Vestibular adaptation to an altered gravitational environment:

Consequences for spatial orientation

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The cover shows a micro CT-scan of a human labyrinth, with the utricular macula in blue and the saccular macula in orange. Courtesy of Hilal Uzun, Allan Jones and Ian Curthoys from the University of Sydney, Australia.

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Contents

Chapter 1

General Introduction

Earth's gravity is an omnipresent factor in human life and provides a strong reference for spatial orientation. It is proposed that a change in this 'background' stimulation requires neuro-vestibular adaptation, including a re-evaluation of this gravitational reference. A persisting change in gravity level is obtained during the weightlessness condition of space flight or when entering another Planet's gravity field, like that of Mars. It can, however, also be induced by a human centrifuge, where the gravito-inertial force level exceeds Earth's gravity. In this thesis the paradigm of sustained centrifugation is used to investigate adaptation to altered gravity levels. This chapter provides a general introduction into the consequences of these gravity transitions and presents a framework to understand these adaptation processes.

Gravity affects our lives more than we think. But because of its ubiquitous nature, we are mostly not aware of this constant force 'pulling everything down'. From the day we are born (and even before that), we have learned to act within the Earth's gravitational field. Although the direction in which the gravitational acceleration acts upon our body varied over time, – depending on our body posture – its magnitude was constant: about 9.8 m/s^2 at the Earth's surface. Gravity has become an omnipresent factor in our behaviour and numerous processes in our body are regulated or affected by gravity; from spatial orientation to blood pressure regulation and bone formation. With gravity being so influential, it may come as a surprise that we do not possess a sense-organ that is sensitive *solely* to the gravitational acceleration. Moreover, this would be impossible because gravitational acceleration is physically indistinguishable from inertial acceleration due to self motion (Einstein's Equivalence principle). Our central nervous system uses additional information to make an estimate of the magnitude and direction of the gravitational part and the inertial part, in order to generate appropriate responses (e.g., for postural control). This process will be explained in more detail below. For now it is sufficient to state that under 'natural' circumstances these estimates are optimal, but outside the natural range the brain comes up with non-veridical solutions leading to several vestibular illusions.

What happens if a constant 'background' force is absent?[1] It is in a condition of persisting weightlessness where we really come to appreciate the fact that we, humans, are 'Earth-like'. Imagine you are orbiting the Earth in a spacecraft: everything that is not attached to an anchored structure – including you – floats. The condition of weightlessness disturbs your vestibular system and, relatedly, your spatial orientation. Moving your head may cause nausea and visual illusions, while finding your way through the spacecraft is not easy, since up, down, left and right are less well defined. So may the same compartment seem unfamiliar to

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[1] It is a common misconception that gravity is absent in space. In fact, at 400 km above the planet, where the International Space Station (ISS) orbits, the gravitational field is only about 12% less than at the Earth's surface. It is in fact gravity that keeps the ISS in its orbit: There is a delicate balance between gravity, the distance at which the ISS orbits (about 400 km from the Earth's surface), and the tangential velocity of the ISS (about 7.7 km/s!). That we experience weightlessness in orbit is because the gravitational acceleration acting on the body's various graviceptors is counteracted by the centripetal acceleration of the rotary motion of the ISS. Although strictly speaking incorrect, in this thesis the terms 'microgravity' and '0G' are used to refer to this state of weightlessness.

you when you enter it in another orientation with respect to the surroundings. And imagine you enter a compartment where all people appear to be up-side-down relative to you: pretty disturbing!

The body possesses the ability to adapt to this new environment, although it will take a few days. It involves neuro-vestibular adaptation to the new gravitational circumstances, since the majority of the effects of space flight on the human body can be attributed to adaptation of neuro-vestibular reflexes in response to weightlessness (for reviews see e.g. Buckey, 2006; Clarke, 1998b; Clément, 1998; Lackner & DiZio, 2000). Although a minority of the astro- and cosmonauts[2] adapt rather smoothly to the condition of weightlessness, about 50 – 70% experiences problems with spatial orientation (Davis et al., 1988; Matsnev et al., 1983). They experience visual or motion illusions and they suffer from motion sickness (i.e., headache, nausea, vomiting, fatigue, apathy, lethargy; see Davis et al., 1988; Homick, 1979; Matsnev et al., 1983; Oman et al., 1986,). This symptomatology is referred to as Space Motion Sickness (SAS) or, using a more generic term, Space Adaptation Syndrome (SAS)[3]. Head movements are particularly provocative, especially pitch and roll movements (e.g., Graybiel, 1980; Oman et al., 1986; Thornton et al., 1987). That is why many astronauts adopt a movement strategy to move the head en bloc with the body. An excellent review on space motion sickness is provided by Lackner & DiZio (2006)

Gravity, however, strikes back at return to Earth, when many processes that were adapted to weightlessness suddenly are inappropriate because they do not reckon for gravity's pull. Among many other problems, astro- and cosmonauts encounter difficulties with postural

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[2] From now on the term 'astronauts' is used as a generic term for space-travelers from all nationalities.

[3] The term SAS is also used to refer to the complex of symptoms in response to extended weightlessness. This includes space motion sickness but also fluid shifts, renal, cardiovascular, and hematological responses. These latter changes take place in every space traveler, while only about 50-70% of them also suffer from space motion sickness.

balance, gait, gaze control and spatial orientation (e.g., Arrot et al., 1990; Benson, 1987; Black et al., 1995; Glasauer & Mittelstaedt, 1998; Merfeld et al., 1994; 1996b; Paloski et al., 1992; Reschke et al., 1998; Young et al., 1984; 1993). Re-adaptation to Earth's gravity is also – again – characterized by motion sickness (now called 'Earth-sickness') and visual illusions.

This space flight example illustrates that Earth's gravity is anchored in our system but that we are, in principal, able to adapt to other gravitational environments within a certain amount of time. This forms the central tenet in this thesis:

> *A persisting altered gravity level evokes neuro-vestibular adaptation and requires a re-evaluation of the constant level of gravitational acceleration that is present.*

Although the condition of weightlessness is a special case within the gravitational continuum, this tenet appears valid for *any* long lasting alteration in the gravitational environment. That is at least suggested by the findings of the three European D1-astronauts who mentioned close similarities between the symptoms of SAS during space flight and the symptoms they experienced after sustained exposure to a higher gravitational level (i.e., 3G) in a human centrifuge (Ockels et al., 1989; 1990). During centrifugation on Earth the body is exposed to the combination of gravitational and centripetal acceleration that exceeds the magnitude of the gravitational acceleration alone. Interestingly, it was not *during* centrifugation that the symptoms arose (since the astronauts were instructed not to move), but *after* return to the 1G environment. The astronauts then suffered from postural instability, motion sickness and motion illusions, similar to their experiences during and after space flight. This phenomenon has been referred to as 'Sickness Induced by Centrifugation' (SIC). It is important to note that the symptoms of SIC were not evoked by the deceleration of the centrifuge – which can be very nauseating as well – but built up after the stop of centrifugation and, importantly, required body motion. Just as during space flight the symptoms were evoked by head movements, specifically those movements changing the orientation of the head relative to gravity (Ockels et al., 1990, Bles et al., 1997). Although the hypergravity exposure itself lasted for 90 minutes, the aftereffects could last for several hours.

The correspondence between SIC and SAS suggests that the transition from hypergravity to Earth's gravity (i.e., after centrifugation) induces similar symptoms as the transition from Earth's gravity to weightlessness (i.e., during spaceflight). This is underscored by the finding that susceptibility to SIC and SAS are correlated: astro- or cosmonauts susceptible to SAS (i.e., during space flight) also suffered from SIC (i.e., after being exposed to centrifugation on Earth) while the ones unsusceptible to SAS did not suffer from SIC either (Bles et al., 1997). Thus, it is not the microgravity environment per se that is a prerequisite for SAS to occur; rather it seems to be a consequence of the adaptation process that is required to operate under new gravitational demands. Apparently, the body adapts to the new gravitational load during centrifugation, and is thus no longer optimally suited to operate under 1G-circumstances. It seems that the system has to re-evaluate the characteristics of the gravitational background and its impact on spatial orientation and posture. This adaptation process forms the focus of this thesis.

AIM OF THIS THESIS

This thesis will explore adaptation to a persisting altered gravity level, using long duration centrifugation as a research tool. Although it is likely that this stimulus will affect all graviceptors in the human body, this thesis focuses on the role of the vestibular system in adaptation to novel gravitational environments. The following two questions formed the basis of the research that is presented:

Q1. Does the hypergravity exposure affect the internal representation *of gravity?*

Q2. Is sustained exposure to hypergravity characterized by a similar adaptation process as adaptation to microgravity?

These issues will be addressed by studying the after effects of sustained centrifugation, while focusing on gravity-related responses like the perception of body-attitude, accompanying orienting ocular responses and the occurrence of motion sickness. These findings can then be compared with similar findings during and after space flight. The next section provides a framework for the experiments described in the later chapters and will explain what is meant by the 'internal representation of gravity'. Adaptation to novel gravitational environments is explained in more detail using an observer model for spatial orientation. The last section of this introduction provides a detailed outline of this thesis.

Investigating these questions is expected to contribute to the fundamental knowledge on the way gravity is dealt with by our central nervous system and how the system reacts when such a constant factor is altered. The study of the effects of sustained centrifugation is also of practical relevance, because astronauts encounter all kinds of gravity transitions during their mission. For instance when entering the gravitational field of the Moon or Mars, when returning to Earth, or when exposed to intermittent artificial gravity during space flight (i.e., on a centrifuge aboard the space station). With the space flights getting longer, exposure to artificial gravity becomes increasingly important to counteract the body's deconditioning. Insight in the adverse effects of gravity transitions will be important for ensuring a mission's safety.

THEORETICAL BACKGROUND

Perception of gravity

Spatial orientation requires an adequate detection or estimation of the body state (how am I oriented, how am I moving?). This is, for instance, important for postural control and for generating appropriate eye movements to keep a stable image of the outer world on the retina during head motion. The most important sensory systems that contribute to spatial orientation are the vestibular, visual, and somatosensory system.

The vestibular system consists of two sets of semicircular canals and two sets of otoliths, located in both inner ears. The semicircular canals are sensitive to rotation. In each ear we have three semicircular canals, which are oriented roughly orthogonal to each other, providing signals related to the three dimensional angular velocity of the head. They show high pass characteristics, in that they respond to changes in angular velocity and not to constant velocity rotation. The otoliths provide signals related to linear acceleration. They consist of the utricle, predominantly sensitive to accelerations in the transverse (head-horizontal) plane, and the saccule, predominantly sensitive to acceleration in the sagittal (head-vertical) plane. The tips of the sensory hair cells of the otoliths are embedded in a layer of crystals (otoconia) and the mass of these crystals makes the hair cells bend during a linear acceleration, generating a sensory response.

Apart from the vestibular system, there are two other important sources of information that contribute to spatial orientation: the visual system and the somatosensory system. The visual system provides information about body motion and attitude in the form of optic flow specifying visual motion, and frame and polarity information specifying visual orientation (see Howard, 1982). The somatosensory system, also referred to as a non-vestibular graviceptor, is assumed to contribute to orientation perception in two ways. First, the kidneys are proposed to be sensitive to linear acceleration, and second the vascular system is proposed to be involved via mechanoreceptors in the structures that support the large vessels (Mittelstaedt, 1996).

As mentioned earlier, acceleration due to gravity is physically indistinguishable from acceleration due to motion (Einstein's equivalence principle). That is why we speak of *gravito-inertial* acceleration. Related to this is the so called *tilt-translation ambiguity*. Taking the otoliths as an example, this refers to the fact that any response of the hair cells can always be caused by translational motion and/or by head tilt (see Figure

1.1).

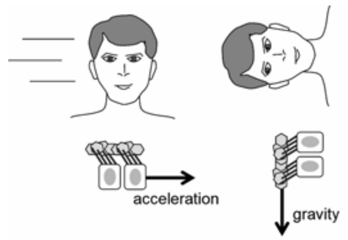

Figure 1.1: Schematic representation of the utricular hair cells with otoconia. Both translation (left) and tilt (right) can induce an equal response of the hair cells.

The resulting otolith signal is thus proportional to the total gravito-inertial acceleration (**f**), which is the sum of gravitational (**g**) and inertial acceleration (**a**):

$$\mathbf{f} = \mathbf{g} + \mathbf{a} \tag{1.1}$$

where bold symbols indicate vectors. On Earth, the downward force of gravity acting on the otoconia is thus equivalent to an *upward* acceleration of the head in the absence of gravity (that is why the acceleration due to gravity acting on the otoliths is pointing upwards, having a positive sign, and not downwards, having a negative sign). To obtain an estimate of the gravitational and inertial acceleration, or, in other words, of tilt and translation, the brain has to use additional information. This is a central issue in spatial orientation and it will also be important for understanding the problems with spatial orientation that occur after gravity transitions.

In 1974, Mayne proposed a solution to this problem that acknowledged the fact that, in an Earth fixed frame of reference, the gravitational acceleration is constant, while inertial accelerations of self-propelled motions have a transient nature. Thus, the gravitational acceleration can be estimated by the low-pass filtered part of the total gravito-inertial acceleration. However, gravity is only constant in an Earth-fixed frame of reference, whereas the neural information comes from sensors in a head-fixed frame of reference. Hence, angular information (from vestibular and/or visual origin) is required to transpose the acceleration information into Earth coordinates before low-pass filtering can be applied. This process can be mathematically formulated by the following differential equation (Glasauer, 1992; Bos & Bles, 2002):

$$\frac{d\mathbf{g}}{dt} = \frac{\mathbf{f} - \mathbf{g}}{\tau_{LP}} - \boldsymbol{\omega} \times \mathbf{g} \qquad (1.2)$$

where $\boldsymbol{\omega}$ is the sensed head angular velocity and τ_{LP} is the time constant of the low pass filter. Solving this equation yields an estimate for **g**, and combining this with Eq. 1.1 yields an estimate for **a**. From Eq. 1.2 it follows that for low frequency movements ($\boldsymbol{\omega} \rightarrow 0$) the estimate of **g** is the low pass response of **f** (first term of Eq. 1.2) whereas for high frequency movements the estimate of **g** is dominated by the second part of Eq. 1.2, and is based on $\boldsymbol{\omega}$. For these frequencies $\boldsymbol{\omega}$ is mainly derived from the semicircular canals (having high-pass characteristics). In order to obtain an estimate of **g** over the whole frequency range, the time constant of the low pass filter, τ_{LP}, has to be in the same order of magnitude as the time constant of the semicircular canals, which is about 4 s in humans (Dai et al., 1999).

Eq. 1.2 also explains the occurrence of several orientation illusions. Without veridical information about angular velocity, the perceived tilt follows low pass characteristics, as is the case in the so-called somatogravic illusion. This illusion can, for example, be experienced by fighter pilots during a catapult-launch. The constant linear acceleration in the horizontal plane together with the gravitational acceleration is interpreted by the brain as ‘gravity’, which induces a sense of tilt when no visual orientation information is present (see Figure 1.2). This illusion can also be experienced during eccentric rotation about a vertical axis, where the centripetal acceleration tilts the gravito-inertial vector in the radial direction, which is perceived as a physical tilt.

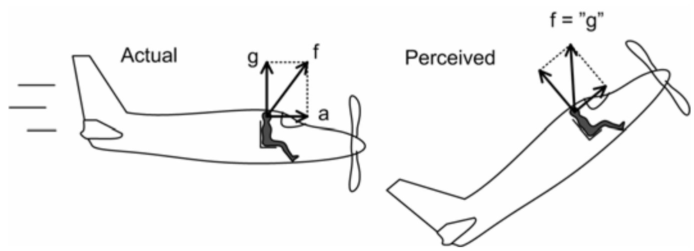

*Figure 1.2: In the somatogravic illusion the total gravito-inertial acceleration **f** is, erroneously, interpreted as gravity, thus inducing a sense of tilt.*

Gravity and motion sickness

The estimate of gravity, or its orientation (further referred to as 'the vertical'), is essential in spatial orientation and also plays an important role in the generation of motion sickness. So is a constant rotation about an Earth vertical axis generally not provocative, whereas rotation about an off-vertical axis is (e.g., Bos et al., 2002; Leger et al., 1981). The fact that after sustained centrifugation only those head movements were provocative that changed the orientation of the head relative to gravity, also illustrates this (Bles et al., 1997). A second aspect involved in motion sickness is expectation: people controlling their own motion, like drivers, usually do not get sick from motion, where passive passengers do (e.g., Rolnick & Lubow, 1991; Stanney & Hash, 1998). And finally, the vestibular system is essential, since people without a functioning inner ear do not get sick from motion (e.g., Irwin, 1881; James, 1882; Money 1970; Reason & Brandt, 1975). These three aspects were combined in the *subjective vertical mismatch* theory on motion sickness (Bles et al., 1998a), which is a refinement of the sensory rearrangement theory of Reason and Brandt (1975). This latter theory proposed that motion sickness was the consequence of a discrepancy between the response pattern stemming from the sense organs and the response pattern that is expected based on past experience (also called 'neural store') Bles and colleagues refined this theory by acknowledging the special role of gravity in motion sickness, and stated that motion sickness was the consequence of a conflict between the vertical based on integrated sensory information and the expected vertical, based on previous experience. The expectation-component was accounted for by using a so-called observer, or internal model, of the sensor dynamics, as first proposed by Oman (1982). The model structure, describing the control of body motion and attitude, is provided in Figure 1.3 (see also Bles et al., 1998a; Bos & Bles, 1998; Bos & Bles 2002). It is related to an earlier model on human spatial orientation presented by Borah and colleagues (1979), using optimal estimation.

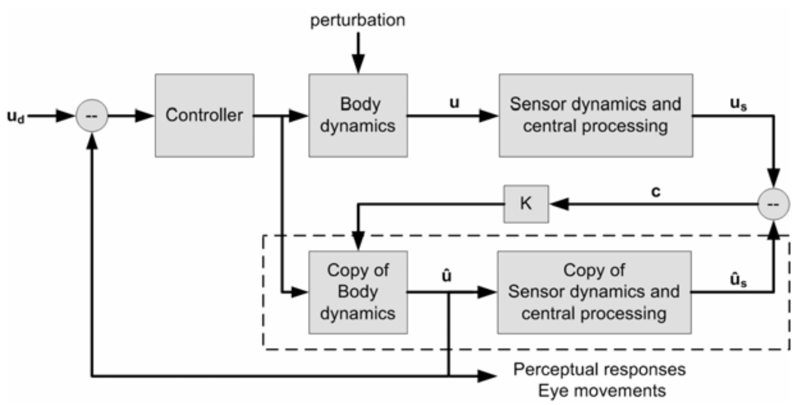

*Figure 1.3: Observer model for spatial orientation. The observer or 'internal model' is indicated by the dashed box. It is proposed that perceptual and ocular responses are derived from an internal estimate of the body state (**û**) instead of sensory output ($\mathbf{u_s}$). The sensory estimates of the body state ($\mathbf{u_s}$) are compared with sensory estimates of the expected body state ($\mathbf{\hat{u}_s}$) to deal with external disturbances. The part of this conflict (**c**) coding for verticality is related to motion sickness.*

To accomplish a certain desired body state, $\mathbf{u_d}$, a set of motor commands is generated by a controller that lead to a certain body state **u**. For an estimate of this body state one could rely on the sensory output $\mathbf{u_s}$, providing an estimate of, e.g., head angular velocity and, via Eq. 1.2, also an estimate of tilt and translation. However, due to neural delays and noisy, imperfect sensors (e.g., the semicircular canals do responding to low frequency rotation) this will yield an imperfect result. A more realistic estimation of the true body state **u** would be the expected body state **û**, obtained by feeding a copy of the input through an exact copy of the body-dynamics. It is assumed that self motion and attitude perception are derived from this expected body state, which includes an internal estimate of gravity. Various eye movements (i.e., reflexive eye movements compensating for head motion) are also assumed to be related to this signal (see e.g. Merfeld, et al. 1993), although recent investigations show that in particular cases perception and eye movements have different dynamics (Merfeld et al., 2005a; 2005b, Wood et al., 2007). To be able to deal with external perturbations acting directly on the body but not on its internal model, this expected state **û** is subsequently fed through an exact copy of the sensor dynamics (plus central processing), leading to a sensed internal estimate $\hat{\mathbf{u}}_s$. In presence of external perturbations, the sensed body state $\mathbf{u}_s$ differs from the sensed internal estimate of the body state $\hat{\mathbf{u}}_s$. This difference (or conflict **c**) is then fed back into the internal model through a gain **K** in order to drive this conflict to zero. **K** is believed to be dependent on the accuracy of $\mathbf{u}_s$: **K** is large when the accuracy of $\mathbf{u}_s$ is high, resulting in fast control loop. This dependence on measurement noise is also a characteristic of optimal estimator models for spatial orientation (Borah et al., 1979). According to the subjective vertical mismatch theory, the difference between sensory and internal model signals coding for verticality is correlated with motion sickness. This model structure proved adequate for modeling sea sickness incidence (Bos & Bles, 1998), but may also be used to explain other kinds of motion sickness, such as cybersickness (Bos et al., 2008).

Internal models in relation to adaptation

The use of an internal model and its expected output has also proven useful in understanding adaptation phenomena. It may be assumed that a persisting conflict triggers our central nervous system to update its internal model in order to reduce the conflict. That happens for instance during disease like an infection of the vestibular nerve: the internal model of the sensor dynamics is no longer adequate, which results in a conflict between the sensed and the expected body state and triggers an immediate sense of dizziness. This sensation fades after several days to weeks, when the internal model parameters have been adequately updated.

How does the model deal with constant 'background' stimuli like the gravitational linear acceleration? An illustrative example is adaptation to a particular wave frequency at sea. During the first days one has to get used to the continuous oscillatory movement caused by the waves, which can be accompanied by sea sickness. It is assumed that after some time this constant pattern of stimulation is 'embedded' in the internal model by updating the expectation pattern. Symptoms of sea sickness then gradually disappear. Once back on land, this expectation pattern is still present but inadequate, often causing motion illusions and motion sickness ('mal de debarquement' or disembarkment syndrome). This requires re-adaptation to the *absence* of this oscillatory linear acceleration.

A similar process is also expected to occur during adaptation to weightlessness. In a microgravity environment, head tilt is no longer accompanied by static otolith stimulation, as it is on Earth. Thus, vestibular signals may have to be centrally re-interpreted (Young et al., 1984) and the astronaut thus has to adapt to an altered sensory response pattern. In other words, the expectation patterns have to be updated. Once that has been done, accompanying symptoms of nausea will also disappear. Back on Earth, however, these new patterns are no longer appropriate and may subsequently cause inadequate responses and 'Earth sickness'. The inappropriate interpretation of otolith signals formed the basis of the so-called 'Otolith-Tilt-Translation-Reinterpretation' (OTTR) theory (Parker et al., 1985; Young et al., 1984), motivated by the finding that astronauts appeared to be more sensitive to linear acceleration than to tilt after space flight (Arrot et al., 1990; Benson, 1987; Merfeld et al., 1994; Merfeld, 1996). Thus, tilt and translation were not appropriately identified (Eq. 1.2).

Given the similarities between SIC and SAS, *it is hypothesized that a similar updating of expectation patterns will also occur during sustained centrifugation* (Q.2). During centrifugation the body is expected to adapt to an increased gravitational reference. Once out of the centrifuge a hyper-G reference is embedded in the expectation pattern, which appears inappropriate for the 1G environment. This may lead to motion sickness, changes in orienting responses and a deteriorated postural stability (e.g. Bles et al., 1997; Bles & De Graaf, 1993; Groen et al., 1996b; Ockels et al, 1990). Thus a second hypothesis is that *sustained centrifugation affects the internal representation of gravity* (Q.1), just as in the case of transitioning to weightlessness. This, in turn, may lead to the responses mentioned above.

Knowledge about these kinds of adaptation processes can be gained by investigating perceptual and ocular responses, which are also the output of the model depicted in Figure 1.3, thus likely sharing the same neuro-vestibular mechanism(s). Motion sickness measures are indicative about the level of mal-adaptation that is still present following centrifugation: if a particular head movement did not cause nausea before centrifugation but does so after, it is clear that the system is not totally re-adapted to the 1G environment.

A last issue that is addressed here is the time scale of these adaptation processes. Adaptation to a novel gravitational background is normally a matter of hours or even days. It cannot go instantly, because it then would make the control of body motion impossible. If we would adapt, for example, within seconds to the state of weightlessness, adaptation would occur every time we jump in the air. As a consequence, we would probably break our legs during landing! This explains why the after-effects of sustained centrifugation, expected to be the result of adaptation, are fundamentally different from the effects of instantaneous gravity transitions as experienced during parabolic or aerobatic flight maneuvers. During these maneuvers the changes in gravitational load last tens of seconds, which is too short for this kind of adaptation to occur. The effects of sustained centrifugation also differ from the motion sickness symptoms that can be caused during deceleration of the centrifuge, where coriolis stimulation may lead to tumbling sensations and nausea. These effects are shortlasting, whereas the symptoms of SIC generally need some time to build up and may last for several hours.

