the Dizziness Handicap Inventory. Arch Otolaryngol Head Neck Surg 1990; 116: 424-7.
71. Jahn K, Strupp M, Schneider E, Dieterich M and Brandt T. Visually induced gait deviations during different locomotion speeds. Exp Brain Res 2001; 141: 370-4.
72. Jáuregui-Renaud K, Yarrow K, Oliver R, Gresty MA and Bronstein AM. Effects of caloric stimulation on respiratory frequency and heart rate and blood pressure variability. Brain Res Bull 2000; 53:17-23.
73. Jáuregui-Renaud K, Villanueva PL and del Castillo MS. Influence of acute unilateral vestibular lesions on the respiratory rhythm after active change of posture in human subjects. J Vestib Res 2005; 15: 41-8.
74. Jáuregui-Renaud K, Villanueva Padrón LA and Cruz Gómez NS. The effect of vestibular rehabilitation supplemented by training of the breathing rhythm or proprioception exercises, in patients with chronic peripheral vestibular disease. J Vestib Res 2007; 17: 63-72.
75. Jokerst MD, Gatto M, Fazio R, Stern RM and Koch KL. Slow deep breathing prevents the development of tachygastria and symptoms of motion sickness. Aviat Space Environ Med 1999; 70: 1189-92.
76. Jones DR, Levy RA, Gardner L, Marsh RW and Patterson JC. Self-control of psychophysiologic response to motion stress: using biofeedback to treat airsickness. Aviat Space Environ Med 1985; 56: 1152-57.
77. Joseph JA and Griffin MJ. Motion sickness from combined lateral and roll oscillation: effect of varying phase relationships. Aviat Space Environ Med 2007; 10: 944-50.
78. Joseph JA and Griffin MJ. Motion sickness: effect of changes in magnitude of combined lateral and roll oscillation. Aviat Space Environ Med 2008; 79: 1019-27.
79. Karnath HO, Ferber S and Dichgans J. The neural representation of postural control in humans. PNAS 2000; 97: 13931–6.

80. Kawakita T, Kuno S, Miyake Y and Watanabe S. Body sway induced by depth linear vection in reference to central and peripheral visual field. Jpn J Physiol 2000: 50: 315-21.
81. Kennedy RS, Berbaum KS, Lilienthal MG, Dunlap WP, Mulligan BE and Funaro F. Guidelines for alleviation of simulator sickness symptomatology. Naval Training Systems Center, Orlando, Florida 1987; Report no.: NAVTRASYSCEN TR-87-007.
82. Kennedy RS, Lane NE, Berbaum KS and Lilienthal MG. Simulator Sickness Questionnaire: An enhanced method for quantifying simulator sickness. Int J Aviat Psychol 1993; 3: 203-20.
83. Kornhuber HH. Vestibular System Part 1: Basic Mechanisms. In: Handbook of Sensory Physiology. Springer Verlag, Berlin. 1974.
84. Kubin L, Alheid GF, Zuperku EJ and McCrimmon DR. Central pathways of pulmonary and lower airway vagal afférents. J Appl Physiol 2006; 101: 618-27.
85. Lang IM. Noxious stimulation of emesis. Dig Dis and Sci 1999; 44 (Suppl.): 58S-63S.
86. Lawther E and Griffin MJ. Motion sickness and motion characteristics of vessels at sea. Ergonomics 1988; 31: 3173-94.
87. Lin M-Y, Timmer FCA, Oriel BS, Zhou G, Guinan JJ, Kujawa SG, Hermann BS, Merchant SN and Rauch SD. Vestibular Evoked Myogenic Potentials (VEMP) can detect asymptomatic saccular hydrops. Laryngoscope 2006; 1165: 987-92.
88. Lipana JG, Fletcher J, Brown W and Cohen G. Effects of various respiratory maneuvers on the physiological response to angular acceleration. Aerosp Med 1969; 40: 976-80.
89. Lombard, M. and Ditton, T. At the Heart of It All: The Concept of Presence. Journal of Computer-Mediated Communication (on-line serial) 1997; 3. Available: http://jcmc.indiana.edu/vol3/issue2/lombard.html.
90. Lucertini M and Lugli V. The Italian air force rehabilitation programme for air-sickness. Acta Otorhinolaryngol Ital 2004; 24: 181-7.
91. Lum LC. Hyperventilation: The tip and the iceberg. J Psychosom Res 1975; 19: 375-83.
92. Mach E. Grundlinien der Lehre von den Bewegungsempfindungen. Engelmann, Leipzig, Germany. 1875.
93. Mast FW, Berthoz A and Kosslyn SM. Mental imagery of visual motion influences the perception of roll-vection stimulation. Perception 2001; 30: 945-57.
94. Matsas A, Taylor N and McBurney H. Knee joint kinematics from familiarised treadmill walking can be generalized to overground walking in young unimpaired subjects. Gait Posture 2000; 11: 46-53.
95. Mayne R. A Systems concept of the Vestibular Organs. In: Kornhuber HH (ed) Handbook of Sensory Physiology. Springer, Berlin. 1974.
96. Mert A and Bles W. Impact of alignment to gravito-inertial force on motion sickness and cardiopulmonary variables. Aviat Space Environ Med 2011; 82: 694-8.

97. Mert A, Hak L and Bles W. Influence of moving visual surroundings on walking. International Conference on Virtual Rehabilitation (ICVR), Rehab Week Zurich. ETH Zurich Science City, Switzerland. June 27-29 2011: 1-4. DOI:10.1109/ICVR.2011.5971845.
98. Mert A, Bles W and Nooij SAE. Hyperventilation in a motion sickness desensitization program. Aviat Space Environ Med 2007; 78: 505-9.
99. Mert A, Bles W and Wertheim W. Presence in virtual environments. Clin Rehabil 2009; 23: 465-6.
100. Mert A, Klopping-Ketelaars I and Bles W. Respiratory impact on motion sickness induced by linear motion. Basic and Clinical Aspects of Vertigo and Dizziness. Ann NY Acad Sci 2009; 1164: 173-9.
101. Miller KE and Muth ER. Efficacy of acupressure and acustimulation bands for the prevention of motion sickness. Aviat Space Environ Med 2004; 75: 224-34.
102. Mills KL and Griffin MJ. Effect of seating, vision and direction horizontal oscillation on motion sickness. Aviat Space Environ Med 2000; 71: 996-1002
103. Moore KL and Dailey AF. Clinically oriented anatomy. Lippincott Williams & Wilkins, New York. 1999.
104. Nobile RL. Symposium on motion sickness. II. Medication for motion sickness prior and during World War II. Int Rec Med Gen Pract Clin 1955; 168: 1-12.
105. O'Hanlon JF and McCauley ME. Motion sickness incidence as a function of the frequency and acceleration of vertical sinusoidal motion. Aerosp Med 1974; 5: 366-369.
106. Oman CM. A heuristic mathematical model for the dynamics of sensory conflict and motion sickness. Acta Otolaryngol (Suppl) 1982; 392: 1-44.
107. Osborne C, Varley J and Gardner W. The range of end-tidal PCO_2 in normal subjects and mild asthmatics using computerized ambulatory capnography. Nineteenth International Symposium from the International Society for the Advancement of Psychophysiology (ISARP); San Diego, Oct 15-17 2000. Available: http://www.ohiou.edu/isarp/conf_00/post_9.htm
108. Pavlou M, Lingeswaran A, Davies A, Gresty MA and Bronstein AM. Simulator based rehabilitation in refractory dizziness. J of Neurol 2004; 251: 983-995.
109. Perkin GD and Joseph R. Neurological manifestations of the hyperventilation syndrome. J R Soc Med 1986; 79: 448-50.
110. Peterka RJ. Sensorimotor integration in human postural control. J Neurophys 2002; 88: 1097–118.
111. Piirtola M. and Era P. Force platform measurements as predictors of falls among older people- a review. Gerontology 2006; 52: 1-16.
112. Previc FH and Ercoline WR (eds). Spatial Disorientation in Aviation. Vol. 203 Progress in Astronautics and Aeronautics. AIAA Inc. Virginia, 2004.
113. Rafferty GF, Saisch SGN and Gardner WN. Relation of hypocapnic symptoms to rate of fall of end-tidal PCO_2 in normal subjects. Respir Med 1992; 86: 335-340.

114. Ramachandran VS & Blakeslee S. Phantoms of the Brain. Harper Perennial, New York. 1998.
115. Reason JT and Brand JJ. Motion Sickness. Academic Press, London. 1975.
116. Rolnick A and Lubrow RE. Why is the driver rarely motion sick? The role of controllability in motion sickness. Ergonomics 1991; 34: 867-79.
117. Sachs O. The Man who Mistook his Wife for a Hat. Summit Books, New York. 1985.
118. Sagawa K, Inooka H, Ino-oka E and Takahashi T. On an ambulance stretcher suspension concerned with the reduction of patient's blood pressure variation. Proc Inst Mech Eng (H) 1997; 211: 199-208.
119. Schneider E, Jahn K, Dieterich M, Brandt T and Strupp M. Gait deviations induced by visual stimulation in roll. Exp Brain Res 2008; 185: 21-6.
120. Schuemie MJ, van der Straaten P, Krijn M and van der Mast CAPG. Research on presence in VR: A survey. Cyberpsychology and Behavior 2001; 4: 183-201.
121. Sherman WR and Craig AB. Understanding Virtual Reality. Morgan Kaufmann Publishers, San Francisco. 2003.
122. Shinder ME and Taube JS. Differentiating ascending vestibular pathways to the cortex involved in spatial cognition. J Vest Res 2010; 20: 3-23.
123. Sinha R. Effect of vestibular coriolis reaction on respiration and blood-flow changes in man. Aerosp Med 1968; 39: 837-44.
124. Slater M. Measuring Presence: A response to the Witmer and Singer Presence Questionnaire. Presence: Teleoperators & Virtual Environments 1999; 8: 560-65.
125. Sugita-Kitajima A, Sato S, Mikami K, Mukaide M and Koizuka I. Does vertigo disappear only by rolling over? Rehabilitation for benign paroxysmal positional vertigo. Acta Otolaryngol 2010; 130: 84-8.
126. Sleight P. Cardiac Vomiting. Br Heart J 1981; 46: 5-7.
127. Stott JRR. Prevention and Treatment of Motion Sickness: Non-Pharmacological Therapy. In: AGARD Lecture Series no. 175: Motion Sickness: Significance in Aerospace Operations and Prophylaxis 1992; 9:1-9.
128. Strongin TS and Charlton SG. Motion sickness in operational bomber crews. Aviat Space Environ Med 1991; 62: 57-9.
129. Tanahashi S, Ujike H, Kozawa R and Ukai K. Effects of visually simulated roll motion on vection and postural stabilization. J Neuoeng Rehabil 2007; 4: 39. DOI: 10.1186/1743-0003-4-39.
130. Teasdale N and Simoneau M. Attentional demands for postural control: the effects of ageing and sensory reintegration. Gait Posture 2001; 14: 203–10.
131. Thurrell A, Jáuregui-Renaud K, Gresty MA and Bronstein AM. Vestibular influence on the cardiorespiratory responses to whole-body oscillation after standing. Exp Brain Res 2003; 150: 325-31.