OUTLINE OF THIS THESIS

In this thesis it is investigated whether the effects of sustained centrifugation reflect a similar adaptation process as adaptation to weightlessness. A strong indicator for the similarity between the system's response to these persisting changes in the gravito-inertial force level is that susceptibility to SAS (i.e., after the transition from 1 to 0G) is correlated with susceptibility to SIC (i.e., after the transition from 3 to 1G). This is important because susceptibility to SAS is *not* correlated with susceptibility to other forms of motion sickness (Graybiel 1980; Homick et al., 1987; Oman et al., 1986). *Chapter 2* starts with an introduction into the centrifuge paradigm and the consequences of sustained centrifugation. It continues with a review of the existing data on the relationship between SIC and SAS obtained so far in 8 astronauts. Subsequently, new data is presented on the SIC-SAS relationship in four more astronauts, using a more standardized approach to rate SAS susceptibility. This data on SIC and SAS enables the evaluation of the hypothesis that SIC and SAS suceptibility are correlated.

In addition to investigating the SIC-SAS relationship, many vestibular tests have been performed previously to gain insight into the adaptation process itself, specifically concerning possible changes in the internal representation of gravity. *Chapter 3* presents an overview of the work that was performed previously, complemented with new data of exploratory tests carried out by both astronaut and non-astronaut subjects.

Chapter 4 focuses on the factors driving the adaptation process during sustained centrifugation, by investigating the interaction between exposure time and applied gravito-inertial load (denoted as G-load). The initial astronaut studies (Ockels et al., 1990) already showed that 60 minutes at 3G was sufficient to induce symptoms of SIC, but other researchers showed that symptoms of SIC were also elicited after exposure to 2G for 90 minutes (Albery & Martin, 1996). Chapter 4 describes a study that systematically investigated the effects of different G-loads and exposure durations on SIC severity in 12 non-astronaut subjects. By monitoring the rate of recovery over time, this research also provided insight into the time course of re-adaptation to Earth's gravity.

Apart from assessing the effect of these different centrifuge conditions on SIC-severity, two tests were included that explored the effect of sustained centrifugation on vestibularly driven eye movements. Ocular responses are assumed to be governed more directly by vestibular signals than perceptual measures reflecting the internal estimate of gravity. Three-dimensional eye position is known to be dependent on head orientation, and it was demonstrated by Groen c.s. (1996b) that sustained centrifugation affects this dependence: they observed a decrease in the gain of ocular counter rolling in response to lateral body tilt. In *Chapter 5* this research is extended by investigating three-dimensional eye position during pitch tilt. Eye position is described by the orientation of the so-called Listing's plane (Tweed & Vilis, 1990), which describes the relationship between torsional eye position (i.e., the rotation about the line of sight) and gaze direction during visual fixations and saccades, when the head is stationary. This relationship is altered during pitch tilt, as is reflected in a change in the orientation of Listing's plane (Bockisch and Haslwanter, 2001; Furman and Schor, 2003; Haslwanter et al., 1992; Hess and Angelaki, 2003). In line with the findings of Groen et al. (1996b), it is expected that sustained centrifugation decreases the effect of head tilt on the orientation of Listing's plane. It is furthermore anticipated that the effects of centrifugation on eye movements are larger in itch than in roll, because this is also the direction of the applied G-load during centrifugation.

Chapter 6 focuses on the effect of sustained centrifugation on the interaction between gravity and rotation, which is indispensable for discriminating tilt from translation (see Eq. 1.2). When viewing a visual scene rotating about the longitudinal body axis, the direction of the slow phase eye velocity (optokinetic nystagmus) is not only dependent on the direction of the visual movement but also on the direction of gravity with respect to the head (or its assumed direction): the eye velocity vector orients towards the gravitational vertical. It is generally assumed that this spatial behaviour is caused by the so-called velocity-storage mechanism (Raphan et al., 1979), and, interestingly, this mechanism is also thought to be related to resolving the tilt-translation ambiguity (Green & Angelaki, 2003; 2004). This makes velocity storage relevant within the current context. Earlier research showed that sustained centrifugation affected the temporal characteristics of the velocity storage mechanism (Groen, 1997), now the focus will lie on its spatial characteristics. Specifically, it is expected that sustained centrifugation decreases the tendency of the eye velocity vector towards gravity.

The data presented in Chapters 2-6 show that, although there was a clear distinction between subjects as it comes to SIC-severity (i.e., either you are sick after centrifugation, or not), changes in perceptual and ocular responses were present in *all* subjects. Thus, the two groups of subjects could not be identified based on differences in vestibular responses after centrifugation. In *Chapter 7* it is investigated whether SIC-susceptibility is determined by individual vestibular characteristics. It has long been proposed that a functional asymmetry between the left and right otolith may be one of the factors determining susceptibility for SAS (Von Baumgarten & Thümler, 1979) and this may thus also apply to SIC. Using a newly developed clinical test to assess this otolith asymmetry (Clarke et al., 1996; 1998; 2001; Wetzig et al., 1990; Wuyts et al., 2003), it was investigated whether susceptibility to SIC was correlated with the level of otolith asymmetry or with other vestibular parameters.

In the final chapter of this thesis the data presented in all chapters is summarized, and it will be discussed whether and how these data underscore the hypothesis that sustained centrifugation affects the internal estimate of gravity. It is concluded that sustained centrifugation evokes a central adaptation process that likely affects sensory integration. In addition, it is concluded that SIC and SAS represent a similar form of motion Sickness, underscored by the finding that susceptibility to SIC and SAS are correlated. This makes sustained centrifugation a valuable tool for the training of astronauts.

Chapter 2

The relationship between SIC and SAS susceptibility

This chapter gives an introduction into the procedures of sustained centrifugation and then focuses on the question whether susceptibility to SIC is correlated with susceptibility to SAS. Where in previous studies susceptibility to SAS was rated after the flight, based on the astronauts' recollection, in recent research susceptibility to SIC and to SAS was scored using a similar head movement protocol, which enabled a more objective comparison between SIC and SAS. Using this method, it was shown that SIC- and SAS-susceptibility are correlated, but that the head movements are more provocative in flight than after sustained centrifugation.

That long duration centrifugation led to symptoms of SAS (and was thus denoted by Sickness Induced by Centrifugation, SIC) was actually discovered by chance. In order to investigate the possible effect of hypergravity on the human immune system the Dutch astronaut Wubbo Ockels, who flew on the D1-mission in 1985, participated in some pilot experiments where long duration centrifugation was applied. While such long centrifuge runs had not been reported on in literature, special care was taken to monitor the astronaut's health every 30 minutes. After a total exposure of 90 min to an acceleration of 3G, the astronaut showed readaptation problems that were similar the symptoms of the Space Adaptation Syndrome experienced during his flight. Subsequently, all three European D1-astronauts participated in a 90 min. centrifuge run, and they all perceived the re-adaptation to Earth's gravity after centrifugation as being similar to adaptation to microgravity (Ockels et al., 1989; 1990).

Ockels and his colleagues experienced that head movements were required to induce the symptoms after centrifugation, just as they were in space. They reported that only the slightest pitch head movement triggered strong visual illusions and nausea. This effect was already present after the first 30 minute exposure, but was significantly increased after the second 30 minute exposure. The last 30 minute exposure (thus adding up to 90 minutes in total) did not increase symptom- severity to large extent. The symptoms lasted for several hours after centrifugation. There was only one difference with their space-experiences: after centrifugation only those head movements that changed the orientation of the head relative to gravity (i.e., pitch and roll when erect) while in space yaw movements were also provocative. This special role of gravity in inducing the symptoms already indicates the involvement of the vestibular system in SIC and SAS. Data of these first experiments showed that a cardiovascular cause for SIC was unlikely (Bles et al., 1989; Bles et al., 1997; Ockels et al., 1990).

Also important was that the individual susceptibilities to SAS were reproduced by SIC suceptibility, suggesting that a similar adaptation process is involved in SIC and SAS. This was an important finding, because up till then it was not possible to assess an astronaut's susceptibility to SAS on Earth before space flight. Although SAS was recognized as a form of motion sickness (Graybiel, 1980) many attempts to predict SAS-susceptibility from susceptibility to other forms of motion sickness failed (e.g., Graybiel 1980; Homick et al., 1987; Oman et al., 1986). Astronauts used to be selected based on their relative insusceptibility to Earthly motion sickness, but nevertheless, about half of them still got sick in space.

Taken together, the research paradigm of sustained centrifugation provided opportunities to investigate vestibular adaptation to gravity transitions on Earth, and to further investigate whether SIC and SAS susceptibility were indeed related. It was therefore the start of a new research program that systematically investigated the after-effects of sustained centrifugation in both astronaut and non-astronaut subjects. The current chapter starts with a description of the centrifuge procedures and then focuses on the relationship between SIC and SAS susceptibility by answering the question whether astronauts suffering from SAS during space flight are also the ones who are susceptible to SIC following sustained centrifugation. An overview of the vestibular research elucidating the mechanism underlying SIC and SAS is provided in the next chapter.

SUSTAINED CENTRIFUGATION

All centrifuge runs performed so far have been carried out at the Center for Man in Aviation[4], Soesterberg, The Netherlands. This centrifuge has a free swinging gondola at a radius of 4 m, so that the direction of the gravito-inertial acceleration (GIA) is always directed perpendicular to the gondola floor[5]. During long duration centrifugation a supine position was chosen, resulting in a G_x stimulation (i.e., GIA directed along the naso-occipetal axis) instead of G_z stimulation (i.e., GIA directed along the longitudinal body-axis), which is generally used in aviation. In this way a reduction of cerebral perfusion and excessive pooling of blood in the lower parts of the body was avoided. To enable a supine body position, a mattress was positioned inside the gondola, inclined over an angle of 10º (see Figure 2.1). Due to the limited size of the gondola, the knees were slightly bent in most subjects (feet pointing in the direction of motion). Ample cushioning was provided for support and comfort. Lying in this position, the GIA was predominantly directed in the *x*-direction, along the

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[4] Formally known as the Netherlands Aerospace Medical Centre, or NLRGC.

[5] The acceleration gradient within the gondola in the radial direction is less than 3% and will further be ignored.

naso-occipetal axis. Electrocardiogram was always continuously monitored by a physician during the entire centrifuge run and video and audio contact with the control room was available. The G-load was increased and decreased with a moderate 0.1G/s, in order to minimize nauseogenic tumbling sensations during acceleration and deceleration. To induce a GIA with a magnitude of 3G a centripetal acceleration (a_c) of 2.8G is required and an angular velocity of 151º/s. Astronauts were instructed to refrain from head movements during centrifugation, in order to prevent nausogenic coriolis stimulation.

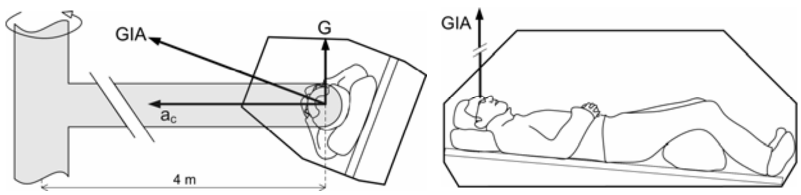

Figure 2.1: The centrifuge gondola swings out during centrifugation, directing the GIA always perpendicular to the gondola floor (see left panel). The subject was lying on a mattress inclined about 10º upwards (see right panel), with the feet pointing in the direction of motion. In this position the GIA was predominantly directed along the naso-occipetal axis.

ARE SIC- AND SAS-SUSCEPTIBILITY CORRELATED?

The relationship between SIC- and SAS-susceptibility has been assessed in a total of 12 astronauts so far. A first group of eight astronauts was tested in the period between 1989 – 1994, as described in Bles et al., 1997. This group included the 3 D1 astronauts who were exposed to a 90 minute centrifuge run at $3G_x$, while the others were exposed to a 60 minute run at $3G_x$. After centrifugation their SIC susceptibility was assessed by means of a head movement protocol: they were to make three head movements about each principal axis (yaw, pitch, roll) and to subsequently rate the experienced level of motion sickness on a 6-point scale (Misery Scale, MISC). In 7 of these eight astronauts their susceptibility to SAS was based on their recollection of symptoms experienced during space flight. In one astronaut a start was made to assess SAS-susceptibility in flight using a similar head movement protocol as used after centrifugation, which enabled a more objective comparison between SIC and SAS. In these eight astronauts a positive correlation between SIC and SAS was demonstrated: *the more they suffered from SAS, the more they suffered from SIC* (Bles et al., 1997).

The second group of four astronauts was tested within the framework of this thesis, in the period between 2003 – 2007. The astronauts participated in different missions (all Russian Soyuz-flights) that were hosted by the European Space Agency (ESA). The experiments were approved by both the TNO and ESA medical ethical boards, and the Russian Space agency. The astronauts gave written informed consent prior to the experiments.

One of the four astronauts already had spaceflight experience, so his susceptibility to SAS was assessed based on his recollection. The other three performed a head movement protocol during flight to assess SAS-susceptibity, and the same protocol was then also used to assess individual susceptibility to SIC after centrifugation. This head movement protocol was part of the Motion Perception questionnaire (MOP, see Figure 2.2), that addressed motion perception (self motion sensations or illusionary motion of the surround) as a consequence of body movements in general, and of head movements in particular. Astronauts were to make 10 self-paced head movements about the yaw, pitch and roll axes ($f \approx 0.25$ Hz, $A \approx \pm 40°$). After each of these stimuli, they described their motion perception and rated any experienced discomfort. The 6-point MISC scale used in the previous astronaut studies was now extended to an 11-point scale, as shown in Table 2.1.

In the ground based part of the experiment, the MOP-questionnaire was filled out just before and after centrifugation (60 min at $3G_x$), and again at two and four hours after the end of centrifugation. All head movements were performed with eyes closed, once while sitting erect and

Motion Perception Questionnaire

You are kindly requested to fill out this questionnaire *at least once a day at the end of the day, but before dinner*. Please write down in your own words whether you experience(d) illusory self and/or surround motion during the past period. Please make explicit note of the following four elements.

1. Did you experience illusory *self motion*?
2. Did you experience illusory *surround motion*?

3a. What is your maximum MISC score? (0 = OK, 10 = vomiting)?
3b. If so, what kind of discomfort did you experience?

4. Which (head)*motions* were most noticeable in these respects?
5. Did you take any anti-motion sickness medication (encircle): Yes / No

If you feel comfortable, you are kindly asked to make some deliberate head movements.

6. Do you object to this for reasons of anticipated discomfort? Yes / No

If Yes, you may skip the remainder of this query.

Please stand (if possible, sit if necessary) and make up to *10 deliberate head movements* over a total *angle of approximately 80º* at a rate of *one cycle per 4 seconds* in *yaw, pitch, and roll*, with your ***eyes open***. Stop whenever you feel uncomfortable. Please answer the following questions.

Yaw

7. What is your MISC score **before** making the yaw head movements? (0 = OK, 10 = vomiting)
8. What is your MISC score **after** making the yaw head movements?
9. Did you experience additional illusory motion? If yes, what kind?
10. How many cycles could you complete (0-10)?
11. Estimate the number of additional cycles you ***could*** have performed before vomiting (encircle): 0 cycles / 1-5 cycles / 6-10 cycles / > 10 cycles

NOTE:
Questions 7 to 11 are repeated for pitch and roll (Q12 – Q21). The order in which the head movements are requested is randomized.

22. Which head movements were **most** provoking? yaw / pitch / roll / N.A.
23. Which head movements were **least** provoking? yaw / pitch / roll / N.A.

END OF QUESTIONNAIRE

Figure 2.2: Questions addressed in the MOP-Questionnaire. The original questionnaire also provided drawings of the requested head movements and the MISC-scale (see Table 2.1).

once while lying in a supine position.

During spaceflight, the astronauts completed the MOP-questionnaire daily (at the end of each day) from 2 days before the launch (denoted by L–2), until at least flight day 7 (denoted by FD7), and subsequently from the day of return (R+0) until six days later (R+6). Because the effects were expected to be largest right after launch and landing, one additional questionnaire was requested as soon as possible on FD1 and on R+0. In order to prevent serious sickness caused by the inflight head movement protocol, astronauts were instructed to stop the experiment as soon as they reached MISC 8: severe nausea. During one mission the maximum amount of head movements per axis was restricted to three (in both the inflight and ground-based testing), whereas during the other missions 10 head movements were requested about each principal axis. Astronauts were considered to suffer from SIC or SAS if they scored 5 or higher on the 11-point MISC.

TABLE 2.1
Misery scale (MISC)

Symptom	Rating
No problems	0
Stuffy or uneasy feeling in the head	1 or 2
Stomach discomfort	3 or 4
Nauseated	5 or 6
Very nauseated	7 or 8
Retching	9
Vomiting	10

Results

The data of this second astronaut group showed that two of the four were not suffering from SAS and not from SIC. The other two developed symptoms, both in space and following sustained centrifugation. The severity of the symptoms was, however, different for SIC and SAS. Figure 2.3 gives an overview of the collected MISC scores, where the astronauts are denoted by *A1 – A4*.

Whereas astronaut *A1* did not suffer from SAS during his flight, astronaut *A2* was seriously affected by the head movements early in flight. The actual number of performed head movements (maximal 10) was inversely related to the MISC score (Spearman rank correlation= –0.72, $p<.05$), but he was able to perform the protocol at FD6 without serious problems. Astronaut *A3* was requested to make only three head movements, and he started with low MISC scores right after launch. However, he was unable to do the experiment again that day due to severe nausea, which was also the case on FD2. He later reported that, from FD3 on, normal daily activities were not really disturbing, but passive 360º body turns that were part of another scientific experiment were very provocative. This suggested that this astronaut was susceptible to SAS, despite his relatively low MISC scores. During the other flight days (3, 6, 7) astronaut *A3* was able to perform the requested head movements without serious problems. These latter two astronauts also experienced serious symptoms on the day of return (R+0). Astronaut A4, who rated his SAS-susceptibility based on his recollection, mentioned that he did not suffer from any symptoms during his spaceflight, except for one single episode of instantaneous vomiting, without preceeding symptoms of nausea. From these data is is concluded that astronauts *A1* and *A4* were considered unsusceptible to SAS, whereas astronauts *A2* and *A3* were considered susceptible.

Before addressing the data on SIC, it is noted that astronaut *A2* rated all head movements as equally provocative during flight, whereas astronaut *A3* showed minor differences between the effects of head movements. He rated yaw as least provocative, and roll as most provocative. Because this was also the order in which the head movements were performed by this astronaut, this could reflect an order-effect. To account for this, the order of the head movements was randomized in the following missions. Notably, right after landing both astronauts rated all head movements equally provocative.

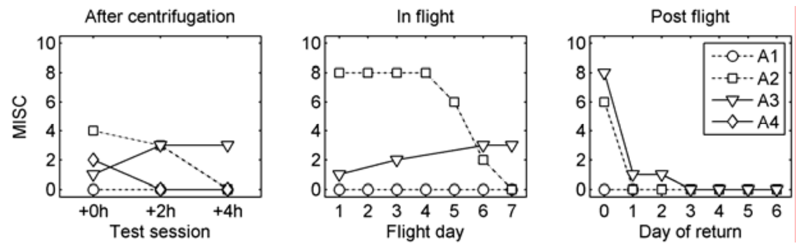

Figure 2.3: MISC scores (maximum from the yaw-, pitch, and roll-score) as elicited by the head movement protocol for the three astronauts, after centrifugation (left panel), in flight (middle panel) and post flight (right panel). No inflight or postflight data was available for astronaut A4. Note that astronaut A3 was not able to perform the head movements on FD2, 4, and 5 due to nausea and that his head movement protocol was restricted to three head movements instead of 10. MISC scores before centrifugation and before flight were 0 in all astronauts.

The two astronauts who developed (mild) symptoms of SAS during space flight also developed symptoms of SIC after centrifugation (see Figure 2.3, left panel). However, after centrifugation the MISC scores remained relatively low: below MISC5, which was,on forehand, defined as the threshold for SIC susceptibility. This indicates that the effects of head movements were less after centrifugation than in space, especially for astronaut *A2*. Despite of this, Figure 2.3 clearly shows that the two astronauts who scored 'positive' on the MISC (i.e., the headmovements raised the average MISC score) after centrifugation, also scored positive in flight *and* post flight. Vice versa, the astronaut who scored 'negative' on the MISC (i.e., the average MISC score was not raised by the head movements) after centrifugation also scored negative in flight *and* after centrifugation. When the value *1* is assigned to a positive score and the value *0* to a negative score, the chance that this distribution (i.e., three times *1* or three times *0*) appears in three subjects is only 1/64, or p=0.01525. Thus, this distribution indicates a relationship between one's susceptibility to these gravity transitions.

Next to the MISC scores, there were marked differences between the overall behaviour of the astronauts. The astronauts who were unaffected by centrifugation behaved normally within minutes and recovered very fast (Astronaut *A4* scored MISC 2 right after centrifugation but recovered quickly) Conversely, the affected astronauts reported motion illusions (floor moving, pushing the stairs down instead of themselves up) and visual illusions (oscillopsia) like ‘the visual surround being attached to the head by rubber bands, lagging the head movement and resulting in an oscillating image’. These astronauts were also careful in their movements, preventing fast (head) movements and turns. In addition, pitch head movements were disturbing postural balance. These examples illustrate that centrifugation did affect their behaviour, despite the relatively low MISC scores. When this overall behaviour is also taken into account, astronauts *A1* and *A4* were considered unsusceptible to SIC, whereas astronauts *A2* and *A3* were considered susceptible. This is in accordance with their individual SAS susceptibility.

DISCUSSION

With the latter four astronauts added to the database, there are now 12 astronauts who participated in a sustained centrifuge run. The data of this second group of four are in accordance with the data of the first group of eight (Bles et al., 1997): the astronauts who did not experience SAS during their flight also did not suffer from SIC Furthermore, although the MISC-scores remained below the preset threshold for SIC-susceptibility, the astronauts who scored positive on the MISC after centrifugation, also did so during, and after space flight. When the astronaut’s general behaviour was incorporated in assessing SIC susceptibility as well, the astronauts who were rated SIC susceptible appeared to be the ones also susceptible to SAS. This thus unscores the correlation between SIC and SAS (see Table 2.2).

TABLE 2.2
Distribution of SIC and SAS-susceptibility in 12 astronauts

	SAS	non-SAS
SIC	5	0
non-SIC	0	7

However, it is clear that is is easier to conclude that someone is *not* susceptible to SIC (nor to SAS) than it is to decide the opposite. After centrifugation the MISC scores of two astronauts remained relatively low, which might suggest that centrifugation did not induce SIC. Nevertheless, these astronauts behaved quite different from the other two astronauts after centrifugation, indicating that they were by no means *un*affected by the centrifuge run. Here we touch upon a difficulty that is connected to this kind of research: if you ask an observer to rate an astronauts susceptibility, he will definitely rate these two astronauts as SIC-susceptible based on their overall behaviour: they move slowly and carefully, they make the head movements with much more precaution and they have more trouble with vertical movements (e.g., sitting or lying down). It is also important to note that the severity of the symptoms is directly related to the amount of movement. In other words: if you don't move, you don't get sick, even if you are susceptible. It is then the experimenter's job to provoke a similar amount of active behaviour in every astronaut, in order to make a fair comparison. Faster or more head movements would have raised the MISC scores, in line with astronaut reports. Thus, based on these considerations astronauts *A2* and *A3* were considered susceptible to SIC, which correlates with their susceptibility to SAS.

The astronauts' reports nicely illustrate the role of anticipation in developing SIC, which is in line with the 'subjective vertical mismatch theory' on motion sickness, presented in Chapter 1. During the debriefing the astronauts noted that the head movements they performed during the head movement protocol were not as disturbing as movements they made *in between* the tests. During the test they were prepared for the movements and they were aware of the fact that these movements could make them sick. In between the tests, they were more relaxed and did not concentrate on every movement they made. Illustrative is the observation that during lunch, one of the astronauts was called by someone standing behind him and he reflexively looked over his shoulder: this was pretty disturbing! Another astronaut remarked that he was able to control his nausea during the head movement protocol, because of anticipation. The head movements, however, decreased his ‘nausea-margin’: any other, unanticipated movement would have made him sick, he reported.

The fact that the symptoms of SIC that were evoked by the prescribed head movements were less after centrifugation than in space suggests that it may be not feasible to score SIC and SAS using the *exact* same protocol. The aforementioned examples illustrate that symptoms of SIC are most evident during a task where fast head and body movement are involved, without a strong anticipatory component. A head movement test where subjects are ‘provoked’ to make head movements in reaction to certain triggers (De Graaf & De Roo, 1993) is expected to decrease this anticipatory component. An adapted version of this latter test will be used in the experiment described in Chapter 4 to provoke symptoms of SIC.

To increase the reliability of the SIC and SAS-assessment it is recommended that head movement characteristics are registered, by means of accelerometers (as was also done by Oman et al., 1986) or by e.g., video-recording. This performance registration is also added in the experiment described in Chapter 4. Of course movement registration during daily activities (in space) or in between the tests (after centrifugation) would also improve the assessment. Alternatively, the MOP-questionnaire could be extended with more questions about experiences during daily activities.

Conclusion

The data showed that a more strenuous head movement protocol is required to elicit symptoms of SIC after centrifugation. Nevertheless, when also the astronauts' behaviour is included in the assessment of SIC and SAS susceptibility, the correlation between the two still holds. With these four astronauts, a positive correlation between SIC and SAS susceptibility has been established in 12 subjects now: five of them were susceptible to SIC and to SAS, whereas seven of them were not. This is comparable to the incidence of SIC as determined in all non-astronaut subjects who participated in any of the centrifuge studies performed so far: 31 out of 67 were considered susceptible to SIC (42%). More importantly, it is comparable to the incidence of SAS (Davis, 1988; Matsnev et al., 1983). Thus, this correlation is in line with the hypothesis that SIC and SAS share a similar underlying mechanism.

Chapter 3

Exploratory research on the effects of sustained centrifugation: an overview

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This chapter provides an overview of the research that was performed in the past to characterize the effects of sustained centrifugation on postural stability, motion and attitude perception and vestibularly driven ocular responses. This is complemented with data on subjective vertical measurements that were performed within the framework of the present thesis. Together, these data did not reveal significant effects of sustained centrifugation on perceptual measures, but ocular responses were found to be affected.

Apart from testing subjects for SIC-susceptibility, several vestibular tests have been performed over the years to quantify the effect of sustained centrifugation on behavioural tasks, and elucidate the mechanism underlying SIC. They all focused on the otolith system and related responses (see Table 3.1 for an overview). Below, the most important results are summarized. For a detailed description of the results the reader is referred to the original manuscripts listed in Table 3.1. This research is then complemented with some new data, described in the second part of this chapter.

TABLE 3.1
Overview of available literature on the effects of sustained centrifugation in humans

Reference	Stimulation	n	Test	Description
Bles et al., 1989	90 min $3G_x$	3	Stabilometry	Postural stability during quiet stance, with and without vision
			Tilting Room	Postural stability in a dynamically tilting visual environment
			Subjective Vertical	Setting oneself upright while seated in a tilted chair
			Visual Motion Perception	Visual motion perception during fore-aft linear oscillation
			Optokinetic Nystagmus	Modulation of horizontal slow phase velocity that is elicited during linear oscillation by optokinetic stimulation
			Double Task Performance	Simultaneous performance of a tracking task and a continuous memory task
			Caloric Nystagmus	Recording of caloric nystagmus in different head orientations in pitch
Bles & De Graaf, 1993	60 min $3G_x$	3	Vision during centrifugation	Effect of vision during centrifugation on SIC-severity
			Head movements supine	Ranking provocativeness of yaw, pitch, and roll head movements in an erect and a supine posture
	60 min 3G	7	Direction of G-load	Difference in SIC severity following G_x, G_y, and G_z centrifugation
			Tiling Room	Postural stability in a dynamically tilting visual environment
	90 min $3G_x$	8	Attitude perception	Attitude perception after deceleration of the centrifuge (while lying in centrifuge gondola)
		8	Stabilometry	Postural stability during quiet stance, with and without vision
Albery & Martin, 1996	90 min $2G_z$	9	Postural stability	Postural stability assessment under different vestibular and visual conditions
De Graaf & De Roo, 1996	60 min $3G_x$	15	Psychomotor Performance	Yaw and pitch head movements while standing in combination with a psychomotor task (placing a peg in a hole)
Groen et al., 1996b	60 min $3G_x$	11	Static Ocular counter rolling	Ocular counter rolling during static lateral body tilt
			Torsional VOR	Ocular counter rolling during dynamic body roll about an Earth vertical and Earth-horizontal axis
Groen, 1997	60 min $3G_x$	9	Subjective Vertical	Indication of the subjective visual vertical during lateral body tilt
		9	Horizontal VOR	Recording of horizontal nystagmus during vertical axis rotation

REVIEW OF PREVIOUS STUDIES

Postural stability

Of all tests performed on the D1-astronauts (Bles et al., 1989), postural stability appeared to be the parameter that was most affected by centrifugation. When deprived of visual information, postural sway was greatly increased during quiet stance. One astronaut showed a major increase in visual dominance after centrifugation, as assessed in a tilting room. The astronaut was standing on an Earth-fixed stabilometer platform, while the visual surround (a 2.5×2.5×2 m cabin) was dynamically tilted about the roll axis located at ankle height. After centrifugation this astronaut was much more de-stabilized by the visual tilt than before centrifugation. Interestingly, similar results were also found in the same astronauts after spaceflight (Bles & Van Raay, 1988).

The effect of sustained centrifugation on postural measurements was further investigated by Bles & De Graaf (1993). They observed an increased postural sway following centrifugation during standing upright with the eyes closed, that markedly increased when head movements were made. In some subjects the head movements resulted in a complete loss of postural control. In addition, subjects reported that standing in the sharpened Romberg position (feet positioned in front of each other, heel to toe) remained very difficult until hours after centrifugation. In these experiments the SIC-susceptible subjects did not behave statistically different from the non-susceptible subjects.

Albery & Martin exposed subjects to $2G_z$ stimulation and observed no real changes in postural stability after a 40 minute exposure, but found a significant reduction after an exposure of 90 minutes.

Subjective Vertical

In addition to a deterioration of postural balance changes were observed by Bles and colleagues (1989) in the perception of the vertical. The astronauts were seated in a chair that was put in a tilted position and the astronauts were to set the chair upright again. After centrifugation they showed a consistent backward bias, indicating that in the *actual* upright position, a forward tilt was perceived. Such a directional bias in the perceived direction of gravity was also suggested by the postural measurements of Bles & De Graaf (1993) mentioned above, where subjects generally showed a tendency to fall backwards.

Groen investigated the effect of sustained centrifugation on the perception vertical in the roll plane. Non-astronaut subjects were to align a visual line with gravity under various angles of lateral body tilt. It was observed that subjects tended to underestimate the tilt at larger tilt angles (A-effect, that is, the visual line was tilted towards the body axis), but no effect of centrifugation was found.

Eye movements

Torsional eye movements were of particular interest, because they are assumed to be predominantly driven by otolith signals (see e.g. Miller, 1962). Groen and colleagues (1996b) recorded ocular counter rolling during static lateral body tilt and found a decrease in the gain of this response after sustained centrifugation. The dynamic torsional response was assessed during angular oscillation of 0.25 Hz about an Earth-vertical axis (no otolith stimulation) and about an Earth-horizontal axis. The gain of the response was found to be increased after centrifugation during rotation about an Earth-horizontal axis (i.e., with otolith stimulation). This might seem to be contradictive with the results of the static measurements, but they are explained by the finding that in these subjects stimulation of semicircular canals alone led to a higher response gain than stimulation of both semicircular canals and otoliths. Thus, apparently the otolith contribution counteracted the canal contribution. Therefore a reduced otolith gain after centrifugation would decrease the counteracting effect of the otoliths, thereby increasing the total gain of the response. This opposite effect of semicircular canals and otoliths on the torsional response was however not replicated in a later study using the same subjects (Groen et al., 1999).

Apart from the torsional vestibulo-ocular reflex (VOR), Groen (1997) also investigated the horizontal angular VOR during constant velocity Earth-vertical axis rotation. The gain of this response was unaffected by sustained centrifugation, but the dominant time constant of the decay-rate of slow phase velocity was found to be significantly decreased.

Head movements

The findings of Bles & De Graaf (1993) showed that in an erect posture only pitch and roll head movements were provocative, while in a supine posture pitch and yaw movements were provocative. This indicated that only those head movements were provocative that changed the orientation of the head relative to gravity, in line with earlier reports of the D1-astronauts.

De Graaf and De Roo (1996) developed a head movement test that included a psychomotor task. Subjects were to turn their head in a visually indicated direction (up, down, left, or right) where another visual trigger was shown. Depending on the latter trigger they either were to press a button or to put a peg in a small hole. It was observed that subjects who were suffering from SIC moved their heads significantly slower than subjects who were not suffering from SIC. Although this velocity decrease was present in both pitch and yaw movements, only the pitch movements were rated provocative. Task performance was not affected by centrifugation.

Mode of centrifugation

Bles & De Graaf (1993) also tested whether the direction of the applied gravitational load affected the aftereffects of centrifugation. To that end they positioned the subjects in a supine body position in the centrifuge while changing the position of the head relative to the GIA. Pitching the head forwards over 90º yielded G_z-stimulation, rotating the head 90º about the longitudinal body axis yielded G_y stimulation and keeping the head in line with the body yielded G_x stimulation. These three conditions, however, had comparable effects on postural stability. The only difference between conditions was that after G_x stimulation pitch head movements were rated as more provocative than roll head movements (while erect) and after G_y stimulation roll was rated more provocative than pitch. Yaw movements, that did not change the orientation of the head relative to the vertical, were not provocative in both cases. The effects of G_z stimulation did not change the rank order of the provocative of head movements and was similar to G_x stimulation.

In three subjects the effect of vision on SIC was investigated and it was observed that SIC-severity was increased when subjects kept their eyes open during centrifugation. (Bles & De Graaf, 1993).

ADDITIONAL EXPLORATORY RESEARCH

Within the framework of this thesis, additional vestibular testing was performed both in the four astronauts who participated in a centrifuge experiment between 2003 and 2007, and in a group of non-astronaut subjects. The two main experiments focused on the effect of sustained centrifugation on ocular responses and are described in Chapters 5 and 6. Here the results of the other additional tests are described.

Provocativeness of head movements

Earlier results, as mentioned above, showed that after centrifugation only those head movements were provocative that changed the orientation of the head relative to gravity. Thus, pitch and roll when erect and pitch and yaw when supine. These results were replicated in a group of 4 astronaut subjects and 11 non-astronaut subjects. They all were exposed to $3G_x$ for 60 min. and rated the provocativeness of yaw, pitch and roll head movements (maximal 10 per axis, performed at a frequency of about 0.25 Hz), both when standing and when lying supine. The effect of the head movements was scored on a 11-point numeric MISC scale (see Table 2.1) A nonparametric ANOVA (Friedman ANOVA by ranks) on these MISC scores showed that pitch movements were ranked as most provocative, while yaw and roll-movements were ranked equally provocative (χ^2=8.44, p=.015). In a supine position there was a trend for roll to be ranked *least* provocative, while pitch and yaw were ranked about equally provocative, (χ^2=4.7, p=.097). When subjects were asked afterwards what they found the most provocative movement, it was generally pitch, both in an erect and supine posture.

Postural stability and visual-vestibular interaction

Postural stability during quiet stance and during dynamic tilt of the visual surround (in the tilting room) was also performed on two of the four astronauts who were tested within the framework of this thesis (exposed to 60 min at $3G_x$). One of them was susceptible to SIC and the other one was not. During all recordings, the astronauts stood on a layer of foam rubber that was placed on the stabilometer platform to reduce the relative weighting of proprioceptive cues. The sway of the centre of pressure was recorded in the fore-aft and the lateral direction, at a sample frequency of 20 Hz. Recordings were obtained during quiet stance with eyes open, with eyes closed and with the neck extended (eyes closed). These conditions were always performed in this order. Figure 3.1 displays the results of the static postural stability recordings of the two astronauts (i.e., stationary visual surround). Shown are values for sway in the fore-aft direction, lateral sway was generally smaller but followed a similar pattern. The astronaut who was not affected by the centrifuge run in terms of SIC exhibited very little postural sway. Only a little increase during the first posttest in the 'Neck extension' condition was observed. In contrast, the other astronaut, who was reasonably affected by the centrifuge run, clearly showed a different pattern over sessions, especially in the 'Neck extension' condition. Instead of a steady decrease of the postural sway over sessions (which is normally observed in repeated recordings) the sway increased in the second and especially in the third session. The third session was also the session were the highest MISC scores were observed. In this astronaut behaviour was not back to baseline within 4 hours after the centrifuge run.

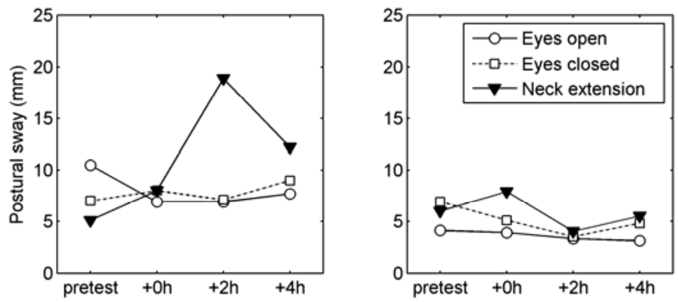

Figure 3.1: Postural stability recordings for the three experimental conditions in two astronauts (Each panel shows the data of one astronaut). Postural sway is expressed as the root-mean-square value of the sway of the centre of pressure.

The dynamic measurements (oscillation of the visual surround at 0.025 Hz and 0.2 Hz) in pitch or roll showed no large increases in postural sway, indicating that the astronauts were not affected by movement of the room. This was also not deteriorated by sustained centrifugation.

Subjective vertical measurements in the pitch plane

In two separate experiments it was investigated whether sustained centrifugation affected the perception of body orientation in space in the pitch plane, as was suggested by earlier findings (Bles et al., 1989; Bles & De Graaf, 1993). They were performed on a total of 10 subjects (2 astronauts and 8 non-astronaut subjects) who were exposed to 60 min at 3Gx. Both experiments were performed shortly before and after centrifugation.

The first experiment focused on the perception of the vertical and of body orientation under different conditions of pitch body tilt, using a tactile indicator. Experiments were perfomed in the TNO tilt-chair, that enabled rotation about the pitch axis through the center of the head. Blindfolded subjects were seated and secured with a five-point belt. They were oriented in different positions and in each position they were to align the manual indicator first with their perceived longitudinal body axis (Subjective Body axis, SB, defined as ‘parallel to your spine”) and subsequently with the gravitational vertical (Subjective Vertical, SV). Figure 3.2 shows the error in these two measurements as a function of tilt.

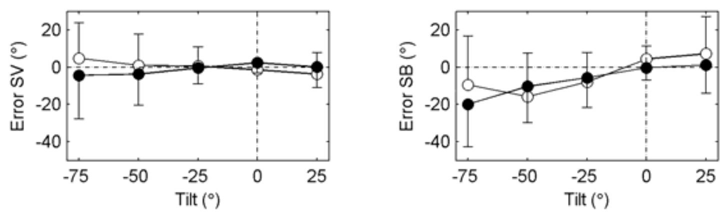

Figure 3.2: Errors in subjective vertical (SV) and subjective body axis (SB). Pretest values (mean and standard deviation) are indicated by the open symbols, values of the first posttest are indicated by the filled symbols.

For backward body tilt a positive error in SV yields an underestimation of tilt, thus the SV is tilted towards the body-axis (A-effect). This is visible for larger tilt angles in the pretest, and appears to be changed into an overestimation of tilt in the posttest. However, these effects of test session or tilt angle were not significant (Factorial ANOVA with Tilt and Test session as within subject factors). Interestingly, for the SB a significant effect of Tilt was found ($F(4, 32)=5.46$, $p<.01$): the body axis was perceived to be more tilted backwards (negative error) and this error increased with tilt angle. No significant effect of centrifugation could be demonstrated. Similar trends for SV and SB were observed in six control subjects who did not undergo centrifugation (see Nooij et al., 2006).

In a second experiment subjects were to reorient themselves to upright after a perturbation in pitch (<30º forward or backward). As in the previous experiment, subjects were blindfolded and seated in the tilt-chair. Each session consisted of six repetitions. The data showed that the magnitude of the error was weakly correlated with the magnitude of the perturbation (r=0.25, p=.01), but because this effect was small in comparison with the error magnitude, the values were not corrected for this trend. Analysis of variance revealed that the sign of the error in the perceived upright was dependent on the direction of the perturbation: when the perturbation was backwards, the perceived upright position was also tilted backwards and vice versa ($F(1, 72)=50.5$, $p<.001$). No effect of test-session (pre-/posttest) could be demonstrated for the error in the perceived upright, and also no differences between the behaviour of SIC-susceptible subjects and non-susceptible subjects. Over all, the error in the perceived upright ranged between −10.8º and +9.7º (mean +0.6º, SD 4.0º), whereas the average absolute error equaled 3.2º (SD 2.42º). In the second session the variability of the responses (standard deviation over the six repetitions) decreased significantly ($F(1,7)=6.4$, $p<.05$), suggesting that subjects got more acquainted with the task.

DISCUSSION

By recording the kinematic characteristics of the head movement, De Graaf and De Roo (1996) nicely showed that head movements were required to provoke SIC following centrifugation: SIC susceptible subjects performed the head movements slower than non susceptible subjects, in an attempt to minimize or prevent increasing symptoms of motion sickness. The results of previous studies regarding the provocativeness of head movements were replicated by new data: pitch head movements were most provocative both when erect and supine. Yaw movements were not provocative when erect, and roll movements were not provocative when supine. The observation that this provocativeness was not altered following G_z stimulation (Bles & De Graaf, 1993) suggests that the magnitude of the G-load is more important than the direction of stimulation, indicating the involvement of a central adaptation process. However, that G_y stimulation altered the order of provocativeness when compared to G_x stimulation suggest that a direction specific element should be involved as well, adding to the effect of the G-magnitude.

Next to symptoms of motion sickness, the second most obvious effect of sustained centrifugation is the deterioration of postural balance. As long as veridical visual information is available, balance could be maintained, but in more challenging situations (with eyes closed or head extended) postural sway increased. Although there were large differences between individuals (i.e., between the two subjects in Figure 3.1), no relationship between SIC-susceptibility and postural sway parameters could be demonstrated (Bles & De Graaf, 1993). This is comparable with the findings in astronauts following space flight. After space flight a similar deterioration of postural balance is found, both in astronauts who suffered from SAS and in astronauts who were free form SAS (e.g., Black et al., 1995; Reschke et al., 1998; Young et al., 1993)

Following centrifugation, head movements often resulted in postural overcorrections and loss of balance (Bles & De Graaf, 1993) showing that dynamic situations were more challenging than static situations. This furthermore hints at a disturbed interaction between semicircular canals and otoliths: both are involved in the estimation of the vertical in this situation. As mentioned in Chapter 1, this is in accordance with the hypothesis that a disturbed perception of the vertical during dynamic head tilt is related to the occurrence of motion sickness after centrifugation.

The perception of the vertical during *static* body tilt was not found to be affected by sustained centrifugation, neither in the roll nor in the pitch plane. The same was true for the perceived body orientation. Many studies demonstrated that the perception of the gravitational vertical can be quite veridical, but that this does not guarantee a veridical perception of body orientation relative to that vertical. The latter requires both ego- and allocentric information and thus, the perceived body orientation in space cannot be inferred from the subjective vertical setting alone (e.g., Mars et al., 2005; Mast & Jarchow, 1996; Van Beuzekom et al., 2001). This was also shown by the perceptual responses to pitch body tilt, as mentioned above. Subjects were able to indicate the vertical with only minor errors, but they made large errors in indicating their subjective body axis. Where subjective vertical settings are predominantly based on otolith input, somatosensory information is known to affect the perception of body posture in space (see e.g., Bisdorff et al., 1995; Bringoux et al., 2000; Ito & Gresty, 1997; Mittelstaedt, 1999). Somatosensory information most likely dominated the perception of the postural vertical in the task where subjects were to set themselves upright.

Although sustained centrifugation did not affect the perception of the vertical during lateral or pitch body tilt, it did affect the ocular response: the gain of ocular counterrolling was decreased. Because this response is mainly dependent on the magnitude of the utricular shear force (e.g., MacDougall et al., 1999; Merfeld et al., 1996a; Miller & Graybiel, 1971; Moore et al., 2001), this would suggest a decrease in otolith sensitivity to head tilt. The absence of an effect on the visual vertical, which is also largely dependent on otolith information, is however not in accordance with this hypothesis. Another possibility is that the otolith sensitivity remains unaltered but that the gain of the orientation response is decreased. Such a decrease would leave the subjective vertical setting unaffected. A general decrease in orientation responses could be a common way of the system to deal with unfamilar response patterns differing from expected patterns, as might be the case following sustained centrifugation. This would also be in accordance with the decrease in ocular counter rolling generally found after spaceflight (Dai et al., 1994; Hoffstetter-Degen et al., 1993; Vogel & Kass, 1986; Young & Sinha, 1998; but see also Moore et al., 2001). To study the effects of gravity on eye position and related orientation responses in more detail, a start was made to measure the orientation of the so-called Listing's plane within the framework of this thesis. As mentioned in the previous chapter, Listing's plane describes three-dimensional eye position during visual fixations and saccades, and its orientation is dependent on head tilt. Therefore the orientation of Listing's plane was expected to be informative about changes in otolith function and related orientational responses too.

Preliminary data in astronaut subjects indeed showed changes in the orientation of Listing's plane following sustained centrifugation. Therefore a separate study was dedicated to the effect of gravity on three dimensional eye position, which will be described in Chapter 5.

A last interesting finding that is discussed here is the decrease in the dominant time constant of the horizontal angular VOR. This dominant time constant specifies the rate of decay of the slow phase eye velocity during constant velocity rotation. For yaw rotation about an Earth-vertical axis it is about 20s, which is longer than expected based on the dynamics of the semicircular canals. The human cupular time constant is about 3.5-7 s (Dai et al., 1999). This prolongation of the VOR is attributed to a central process called *velocity storage* (Raphan et al., 1979), which is known to be dependent on otolith input too. For example, the time constant decreases with tilt angle: during Earth horizontal axis rotation the time constant is smaller than during Earth vertical axis rotation (see e.g., Haslwanter et al, 2000; Tweed et al., 1994, but see also Bos et al, 2002). Thus the decrease of the dominant time constant suggests that sustained centrifugation affects the interaction between otoliths and semicircular canals. Investigation of the velocity storage mechanism is also interesting given the observed relationship between the velocity storage time constant and motion sickness (e.g., Bos et al, 2002; Dai et al., 2003). This thus incited a separate study, that will be described in Chapter 6.

Conclusion

It can be concluded that gravity plays a major role in SIC: only those head movements are provocative that change the orientation of the head relative to the vertical. Furthermore, that the speed of those movements affects both SIC and postural balance hints at a disturbed interaction between canals and otoliths. Ocular responses that are mediated by gravity may shed more light on the exact mechanism underlying the observed effects.

Chapter 4

Effect of G-load and duration of centrifugation on the symptoms of SIC

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*The study described in this chapter investigated the characteristics of the gravito-inertial stimulus that is required for SIC to occur. Twelve non-astronaut subjects were exposed to centrifugation at 2 and 3*G_x*, for a duration of 45 and 90 minutes. A standardized head movement protocol was used to evoke SIC after centrifugation. The results show that in six out of 12 subjects (50%) no serious symptoms were elicited. In the other subjects, the effects of the 3G runs exceeded those of the 2G runs, and within each G-level symptom intensity was higher for the 90 min. exposure than for the 45 min. exposure. An exponential fit on this data showed that the time constant of adaptation to the gravito-inertial stimulus was about one hour.*

This chapter describes a study that looked further into the nature of the gravitational stimulus that evokes vestibular adaptation and the accompanying symptoms of SIC. Generally speaking, adaptation takes time and it may be anticipated that a very short exposure to an altered gravito-inertial state will not result in SIC. The transitions following the rather short lasting hyperG exposure as experienced by a fighter pilot, for instance, do not trigger any symptoms of SIC, neither do the phases of parabolic flight[6]. The experiences of the D1-astronauts indicated that 30 minutes of centrifugation at 3G is already sufficient to evoke SIC, but symptom-severity markedly increased after another 30 minutes of exposure. Apart from the duration of centrifugation, the magnitude of the gravito-inertial difference might be a second factor affecting the adaptation process. The fact that Albery and colleagues (1996) observed symptoms of SIC in subjects who were exposed to a load of $2G_z$ for a duration of 90 minutes furthermore suggests an interaction between the applied G-load and duration of centrifugation.