132. Tijssen MA, Straathof CS, Hain TC and Zee DS. Optokinetic afternystagmus in humans: normal values of amplitude, time constant, and asymmetry. Ann Otol Rhino Laryngol 1989; 98: 741-6.
133. Tinetti ME, Speechlev M and Ginter SF. Risk factors for falls among elderly persons living in the community. N Eng J Med 1988; 319: 1701–7.
134. Treleaven J. Dizziness Handicap Inventory (DHI). Aust J Physiother 2006; 52: 67.
135. Turner M and Griffin MJ. Motion sickness in public road transport: their relative importance of motion, vision and individual differences. Br J Psychol 1999; 90(pt 4): 519-30.
136. Turner M and Griffin MJ. Motion sickness in public road transport: the effect of driver, route and vehicle. Ergonomics 1999; 42: 1646-64.
137. Van Dixhoorn J and Duivenvoorden HJ. Efficacy of Nijmegen questionnaire in recognition of the hyperventilation syndrome. J Psychosom Res 1985; 29: 199-206.
138. Vibert D, Häusler R and Safran AB. Subjective visual vertical in peripheral unilateral vestibular diseases. J Vestib Res 1999; 9: 145-52.
139. Volpato S, Maraldi C and Fellin R. Type 2 diabetes and risk for functional decline and disability in older persons. Curr Diab Rev 2010; 6: 134-43.
140. Waddell G, Scott PDR, Leed NW and Ledingham I. Effect of ambulance transport in critically ill patients. BMJ 1975; 1:386-9
141. Wertheim AH, Ooms J, de Regt GP, Wientjes CJE. Incidence and severeness of seasickness: validation of a rating scale. TNO Human Factors Research Institute, Soesterberg, The Netherlands 1992. Report no.: IZF-1992-A-41.
142. Whitney SL, Wrisley DM, Brown KE and Furman JM. Is perception of handicap related to functional performance in persons with vestibular dysfunction? Otol Neurotol 2004; 25:139-43.
143. Yates BJ and Miller AD. Physiological evidence that the vestibular system participates in autonomic and respiratory control. J Vestib Res 1998; 8: 17-25.
144. Yates BJ, Miller AD and Lucot JB. Pysiological basis and pharmacology of motion sickness: an update. Brain Res Bull 1998; 47: 395-406.
145. Yen Pik sang FD, Golding JF and Gresty MA. Suppression of sickness by controlled breathing during mildly nauseogenic motion. Aviat Space Environ Med 2003; 74: 998-1002.
146. Yen Pik Sang F, Billar J, Gresty MA and Golding JF. Effect of a novel motion desensitization training regime and controlled breathing on habituation on motion sickness. Percept Mot Skills 2005; 101: 244-56.
147. Yokota Y, Aoki M, Mizuta K, Ito Y and Isu N. Motion sickness susceptibility associated with visually induced postural instability and cardiac autonomic responses in healthy subjects. Acta Otololaryngol 2005; 125: 280-285.
148. Zabara J, Chaffee RB, Tansy JR and Tansy MF. Neuroinhibition in the regulation of emesis. Space Life Sci 1972; 3: 282-92.

9. Summary

In the introductory chapter the importance of congruent sensory function is emphasized and especially how this relates to vestibular functioning in health and disease. The focus is laid on motion sickness and chronic peripheral vestibular disease. In these areas we see that people habituate to the new situation, which is also called equilibrium reprocessing. Focus in this thesis was laid on the potential respiratory impact on motion sickness and the possible consequences for the design of military motion sickness desensitization programs. Furthermore, it is hypothesized that these principles of military motion sickness desensitization might be transferred to the treatment of vestibular disease. In fact, this approach for motion sickness desensitization and vertigo treatment could be summarized as Motion-based Equilibrium Reprocessing Therapy.