The aim of the study described in this chapter was therefore to systematically investigate the interaction between the G-level difference and duration of centrifugation in the occurrence of SIC. Apart from contributing to the fundamental knowledge about adaptation to altered gravito-inertial states, insight in this dose-effect relationship helps to determine the G-dose minimally required for SIC to occur in the first place, which is of help for future ground based research on SIC and SAS. It may also be of interest for selecting, training, and habituating future astronauts before their space flights. In addition, the (neuro-vestibular) consequences of gravity transitions relate to the application of intermittent artificial gravity (AG) during space flight and to the risks that are present during and after (re-) entry into Planet's gravity. These two topics are both identified as highly relevant for space research (see e.g. Clément & Bukley, 2007, and the Bioastronautics Roadmap[7]).

As the most simple model, it was hypothesized that at low to moderate G-levels the level of SIC is related to the product of the G-level *difference* and the time of exposure, $\Delta G{\cdot}t$. To validate this hypothesis subjects were repeatedly exposed to a hypergravity-load, using four different combinations of G-load and duration. A head movement

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[6] Although the repeated GIA changes occurring during parabolic flight may induce motion sickness symptoms too, these changes will not trigger adaptation processes similar to those involved in SIC.

[7] NASA/SP-2004-6113, available at http://bioastroroadmap.nasa.gov/.

protocol was used to trigger symptoms of SIC after centrifugation. Instead of letting the subjects perform self-paced head movements (as was the case in the astronaut studies), head movements were provoked using a stimulus-response paradigm (De Graaf & De Roo, 1996). Using this test, De Graaf & De Roo showed that head movement performance and symptom severity are mutually dependent: the severity of the symptoms is dependent of the velocity and amount of head movements, but, on the other hand, SIC susceptible subjects showed to move their heads slower than non-susceptible subjects. Thus, in order to compare the effect of the four centrifuge conditions, head movement performance was taken into account in the determination of SIC-severity.

The experiments to be described in Chapters 5 and 6 were carried out as a part of the same study, using the same subjects.

METHODS

Twelve male (non-astronaut) subjects participated in this study (aged 23.0±3.2 yrs.). All were free from any vestibular, cardiovascular, neurological and pulmonary disorders, as checked by a MD. The study was approved by the Medical Ethics Committee of the Utrecht University Hospital, The Netherlands. All subjects gave written informed consent prior to the study. In the selection procedure that preceded the experiment, the subjects were medically checked and then familiarized with the centrifuge during a run at $3G_x$ for 10 minutes only (see Chapter 2 for a description of the centrifuge facility). From all subjects their susceptibility to Earthly motion sickness was assessed by the Motion Sickness Susceptibility Questionnaire (Golding, 1998).

Centrifuge conditions and design

The four centrifuge conditions that were used in this study are depicted in Table 4.1. By using the levels of 2 and 3G for centrifugation, the G-level *difference* relative to Earth's gravity (*ΔG)* equaled 1 and 2G respectively.

In combination with the chosen durations, the product *ΔG·t* was equal in two of the four conditions (45, 90, 90 and 180 G-minutes respectively).The conditions will be referred to as 2G45, 2G90, 3G45 and 3G90, respectively.

Subjects came in one day a week for four subsequent weeks and received each load-duration combination once. The order in which the conditions were presented was determined by a digram balanced Latin square design. Subjects were uninformed about the stimulus characteristics, except for the maximum duration (90 min.) and the maximum G-load (3G). Although body and head movements were possible during centrifugation to a small extent, the subjects were instructed to refrain from making head movements. They were allowed to close their eyes, but sleeping was prevented.

TABLE 4.1
Characteristics of the four centrifuge runs.

Condition	Total gravito-inertial load during centrifugation (G-units)	Duration (min)	Magnitude of the G-transition after centrifugation (*Δ*G, in G-units)	Dose (*ΔG·t,* in G-minutes)
2G45	2	45	1	45
2G90	2	90	1	90
3G45	3	45	2	90
3G90	3	90	2	180

After centrifugation the subjects were transported to the test-facility by wheelchair (approximately 200 m from the centrifuge) to minimize variability in the amount of body motion before the SIC assessment. Using a head movement protocol to evoke symptoms of SIC (see below), one entire test day consisted of a pretest, a centrifuge run and four posttest measurements approximately at 15, 60, 120, and 210 min. after centrifugation. The eye movement tests described in Chapters 5 and 6 were also part of the protocol, as depicted in Figure 4.1. During the breaks in between test sessions no restrictions were imposed on the subject's behaviour. After every test day, an evaluation form was deployed assessing the time they were free of symptoms.

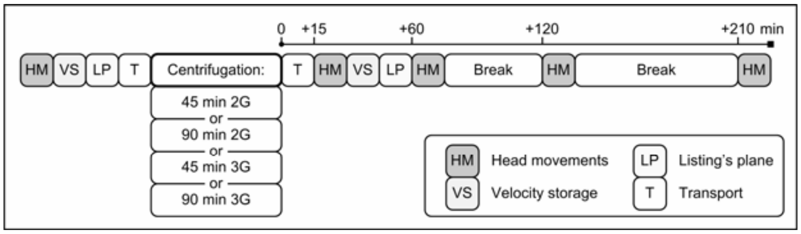

Figure 4.1: Time line of the experiment. The head movement test (HM) to assess SIC-severity was carried out before and repeatedly after the centrifuge run. The measurements on Listing's plane (LP) are further described in Chapter 5, the measurements on velocity storage (VS) in Chapter 6.

Head movement protocol

A standardized head movement protocol was used to test subjects for SIC, adapted from De Graaf & De Roo (1996). In this protocol the subject stood erect with the head in the center of a rectangular box (dimensions 1.4×0.7×0.7 m, front and bottom open, see Figure 4.2). In front of the subject, a cue display was mounted at eye level with four LED's to indicate the desired direction of head movement: up, down, left, or right. Four target displays showing random numbers were attached to the upper, left, and right side of the box and a fourth display below, on a small stand right in front of the subject. In order to see the target displays, the head had to be rotated over an angle of at least 50°.

Subjects were instructed to look at the cue display and turn their head in the indicated direction, read the random number that appeared on the target display, and turn the head back to its original position. They were to move 'reflexively', as if they were tapped on the shoulder or someone called their name. They had 5 s to complete each movement, followed by a 2 s break. Each test session consisted of a maximum of 40 head movements, 10 in each direction, presented in random order. During the test, head orientation and velocity were measured using a small magneto-inertial motion and tilt sensor that was attached to the subject's head (Xsens MT9, Xsens Technologies BV, The Netherlands). Signals were digitized at 50 samples/s.

Figure 4.2: Experimental set-up for the head movement test. The cue display, positioned in front of the subject, is shown in the upper left inset. This display indicated the direction of the required head movement. Three target displays are visible; the fourth was positioned below and in front of the subject. The subject wore a movement registration device to measure head position and velocity.

Symptom scores

To describe the symptoms that were evoked by the head movements, subjects completed the Simulator Sickness Questionnaire (SSQ, see Kennedy et al., 1993) after each head movement test. To the 16 motion sickness related symptoms that are rated in this questionnaire two SIC-specific symptoms were added: emesis and oscillopsia.

Because the SSQ does not provide insight into the temporal build up of symptoms *during* the test, the level of sickness was also scored on the Misery Scale (MISC). The version used in this study differed slightly from the scale used in the astronaut studies, in that it clarifies the meaning of the scores, especially in the lower range (see Table 4.2).

TABLE 4.2
Misery Scale (MISC).

Symptoms		Score
No problem		0
Uneasiness (no typical symptoms)		1
Dizziness, warmth, headache, stomach awareness, sweating, ...	vague	2
	slight	3
	fairly	4
	severe	5
Nausea	slight	6
	fairly	7
	severe	8
	retching	9
Vomiting		10

Subjects were instructed about all symptoms possibly anticipating nausea (Graybiel et al., 1968; Reason & Brandt, 1975, pp38-54) leading to scores 2-5, which are also listed in the SSQ (Kennedy et al., 1993). The new MISC also takes into account that the order of symptoms other than nausea generally varies over subjects, while nausea, if present, always directly precedes retching and vomiting. It is equal to the MISC used and validated by Wertheim et al. (1998), with the exception that once nausea is experienced, a minimum MISC of 6 is rated (instead of 5), and the symptoms below a rating of 6 are pooled instead of ordered. As with the previously applied MISCs, this new MISC is easy to use during the test and has the advantage that it reflects the momentary subjective score (De Graaf & De Roo, 1996; Bles et al., 1997; Bos et al., 2005). It was the main sickness measure used in the current study. MISC scores were collected prior to the test and after every 10 head movements. The test was aborted when the MISC exceeded 7.

Data analysis

Head movement performance was described by the maximum head angular velocity (ω_{max}), defined as the maximum magnitude of the 3D angular velocity vector. For every subject, ω_{max} was averaged over all yaw and pitch trials within one session. Head position data (i.e., head orientation) was used to check whether the task was performed properly.

As stated in the introduction of this chapter, MISC scores are affected by head movement velocity and vice versa. Because a particular head movement velocity was not strictly prescribed during the test, there is a chance that head movements were performed deliberately at a low rate in order to prevent sickness. This would lead to an underestimation of MISC scores, which could hamper the comparison of centrifuge conditions. Such behaviour (i.e., low MISC scores and low angular velocity) would deviate from the inverse relationship between MISC scores and movement velocity that normally is observed. It would also result in a low linear correlation between MISC scores and maximum angular velocity. When such deviating behaviour is indeed found, and the correlation between MISC scores and maximum angular velocity is low, both measures have to be taken into account to enable a consistent comparison of centrifuge conditions. Thus, depending on the results of a linear regression analysis between MISC scores and ω_{max}, the data will be combined in a single measure. This measure then, will be used to determine the subject's susceptibility to SIC and to investigate the effects of ΔG and duration of centrifugation on the occurrence of SIC.

RESULTS

The head movement data of one subject had to be disregarded for further analysis. This subject was so disturbed by his first centrifuge run (2G90) that he also refrained automatically from making any rapid head movements following the other runs, regardless of the gravito-inertial stimulus. Such behaviour was not observed in the other subjects. A second subject was so disturbed by the first posttest following the 3G90 run (terminated after 9 head movements) that he was unable to perform the second test session 45 minutes later (MISC>7). Missing head movement performance data for this session was replaced using linear interpolation.

The symptom scores obtained after each centrifuge run showed large differences between centrifuge conditions and between subjects. Where none of the subjects experienced nausea (MISC≥6) following the head movement test after the 2G45 centrifuge condition, 5 of the 12 subjects did so after the 3G90 run. However, before we could identify subjects as SIC-susceptible and subsequently compare the effect of the four centrifuge conditions, it was checked whether head movement performance was deteriorated after centrifugation. As mentioned in the Methods section, a deterioration of head movement performance could lead to an underestimation of the MISC scores. Therefore we will start this section with an analysis of head movement performance. It will be shown that ω_{max} was indeed decreased after centrifugation, but that the correlation between ω_{max} and MISC scores was low. This necessitated a correction of the MISC scores, as described below.

Head movement performance

The head movement velocity data is shown in Figure 4.3. A 2(ΔG) × 2(duration) × 5(session) × 2(movement plane) within subjects ANOVA revealed that ω_{max} was lower for pitch than for yaw movements ($F(1,10)=407$, $p<.001$). Inspection of head position data learned that the amplitude of yaw movements was higher than the pitch amplitude (65±7° vs. 53±8°). Apparently, subjects voluntarily rotated further than necessary in yaw. The interaction of G × session was significant ($F(4,40)=7.78$, $p<0.001$) and a posthoc Tukey test indicated that ω_{max} was significantly lower after 3G stimulation, but not following the 2G runs. Large interindividual differences are reflected by the many outliers in Figure 4.3. These outliers indeed correspond to the behaviour of SIC-susceptible subjects, as will be shown later. The absence of a significant interaction of G-load × movement plane × session indicated that the velocity decrease was present in both yaw and pitch movements.

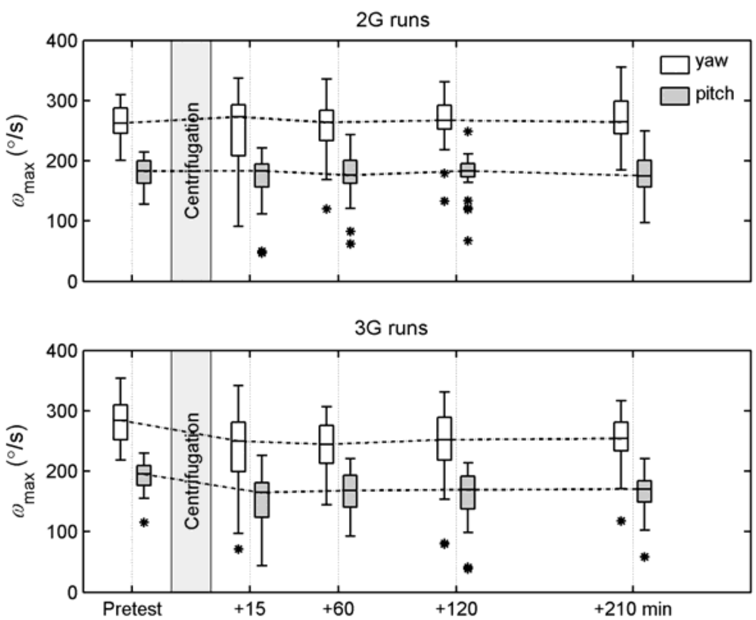

Figure 4.3: Boxplot of the averaged ω_{max} for the two G-levels. Pitch head velocity was lower than yaw velocity, and both were affected by the 3G-condition. Stars indicate extremes.

As to symptom severity, subjects who experienced nausea after centrifugation indicated that only the pitch movements were provocative and that their experienced level of nausea decreased again after a few yaw movements. This implies that the build up of symptoms was directly related to movements involving changes in head orientation with respect to gravity. It also explains the absence of a gradual MISC increase within one session. Therefore, the maximum MISC score within each session ($MISC_{max}$) was taken as a measure for SIC-severity, rather than the score at the end of the test. The $MISC_{max}$ scores of the first posttest are shown in Figure 4.4, plotted against head movement performance (ω_{max}, averaged for pitch and yaw). The focus will lie on the results of the first post test, since in this session the effects are largest.

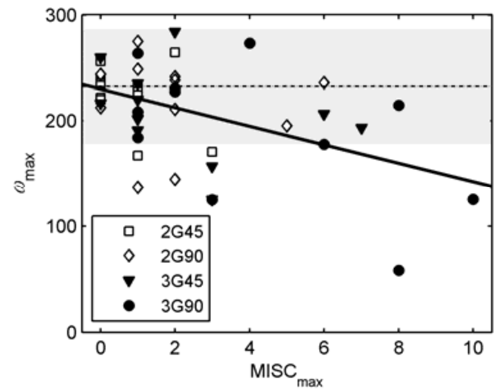

Figure 4.4: Mean ω_{max} vs. the maximum MISC score of the first post test following each centrifuge run (n=11). The regression line (solid) and the mean velocity of the pretest (dashed) are indicated. The gray area represents the mean pretest velocity ±2SD.

A linear regression analysis revealed the anticipated inverse relationship between maximum head velocity and MISC scores (ω_{max} = 229.7 – 8.8·$MISC_{max}$, r= –0.47, p<.01): subjects suffering from nausea (i.e., high MISC scores) generally prevented rapid head movements (i.e., low ω_{max}). For clarity, the average pretest performance (± 2SD) is also depicted in Figure 4.4 by the dashed line and shaded area. The fact that the accounted variance of the regression equation is low (r^2 = 0.22) indicates that different behaviour (e.g., high MISC scores with high ω_{max}) is observed as well, depending on the received stimulation and the subject's susceptibility. Most obvious in this respect are the data points in the lower left corner of Figure 4.4: ω_{max} is well below the pretest average *despite* a low $MISC_{max}$ score. These points represent subjects who most likely refrained from rapid head movements to prevent serious nausea. It is likely that $MISC_{max}$ scores in this latter group would have been higher when head movements were performed at a higher rate.

Corrected MISC score

Given the weak correlation between $MISC_{max}$ and ω_{max} , and the fact that these variables are mutually dependent, they both had to be taken into account in the comparison of centrifuge conditions. To that end, MISC scores were corrected for the level of performance: the scores were increased when the head movement velocity was lower than the pretest average. Thus, it was assumed that the performance decrease was due to (anticipated) nausea. As such, the corrected measure should estimate the symptom level that would have been reached when the head movements had been performed at the pretest level. The magnitude of the correction was based on the regression analysis presented above. On average, a 1-point increase in $MISC_{max}$ was accompanied by a decrease of 8.8 °/s in ω_{max} (slope of the regression line). This would be a perfect correction factor when the variance in $MISC_{max}$ was totally accounted for by the variance in ω_{max}, i.e. r^2=1. However, r^2 was in fact only 0.22, implying that the decrease in head movement velocity was also affected by other factors and thereby making the correction of 1 MISC-point per 8.8 °/s too strenuous. Instead, the variance accounted for was taken into account by dividing the slope of the regression line by r^2. This resulted in a correction of 1 *MISC*-point per 40°/s decrease in ω_{max}. The group average of the pretest ($\overline{\omega}_{\max\,pretest}$, equal to 232º/s) was taken as a reference velocity relative to which the velocity change of each subject and each centrifuge condition was determined. The corrected score, denoted by *CMISC*, then became:

$$CMISC = MISC_{\max} + \frac{\overline{\omega}_{\max\ pretest} - \omega_{\max\ posttest}}{40} \tag{4.1}$$

For example, a MISC score obtained after head movements performed with an average velocity of only 152º/s instead of the pretest average of 232º/s would be increased with 2 MISC points. Since one cannot get sicker than sick, scores were ceiled at a *CMISC* of 10. This corresponded to the assumption that if a subject would have made a more vigorous head movement, he would have vomited.

This new variable has subsequently been used to categorize the subjects. Subjects were considered susceptible to SIC if their *CMISC* of the first posttest following the 3G90 centrifuge run was 6 or higher, i.e. if they were suffering from nausea (or would be if they had made more vigorous head movements).

Comparison of centrifuge conditions

Based on their *CMISC* scores, six out of 12 subjects were considered susceptible to SIC. Figure 4.5 summarizes their CMISC scores. These scores were submitted to a 2(ΔG) × 2(duration) × 5(session) within subjects factorial ANOVA, with SIC-susceptibility as a between-subjects factor. The results show that the effects of the 3G runs exceeded those of the 2G runs ($F(1,9)=43.7$, $p<0001$) and the effects of the 90 minute exposure exceeded those of the 45 minute exposure ($F(1,9)=17.9$, $p<.01$). Also a main effect for test session was found ($F(4,36)=40.2$, $p<.0001$). Given the large differences between the SIC and non-SIC group ($F(1,9)=22.8$, $p<.01$) it is not surprising that the interaction between SIC and respectively ΔG ($F(1,9)=21.1$, $p<.01$), duration ($F(1.9)=9.4$, $p<.05$), and session ($F(4,36)=18.6$, $p<.0001$) were also significant. Furthermore, an interaction-effect was found for ΔG × session ($F(4,36)=19.4$, $p<.0001$), duration × session ($F(4,36)=8.5$, $p<.0001$) and ΔG × session × SIC ($F(4,36)=11.1$, $p<.0001$). Post hoc testing revealed that for the non-SIC group, no significant differences were found; centrifugation did not significantly increase the *CMISC* scores. For the SIC-group, on the other hand, *CMISC* scores were significantly increased after the 2G90 run and both 3G runs. Comparing the magnitude of the effect measured in the first posttest between centrifuge conditions, the 2G90 run did not differ significantly from the 3G45 run, whereas the 3G90 run effects exceeded all other runs.

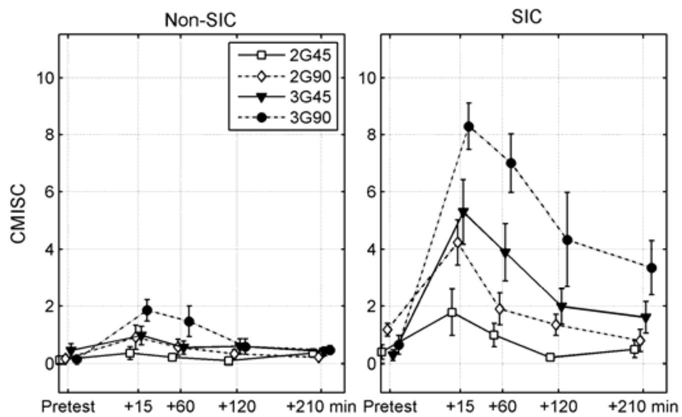

Figure 4.5: Mean CMISC scores for each test session and centrifuge condition. Error bars indicate standard error of mean.

The recovery rate differed per condition. For the 2G90 run the scores were already back to the pretest level in the second posttest, whereas for the 3G45 run this has occurred in the third posttest. In the 3G90 condition recovery has begun (scores in the third posttest are significantly lower than the first posttest) but was not yet complete in the last posttest. The scores then were still higher than the pretest level. To estimate the time constant of the recovery process, the post-centrifugation data of the SIC-group was fitted with an exponential decay curve ($CMISC(t) = A \cdot e^{t/\tau}$). Time constants equalled 74 and 85 s (2G) vs. 135 and 194 s (3G) for respectively the 45 and 90 min. exposure. The amplitude *A* increased in a same manner, 2, 5, 6, and 9 *CMISC*-points, respectively.

Other symptoms

Although motion sickness is the most prominent component of SIC, a range of other symptoms were observed. Subjects often could not walk in a straight line and had difficulties with taking corners and maintaining balance. Some subjects reported motion illusions during vertical movements. Figure 4.6 shows the incidence of the symptoms that were scored after the head movement test following each centrifuge run. Many subjects were not completely free of symptoms after the end of the last post test, especially after the heaviest condition. Subjects were still suffering from nausea, dizziness and fatigue for the rest of the day. In one subject, head movements remained provocative up to 6 hrs after the run. Another subject experienced motion illusions when lying in bed at night. In all cases symptoms had vanished completely the following morning. It is interesting to note that sleep in between the test-sessions also had a positive effect on recovery.

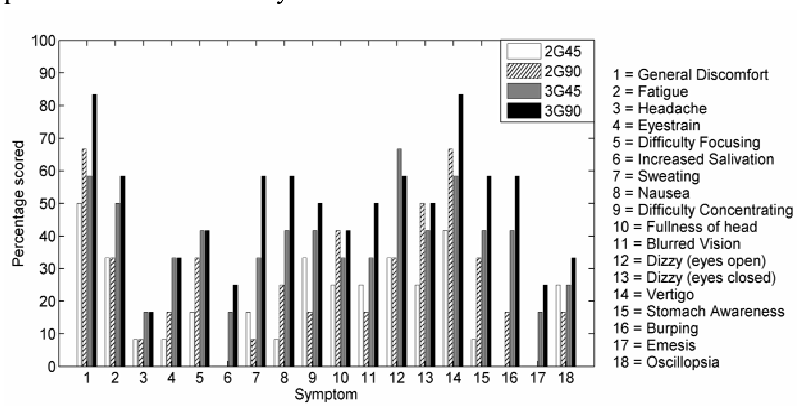

Figure 4.6: Histogram of symptom scores for each centrifuge condition in the first posttest (n=12). Symptoms are listed on the right.

Susceptibility to Earthly motion sickness

Six out of the 12 subjects were considered susceptible to SIC. Following the MSSQ (Golding, 1998), all subjects rated themselves as not (*n*=10) or slightly susceptible (n=2) to *Earthly* motion sickness. MSSQ scores ranged from 0 to 60.5, (mean=18.5, SD=21.5) with the mean score being equal to the 20th percentile score (Golding, 1998). Although the MSSQ scores were fairly low, the SIC-susceptible group had significantly higher MSSQ scores than the non-susceptible group (t=3.1, p<.01). Furthermore, the MSSQ scores were significantly correlated with the CMISC scores of the first posttest after the 3G90 run (r=0.83, p<.01).

DISCUSSION

The re-introduction to Earth's gravity following a sustained exposure to hypergravity can elicit symptoms that resemble those of SAS (e.g. nausea, dizziness, visual illusions). The present study looked further into the nature of the gravito-inertial stimulus that is a prerequisite for the symptoms to occur, by investigating the interaction between G-level and exposure duration on the experienced symptom level (SIC). Subjects were exposed to centrifuge runs at $2G_x$ and $3G_x$ for 45 and 90 minutes and carried out a head movement protocol to elicit SIC.

The results showed that 50% of the subjects were suffering from SIC after one or more centrifuge conditions. This corresponds to the amount found in previous studies (Bles et al., 1997; De Graaf & De Roo, 1996) and is in the same order as the incidence of SAS (e.g. Davis et al., 1988; Homick, 1979; Matsnev et al., 1983). In line with the findings of De Graaf & De Roo (1996), the present results show that both yaw and pitch movements were performed at a significantly lower rate after centrifugation, whereas only the latter provoked nausea. Apparently, susceptible subjects adopted a strategy to limit *all* head motion, regardless of its direction. Although the main trend in our data was that head velocity decreased with an increasing symptom severity, other behaviour was also observed (see Figure 4.4): subjects moving slowly, while experiencing only mild symptoms. This resulted in a weak correlation between $MISC_{max}$ and ω_{max}. As such, the data necessitated the correction of the symptom scores for performance, by means of the

CMISC. Although there are obviously more ways to combine the two measures, the method used here is simple, and based on the statistical analysis. This correction yielded a more pronounced distinction between the SIC- susceptible subjects and the non-susceptible ones as well as a more consistent comparison between centrifuge conditions.

The main finding of this study is that, within the measured range, both G-level and duration affected the symptom level as defined by the *CMISC* scores. The scores following the 3G exposures exceeded those of the 2G exposures and the effects of the 90 minutes exposure exceeded those of the 45 minute exposure. However, it was after the 3G90 exposure only that the average *CMISC* of the SIC-susceptible group was substantially higher than 6 (“mild nausea”). The remainder of this discussion will elaborate on the parameter driving the adaptation process, and possible implications for space flight are discussed.

Time course of adaptation

The results of the current study suggest that the G-level difference is the signal that drives the adaptation during centrifugation and re-adaptation to 1G. The *CMISC* scores of the SIC-susceptible group are higher after 45 minutes centrifugation at 3G than at 2G. The adaptation to 3G is however not yet complete after 45 minutes, given the increase in *CMISC* scores with prolongation of the exposure. It is, however, likely that the effects saturate at a certain time interval, that is, when adaptation is complete. This is in line with the preliminary qualitative results from Bles and colleagues, who showed that the difference between an exposure of 60 and 90 minutes to $3G_x$ was small as compared to the difference between a 30 and 60 minute exposure. This suggests a nonlinear interaction between ΔG and duration. To make a first order estimation of the time constant of the adaptation process, an exponential function of the form $CMISC = A \cdot (1 - e^{-t/\tau})$ was fitted through the data of the first posttest (SIC-group only). These first posttest data were assumed to reflect the status of adaptation just at the end of the centrifuge run. It was furthermore assumed that the time constant of adaptation (τ) was independent of ΔG, but that ΔG did affect the amplitude A, the saturation value of *CMISC*. For instance, it is plausible that a prolongation of centrifugation at 2G does not significantly increase the *CMISC*, so that this value saturates well below 10. At a level of 3G, a level of 10 may be reached. As a first step, A was taken linearly dependent on ΔG so that the function to fit became $CMISC = c \cdot \Delta G \cdot (1 - e^{-t/\tau})$. When the parameter c was fixed at 5, implying a maximal value of 10 for *CMISC*, the time constant τ came to 58 minutes (see Figure 4.7). As can be seen in Figure 4.7, both the 2G and 3G curves intersect the SEM error bars, indicating that the adaptation process can be described by this simple model based on the difference between gravity levels and exposure duration only. Although this is just a first step in modelling the role of ΔG and exposure duration in adaptation, it already may give a fair indication of the order of magnitude of the adaptation time constant.

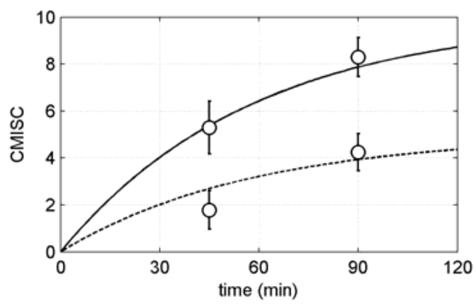

Figure 4.7: Fits on the CMISC data (SIC-susceptible group) as a model for adaptation to 2G (dashed line) and 3G (solid line). Bars indicate standard error of mean.

Interestingly, a time constant of about one hour would imply that the effects after 90 minutes of stimulation would differ significantly from the effects of 60 minutes stimulation. Although this latter stimulus was often used in other centrifuge experiments (De Graaf & De Roo, 1996; Bles et al., 1997), the MISC data obtained there cannot be compared easily with the CMISC scores reported here, because the scores are heavily dependent on the amount, the amplitude and the velocity of head movements made. To the experimenter's observation, the amount of movement required to elicit a particular MISC scores was less after an exposure duration of 90 minutes. A systematic comparison is however needed to be conclusive about this issue.

It can be assumed that different dynamics have to be incorporated in the model when higher G-levels are used. Obviously, there are limits to adaptation speed and to the saturation level of adaptation. Furthermore, the model does not incorporate the dynamics between the level of mal-adaptation and the eventual build up of sickness symptoms (see e.g Oman, 1982; 1990; Bos & Bles, 1998). Admission to more direct adaptation measures would be useful in this respect, especially when they can be monitored during centrifugation. Such a measure would probably also reveal more about the adaptation process in non-susceptible subjects. It is possible that they re-adapt more quickly, too fast to measure any effects, or that this group uses a different strategy to cope with G-transitions disregarding vestibular input altogether. Nevertheless, it can be concluded that the order of conditions showing increasing levels of sickness as revealed by the *CMISC*, i.e., 2G45, 2G90, 3G45 and 3G90, can well be explained by a first order approximation of the adaptation process based on the difference between gravity levels and exposure duration only.

Consequences for Artificial Gravity

The fact that G-transitions can cause disorientation and motion sickness has implications for space flight. Intermittent Artificial Gravity (AG) is currently a promising countermeasure against physiological deconditioning during space flight. However, the exact characteristics of the stimulus, like the optimal body position, frequency, duration, and load, still need to be determined (Clément & Pavy-Le Traon, 2004; Clément & Bukey 2007; see also the Bioastronautics Roadmap[7]). The results of this study show once more that, from a vestibular point of view, locating the vestibular system on or close to the rotation centre is preferred in order to prevent repetitive G-transitions. The fact that both G_x and (the more often used) G_z stimulation may elicit symptoms of SIC (Albery & Martin, 1996; Beier, 1999; Beier et al., 2002; Takeda et al., 1996) suggests that the direction of stimulation is of minor importance as compared to the magnitude. Although the G-transitions experienced after AG exposure or entry into a planet's gravity field are generally smaller than the provocative 2G transition (i.e. from 3 to 1G) used in this study, one should keep in mind that adaptation to the *absence* of gravity forms a singular case within the gravitational continuum. During the stay in microgravity, the astronauts become more visually dependent and some of them eventually adopt a body centred reference frame instead of a gravity based reference frame (e.g. Glasauer & Mittelstaedt, 1998; Oman et al., 1986). Due to this adaptation, orientational responses are no longer required. Re-entry into any gravity field requires regaining of those responses, which can be accompanied by SIC. It is to be verified in space what G-difference is required for this process to occur.

Relation with Earthly motion sickness

A last issue that will be touched upon is the relation between SIC and Earthly motion sickness. Although susceptibility to SAS is correlated with that to SIC (see Chapter 2), no such correlation was found between SAS and Earthly motion sickness (Homick et al., 1987; Oman et al., 1986). The finding that the SIC-susceptible subjects had significantly higher scores on the MSSQ seems to contradict this. In may be too premature to draw conclusions based on our limited sample of subjects, whose MSSQ ratings were all low. Although in previous centrifugation experiments the MSSQ was not administered explicitly, it is known that there are subjects who are very susceptible to Earthly motion sickness, but not to SIC, and vice versa (Bles et al., 1995; Bles, personal communication).

Conclusion

The current study showed that the magnitude of the G-transition and the exposure duration both contribute to the experienced level of SIC after centrifugation. By means of a simple but adequate curve fit, the time constant of adaptation was estimated at about one hour. Although previous studies indicated that a stimulus of 60 minutes at 3G is sufficient to make the symptoms of SIC visible, these results imply that adaptation to 3G is not yet complete after this exposure duration.

Chapter 5

The effect of sustained centrifugation on the orientation of Listing's Plane

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*The orientation of Listing's plane in the head specifies the amount of ocular torsion in each gaze direction, which is known to be affected by gravity. In the search for physiological parameters reflecting the vestibular adaptation process, this chapter therefore investigates whether the orientation of Listing's plane is affected by sustained exposure to hypergravity. Non-astronaut subjects were exposed to the four centrifuge conditions described in Chapter 4. The orientation of LP was determined shortly before and after each centrifuge run, with the head erect and tilted in pitch. The results show that exposure to 3*G_x *for 90 min. induced a backward tilt of LP when the head was erect. Pitch head tilt induced a counter-pitch of LP, which was found to be less pronounced after centrifugation. The results are explained by a model indicating that sustained centrifugation decreases the effect of gravity on orientation responses.*

In Chapter 3 it was described that the subjective vertical measurements did not provide evidence for a consistent bias in the internal representation of the vertical as related to the direction of the applied centrifugal load, nor for a decrease in otolith sensitivity. However, ocular orienting responses were found to be affected by sustained centrifugation (e.g., ocular counter rolling; Groen et al., 1996b). To investigate the effect of sustained centrifugation on orienting ocular responses in more detail, a study was performed that focused on the effect of sustained centrifugation on the orientation of Listing's plane (LP). Listing's law states that, during saccades and fixations, the amount of ocular torsion is determined by the gaze direction, thereby reducing the eye's three degrees of freedom to two. This can be visualised by describing all eye orientations by a particular rotation vector. This vector represents the rotation required to bring the eye from a certain chosen three dimensional reference position to the desired, three dimensional eye position[8]. Instead of filling up a 3D space, these axes, or rotation vectors, generally lie in a single plane, called a *displacement plane* (DP, Tweed and Vilis, 1990). Obviously, the displacement plane is dependent on the choice of the reference position: expressing the *same* eye positions with respect to a different reference position leads to a different DP (i.e., having a different orientation). Changing the orientation of the reference position by an angle of $2\alpha°$ upward or downward, leads to a change in the orientation of the displacement plane of $\alpha°$ in the same direction (Tweed et al., 1990). The term *Listing's plane* (LP) is generally reserved for the DP that is formed by rotation vectors expressed relative to a specific reference position called the 'Primary Position', which is, by definition, orthogonal to LP (Haslwanter, 1995, Tweed and Vilis, 1990).

Interestingly, the orientation of LP in the head is not fixed, but depends on the orientation of the head relative to gravity. Head tilts to the side induce a shift of LP along the torsional (or *x*-) axis while a pitch tilt of the head induces a counter rotation of LP (in monkey: Haslwanter et al., 1992; Hess and Angelaki, 2003; in human: Bockisch and Haslwanter, 2001; Furman and Schor, 2003). The dependence of the orientation of LP on gravity suggests that it is mediated by the otoliths. More specifically, Hess & Angelaki showed that the primary eye position is not governed by

[8] Here eye *position* refers to the eyes' three-dimensional orientation in the head.

the gravito-inertial acceleration, but by the estimate of gravity (Hess & Angelaki, 1997; 1999). Clarke & Haslwanter (2007) also investigated the effect of gravitaty on the orientation of LP, and observed a consistent immediate backward tilt of LP when entering the 0G phase in parabolic flight, which disappeared again in the subsequent 1G phase. This suggests that the orientation of LP is not only dependent on the direction of gravity (i.e. head tilt) but also on its magnitude. Regarding the study described in this chapter, it was thus hypothesized that centrifugation-induced otolith adaptation is reflected in the pitch orientation (elevation) of LP. Because LP forms the coordinate system for the oculomotor system (Crawford & Vilis, 1992; Crawford, 1994; Crawford et al., 1997), such changes would consequently affect oculomotor responses.

Displacement planes (DP, with the reference position straight ahead) were therefore obtained in different head orientations (–45, 0, and 45° pitch tilt) and it was investigated whether the elevation was changed after sustained centrifugation. Changes in the head pitch dependency could indicate a reduced reaction to head tilt (possibly a reduced otolith sensitivity), whereas changes in the absolute orientation of the DP, regardless of pitch head orientation, could indicate a shift in the spatial properties of the oculomotor coordinate system. Such a change could then be the consequence of a direction specific effect of centrifugation.

METHODS

This experiment was carried out as part of the experiment described in Chapter 3, where a detailed description of the study design can be found. In short, 12 non-astronaut subjects were exposed to four different centrifuge conditions on four different days. The centrifuge conditions differed in G-load and duration and consisted of a 45 or 90 min. exposure to $2G_x$ or $3G_x$ (denoted by 2G45, 2G90, 3G45 and 3G90, respectively). DP recordings were performed within 30 min. before and within 45 min. after the centrifuge run. Centrifugation procedures have been described in Chapter 2.

Eye movement recordings

Binocular eye movements were recorded using video-oculography (VOG, Eye Tracking Device, Chronos Ltd, Berlin), at a sampling rate of 100 Hz. The subject was seated and head position in space was fixed by means of a personal bite board (see Figure 5.1). This bite board was attached to a standard that could be adjusted to the desired head position: erect, 45° backward or 45° forward tilt. For calibration purposes, a small laser was attached to the bite-board, projecting a cross-hair (extending 3.0° up, down, left, and right) in front of the subject. By locating this device between the eyes, the reference position was always the straight ahead position. This allowed for calibration in all head orientations.

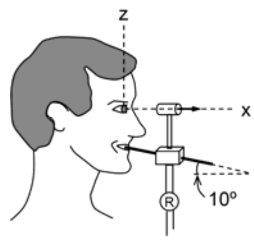


Figure 5.1: Schematic drawing of the experimental setup (calibration 'Head-fixed'). The bite-board was oriented 10° upward, to ensure a comfortable "head erect" position. A laser was positioned in between the eyes, projecting calibration targets along the line of sight. The whole device could be rotated in the sagittal plane about 'R' into a 45° forward or backward position, inducing the desired head tilts.

Due to technical problems with the calibration device during the first 2 days of the experiment, an additional recording was made using a slightly different set-up. The set-up described above will be referred to as 'Head-fixed' and the set-up described below will be referred to as 'Earth-fixed'. In the latter, the subject was seated 60 cm from a backlit projection screen with the head in the erect position (head fixation as described above). Predefined calibration targets (7.0° up, down, left and right) were presented for the left and right eye separately. Because the screen was Earth-fixed, this set-up only allowed for measurements with the head in the erect position.

First, a DP recording was performed using the 'Earth-fixed' method (head erect only). After calibration, eye movements were elicited by a visual target jumping over the screen within a range of ± 15º horizontally and vertically. Second, (when possible) the recordings were performed with the 'Head fixed' method. The screen was removed and the head was randomly positioned into one of the three tilt conditions. Subsequently, calibration was performed with the laser device projecting calibration targets parallel to the line of sight. After calibration, the subject was to make voluntary eye movements for about 45 s. This procedure was then repeated for all head tilt conditions. All measurements were performed in the dark, with only the (calibration) targets visible.

Data analysis: determination of the Displacement Plane

3D eye position (Fick angles) was obtained using dedicated software (Iris Tracker, Chronos Ltd, Berlin). Horizontal and vertical eye position was based on automatic pupil tracking. The torsional position (rotation about the line of sight) was computed by a polar cross correlation algorithm of iris segments (Clarke et al., 2002). Measured with an artificial eye, the measurement accuracy of the Chronos VOG system is 0.1° for the horizontal and vertical eye position and 0.4° for the torsional eye position (within a measurement range of ±20°, see Clarke et al., 2002). However, especially the torsional eye position is subject to measurement errors, that depend on the quality of the iris segments (i.e., the amount of structure present) and the exact location of the pupil centre. Where the first source of error is dependent on characteristics of the individual iris (and can thus not be accounted for), errors in torsional position due to misdefined pupil centres were accounted for by evaluating 36 iris segments for each video frame. These 36 local estimates were then subjected to an iterative sine-fit algorithm that resulted in a more veridical estimate of ocular torsion (Bos and De Graaf, 1994; Groen et al., 1996a). 3D eye position data were subsequently transformed into rotation vectors [r_x, r_y, r_z] (see Haustein, 1989; Haslwanter, 1995), expressed in a head fixed, right-handed, orthogonal coordinate system with the *x*-axis aligned with straight ahead gaze (see Figure 5.2). Each dot in Figure 5.2 represents the tip of a rotation vector, decribing one particular eye position. For example, using the right hand rule, an upward gaze direction with no ocular torsion component is represented by a rotation vector that is aligned with the negative y-axis in Figure 5.2 (left panel), with the vector magnitude equal to the angle of rotation. The DP was obtained from a least squares planar fit ($r_x = ar_y + br_z + c$) through the data. Pitch tilt (elevation, β) of the plane was defined as the tangent of *b* and is the angle between the plane fit and the *z*-axis (see Figure 5.2, right panel). Thickness of the DP, which can be taken as a measure of accuracy, was defined by the standard deviation of the distance from the data to the fitted plane. Planes of which the ratio between the thickness and the vertical range exceeded 0.08 °/° (matching the average thickness divided by 15° assumed to be a useful range) were not taken into account for further analysis. Furthermore, elevation values deviating more than 2·SD from average were considered outliers too. For statistical analysis DP elevations of both eyes were averaged.

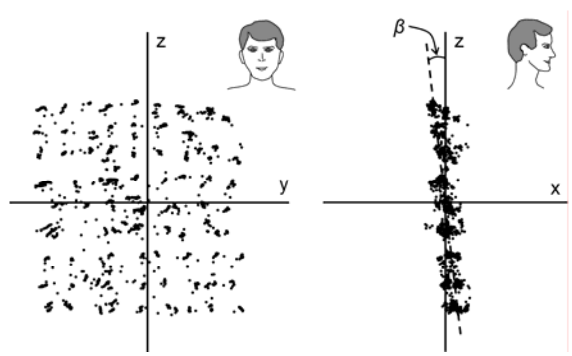


Figure 5.2: Example of recorded data. Eye position is expressed as rotation vectors relative to the straight ahead position. The front view (left panel) shows the gaze directions while the side view (right panel) shows that torsional position is restricted to a displacement plane (DP). DP-elevation is characterized by the angle β, the tilt of the plane relative to the z-axis.

RESULTS

Of the data recorded with the 'Head-fixed' method (i.e., head tilted –45, 0 and +45°), 12.5% was missing due to technical problems (see Methods) while 8% did not meet the inclusion-criteria. The 'Earth-fixed' data set (i.e., head erect only) was complete and allowed an assessment of the repeatability of the DP-elevation in general. The average variability within subjects, as expressed by the standard deviation of DP-elevation of the four consecutive individual pre-tests, equalled 1.6°. The intra-class correlation coefficient for these four repetitions was 0.92. DP-elevation differed considerably between subjects, ranging from –6.2 to +8.0° in the pre-tests (mean 0.0°, SD 2.9°, head erect). The correlation between DP-elevation obtained with the two calibration methods (i.e., 'Head-fixed' and 'Earth-fixed', see Methods) was 0.66 ($p<0.0001$). Average thickness of DP equalled 1.2° (SD 0.4).

Effect of head tilt on DP-elevation

DP-elevation significantly depended on head tilt as indicated by a within subject main effect ANOVA on the data of the pre-tests ($F(2, 147)=12.09$, $p<.001$): the DP tilted backward when the head tilted forward and vice versa (see Figure 5.3, open symbols). To assess the effect of the different centrifuge conditions on this tilt-dependency we calculated the slope of the regression line (° DP tilt/° head tilt) through the available data for each subject and condition. This data was then submitted to a within subjects, 4 (centrifuge condition) × 2 (session) ANOVA, where session refers to the pre- and post-test. Despite the small number of subjects having a full data-set on slope ($n=5$), the effect of session was significant ($F(1,4)=8.2$, $p=.046$). Averaged over all data, mean slope changed from –0.02°/° (SD = 0.02) in the pre-test to –0.01°/° (SD = 0.02) in the post-test (see Figure 5.3, filled symbols). The analysis did not reveal significant differences between the effects of the four centrifuge conditions on slope. Because this could be due to the limited number of subjects having a full dataset on slope, an additional analysis was performed, using a main effect ANOVA with subject as random factor and centrifuge condition and session as fixed factors. An interaction term centrifuge condition × session was added to the model. However, no differences between the effects of centrifuge condition could be demonstrated. Again, only the effect of session appeared significant ($F(1, 59) = 4.22$, p=.044).

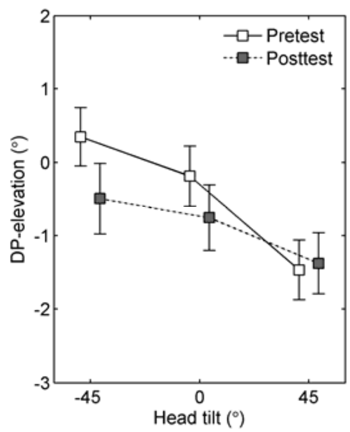


Figure 5.3: Mean DP-elevation as a function head tilt, averaged over the four centrifuge conditions (bars indicate standard error of mean). According the right-hand-rule, negative angles indicate backward tilt of the DP relative to the z-axis.

Absolute orientation of DP

The data in Figure 5.3 suggests that not only the effect of head tilt is affected by centrifugation, but also the absolute orientation of the DP in the head. Figure 5.4 shows the average difference between the pre- and post-tests for these head erect conditions for the four centrifuge conditions. Note that the difference depends on the applied centrifuge condition: a significant difference of −1.0° (SD 1.5°) was found in the 3G90 condition ($t(11) = -2.34$, p=.039), indicating a backward tilt of DP when the head was erect.

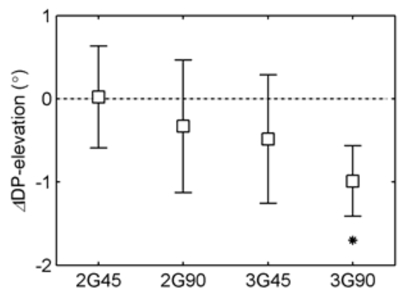


*Figure 5.4: Mean difference in DP-elevation between the pre- and posttest for the 4 centrifuge conditions (Bars indicate standard error of mean). A negative change indicates a backward tilt of DP relative to the pretest value. Statistical differences are indicated by *.*

DISCUSSION

In the current study displacement planes (DP, with the reference position defined as the straight ahead gaze) were recorded in different head orientations and it was investigated whether 1) the dependency of DP-elevation on pitch head tilt was affected by sustained centrifugation, and 2) whether sustained centrifugation induced changes in the spatial properties of the oculomotor coordinate system. The results indicate that both questions can be answered in the positive. Averaged over all conditions, centrifugation decreased the counter pitch of DP in response to head tilt. Furthermore, 90 minutes of $3G_x$ stimulation induced a small but significant backward tilt in the absolute orientation of DP when the head was erect. Shorter exposures or exposures at a lower G-level only induced marginal changes in the absolute orientation of DP.

Methodological issues

Average thickness of the displacement planes recorded in the current study was in the upper range of the values generally obtained for recordings made with scleral search coils (Bockisch & Haslwanter 2001:

0.4°; Furman & Schor, 2002: 1.0°; Haslwanter et al., 1994: <1°; Melis et al, 1997: 0.69°). This can be attributed to the fact that the determination of ocular torsion using video-based systems is slightly less accurate than obtained from scleral search coils (Houben et al., 2006, but see also Merfeld et al., 1996). Nevertheless, the day to day variability of DP-elevation was similar to the variability found by others (Clarke & Haslwanter 2007: 2.1°; Haslwanter et al., 1994: 3.4°; Melis et al., 1997: <3°). In addition, the effect of pitch head tilt on DP-elevation as found by Bockisch and Haslwanter (2001) and Furman and Schor (2003) was replicated. Therefore it is concluded that video-oculography is suitable to determine DP-elevation in humans.

Interestingly, the magnitude of DP counterpitch found in the pre-tests seems to exceed the effect reported by Furman and Schor (2003), who measured the orientation of Listing's plane in response to whole body tilts up to 30°. The effect of body tilt on the orientation of Listing's plane found by Bockisch and Haslwanter (2001) also seemed somewhat smaller, although it is hard to judge the data based on their figures and the limited amount of subjects. Because both studies used whole body tilt instead of head tilt, as was the case in our study, it is tempting to ascribe differences to the contribution of the neck. Influences of the neck on ocular orientation responses (OCR) have, for example, also been described by Bles et al. (1998b). Furthermore, it may be assumed that a head-tilt paradigm represents a more natural situation than a body tilt paradigm. The neck provides additional information about the orientation of the head relative to the vertical and may therefore affect the orientation of oculomotor responses.

Are the changes in DP orientationrelated to vestibular adaptation?

Do the results of the current study reflect changes in the oculomotor system that can be related to adaptation-induced phenomena? The centrifugation induced effects were small and it does not seem plausible that such small changes would be the cause of major behavioural changes that are observed after sustained centrifugation. Given the large intra-subject variability of DP-elevation, the effects are in any case not large enough to monitor adaptation at an individual level. Nevertheless, the results may contribute to our understanding of vestibular adaptation in general. In the next paragraphs a hypothesis is proposed that might provide an explanation for these results.