In chapter 2 cardiorespiratory parameters on a rotating chair are investigated as the fore-aft torso movements are part of the motion sickness desensitization programs and respiratory relaxation techniques are applied successfully in these courses. It is hypothesized whether these repetitive trunk movements by themselves may induce hyperventilation and consequently add to the motion sickness. The hyperventilation provocation test, performed prior to the actual experiment, did not result in nausea. During the rotation of the chair none of the cardiorespiratory parameters was significantly different from baseline measures. On an individual level, however, sustained hyperventilation was seen. The findings show that hyperventilation is not the main cause of nausea during Coriolis effects on a rotating chair. It is concluded that measuring cardiorespiratory parameters is not necessary during motion sickness desensitization programs, but as hyperventilation does occur on an individual basis it is advised to pay attention to respiratory parameters.

In chapter 3 the effect of alignment to the gravito-Intertial Force (GIF) on the development of motion sickness during low-frequency horizontal motion was investigated. Subjects were seated on the ESA-sled while a sinusoidal movement (0.176 Hz) across the 6 m long track was performed. There were three experimental conditions in which the ESA-sled cabin was either not, partially or fully compensated for the GIF. There were no significant differences between the conditions, although a survival series pointed towards a possible temporary protection for the development of motion sickness in the condition that partially compensated for the GIF. An analysis of predictive values revealed that initial symptoms (but no nausea) or absence of these initial symptoms early in the runs predicted the occurrence or absence of nausea during the experiment. It was concluded that there seems to be a rationale to partially compensate for the GIF while trying to prevent motion sickness. Lastly, a significant drop in relative end-tidal CO_2 levels is seen. It is hypothesized that this might be a sign for pulmonary compensation for the nauseating stimulus.

In chapter 4 the 6DoF DESDEMONA motion platform was used to investigate the role of the frequency of oscillatory linear motion on the development of motion sickness, the impact on respiratory variables and the occurrence of enforced breathing due to

the motion stimulus. A special interest went out to the relative high motion sickness incidence found in the literature at 0.167 Hz as normal breathing frequency is close to this frequency. The results show that with increasing stimulus frequency (0.05 Hz- 0.8 Hz) an increased likelihood for synchronization of the breathing frequency with the stimulus frequency seems to be present. With increasing stimulus frequency a steady increasing drop in end-tidal CO_2 levels is seen. Also there seems to be a maximum incidence of motion sickness around the 0.2 Hz range and this is in accordance with the available literature. It is concluded that the high motion sickness incidence at 0.167 Hz is not due to enforced breathing, since enforced breathing increases with higher stimulus frequencies. At an individual level it was seen that an induced hyperventilatory response through the motion stimulus can result in 'sickness during motion' and it is stressed out that this should not be confused with motion sickness.

In chapter 5 the 6DoF CAREN motion platform was used to investigate the possibilities to extrapolate principles of military aviation vestibular desensitization programs to chronic peripheral vestibular disease. Preliminary results of the Motion-based Equilibrium Reprocessing Therapy are presented. Patients were exposed to sinusoidal vertical passive whole body motion in increasing intensity for a maximum of 10 sessions. The therapy was well tolerated and a dramatic symptom change occurred. Subjects experienced less handicap and an increase in level of functioning.

In chapter 6 the extended possibilities of the CAREN motion platform were used to qualitatively and quantitatively investigate the influence of optokinetic roll stimuli on walking stability. In front of the subjects a virtual roll dome was projected on a 6 m 180° field-of-view screen. Subjects walked at a constant speed. Subjects experienced severe gait disturbances, tilt and an impossibility to compensate for the roll stimulus. It is concluded that optokinetic roll stimuli decrease walking stability and most probably increase the risk of falling. This study also demonstrates the importance of well-calibrated visual stimuli while using simulation techniques within the field of rehabilitation.

In Chapter 7 the results of the thesis are put in perspective and future prospects are given. It is concluded that the peak motion sickness incidence seen at 0.2 Hz is not due to enforced breathing. The financial and practical reasons why a follow-up study at larger g-levels is not possible in the near future are discussed. Furthermore it is advised to substantiate the results of Motion-based Equilibrium Reprocessing Therapy in a larger study, preferably a randomized clinical trial. As the use of virtual reality in rehabilitation practice becomes more common important aspects of successful use of virtual reality are highlighted. Lastly, the reasons why a combined transdisciplinary approach in vestibular research should be strived for is stressed out.