The decreased DP-counterpitch found after sustained centrifugation suggests a decreased sensitivity or gain of the orientation response. This is in accordance with findings of Groen et al. (1996b), who measured the otolith driven ocular response (Ocular Counter Roll, OCR) to lateral body tilt and found that the gain of this response was decreased after a 60 min exposure to 3G. Interestingly, as was already mentioned in Chapter 3, a similar decrease in OCR gain was generally also observed after spaceflight (Dai et al., 1994; Hoffstetter-Degen et al., 1993; Vogel & Kass, 1986; Young & Sinha, 1998; but see also Moore et al., 2001). This down-scaling of orientation-responses may be a common reaction of the system to deal with novel gravitational states. Instead of the gravitational cue, the body or the visual environment is taken as a spatial reference. Associated to this is Mittelstaedt's concept of the idiotropic vector (Mittelstaedt, 1983), which is the tendency to take the longitudinal body axis as a reference for verticality. It is already known from spaceflight that astronauts tend to shift to a body-centric frame of reference and interestingly, there is also evidence that this occurs after the transition to hypergravity as well. Jenkin and colleagues (2005) measured the perceived direction of 'up' in the different phases of parabolic flight and found that *both* in the micro- and hypergravity phase subjects shifted towards a body-centric frame of reference.

This shift towards a more body-centric frame of reference could also apply to Listing's plane (LP) Let us assume that LP takes a certain orientation in the head, which is modulated by the direction of gravity relative to the head. As such, the orientation of LP is determined by a head-fixed component and a space-fixed component. This can be visualized by denoting the head-fixed component by the vector $\mathbf{LP_h}$, comparable to an 'idiotropic vector', and the space-fixed component by the vector $\mathbf{LP_g}$. The resulting elevation of LP follows from the addition of these two vectors (see Figure 5.5, left panel). Modulation of LP-elevation by head tilt is accomplished by varying the direction of $\mathbf{LP_g}$ relative to $\mathbf{LP_h}$, resulting in the counterpitch of LP during head tilt. The strength of this modulation is given by the length of $\mathbf{LP_g}$ relative to $\mathbf{LP_h}$: If there would be no effect of head tilt on LP-elevation, $\mathbf{LP_g}$ would be 0, whereas if LP would perfectly orient to gravity, $\mathbf{LP_g}$ would be large relative to $\mathbf{LP_h}$. Now the effect of centrifugation can be understood by decreasing the effect of gravity on LP-elevation, in favour of the head-fixed orientation $\mathbf{LP_h}$. Decreasing the length of $\mathbf{LP_g}$ results in a backward tilt of LP (see Figure 5.5, right panel), together with a smaller effect of head tilt on LP-elevation. This is accordance with the results of the current study.

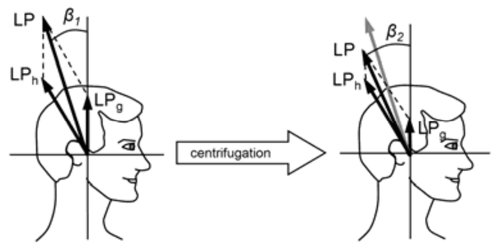


Figure 5.5: Proposed model determining LP-elevation. The orientation of LP (β) results from vector addition of a head-fixed vector $\mathbf{LP_h}$*, combined with a vector* $\mathbf{LP_g}$ *that is parallel to gravity (left panel). The length of* $\mathbf{LP_g}$ *denotes the strength of the gravitational modulation. If the head is tilted, the vector* $\mathbf{LP_g}$ *induces a counterpitch of LP. If the effect of gravity on LP-elevation is decreased after centrifugation (right panel), this would result in a backward tilt of LP* ($\beta_1<\beta_2$)*, together with a decrease of head tilt induced modulation of LP-elevation.*

Furthermore, the model also predicts a backward tilt of LP in 0G: in absence of $\mathbf{LP_g}$, LP would be equal to $\mathbf{LP_h}$. However, the extent of this effect has been shown to exceed the effect of body tilt on the orientation of LP (Clarke & Haslwanter, 2007), which is not (yet) reproduced by the model. Possibly, a zero gravity condition leads to a qualitatively different response than conditions where a gravity vector is present.

Interestingly, the hypothesis that LP-elevation is determined by a head-fixed and a space-fixed component also matches experimentally obtained results on the effect of head pitch on LP-elevation. These studies reported on the effect of a full revelation of head tilt on LP-elevation and showed an asymmetric response (e.g., Bockisch and Haslwanter, 2001; Haslwanter et al., 1992). That is, elevation when the head is erect differs from elevation in the up-side-down position, and forward head tilt often leads to greater changes than backward head tilt, which is qualitatively simlar to the effect of pitch tilt on LP-elevation as shown in Figure 5.6. This figure shows the orientation of LP (OLP) that is predicted from the proposed model, and clearly shows this asymmetrical behaviour. Nevertheless, it is clear that this hypothesis requires further elaboration. Considering the large variability of LP-elevation within, and between subjects, a larger amount of data is required for a quantitative analysis.

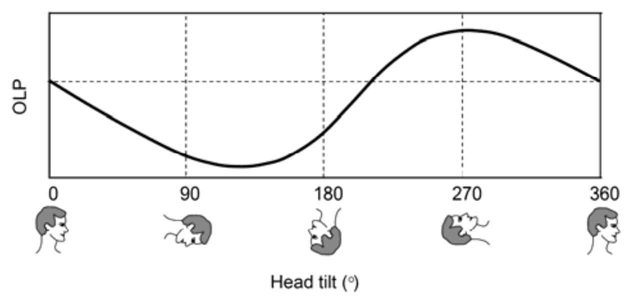


Figure 5.6: Predicted elevation of Listing's plane (OLP) as a function pitch head tilt. Note that this type of behaviour is also observed experimentally (Bockisch & Haslwanter, 2001; Haslwanter et al., 1992)

Alternatively, the two effects of sustained centrifugation could also be caused by two separate mechanisms: 1) a direction-specific bias in the estimate of the gravitational vertical, responsible for the backward tilt of LP when the head is erect, and 2) a decreased effect of head tilt on the spatial behaviour of LP. The hypothesis mentioned above is elegant in that it links these two effects to a single cause: a shift towards a more body centred frame of reference.

Conclusion

It was shown that after centrifugation the DP tilts backward, and the effect of head tilt on DP-elevation is decreased. This suggests that the gain of orientation responses is decreased after sustained centrifugation, which can be understood as a shift towards a more head-centric frame of reference. Nevertheless, because the effects were small relative to the within-subject variability, DP-elevation was not considered to be informative about otolith adaptation to hypergravity at an individual level.

Chapter 6

The effect of sustained centrifugation on the spatial characteristics of velocity storage

This chapter focuses on the effects of sustained centrifugation on the velocity storage (VS) mechanism, which is associated with the interaction between otolith and semicircular canal signals in the low frequency range. Recently it has been proposed that this VS mechanism plays a role in the discrimination of gravitational and inertial acceleration during dynamic mid-frequency head movements as well. The effects of sustained centrifugation found so far may therefore be related to inadequate processing of these vestibular signals. In humans, the VS mechanism is also responsible for the reorientation of the eye velocity vector (EVV) towards gravity during off-vertical optokinetic and vestibular stimulation. It was therefore investigated whether these spatial eye movement properties were affected after sustained centrifugation. To that end, yaw optokinetic nystagmus was recorded with the head erect and tilted to the side. The results indicated a reduction in the reorientation of the EVV following sustained centrifugation, which suggests a decrease in velocity storage activity.

This chapter tries to link the aftereffects of sustained centrifugation, like motion sickness and disorientation, to changes in canal-otolith interaction. More specifically, it focuses on a process called velocity storage (VS) which, as will be described below, appears to play a role in solving the tilt-translation ambiguity. As mentioned in Chapter 1, the tilt-translation ambiguity refers to the fact that inertial (i.e., translation) and gravitational acceleration (i.e., tilt) are physically indistinguishable.

The so called VS-mechanism or -integrator (Raphan et al., 1979) refers to a brain stem network with integrative properties that traditionally is believed to improve the dynamics of the angular vestibulo-ocular reflex (aVOR) at low frequencies. When rotating at a constant velocity, for example, it extends the duration of effective compensation for head movement by increasing the dominant time constant of the aVOR, as was also mentioned in previous chapters. The VS-integrator is also responsible for the dynamics of the nystagmus observed during and after optokinetic stimulation (Cohen et al., 1977; Cohen et al., 1981; Raphan et al., 1979). Nevertheless, several researchers suggested that, apart from these properties, the actual purpose of this network is to integrate multiple sensory signals to provide a spatially referenced estimate of head velocity (Angelaki & Hess, 1994; 1995; Jaggi-Schwarz et al., 2000), likely aimed at stabilizing gaze during locomotion (Dai et al., 1991; Solomon & Cohen 1992). The properties of the VS-integrator remained, however, associated with low frequency behaviour, outside the range of natural movements.

Interestingly, Green and Angelaki (2003, 2004) proposed a new role for the VS-integrator in spatial orientation. They suggested that its main function is to process (temporally integrate) spatially referenced extra-otolith information, necessary for the discrimination of gravitational and inertial acceleration (see Chapter 1). Thus, in order to generate appropriate responses, our central nervous system has to use additional (extra-otolith) information to distinguish between gravity and inertia. The temporal integration of angular velocity signals (e.g. originating from the semicircular canals) ensures the appropriate eye movements during combined translational and tilt movements.

The idea that angular velocity signals are necessary to discriminate tilt from translation is not novel (Mayne, 1974), and has been applied in many models for spatial orientation (e.g., Angelaki et al., 1999; Merfeld et al., 1993; 1999; Bos & Bles, 2002; Zupan et al., 2002). New is the idea that the required temporal integration could well be performed through the VS-integrator, as suggested by Green and Angelaki (2003; 2004). This would especially apply to movements in the mid-high frequency range (i.e., the range of natural movements), which opens up a new perspective for understanding the problems with spatial orientation induced by sustained centrifugation. These problems, in particular the occurrence of motion sickness, usually arise during mid- to high-frequency movements, and especially when head tilt is involved (Bles & De Graaf, 1993; De Graaf & De Roo, 1996; Bles et al., 1997). Interestingly, it has been demonstrated that VS-activity is related to motion sickness susceptibility: subjects showing a long aVOR time constant during vertical yaw axis rotation (horizontal aVOR) were found to be more prone to motion sickness than subjects showing shorter time constants (e.g. Bos et al., 2002; Cohen et al., 2003; Dai et al., 2003; De Wit, 1953; Quarck et al., 1998). In addition, Dai and colleagues (2003, Cohen et al., 2003) demonstrated a relationship between the *spatial* properties of VS and motion sickness induced by Coriolis stimulation. The spatial properties of VS emerge during rotation about an off-vertical axis, where the eye velocity vector (EVV) shows a tendency to align with gravity (e.g., Dai et al., 1991; Raphan & Cohen, 1989; Raphan & Sturm, 1991, see Cohen et al., 1999 for a review) instead of remaining aligned to the stimulus-axis. Dai et al. (2003) suggested that the misalignment between the EVV and the Earth vertical was responsible for the experienced motion sickness. They therefore proposed that VS is the critical element in the generation of motion sickness.

Given the proposed relationship between VS activity, the tilt/translation ambiguity and motion sickness, it was hypothesized that sustained centrifugation affects the VS mechanism, which, in turn, may be responsible for some of the phenomena observed after sustained centrifugation. There is already some evidence that VS is indeed affected by exposure to altered gravitational states. DiZio and Lackner showed in a series of experiments that the dominant time constant of the horizontal aVOR was reduced during the both the 1.8 and 0G phase of parabolic flight (1987; 1988; 1991; 1992). And, as was already mentioned in Chapter 3, sustained centrifugation (60 min at $3G_x$) also led to a reduction of this time constant (Groen, 1997), suggesting a reduction of velocity storage activity.

The current study focuses on the spatial properties of VS, that is, the tendency of the EVV to align with gravity. In humans this becomes apparent during horizontal optokinetic nystagmus (OKN) with the head tilted to the side: apart from a horizontal eye movement, a vertical component is often present as well (Arai & Cohen, 1999; Gizzi et al., 1994; Moore et al. 2005). This phenomenon is called cross-coupling. Although the resulting reorientation of the EVV is far from perfect (about 20% of the head tilt), the amount of reorientation can serve as a measure for the VS activity. Given the results of Groen (1997) mentioned above, sustained centrifugation was expected to reduce this effect of head tilt on EVV-reorientation.

For this study, OKN was recorded during optokinetic stimulation about the subject's yaw axis as a function of lateral head tilt, and it was investigated whether the responses were affected by sustained centrifugation. After showing that the amount of cross-coupling is reduced following sustained centrifugation, a model will be presented that relates the observed changes in cross-coupling with a decrease in the VS-contribution to the spatial orientation of the EVV. The discussion will finally elaborate on the possible consequences for spatial orientation.

METHODS

The assessment of velocity storage activity through the recording of optokinetic nystagmus was part of the experiment described in Chapter 3 (see Figure 3.4 for the design of this experiment). In short, 12 non-astronaut subjects were exposed to four different centrifuge conditions on four different days. The centrifuge conditions differed in G-load and duration and consisted of a 45 or 90 min. exposure to $2G_x$ or $3G_x$ (denoted by 2G45, 2G90, 3G45 and 3G90, respectively). Optokinetic nystagmus was recorded within 45 min. before and 30 min. after the centrifuge run. The centrifugation procedures have been described in Chapter 2.

Recording of optokinetic nystagmus

Binocular eye movements were recorded at a sampling rate of 100 Hz using a head-mounted video-based eye tracking device (ETD, Chronos Ltd, Berlin). The subjects were seated on a height-adjustable chair, placed in front of a backlit projection screen (110 by 150 cm). Viewing distance was 65 cm. Head position in space was fixed by means of a personal bite board, attached to a standard that could be placed in one of the desired head positions: erect, or tilted 45º to the left or right.

To drive horizontal eye movements while allowing vertical eye motion, the optokinetic stimulus consisted of a symmetrical vertical black and white stripe pattern that was projected in a circular field of view, extending over a viewing angle of 74º (see Figure 6.1). The centre of the stimulus area was always located straight ahead. Stripe width was 3º in all viewing angles, thus simulating a drum rotating about the subject's yaw axis. Edges of the stripes were blurred to minimize visual tracking. The pattern was always aligned with the head's yaw axis, and moved at 35º/s. The experiments took place in an otherwise darkened room.

Figure 6.1: The optokinetic stimulus in the three head tilt conditions. The pattern moved along the interaural axis, either from left to right or from right to left.

After positioning the subject in one of the three head tilt conditions a calibration was performed for the right and left eye separately.

Subsequently, a fixation dot was presented at the centre of the screen for 3 s, followed by 30 s of optokinetic stimulation. After that, the stimulus was switched off (thus leaving the subject in total darkness), while the eye movement recording continued for 10 s. Subsequently, the measurement was repeated with the pattern moving in the opposite direction. Tilt conditions (3) and stimulus direction (2) were presented in a random order, amounting to six trials per test (pre and post centrifugation) in total.

Data analysis: determination of the eye velocity vector

3D eye position (Fick angles) was obtained using dedicated software (Iris Tracker, Chronos Ltd, Berlin). Horizontal and vertical eye position was based on automatic pupil tracking, whereas the torsional position (rotation about the line of sight) was computed by polar cross correlation of iris segments (Clarke et al., 2002), as described in Chapter 5. The 3D eye velocity vector (EVV) was calculated from the eye position data and their time derivatives (Goldstein, 1980; Haslwanter, 1995). Yaw eye velocity (ω_z) was defined as the component generating left-right eye movements and pitch eye velocity (ω_y) as the component generating up-down eye movements. A right-handed, head-fixed frame of reference was used throughout, with the x-axis aligned with the straight ahead gaze, and the y-axis aligned with the inter-aural axis.

The amount of cross-coupling during OKN was characterized by the median orientation of the EVV relative to the stimulus axis (i.e. the head longitudinal axis, see also Figure 6.2). The first 10 seconds of each trial were disregarded from the analyses, to ensure full build up of velocity storage (Fletcher et al., 1990). After removing the saccades of the remaining 20s interval, the mean eye velocity per nystagmus beat was calculated from a linear fit on the raw eye velocity data. The orientation of the EVV was then defined as $\alpha = \mathrm{atan}\left(\mathrm{med}(\omega_y)/\mathrm{med}(\omega_z)\right)$. For statistical analysis results of the left and right eye were averaged. OKN gain was defined as the median of ω_z divided by the stimulus velocity.

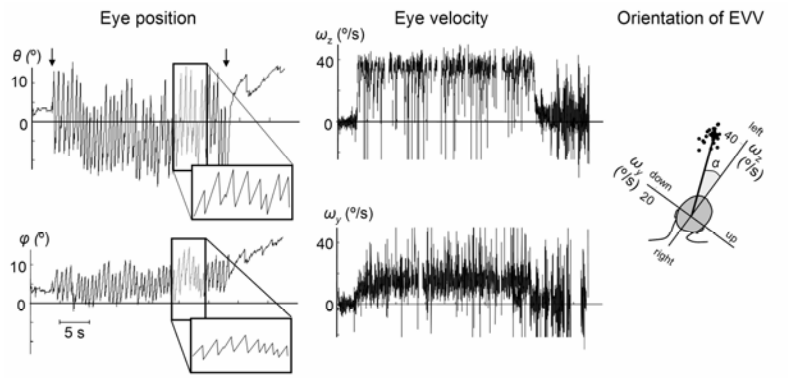


Figure 6.2: Example of a recording when the head was tilted to the right and the stripes were going from right to left. The left panel shows the horizontal (θ) and vertical (φ) eye position (Fick angles, where positive values indicate leftward and downward eye positions). The start ("lights on") and stop ("lights off") of the optokinetic stimulus are indicated by vertical arrows. The middle panel shows the corresponding components of eye velocity. The resulting orientation of the EVV (denoted by α) is shown in the right panel. Here, each dot represents the mean eye velocity of one nystagmus beat. The pitch-down component induces a reorientation of the EVV towards the spatial vertical. Note that downward eye movements result in EVV endpoints left of the z-axis.

RESULTS

An example of a recording is given in Figure 6.2 (head tilt to the right, stripes from right to left). At the start of the optokinetic stimulus (first arrow in upper-left panel of Figure 6.2) yaw eye velocity builds up almost immediately. A pitch-down component (i.e., cross-coupling) is also present, taking several seconds to build up. Due to this pitch component, the EVV shifts towards the spatial vertical (see Figure 6.2, right panel). When the stimulus is switched off (second arrow in upper-left panel of Figure 6.2) a small optokinetic after nystagmus (OKAN) is present. In the following section the data on cross-coupling during OKN is presented, reflecting the spatial properties of VS. Subsequently the second section presents a model describing these results, in order to quantify the effects found.

Cross-coupling during OKN

Figure 6.3 shows the average orientation of the EVV in the six experimental conditions as measured before and after centrifugation (3G90 condition). The other centrifuge conditions gave similar results. The EVV is expressed relative to the head yaw axis. A deviation of the EVV from the ordinate in Figure 6.3 indicates the presence of a pitch eye movement, i.e., cross-coupling.

Surprisingly, a small but significant amount of cross coupling is present when the head is erect: A pitch down eye movement is observed that is independent of the direction of the optokinetic pattern. This was consistent over all conditions and subjects and tilted the EVV away from the head yaw axis over an angle of 5.0° (mean over 192 observations, SD=4.0º, $t(11)=5.46$, $p=.0002$). Due to this component, the reorientation of the EVV caused by the lateral head-tilt is biased in the pitch-down direction, but it still induces an additional shift towards the spatial vertical: a downward eye velocity component was present when the stimulus velocity had an upward component with respect to gravity, and an upward eye velocity component was present when the stimulus velocity had a downward component relative to gravity. As such, the six conditions can be divided into three groups, based on the characteristics of the optokinetic stimulus velocity with respect to gravity (see also Figure 6.3): 'G-neutral' (stimulus velocity axis is aligned with gravity), 'Against-G' (stimulus velocity axis is tilted away from the Earth vertical, having an upward component with respect to gravity) and 'With-G' (stimulus velocity axis is tilted away from the Earth-vertical, having a downward component with respect to gravity). These G-conditions are also graphically indicated in Table 6.1.

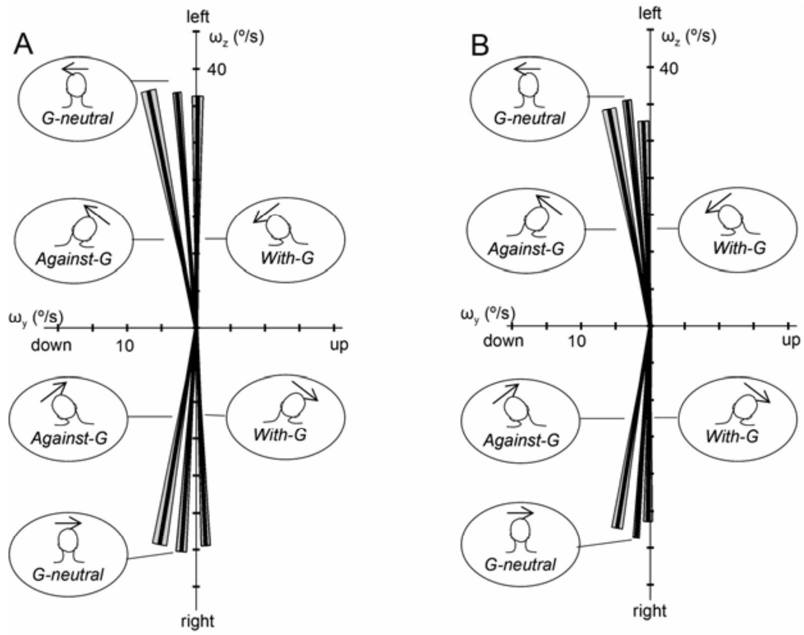


Figure 6.3: Orientation of the eye velocity vector (α in Fig. 6.2) relative to the head-longitudinal axis, for the six experimental conditions. The drawings indicate the corresponding head orientation and direction of the optokinetic stimulus. 'G-neutral' denotes the conditions where the stimulus velocity vector is aligned with gravity, 'With-G' denotes the conditions where the stimulus velocity vector has a downward component relative to gravity (thus requiring an upward eye velocity component to shift the EVV towards gravity), and 'Against-G' denotes the conditions where the stimulus velocity vector has an upward component relative to gravity (thus reguiring a downward eye velocity component to shift the EVV towards gravity). Panel A shows the pretest values of the 3G90 condition, panel B the post-test values. Mean orientation of the EVV (n=12) is indicated by the thick solid line, where its length indicates the mean gain. The gray patches indicate standard error of mean of α.

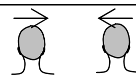
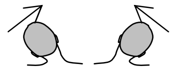
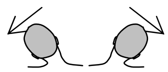
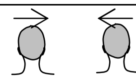
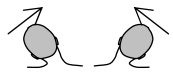
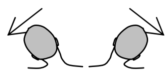
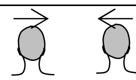
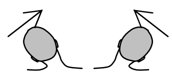
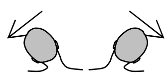
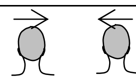
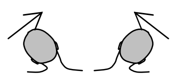
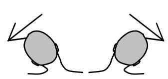
That head tilt indeed induced significant reorientation of the EVV was confirmed by the statistical analysis: when submitted to a within subjects factorial ANOVA (Centrifuge-condition (4) × measurement condition (6) × test-session (2)), the effect of measurement condition was significant

($F(5, 50)=33.2$, $p<.0001$). A Tukey posthoc test indicated that the two G-neutral conditions, the two With-G conditions and the two Against-G conditions did *not* differ from each other, whereas the head-tilt conditions differed from those with the head erect. The results show that the orientation of the EVV relative to the head yaw axis depended on head tilt and the orientation of the optokinetic stimulus relative to gravity (i.e, Against-G or With-G). In both conditions a significant crosscoupling was induced. Table 6.1 lists the EVV orientation values for the 4 centrifuge conditions, pooled into the G-neutral, With-G and Against-G groups.