9.1 Samenvatting

In het inleidende hoofdstuk wordt het belang van congruente zintuiglijke informatie benadrukt en vooral hoe dit zich verhoudt met betrekking tot het functioneren van het gezonde vestibulaire systeem buiten de dagelijkse bewegingsenvelop en van het zieke vestibulaire systeem binnen de dagelijkse bewegingsenvelop. De focus wordt dus gelegd op bewegingsziekte en op chronische perifeer vestibulaire aandoeningen. In beide omstandigheden passen mensen zich aan de nieuwe situatie aan en dit wordt ook wel equilibrium reprocessing genoemd. De nadruk in dit proefschrift is gelegd op potentiële respiratoire effecten op bewegingsziekte en de mogelijke gevolgen hiervan voor militaire bewegingsziekte desensitisatie programma's. En vervolgens is gekeken of de principes van deze desensitisatie programma's voor de behandeling van vestibulaire aandoeningen ingezet kunnen worden. Een dergelijke benadering voor de desensitisatie van bewegingsziekte en vertigo-behandeling kan men vangen onder de benaming Motion-based Equilibrium Reprocessing Therapy.

In hoofdstuk 2 zijn cardiorespiratoire parameters onderzocht bij bewegingen zoals die tijdens het desensitisatieprotocol succesvol toegepast worden. De vraag was of het repetitief vooroverbuigen van de torso op de ronddraaiende draaistoel de ademhaling negatief zou beïnvloeden door het veroorzaken van een hyperventilatoire respons en zodoende zou bijdragen aan de optredende bewegingsziekte. De vóór het eigenlijke experiment verrichte hyperventilatieprovocatietest resulteerde niet in misselijkheid, en tijdens het experiment op de draaistoel waren geen van de cardiorespiratoire parameters significant verschillend van de rustparameters. Op individueel niveau echter werd volgehouden hyperventilatie waargenomen. De bevindingen laten zien dat hyperventilatie niet de hoofdoorzaak is van misselijkheid tijdens Coriolis effecten op een draaistoel. Geconcludeerd wordt dat het meten van cardiorespiratoire parameters niet nodig is tijdens bewegingsziekte desensitisatieprogramma's, maar aangezien hyperventilatie op individuele basis voorkomt wordt geadviseerd wel aandacht voor de ademhaling te hebben.

In het derde hoofdstuk wordt het effect van het uitlijnen van de gravito-inertiële kracht (GIK) tijdens laagfrequente horizontale oscillerende bewegingen op de ontwikkeling van bewegingsziekte onderzocht. Proefpersonen namen plaats op de ESA-slee en werden blootgesteld aan een sinusoïdale beweging (0,176 Hz) op een ca. 6 meter lange baan. De uitlijning tijdens het experiment omvatte drie experimentele condities, te weten geen, gedeeltelijke en volledige uitlijning. Significante verschillen tussen de condities werden niet gevonden, hoewel een overlevingscurve in de richting wees van een tijdelijke bescherming tegen bewegingsziekte voor de conditie met gedeeltelijke uitlijning. Een analyse van voorspellende waarden bracht naar voren dat vroeg optreden of afwezig zijn van initiële symptomen (zonder misselijkheid) of de

afwezigheid van deze initiële symptomen het optreden van misselijkheid tijdens het experiment kon voorspellen. Er werd geconcludeerd dat een rationale bestaat voor het gedeeltelijk compenseren voor de GIK om bewegingsziekte te voorkomen. Tenslotte, een significante afname in relatieve eindteug CO_2 niveaus wordt gezien. Verondersteld wordt dat dit een teken voor pulmonale compensatie voor de misselijkmakende stimulus kan zijn.

In het vierde hoofdstuk werd met gebruikmaking van het 6-vrijheidsgraden bewegingsplatform DESDEMONA het volgende onderzocht: de invloed van de bewegingsfrequentie van een oscillerende lineaire beweging op het ontstaan van bewegingsziekte, de impact op respiratoire variabelen, waaronder het optreden van door de beweging veroorzaakte beïnvloeding van de ademhalingsfrequentie. Bijzondere aandacht is uitgegaan naar de relatief hoge incidentie van bewegingsziekte rond het 0,167 Hz gebied, aangezien de normale adehamhalingsfrequentie dichtbij deze frequentie ligt. De resultaten laten zien dat met toenemende stimulusfrequentie (0,05 Hz-0,8 Hz) een toenemende waarschijnlijkheid is dat synchronisatie van de ademhaling met de stimulusfrequentie zal optreden. Ook wordt met toenemende stimulusfrequentie een toenemende daling van de eind-teug CO_2 niveaus gezien. Daarnaast lijkt een maximum incidentie van bewegingsziekte rond het 0,2 Hz gebied te liggen en dit is in overeenstemming met de aanwezige literatuur. Geconcludeerd wordt dat de hoge bewegingsziekte incidentie rond 0,167 Hz niet het gevolg is van een door de beweging opgelegde ademhaling, aangezien een opgelegde ademhaling juist bij hogere bewegingsfrequenties optreedt. Op individueel niveau wordt gezien dat een door de bewegingsstimulus geïnduceerde hyperventilatoire respons kan resulteren in 'ziekte tijdens bewegen', waarbij benadrukt wordt dat dit niet verward dient te worden met bewegingsziekte.

In het vijfde hoofdstuk worden met het 6-vrijheidsgraden bewegingsplatform CAREN de mogelijkheden onderzocht voor het extrapoleren van principes van de in de militaire luchtvaart gebruikte vestibulaire desensitisatie programma's voor de behandeling van perifeer vestibulaire aandoeningen. De eerste resultaten van de Motion-based Equilibrium Reprocessing Therapy worden gepresenteerd. Patiënten werden blootgesteld aan maximaal tien sessies van, in toenemende intensiteit, sinusoïdale verticale passieve bewegingen van het gehele lichaam. De therapie werd goed verdragen en de eerste resultaten zijn zeer positief te noemen. De patiënten ervoeren nadien minder klachten en beperkingen en vertoonden een toename in niveau van functioneren.

In hoofdstuk 6 worden de uitgebreide mogelijkheden van het CAREN systeem gebruikt om kwalitatief en kwantitatief het effect van optokinetische rolstimuli op loopstabiliteit te onderzoeken. Voor de proefpersonen werd op een 6 meter breed scherm met een

gezichtveld van 180 graden een virtuele roll-dome geprojecteerd. De proefpersonen liepen met een vaste loopsnelheid en ervoeren duidelijke loopstoornissen, 'tilt' en een onmogelijkheid om de rolstimulus adequaat te compenseren. Geconcludeerd wordt dat optokinetische rolstimuli de loopstabiliteit verminderen en hoogstwaarschijnlijk het risico op vallen doen toenemen. Dit onderzoek demonstreert tevens het belang van adequate visuele stimuli bij het gebruik van simulatietechnieken binnen de revalidatie.

In hoofdstuk 7 worden de resultaten van het proefschrift in perspectief geplaatst en toekomstige vooruitzichten geschetst. Geconcludeerd wordt dat de piek die rond 0,2 Hz in bewegingsziekte-incidentie wordt gezien niet het gevolg is van een opgelegde ademhaling. De financiële en praktische redenen waarom een vervolgstudie in de nabije toekomst niet mogelijk is worden besproken. Daarnaast wordt geadviseerd om van de Motion-based Equilibrium Reprocessing Therapy een grotere studie te verrichten en bij voorkeur een klinisch experiment. Aangezien het gebruik van virtual reality in de revalidatiepraktijk gewoner wordt, worden belangrijke aspecten voor het succesvol toepassen ervan belicht. Tenslotte worden redenen gegeven waarom gestreefd zou dienen te worden naar een transdisicplinaire benadering van vestibulair onderzoek.

9.2 Özet

İlk bölüm uyumlu sensorik bilgi önemini ifade edip ve daha çok bunun sağlık ve hasta vestibuler fonksiyonla ilişkisini gösterir. Hareket hastalığı (yol tutması) ve kronik periferik vestibuler hastalıkları odak içine alınmıştır. Bu durumlarda insanların yeni duruma adapte edildiği görülür ve buna "Equilibrium Reprocessing" ile tabir edilir. Bu tez, hareket hastalığının potansiyel solunum etkisini ve bunun askeri hareket hastalığı desensitizasyonuna olabilen etkileri vurgular. Ayrıca, bu ilkelerin vestibuler hastalıklar tedavisinde' de uygulanması hipotez edilir. İncelendiğinde, hareket hastalığı desensitizasiyonu ve baş dönmesine bu tür bir yaklaşımla, Motion- based Equilibrium Reprocessing Therapy olarak özetlenebilir.

İkinci bölüm dönen sandalye deneyiminin kardiyorespiratuar parametrelerini araştırır, çünkü dönerken ileri geri hareketleri ve solunum egzersizleri hareket hastalığı desensitizasyon programı içerisinde başarıyla uygulanmaktadır. Bu tekrarlı dönme hareketinin kendisi hiperventilasyon oluşturup hareket hastalığının semptomlarına katkıda bulunması hipotez edilir. Gerçek deneyimden önce yapılan hiperventilasyon provokasyon testi mide bulantısı göstermemiştir. Dönen sandalye deneyiminin kardiyorespiratuar parametreleri, sakin kardiyorespiratuar parametrelerden önemli bir fark ifade etmez. Bireysel düzeyde hiperventilasyon tespitlenmiştir. Sonuçlar hiperventilasyonun Karolis etkilerinin ana sebebi olmadığını gösterir.

Sonuçta kardiyorespiratuar parametrelerinin ölçümünün hareket hastalığı desensitizasyon programında gereksiz olarak görülür ancak bireysel düzeyde hiperventilasyon tespiti, solunuma dikkat önerilir.