Effect of centrifugation on crosscoupling

Figure 6.3B shows the EVV orientation after centrifugation, where changes were found in the orientation of EVV in both With-G conditions: the small upward velocity component changed into a downward velocity component ($F(5,50)=6.61$, $p<.0001$, with Tukey posthoc test). The effect of head tilt on EVV reorientation was analyzed further by calculating the difference in EVV orientation relative to the head-erect condition, thus eliminating the pitch down bias found when the head was erect. The reorientation values for the two With-G and the two Against-G conditions were subsequently submitted to a within subjects factorial ANOVA (Centrifuge-condition (4) × measurement condition (4) × test-session (2)). Here the four measurement conditions indicated the four conditions where the head was tilted. The ANOVA revealed a significant main effect for session ($F(1, 11)=21.3$, $p=.00075$): the head tilt induced reorientation of the EVV was decreased after centrifugation. No differences were found between the four head tilt conditions, indicating that the decrease in reorientation was present in *all* conditions. The mean amount of head tilt induced reorientation (averaged over the four centrifuge conditions and four tilt conditions) equaled 6.5º in the pretest (SD=4.3º, 95% confidence interval = [5.9, 7.1]) versus 5.0º in the posttest (SD=4.0º, 95% confidence interval = [4.5, 5.6]).

TABLE 6.1
Mean EVV orientation (α) and OKN gain, pooled into G-neutral, Against-G and With-G groups.

Centrifuge condition	G-condition		Pretest α(°)	Pretest OKN gain	Posttest α(°)	Posttest OKN gain
2G45		G-neutral	5.0 (3.9)	0.85 (0.15)	6.0 (4.0)	0.89 (0.12)
		Against-G	11.6 (7.9)	0.84 (0.19)	11.6 (6.5)	0.87 (0.19)
		With-G	−1.9 (5.6)	0.85 (0.15)	0.7 (6.3)	0.85 (0.15)
2G90		G-neutral	4.6 (3.8)	0.90 (0.14)	5.4 (3.5)	0.87 (0.17)
		Against-G	11.7 (6.5)	0.87 (0.19)	11.1 (6.9)	0.88 (0.19)
		With-G	−1.1 (5.7)	0.85 (0.18)	1.2 (5.1)	0.82 (0.16)
3G45		G-neutral	4.1 (4.8)	0.89 0.13)	4.6 (3.7)	0.89 (0.15)
		Against-G	11.2 (7.7)	0.87 (0.16)	10.7 (6.2)	0.88 (0.17)
		With-G	−1.9 (5.6)	0.82 (0.16)	0.2 (5.1)	0.81 (0.17)
3G90		G-neutral	4.5 (4.3)	0.89 (0.10)	5.2 (3.8)	0.85 (0.19)
		Against-G	11.2 (6.7)	0.89 (0.12)	10.7 (5.9)	0.82 (0.19)
		With-G	−1.5 (4.8)	0.87 (0.11)	1.4 (5.1)	0.77 (0.20)

The ANOVA did not reveal a significant effect of centrifuge condition, indicating that all conditions had a similar effect on EVV reorientation. Inspection of the data revealed that the average decrease of head tilt induced reorientation was largest in the most strenuous condition (3G90, see Figure 6.4), but differences between conditions were small.

Averaged over all observations, mean OKN-gain equaled 0.86 (SD 0.16, see also Table 6.1). Although no differences were found between the pre- and posttest, the tilt-condition (G-neutral, With-G or Against-G) significantly affected OKN gain ($F(2,22)=16.7$, $p<.001$). A post-hoc Tukey test indicated that the gain in the With-G condition was significantly lower than the other two conditions.

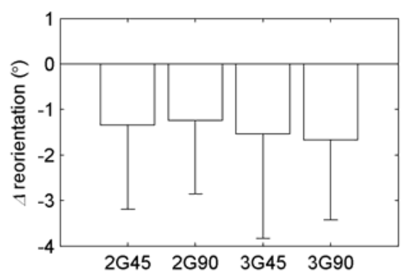


Figure 6.4: Difference in the head tilt induced EVV-reorientation between the pre- and the posttest, for the four centrifuge conditions.

Vector model for OKN

In this section a model is proposed that accounts for the results regarding the orientation of the EVV, both before and after centrifugation. By means of this model, the observed changes in cross-coupling can be related to a decrease in the contribution of VS to the orientation of the EVV.

During optokinetic stimulation, the orientation of the resultant eye velocity vector is determined by the direction of the stimulus and, through VS, by the direction of gravity relative to the head. The current results suggest that there is a third determinant present: regardless of the head orientation, the eye showed a tendency to move down in the head. These three components were combined in a model possibly explaining these observations.

It is proposed that the orientation of the EVV is determined by the sum of the vectors **S**, indicating the stimulus-induced component, **VS** indicating the velocity storage-induced component, and **B** indicating the downward bias. Figure 6.5 depicts the model for the three tilt conditions. **S** is related to the angular velocity of the optokinetic pattern and is always aligned with the head yaw axis, **VS** is hypothesized to be aligned with the Earth-vertical, and **B** is assumed to be aligned with the interaural axis to account for the downward eye motion. The orientation of the EVV (α) then is determined by:

$$\alpha = \arctan\left(\frac{|\mathbf{B}| + |\mathbf{VS}| \cdot \sin(\beta)}{|\mathbf{S}| + |\mathbf{VS}| \cdot \cos(\beta)}\right) \tag{6.1}$$

with β the angle of head tilt.

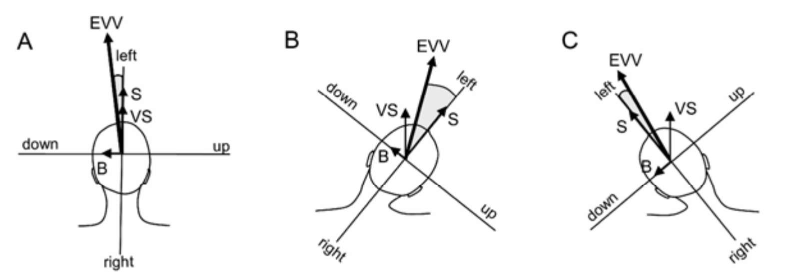


*Figure 6.5: Vector model for OKN, specified for the G-neutral condition (A), the Against-G condition (B) and the With-G condition (C). The stimulus vector **S** is always aligned with the head-longitudinal axis, the velocity storage **VS** vector with gravity, and the bias vector **B** with the inter-aural axis. The sum of these vectors determines the orientation of the resulting EVV (α), indicated by the shaded arcs.*

With the bias-vector included in the model, the different effects of centrifugation in the With-G and the Against-G conditions can be understood. Recall that centrifugation changed the *absolute* orientation of the EVV in the With-G conditions only. For illustration puposes, a complete absence of **VS** is Figure 6.6, depicting a theorectical effect of sustained centrifugation (as is shown later, the actual decrease in VS is obviously less than 100%). When the head is erect, the EVV is shifted further away from the stimulus-axis (Figure 6.6A, compare the orientation of EVV_{pre} with that of EVV_{post}), while it is shifted closer to the stimulus-axis in the Against-G condition (Figure 6.6B). The change in EVV-orientation is largest in the With-G condition, where the EVV shifts to the other side of the ordinate (Figure 6.6C). These changes are qualitatively all in accordance with the experimental data (see Table 6.1 and Figure 6.3).

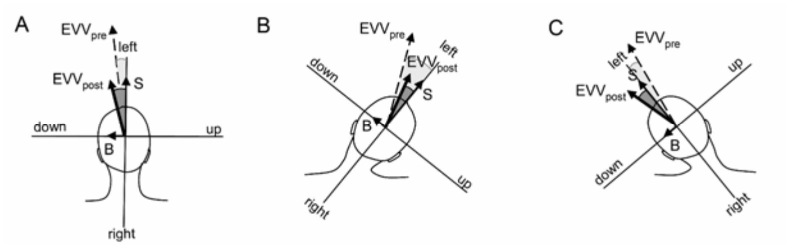


Figure 6.6: Vector model for OKN, specified for the G-neutral condition (A), the Against-G condition (B) and the With-G condition (C). Centrifugation is hypothesized to decrease the effect of velocity storage on the orientation of the EVV. In this example ***VS****=0, leading to changes in the orientation of EVV that are consistent with the data. The orientation of the EVV before centrifugation,* EVV_{pre}*, is indicated by the shaded arc in light-gray whereas the orientation after centrifugation,* EVV_{post} *is indicated in dark gray.*

To analyze this model quantitatively, it was fitted to the data of the most strenuous centrifuge condition (3G90) for each individual subject and assuming variable vector lengths. The length of **S** was set to unity and the relative lengths of **VS** and **B** were determined using Eq. 6.1. The model described the data very well: a comparison of the observed and the predicted values yielded a correlation of r=0.99. The residual sum of squares was 0.06° on average (SD 0.09°). Averaged over all subjects, the lengths of **S** : **VS** : **B** equaled 1 : 0.19 : 0.10 in the prestest (SD_{VS} 0.08; SD_B 0.10) versus 1 : 0.13 : 0.11 in the posttest (SD_{VS} 0.04; SD_B 0.08). This implies a significant reduction in the contribution of VS of 31% after centrifugation ($t(11)=3.19$, $p=.0086$). The change in **B** was not significant.

DISCUSSION

The study described in this chapter focused on the spatial properties of velocity storage (VS) in humans. Because the spatial orientation of the eye velocity vector (EVV) during optokinetic nystagmus is governed by VS-activity (Cohen et al., 1977; Raphan et al., 1979) this parameter was used to determine whether sustained centrifugation affected the VS-mechanism. The results showed that lateral head tilt of 45° induced a reorientation of the EVV of about 6.5° towards the Earth's vertical. This reorientation was independent of the direction of head tilt and was significantly reduced after centrifugation to an amount of 5° on average. However, when the head was erect, a pitch-down bias was observed, already shifting the EVV 5.0° away from the stimulus axis. This caused an asymmetry in the absolute orientation of the EVV relative to the stimulus axis between the conditions where the slow phase was directed against gravity (Against-G, requiring a downward velocity component for alignment with gravity) and where the slow phase was directed in the direction of gravity (With-G, requiring an upward component for alignment with gravity) .

A pitch-down bias and the resulting gravity-dependent asymmetry in EVV orientation have been described before, although the magnitudes of these effects differed per study. Gizzi and colleagues (1994) reported that the EVV was 'closely aligned' with the spatial vertical when the head was erect (mean deviation = 0.5º over 6 subjects, but with a maximum of 9º), and found a large gravity dependence during a 45º head tilt. Relative to the stimulus axis, reorientation of the EVV was 23.5º in their Against-G condition while it was 12.7º in their With-G condition. Moore and colleagues (2005) observed a mean deviation of the EVV of 7.4º (4 subjects) when the head was erect, and an additional 8.9º reorientation due to G_y centrifugation (i.e., tilting the gravito-inertial acceleration 45º to the left and right). These investigators also studied the spatial characteristics of VS during spaceflight, which is discussed below. They suggested that the large magnitude of reorientation as found by Gizzi could be attributed to the contribution of the neck stretch receptors (Mittelstaedt & Glasauer, 1993), because Gizzi used active head tilt as opposed to whole body tilt which was used by Moore c.s.. The current results contradict this hypothesis, because they were obtained using a similar head tilt paradigm. Alternatively, it is possible that the use of electro-oculography, which is known to be prone to crosstalk between horizontal and vertical channels, might have affected their results.

Effect of sustained centrifugation

The most important result of this study was that sustained exposure to hypergravity and the following transition to Earth's gravity led to a reduction of the amount of head-tilt induced reorientation of the EVV. This suggests a decrease in VS-activity, which, when quantified by means of a vector model, was estimated at 31%.

Although this reduction of the reorientation induced by head tilt was present in both the With-G and the Against-G conditions, a significant change in the *absolute* EVV orientation was only found in the With-G condition. This apparent contradiction can be explained by changes in the absolute values for the G-neutral and Against-G conditions. As could be seen in Table 6.1, the angle between the EVV and the head yaw axis increases slightly for the G-neutral conditons where it decreases slightly for the With-G conditions. Although these changes by themselves are too small to become significant, they make that the *difference* between the two vectors (i.e., the reorientation due to head tilt) becomes less after centrifugation.

By incorporating a pitch down bias in the vector model, the experimental results could be replicated very well. This pitch-down bias appeared to be a constant factor in the determination of the EVV-orientation, and both the gravity-dependent asymmetry in EVV-orientation (pretest data), as well as the effects of centrifugation (posttest data) were in accordance with the observed results. It was because of this pitch down bias that a decrease of the VS-vector had a larger effect on the absolute EVV orientation in the With-G conditions than in the Against-G conditions (see Figure 6.6). In addition, the changes in the EVV orientation in the G-neutral condition (head erect) were also in accordance with the data.

This suggests that the EVV-orientation is determined by 1) the direction of the stimulus (which was, in this case, always head-fixed), 2) the direction of gravity relative to the head (Earth-fixed), and 3) the pitch-down bias. Taking the latter component head-fixed as opposed to Earth-fixed yielded a significantly smaller sum of residuals in the data fits ($t(23)=2.41$, $p<0.05$), thus suggesting a head-fixed bias as has been used in the current analyses. It remains unclear whether this bias has a functional meaning or results, for example, from a kinematic constraint. The head-fixed nature of this behaviour, together with the observation that this pitch down bias is also present during vertical axis rotation in humans (Haslwanter et al., 1996), appears to favour the latter explanation. An exact answer is, however, still lacking.

It should be stressed that the model only estimates the *orientation* of the EVV and not its magnitude. The OKN gain was affected by head tilt, as it was smallest in the With-G conditions (i.e., horizontal slow phase eye velocity has a downward component relative to gravity). Such a gravity-dependent difference in horizontal OKN-gain has been observed before (Kitama et al., 2004; Lafortune et al., 1991) and is also present in vertical OKN. With the head erect, slow phase velocity is usually greater during an upward stimulus than during a downward stimulus, although this asymmetry is larger in monkeys than in humans (e.g., Matsuo & Cohen, 1984; Ogino et al., 1996; Van den Berg & Collewijn, 1988). Nevertheless, this suggests that gravity has an effect on OKN-gain, whereas velocity storage predominantly affects the spatial properties of OKN.

As mentioned before, sustained centrifugation is also known to affect the temporal properties of VS. Groen (1997) found a reduction of the horizontal aVOR time constant after exposure to a $3G_x$ load for 60 min. Such temporal effects should then also be present in the optokinetic afternystagmus (OKAN), which is the prolongation of nystagmus when the visual stimulus is switched off (Cohen et al., 1977; 1981; Raphan et al., 1979). However, inspection of the current data revealed that we were not able to induce a reliable and robust OKAN response in all subjects. Responses generally were short and variable. This might be due to the fact that we used a flat projection screen with a limited field of view instead of a rotating drum with an unlimited field of view. Nevertheless, we analyzed the available OKAN-data of the G-neutral condition and found a small reduction of the VS-time constant[9]. Although this reduction is in accordance with the results of Groen (1997), and with the hypothesized reduction in VS-activity, a more compelling stimulus is necessary to substantiate these results.

Does spaceflight also lead to changes in velocity storage characteristics? A reduction of the dominant aVOR time constant have been observed, although the results varied between astronauts (Oman & Weigl, 1989; Oman & Balkwill, 1993; Oman et al., 1996). Moore and colleagues (2005) investigated the spatial orientation of optokinetic nystagmus during G_y centrifugation in four astronauts during the Neurolab mission, but observed no significant changes in EVV reorientation during or after the flight. It was concluded that the EVV

[9] To that end, horizontal OKAN slow phase velocity (SPV) was fitted by a double exponential curve ($SPV=A_1 \cdot e^{-t/\tau 1} + A_2 \cdot e^{-t/\tau 2}$, see Jell et al., 1984). The first and smallest time constant accounts for the rapid decay in SPV at the end of stimulation, whereas the longer time constant is associated with VS-activity. Averaged over the available data, this latter time constant equaled 9.1s (SD 8.9) in the pretest and 6.5s (SD 5.9) in the posttest.

reorientation depended on the magnitude of the interaural stimulation, which was similar before, during, and after the flight. A post flight decrease in the spatial characteristics of velocity storage was, on the other hand, observed in 2 monkeys (Dai et al., 1998). The small amount of astronauts tested during the Neurolab mission might have contributed to the lack of space flight effects. The data of the current study show that responses do vary between subjects, and changes are relatively small.

Velocity storage is a central, i.e., merely neural mechanism (Raphan et al., 1979). The fact that the hypergravity load was applied in the fore-aft direction (i.e., G_x-load) whereas we measured an effect in the plane orthogonal to this direction (i.e., the roll plane) illustrates that adaptation to a novel gravitational environment is a central process too. Possibly, the effects on VS would have been larger when the G-load would have been applied along the interaural axis (i.e., G_y, parallel to the roll plane), by having the subject lying on their side in the gondola. Alternatively, G_x stimulation during centrifugation could have been combined with OKN recordings during pitch body tilt, inducing a reorientation of the EVV in the sagittal plane (crosscoupling from horizontal to torsional eye movements).

Is VS-activity related to spatial orientation?

In the remaining part of this chapter we will return to the tilt/translation ambiguity and discuss how a reduction of VS-activity may relate to spatial disorientation as experienced after sustained centrifugation. As mentioned in the introduction, many models for spatial orientation are based on the idea that the brain uses information about angular velocity to discriminate translation from tilt (e.g., Angelaki et al., 1999; Bos & Bles, 2002; Merfeld et al., 1993; Merfeld et al., 1999; Zupan et al., 2002). Although the models may differ in detail, they are all based on similar equations that incorporate the interaction between otolith and semicircular canal signals in order to obtain an estimate of gravity (see also Chapter 1, Eq. 1.2). Investigation of neural activity of motion sensitive neurons in monkeys showed that the observed neural firing rates could well be described by these equations of motion, suggesting that these equations are indeed used by the brain (Angelaki et al., 2004; Green et al., 2005; Shaikh et al., 2004; Yakusheva et al., 2007)[10]. An important aspect of this strategy to solve the tilt/translation ambiguity is that it requires a *temporal integration of angular velocity information*. Green and Angelaki (2003, 2004) suggested that this integration could well be performed by the VS-integrator. By recording the eye movements of monkeys during combined tilt and translational movements, they showed that these integrated angular velocity signals were necessary to generate the appropriate ocular responses (i.e., ocular counter roll and/or linear VOR). The behaviour classically attributed to the VS-integrator (like improving the low frequency behaviour of the VOR) can then be seen as a by-product of this integrative action rather than as its main purpose.

Although evidence for the role of the VS integrator in spatial orientation remains to be substantiated both theoretically and experimentally, it is a promising hypothesis because it links a number of findings regarding adaptation to a new gravitational environment. First of all, the symptoms that are usually observed after sustained centrifugation all relate to a disturbed spatial orientation. Subjects show a deteriorated postural stability (Bles & De Graaf, 1993), and experience all kinds of motion illusions, suggesting a disturbed sense of self motion. As a result, they also suffer from motion sickness, which is closely related to spatial disorientation (Blest et al., 1998a, see also Chapter 1).

Second, a disturbed canal-otolith interaction has earlier been suggested as a contributor to the centrifugation induced effects (Bles & De Graaf, 1993; Bles et al., 1997). This is illustrated by the finding that motion sickness is especially provoked by head movements that tilt the head with respect to gravity (i.e., pitch and roll when erect, Bles & De

[10] These studies used a slightly different version of Eq. 1.2, that was suitable for the frequency domain of the semicircular canals: $\frac{d\mathbf{g}}{dt} = -\boldsymbol{\omega} \times \mathbf{g}$

Graaf, 1993; see also Chapter 2), and not by head movements without a tilt component. Importantly, static or slow tilt (<0.1 Hz) is not provocative, which is also outside the frequency range where the semicircular canals contribute to resolving the tilt/translation ambiguity (Angelaki et al., 1999).

Third, a disturbed ability to discriminate tilt from translation has recently been recognized as a factor contributing to disorientation experienced by astronauts returning to Earth (Merfeld, 2003). Merfeld suggested that “the functional role played by the neural networks that perform the calculations (i.e., to solve the tilt/translation ambiguity) will deteriorate in the absence of a gravitational field”. Although this is a perfectly functional adaptation to the microgravity environment, it obviously leads to an inadequate spatial orientation perception when back on Earth. Accordingly, it has been shown that the ability to control dynamic roll tilt (i.e., keep yourself upright while exposed to pseudo-random motion in roll) was deteriorated in astronauts after spaceflight, while the ability to counteract *static* roll was unchanged (Merfeld, 1996). This again stresses the importance of dynamic rotational cues in solving the tilt/translation ambiguity in movements within the mid-frequency range.

Conclusion

Taken all together, the arguments presented above suggest that the spatial disorientation occurring after sustained centrifugation and possibly also after space flight are, at least in part, associated with a deteriorated ability to discriminate translation from tilt. The results of the present study add to the data showing that the gravity transitions mentioned above also affect the VS-mechanism. Linking the VS-integrator directly to spatial orientation would be an important next step in understanding the cause of the disorientation after both gravity transitions. As suggested by Green & Angelaki (2004), further evidence for such a link can be obtained by studying how modifications in VS-activity, associated with lesions in the associated brain areas like the nodulus/uvula or the vestibular commissural pathways (e.g. Angelaki & Hess, 1995; 1998; Katz et al., 1991; Wearne et al., 1997) affect the ability to discriminate tilt from translation.

Chapter 7

Is SIC-susceptibility related to otolith asymmetry?

A functional asymmetry between the left and right otoliths has long been thought to contribute to an astronauts susceptibility to SAS. This hypothesis is verified using SIC as a ground based model for SAS. To that end, vestibular asymmetries (from a semicircular canal or otolith origin) were investigated in a group of 15 subjects for whom SIC susceptibility had been established. SIC susceptible subjects showed a higher degree of utricular asymmetry, but this parameter alone did not discriminate between the susceptible and the un-susceptible group. However, when otolith parameters were combined with semicircular canal parameters in a single regression model, the two groups could be perfectly separated. This implies that SIC susceptibility can be predicted based on vestibular parameters.

The previous chapters showed that, although there was a clear distinction between subjects as it comes to SIC susceptibility, this distinction was not observed in the ocular orienting responses. This chapter addresses the question whether the susceptible subjects can be discriminated from non-susceptible subjects on the basis of vestibular function. It was first thought that susceptibility to SAS could be predicted from susceptibility to other forms of Earthly motion sickness, but these attempts failed (e.g., Graybiel 1980; Homick et al., 1987; Oman et al., 1986). That susceptibility to SAS is related to vestibular function was suggested by the so-called "otolith asymmetry hypothesis" (Baumgarten & Thümler, 1979; Von Bechterew, 1909). It was argued that a functional asymmetry between the left and right otoliths might contribute to susceptibility to SAS in astronauts. It was shown in 1969 by Yegorov amd Samarin that the otolithic pairs in fish (having an otolithic system homologous of that of humans), can actually be very different in size and weight (in Von Baumgarten & Thümler, 1979). While these asymmetries may be centrally compensated during normal life on Earth, they become unmasked in novel gravitational environments (like microgravity), where the compensation is inadequate. Such a misbalance within the otolith system would lead to the conflict causing motion sickness.

In humans, the only relatively pure indicator of otolith function is ocular counter roll (OCR). Vogel & Krass (1986) reported that the SL−1 crew member most prone to SAS during orbital flight also showed a marked asymmetry between OCR-gain in response to rightward and leftward body tilt before flight (see also Diamond & Markham, 1988). Young & Sinha (1998) report that all SLS−2 crewmembers had a symmetric ICR response to left- and rightward body tilt preflight, but showed a marked asymmetric response on the first day after return. They do not report upon a relationship with SAS-susceptibility. In addition, a relationship between gain asymmetry and SAS-susceptibility was not observed in a later study (Diamond et al, 1990). Instead, Diamond & Markham (1991) proposed that an otolith asymmetry would be observable during the novel G-states of parabolic flight as it would elicit a gravity dependent asymmetry in the torsional position of the right and left eye. In 13 astronauts they calculated a so-called level of torsional disconjugacy during parabolic flight (i.e., the left-right difference in 1.8 G relative to the left-right difference in 0G), and related this to the astronauts' individual susceptibility to SAS. Astronauts who had not been suffering from SAS during orbital flight appeared to have lower disconjugacy scores and vice versa (Diamond & Markham 1991; Markham & Diamond, 1992; 1993). A drawback of the procedures mentioned above is that the otoliths were always stimulated *bilaterally*, making it difficult to discriminate directly between right and left otolith function. With the development of tests for the *unilateral* assessment of otolith function, it became possible to evaluate the otolith-asymmetry hypothesis in more detail.

Unilateral *utricular* function can be evaluated using eccentric centrifugation (Clarke et al., 1996; 1998; 2001; 2003; Wetzig et al., 1990; Wuyts et al., 2003). This is a paradigm using high speed vertical axis rotation, while changing the location of the rotation axis relative to the centre of the head. When the axis of rotation is aligned with one of the utricles the contra-lateral utricle is exposed to centrifugal acceleration, while the ipsilateral is not. The centrifugal acceleration tilts the gravito-inertial acceleration away from the vertical, inducing ocular counterrolling (OCR). Utricular asymmetry can thus be assessed by comparing the OCR elicited by both left and right utricular stimulation.