Üçüncü bölüm hareket hastalığının oluşmasında düşük frekans ileri geri hareketlerinde gravatif atıl gücünün hizalanmasının etkisini araştırır. Test adayları ESA kızağında altı metrelik bir pist üzerinde sinüs hareketine (0.176 Hz) konulur. Bu deneyimde hizalamak üç araştırma koşulu kapsar: hiç hizalanmamış, yarım ve tam hizalanmış. Bu kondisyonlar arasında önemli fark bulunmamıştır ancak yarım hizalanmış deneyimler hareket hastalığına karşı geçici bir koruma sağlar. Prediktif değer araştırması erken yada hiç başlangıç semptomlarının bulunmaması bu deneyimde mide bulantısının tahmin edebildiğini öne sürer. Kısmen gravatif atıl gücünün tazminatı hareket hastalığının önlenmesinde ilişkilidir. Son olarak tidal-volüm sonrası CO_2 düzeyinde önemli bir iniş görülür. Hipoteze göre, bu veriler pulmonal tazminatın mide bulantısını önlediğine dahil varsayımdır.

Dördüncü bölüm DESDEMONA 6 serbestlik derecesi hareket platformu ile sonrakileri araştırır: doğrusal titreşimde hareket frekansı hareket hastalığının oluşmasını ve nefes frekansı ve nasıl diğer respiratuar değişkenleri etkilediğini. Normal nefes frekansının

etrafında, 0.167 Hz alanında görülen hareket hastalığının yüksek vakaları özel önem verildi. Sonuçlar yükselen uyarım frekansı (0.05 Hz - 0.8 Hz) ile nefes frekansının senkronizasyonu ihtimalinin yükseldiğini gösterir. Ayni zamanda uyarım frekansının yükselmesi tidal volüm sonrası CO_2 düzeyinde düşüklük gösterir. Bunun dışında hareket hastalığının maksimum vakaları 0.2 Hz alanında ispatlanır ve bu şimdiye dek yayınlanan makalelere eşittir. Hareket hastalığının 0.167 Hz civarındaki yüksek vakaları, hareketin empoze ettiği nefes frekansınla ilişkili almadığı sonuçlandırılır, çünkü nefes frekansı devamlı hareket frekansı ile yükselir. Hareket uyarım bireysel düzeyde empoze ettiği hiperventilasyon "hareket esnasında hastalık" gösterir ancak bunu hareket hastalığı ile karıştırılmaması vurgulanır.

Beşinci bölüm CAREN 6 serbestlik derecesi hareket platformuyla askeri havacılıkta kullanılan hareket hastalığına karşı vestibuler desensitizasyon programlarının prensipleriyle periferik vestibuler patolojiler tedavi uygulamak imkanlarını araştırır. Motion-based Equilibrium Reprocessing Therapy tedavisinin ilk sonuçları sunulur. Hastalara yükselen keskinlikle en azami on oturum, tüm vücutları ile dikey sinüsoidal pasif hareketler yaptırılır. Tedavi iyi tolere edilmiştir ve ilk sonuçlar çok pozitif olduğu söylenebilir.
Hastalar daha az şikayet ve kısıtlamalar yaşar ve daha yüksek fonksiyon derecesi gösterir.

Altıncı bölüm CAREN sisteminin genişletilmiş imkanları kullanılarak optokinetik rolleri uyarımının yürüme stabilize üzerindeki kantitatif ve kalitatif etkilerini araştırır. Test adaylarına 180 derece görüş alanı ile 6 metre büyüklüğünde bir ekranın üzerine sanal 'roll-dome' proje edilir. Test adayları sabit bir tempoyla yürür ve yürümekte zorluk,eğim ve dönüş uyarımının karşılamak imkansızlığını yaşar. Optakinetik dönüş uyarımının yürüme stabilizasyonunu düşürür ve büyük bir olasılıkla düşme riskinin yükseltir. Bu araştırma aynı zamanda görsel uyarımının rehabilitasyondaki sanal tekniğinin vurgular.

Yedinci bölüm bu tezin sonuçlarını perspektif içerisine alır ve ileriye dönük görüşleri çizer. Hareket hastalığının 0.2 Hz civarındaki yüksek vakaları, hareketin empoze ettiği nefes frekansının sonucu olmadığı sonuçlandırılır. Bir izlen çalışmasının yakın gelecekte mali ve pratik nedenlerden dolayı imkansızlığı tartışılır. Bunun dışında 'Motion-based Equilibrium Reprocessing Therapy' tedavisinin daha büyük bir çalışma ile yahut bilimsel bir deneyle araştırılması önerilir. Sanal gerçeklik kullanımı rehabilitasyon kliniğinde kullanıldığı için, önemli yönleri ve başarılı kullanılışı vurgulanır. Son olarak vestibuler araştırmaların trans-disipliner yaklaşımının önemi belirtilir.

Dankwoord

Hoe ver moet je teruggaan in de tijd om mensen te bedanken? Mijn ouders, in ieder geval omdat ze ongeveer veertig jaar geleden uit een onbeduidend dorpje in Noordoost Turkije zijn vertrokken voor een ongewis avontuur. En om talloos andere redenen. Misschien zelfs mijn grootouders omdat ze uiteindelijk accepteerden dat het land niet meer door mijn ouders bewerkt zou hoeven worden.

Misschien moet ik ook wel de NS of Deutsche Bahn bedanken voor het feit dat mijn lieve Astrid meer dan tien jaar geleden tijdens een treinvakantie in mijn leven kwam. Ondertussen is het een heel fantastische rit met mooie vergezichten geworden met een dochtertje die ondanks haar geringe leeftijd ook een dankwoordje verdient. Isis, bedankt voor het verruimen van mijn horizon met de Jellabies, Nijntje en K3. De mediterende en stimulerende werking ervan mag niet onderschat worden. Hoe dan ook hebben de afgelopen jaren, waarin het proefschrift 'tussen de bedrijven door' tot stand is gekomen veel invloed gehad en je liefde, steun en toewijding waren onontbeerlijk.

Over Wim Bles kan ik veel schrijven, misschien zelfs een hoofdstuk in mijn proefschrift eraan wijden, maar waar te starten? Waarschijnlijk met een titel als "Hoe één man de verticaal subjectief maakte" of "Het motiveren van een vliegerarts tot het monnikenwerk van een proefschrift" of misschien wel "Het leven begint pas na je pensioen". In de tekst zouden dan dingen dienen te staan over humor, kritische blik, boven de stof staan en vriend. Het is duidelijk dat het zonder hem niet was gelukt.

Prof René Leemans, mijn promotor en prof Jelte Bos, mijn mede co-promotor, ook jullie bedankt voor het mogelijk maken van de wetenschappelijke promotie en voor het kritisch meedenken over de inhoud ervan.

Een woord van dank dient ook uit te gaan naar Felix van Hootegem, lkol-vliegerarts b.d., die als leidinggevende mij in staat wilde stellen om bij TNO onderzoek te gaan doen en in de beginfase van groot belang is geweest voor het onderzoek. Ook de kolonel-vliegerarts John van der Hoorn en kolonel-vliegerarts b.d. Willem Tielemans voor het steunen van mijn onderzoek en ook om experimenten op DESDEMONA mogelijk te maken.

Niet te vergeten mijn huidige collega's, het hoofd revalidatiezorg luitenant-kolonel Kees van Leeuwen en de commandant luitenant-kolonel Jos van 't Root van het Militair Revalidatiecentrum die mijn ambities om onderzoek te doen naar virtual reality binnen de revalidatie stimuleren.

Een speciaal woord van dank dient uit te gaan naar de kolonel-arts b.d. Willem Wertheim, die een belangrijke motor is geweest om het CAREN systeem naar het MRC te halen: In eerste instantie uiteraard voor de innovatieve behandeling van de militaire patiënt, maar onbedoeld maakte het de weg vrij voor de laatste twee hoofdstukken van het proefschrift en bood het de mogelijkheid een bijzondere onderzoekslijn op het gebied van virtual reality en revalidatie op te zetten.

Tessa Frunt en Roos vd Lint dienen in dit verband niet vergeten te worden. Tessa bedankt voor het programmeren van, de inmiddels vele, applicaties voor het CAREN systeem. Roos bedankt voor je optreden als operator en soms ook als proefpersoon 0 bij de uitvoering van de nieuwe applicaties. Ook bedankt dat je de uitspraak “en zo is het” op waarde weet te schatten.

Ook wil ik Vedat Topsakal, KNO-arts in het UMC Utrecht, en Ayhan Sik bedanken voor hun actieve inzet voor het mogelijk maken van een Turkse samenvatting.

Marlies Diederen verdient een speciaal woord van dank omdat zij het proefschrift heeft voorzien van hele mooie illustraties. De kunstwerkjes maken het proefschrift helemaal af. Het zijn de kersen op de taart. Superbedankt daarvoor!

Ook wil ik graag mijn vrienden, broer en zus bedanken, gewoon omdat ze er zijn.

Curriculum Vitae

Agali Mert was born March 5th 1973 in Eindhoven, The Netherlands and lived in Best where he went to "Heydonck" primary school and the Heerbeeck college high-school. After finishing high-school in 1991 he went to Maastricht University to study Health Sciences. In 1993 he also started going to Medical School at Maastricht University. After finishing his master in Health Sciences in 1996 and Medical School in 1999, he started working as a physician for the Royal Netherlands Air Force (RNLAF). He enrolled for his military specialist training at the Royal Military Academy in 2000. After finishing his flight-surgeon education at Brooke's Air Force base in San Antonio, Texas USA, he started working at the primary health center at the HQ of the RNLAF. In 2002 and 2003 he was deployed in Kirgizstan and Iraq respectively. In that period he also started doing research at TNO Soesterberg. In 2005, being a major, he applied for his medical specialist training in Physical Medicine and Rehabilitation. He finished his training in 2009 at de Hoogstraat, Utrecht, and started working as a PM&R specialist at the Military Rehabilitation Center Aardenburg in Doorn. He is responsible for the orthopedic rehabilitation at the center and also for research on virtual reality for the benefit of the military patient.