Unilateral *saccular* function can be assessed by recording vestibular evoked myogenic potentials (VEMPs, Colebatch et al, 1994). VEMPs are averaged inhibitory responses of the tonically contracted sternocleidomastoid muscle (SCM), and result from stimulating the saccule through loud acoustic stimuli. The VEMP waveform is biphasic, with a positive peak after 13 ms (*p13*) and a negative peak after 23 ms (*n23*). A saccular asymmetry would result in a difference between the peak-to-peak amplitude during rightward and leftward stimulation.

The otolith asymmetry-hypothesis was reinvestigated using sustained centrifugation as a ground based model for SAS. To that end, a group of subjects was selected that previously participated in one of the centrifuge-studies and for whom the susceptibility to SIC had been assessed. VEMPs were recorded to assess saccular asymmetry, while utricular asymmetry was tested through unilateral centrifugation. Originally, the latter test applied a semi-static trapezoid translation profile, where the rotation axis of the chair remained aligned with one of the utricles for a period of 30 s before translating to the other side (Wuyts et al., 2003). The current study used a novel sinusoidal translation profile, that has shown to generate more robust responses (Wuyts et al., in preparation). A new mathematical model was developed to analyse these data, described in the method section. In addition to the two otolith tests, semicircular canal function was assessed through standard electro-nystagmographic procedures.

METHODS

15 Dutch subjects from the Soesterberg region (mean age 27, SD=7.8) volunteered to participate in this experiment and gave written informed consent. They were selected from a pool of 67 subjects that participated in one of the previous centrifuge-experiments, in which their susceptibility to SIC was assessed (see Chapters 1 and 2 for procedures) Seven of the 15 subjects were susceptible to SIC, whereas eight were not. The study-protocol was approved by the Medical Ethical Board of the Antwerp University Hospital.

Vestibular testing took place in the Antwerp University Research center for Equilibrium and Aerospace (Belgium). Apart from the unilateral assessment of otolith function (see below), hearing sensitivity was measured (Green, 1978), and a standard electro-nystagmography (ENG) protocol was performed to evaluate the unilateral functionality of the horizontal semicircular canals.

Testing of the horizontal semicircular canals

Standard electro-nystagmographic recording techniques were used for the evaluation of the horizontal semicircular canal function (Van der Stappen et al., 2000). The ENG test battery consisted of the recording of spontaneous nystagmus, followed by tests for gaze-evoked nystagmus, saccades, optokinetic nystagmus, smooth pursuit and positional nystagmus (Dix Halpike manoeuvre). Possible asymmetries between the left and right horizontal semicircular canals were assessed by a caloric test. During this test both ear canals were consecutively irrigated with warm (44°C) and cold (30°C) water for 30 seconds with a volume of 180 cc. Warm water in the right ear (WR) and cold water in the left ear (CL) both evoke nystagmus with fast phases to the right, whereas warm water in the left ear (WL) and cold water in the right ear (CR) both evoke nystagmus with fast phases to the left. Labyrinth preponderance (LP_{SCC}) was calculated by Jonkees' formula, based on the maximum slow phase velocities:

$$LP_{SCC} = \frac{(WL + CL) - (WR + CR)}{WL + CL + WR + CR} \tag{7.1}$$

where a positive value indicates a preponderance for the left labyrinth. The sum of the responses to the four irrigations (i.e., the numerator of Eq. 7.1, denoted by S_{SCC}) was taken as a measure for the total responsiveness of the horizontal semicircular canals.

The angular yaw VOR was measured during sinusoidal vertical axis rotation in total darkness with a maximum velocity of 50°/s and with a frequency of 0.05 Hz. Both head position and slow phase velocity (SPV) were described by a sine-function, where the offset in SPV determines the directional asymmetry (indicating that the SPV is higher in one movement-direction than the other). VOR gain was defined as the ratio of the SPV over head velocity.

Testing the saccules

Unilateral saccular function was assessed by the VEMP-test, as described by Vanspauwen et al (2006a, 2006b). After cleansing the skin with an impedance lowering gel, Ag/AgCl surface electrodes (Blue Sensor, Ambu), were placed on the medial portion of the contracted sternocleidomastoid muscle SCM' muscle belly (negative electrodes), the reference electrode on the upper part of the sternum and the ground electrode on the forehead. The subject was seated upright, with the head pitched forward over about 30°. Baseline contraction of the (SCM) was obtained by pressing the jaw against the hand-held inflated cuff of a blood pressure manometer. Because the VEMP response amplitude is dependent on the SCM contraction level (Colebatch et al, 1994; Lim et al., 1997; Robertson & Ireland, 1995), care was taken to keep the contraction level of the SCM constant throughout the trial. To that end, the cuff pressure could be monitored by subject and investigator and the subject was to maintain a steady level throughout the trial. An auditory evoked potential system (Nicolet Viking) equipped with EMG-software was used to record the responses. Prior to the actual VEMP measurement, mean rectified voltage (MRV) values were recorded in this way, over a period of 15 s, as an indicator of SCM contraction level. Subsequently two series of 100 tone bursts (frequency 500 Hz; loudness 95 dBnHL; repetition rate 5.1 Hz) were presented unilaterally through insert earphones while averaging the resulting biphasic VEMP responses. During the VEMP recording, the cuff method was used at the same pressure level as during the MRV measurements. Peak-to-peak amplitude (*p13-n23,* see Figure 7.1) and absolute latencies (*p13, n23*) were obtained from the average response of the two series. The peak-to-peak amplitude was divided by the mean MRV value (as measured prior to the VEMP recording) to correct for the contraction level of the SCM. The whole procedure was performed separately for the left and right SCM.

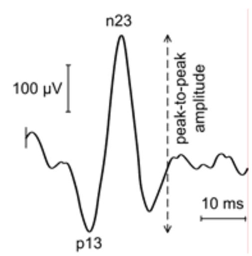


Figure 7.1: Example of a VEMP recording, with the negative peak, p13, and the positive peak, n23, indicated.

To determine saccular asymmetry, an asymmetry-factor ASF_{SAC} was defined as:

$$ASF_{SAC} = \frac{\left|A_S - A_D\right|}{A_S + A_D} \tag{7.2}$$

where *A* denotes the corrected peak-to-peak amplitude, with the subscript *S* for *sinister* (left) and *D* for *dexter* (right). A_S and A_D are both positive so ASF_{SAC} ranges between 0 (perfect symmetry) and 1 (complete unilateral loss).

Testing the utricules

Utricular function was assessed by unilateral centrifugation (UC). The subject was seated in a vertical axis rotating chair (Neurokinetics, USA) and secured with a five-point belt. The head was stabilised with a head-rest and three flexible arms (Mitutoyo) pressing against the forehead. Eye movement recordings were made by 3D video-oculography (VOG)[11] at a sampling frequency of 50 Hz. During the measurement, the subject was instructed to look at a chair-fixed fixation light, presented at a distance of 1 m. At the beginning of the trial, the axis of rotation was aligned with the centre of the head and the chair was accelerated with 3°/s^2 to a constant velocity of 400°/s. Then, after a period of 90 s at this velocity, the chair was sinusoidally translated along the inter-aural axis at a frequency of 0.013 Hz. Maximum displacement was 4 cm to either side. Measured at the centre of the head, this induced a maximum interaural acceleration of 1.95 m/s^2 (=0.2 G), which is equivalent to a tilt of the gravito-inertial acceleration (GIA) of 11.2°. After 4 cycles (equivalent to 307.7 s) the rotation axis was again aligned with the centre of the head and the chair was brought to a stop with a deceleration of 2.5°/s^2. The protocol is depicted in Figure 7.2A-C, together with an example of the OCR-response (Figure 7.2D). The whole test was performed in the dark, with only the fixation light visible.

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[11] The VOG-system used was developed by the Antwerp University Center for Equilibrium and Aerospace, based on a prototype by Kingma et al. (1995, 1997)

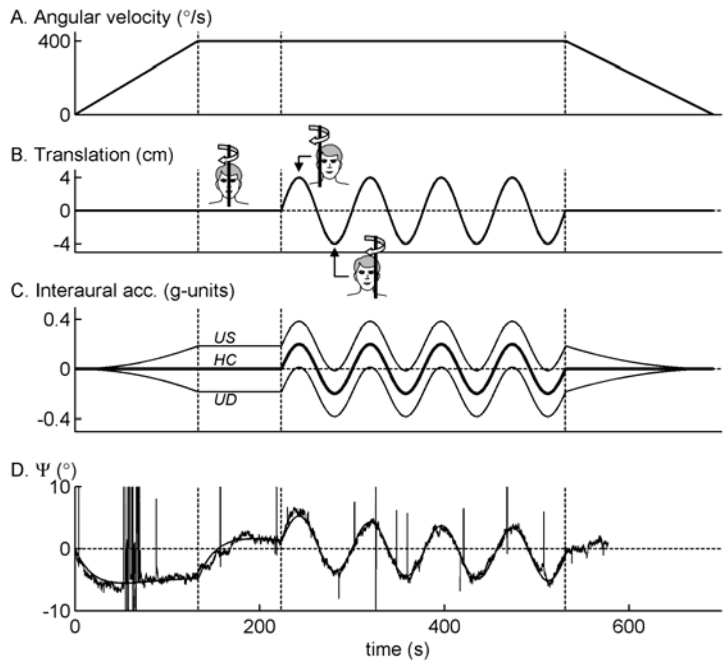

Figure 7.2: Unilateral centrifugation. A: Angular velocity profile. B: Interaural translation profile. C: Centripetal acceleration (in g-units) at the level of the left utricle (US), right utricle (UD) and head centre (HC). D: Example of an OCR response (Ψ). Note that the start (t=0 s) and stop (t=133.3 s) of angular yaw-acceleration of the chair elicit an OCR response that is still present at the start of translation (t=223.3 s). The fit of the model described by Eq. 7.3 - 7.8 is overlaid.

Modeling of the ocular response during unilateral centrifugation

Ocular responses were fitted to a mathematical model to determine the level of utricular asymmetry. Figure 7.2D clearly shows that both the angular acceleration of the chair and the lateral translation induce an OCR response. Most likely, only the part of the response induced by lateral translation (centripetal acceleration) can be attributed to the utricles, while the angular acceleration induced component has been attributed to the semicircular canals (Smith et al., 1995). In order to isolate the utricular response, it is necessary to include the angular acceleration induced contribution in the model, because it has not died out fully at the start of translation. Thus, the total OCR response (Ψ) can be described by:

$$\Psi = \Psi_\alpha + \Psi_u \tag{7.3}$$

where the subscript u represents the utriclar contribution that is related to the centripetal acceleration, and α the response related to the yaw angular acceleration.

To investigate the dynamics of the component Ψ_α, some trials were recorded using the velocity profile of Figure 7.2A, but without the translation (see Figure 7.3). When the left and right utricles are assumed equally sensitive to centripetal acceleration the net utricular contribution equals zero (see Figure 7.2C), leaving only the semicircular canals to contribute to OCR. The OCR-response showed characteristics that resembled those of the slow phase velocity of horizontal nystagmus during vertical axis acceleration. It contained a velocity storage component (Raphan et al., 1979) that prolonged the effective time constant of the response, and an adaptation component, accounting for the gradual decay during continuation of the acceleration (Malcolm & Melvill-Jones, 1970; Young & Oman, 1969).

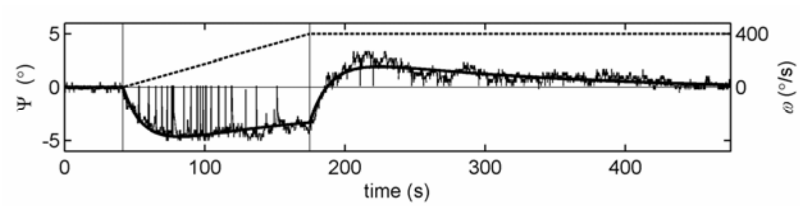

Figure 7.3: Example of an OCR response (Ψ) during acceleration of 3°/s^2 to 400°/s. The velocity profile is indicated by the dotted line (abscissa on the right). The frequent spikes in the first part of the data are due to eye blinks. The OCR-pattern shows a clear response to the start and stop of acceleration, indicated by the vertical lines. The fit of Eq. 7.5 is overlaid (A_α= 0.4, k=0.7, τ_C= 7.4 s, τ_A = 173.9 s).

Combining these properties with a first order model of the cupular dynamics yielded the following transfer function: (Laplace notation, see also Robinson 1981; Furman et al., 1989):

$$\frac{\Psi_\alpha(s)}{\omega_{head}(s)} = A_\alpha \cdot \frac{1}{1-k} \cdot \frac{\tau_A s}{\tau_A s+1} \cdot \frac{\tau_C s}{(\tau_C/1-k)s+1} \tag{7.4}$$

where A_α is a gain factor, τ_A the adaptation time constant, and τ_C the cupular time constant. The factor k assumes a value between 0 and 1 and accounts for velocity storage. The velocity storage time constant, τ_{VS}, is then given by:

$$\tau_{VS} = \frac{\tau_C}{1-k} \tag{7.5}$$

Transforming Eq. 7.4 to the time domain yields the following equation for Ψ_α that consists of a sum of four exponentials, two for the start of angular acceleration and two for the stop of angular acceleration:

$$\Psi_\alpha(t) = A_\alpha \cdot \left(\frac{\tau_C \cdot \tau_A}{\tau_C - \tau_A + k \cdot \tau_A} \cdot \left(e^{\frac{-t}{\tau_A}} - e^{\frac{(-1+k)\cdot t}{\tau_C}} \right) \right) + \ldots \tag{7.6}$$
$$A_\alpha \cdot K_1 \cdot \left(\frac{\tau_C \cdot \tau_A}{\tau_C - \tau_A + k \cdot \tau_A} \cdot \left(e^{\frac{-(t-t_{stop\_acc})}{\tau_A}} - e^{\frac{(-1+k)\cdot(t-t_{stop\_acc})}{\tau_C}} \right) \right)$$

The second part of Eq. 7.6 only contributes to the response when the chair has reached its final angular velocity (t_{stop_acc}). K_1 is thus an inclusion parameter, where $K_1 = 0$ as $t<t_{stop\_acc}$ and $K_1 = 1$ as $t \geq t_{stop\_acc}$.

The utricular induced OCR is assumed proportional to the magnitude of the interaural acceleration:

$$\Psi_u(t) = \alpha_{us} \cdot \omega(t)^2 \cdot \left(R_u + R(t)\right) + \alpha_{ud} \cdot \omega(t)^2 \cdot \left(-R_u + R(t)\right) \tag{7.7}$$

where the first part of the right-hand side describes the contribution of the left utricle (subscript *us*), and the second part describes the contribution of the right utricle (subscript *ud*). The parameter α is a proportionality constant, and $\omega(t)$ is the angular velocity of the chair. R_u is the distance between the utricle and the centre of the head, being positive for the left side and negative for the right side. The utricles are assumed to lie symmetrically around the centre of the head (Nowé et al, 2003) with the mean inter-utricular distance equal to 7.45 (SE 0.08) cm for males and 6.99 (SE 0.06) cm for females (Nowé et al, 2003). $R(t)$ is the distance between the axis of rotation and the centre of the head. It equals 0 when the chair is on centre, and during the translation-phase $R(t)$ is given by:

$$R(t) = R_{\max} \cdot \sin(2\pi f(t - dt)) \tag{7.8}$$

where R_{max} is the translation amplitude (0.04 m) and f the translation frequency (0.013 Hz). The term dt is incorporated to account for possible phase differences between the actual translation of the chair and the ocular response. Combining Eq. 7.7 and 7.8 yields the following expression for Ψ_u:

$$\begin{aligned}\Psi_u(t) = &\left((\alpha_{us} - \alpha_{ud}) \cdot \omega(t)^2 \cdot R_u\right) + \ldots \\ &K_2 \cdot \left((\alpha_{us} + \alpha_{ud}) \cdot \omega(t)^2 \cdot R_{\max} \cdot \sin(2\pi f(t - t_{start\_trans} - dt))\right)\end{aligned} \tag{7.9}$$

where $K_2 = 0$ for $t < t_{start\_trans}$ (i.e., the start of lateral translation) and $K_2 = 1$ for $t \geq t_{start\_trans}$.

The total OCR-response can thus be described by combining Eq. 7.6 and 7.9. Figure 7.4 shows the four components of the model: the response to the start of angular acceleration, the response to the stop of angular acceleration, the response from the left utricle to chair translation and the response of the right utricle to chair translation. The sum of these four components equals the measured OCR response.

A utricular asymmetry is characterized by the values of α_{us} and α_{ud}. When these values are equal, both utricles are equally sensitive, and when they differ in magnitude, an asymmetry exists. A utricular asymmetry factor was defined as:

$$ASF_u = \frac{|\alpha_{us} - \alpha_{ud}|}{\alpha_{us} + \alpha_{ud}} \tag{7.10}$$

Again, α_{us} and α_{ud} are both positive so ASF_U ranges between 0 (perfect symmetry) and 1 (complete unilateral loss). The offset of the sine function (i.e., first part of Eq. 7.9) was taken as an additional measure for utricular asymmetry. Note that the sensitivity of the utricles is also characterized by α_{us} and α_{ud}: higher values indicate a larger sensitivity. The amplitude of the response (A_u, derived from the second part from Eq. 7.9) was taken as a measure for utricular sensitivity. Other parameters of interest were the maximum amplitude of Ψ_α, and the time constants τ_C, τ_A, and τ_{VS}.

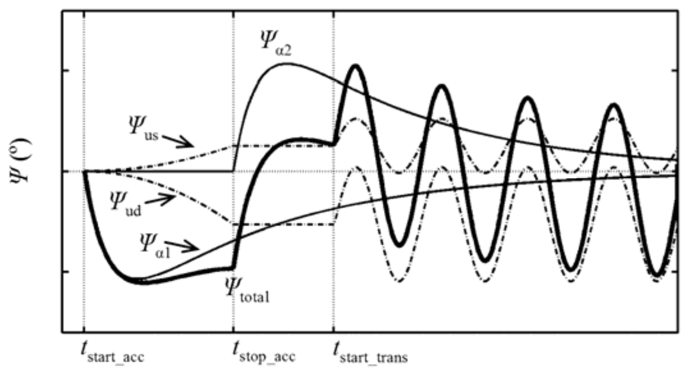

Figure 7.4: Components of the model to fit the OCR data, for the data presented in Figure 7.2D. t_{start_acc}=start of angular acceleration; t_{stop_acc}=stop of angular acceleration (constant velocity); t_{start_trans}=start lateral translation; $\Psi\alpha 1$=response to first angular acceleration step; $\Psi_{\alpha 2}$=response to second angular acceleration step; Ψ_{us}=response from left utricle; Ψ_{ud}= response from right utricle; Ψ_{total}= sum of all components. Model parameters are τ_C=4.4 s; τ_A=144.6 s; A_α=0.35; k=0.80; dt=0.42 s; α_{us}=0.70; α_{ud}=1.45. Note that in this case the left utricle is less sensitive than the right utricle.

The model of Eq. 7.6 and 7.9 was fitted to the mean ocular torsion position data (left + right eye) to obtain individual values for different parameters. An example of a model-fit was already shown in Figure 7.2D. By using the average data of the two eyes the model does not account for prevalence or preponderance, that is, a dominant utricular impact on the ipsilateral eye (Wetzig et al., 1990). However, earlier studies showed that the responses of both eyes are reasonably equivalent in normal subjects (Clarke & Engelhorn, 1998; Wuyts et al., 2003). Close inspection of the data showed that this was also the case in the present data.

RESULTS

Reliable responses for utricular and saccular parameters were obtained in 12 subjects. In two of those 12 subjects the OCR data of the acceleration phase of the UC-test contained too many eye blinks to obtain reliable parameters for the first part of the response (τ_C, τ_A, τ_{VS}, and max. Ψ_α). For these subjects utricular parameters were obtained from a fit (Eq. 7.9) on data of the last two translation cycles only. In one subject the caloric test had to be aborted due to severe nausea. The VOR-data was not used for further analysis, because the gain was found to be below the normal range (Van der Stappen et al., 2000) in seven of the 15 subjects. The most plausible explanation for the low VOR gain would be fatigue, caused by the busy test-schedule and the journey from Soesterberg to Antwerp.

Evaluation of the model assessing utricular function

The model describing the ocular response of the UC-test provided an adequate description of the data, the R^2 values ranged between 0.88 and 0.92. More imporant, the utricular parameters α_{us} and α_{ud} that determine both the utricular asymmetry (ASF_U) and utricular sensitivity (A_u) could be estimated adequately. Individual parameter values and confidence intervals are listed in Table 7.1. This was different for the parameters describing the angular acceleration induced part of the response. Confidence intervals of these parameters (time constants τ_C, τ_A, and τ_{VS})

were an order of magnitude larger than the actual parameter values. Because the overall fit of the model to he data was good, this means that the same ocular response pattern could be obtained using different combinations of time constants. This was also verified by model simulations. Thus, although the model gave a good description of the angular acceleration-induced response, it does not provide a reliable estimation for individual time constant values. Therefore these values are ignored in further analysis.

TABLE 7.1
Individual values for the estimated utricular parameters α_{us} and α_{ud} and 95% confidence intervals (CI)

Subject	α_{us}	CI	α_{ud}	CI
1	0.846	[0.814, 0.878]	0.122	[0.090, 0.154]
2	0.584	[0.582, 0.587]	0.301	[0.298, 0.303]
3	0.370	[0.366, 0.373]	1.020	[1.016, 1.022]
4	0.530	[0.526, 0.534]	0.549	[0.544, 0.553]
5	0.609	[0.602, 0.616]	1.096	[1.090, 1.101]
6	0.058	[0.054, 0.063]	1.209	[1.205, 1.213]
7	0.342	[0.339, 0.345]	0.584	[0.581, 0.586]
8	0.154	[0.150, 0.157]	0.755	[0.752, 0.758]
9	0.492	[0.488, 0.496]	0.445	[0.441, 0.449]
10	0.279	[0.253, 0.295]	0.878	[0.862, 0.903]
11	0.766	[0.746, 0.787]	0.382	[0.361, 0.402]
12	0.216	[0.218, 0.238]	0.696	[0.677, 0.695]

Differences between SIC-susceptible and non-susceptible subjects

Table 7.2 provides descriptive values for the relevant vestibular parameters from all vestibular tests. Note that the values for the time constants are also included in Table 7.2, but that these have to be treated with care.

TABLE 7.2

*Descriptive statistics for the relevant vestibular parameters. Parameters marked with * show differences between the SIC-susceptible group and the non-susceptible group (p<.1)*

		n	**mean**	**SD**	**min**	**max**
VOR	Gain	15	0.41	0.25	0.12	1.04
Caloric test	Abs. directional asymmetry (º/s)	9	5	4	2	11
	* Responsiveness, S_{SCC} (°/s)	14	86	34	47	169
	Abs. labyrinth preponderance, LP_{SCC}	14	0.10	0.06	0.02	0.20
VEMP-test	*p13* (ms)	12	15.8	1.4	14.2	19.2
	n23 (ms)	12	23.6	2.0	21.0	28.4
	Baseline MRV value (μV)	12	86.3	27.6	43.1	131.6
	Peak-to-peak amplitude VEMP	12	104.1	63.6	28.6	278.6
	Amp. corrected for MRV	12	1.3	0.8	0.3	3.9
	Abs. saccular asymmetry, ASF_{sac}	12	0.19	0.12	0.04	0.44
UC-test	Cupular time constant, τ_C (s)	10	5.1	0.8	4.0	6.5
	Adaptation time constant, τ_A (s)	10	228.0	169.7	77.0	671.1
	Velocity storage time constant, τ_{VS} (s)	10	83.1	119.4	11.1	400.7
	Max. amplitude Ψ_α,(°)	10	2.1	1.3	0.6	4.5
	* Amplitude Ψ_u, A_u (°)	12	2.1	0.5	1.7	3.3
	Abs. offset Ψ_u (°)	12	0.7	0.5	0.1	2.1
	* Abs. utricular asymmetry, ASF_u	12	0.43	0.25	0.05	0.91

Of the subjects selected for this study, seven were susceptible to SIC, while the other eight were not. Non-parametric statistics (Mann-Whitney U test) were used to investigate differences between the groups. Although none of the parameters showed differences between the groups that were significant at the p<.05 level, four of them showed significant differences at the p<.1 level. Regarding the utricular parameters, the SIC susceptible group showed a higher level of utricular asymmetry (ASF_U, p=.065), and a higher amplitude of the utricular response (p=.093). In addition, the caloric responsiveness of the semicircular canals, S_{SCC}, was higher in the SIC-susceptible group (p=.059). These differences are also depicted in Figure 7.5. The VEMP test reveiled no differences between the SIC-susceptible group and the non-susceptible group for saccular paramterers.

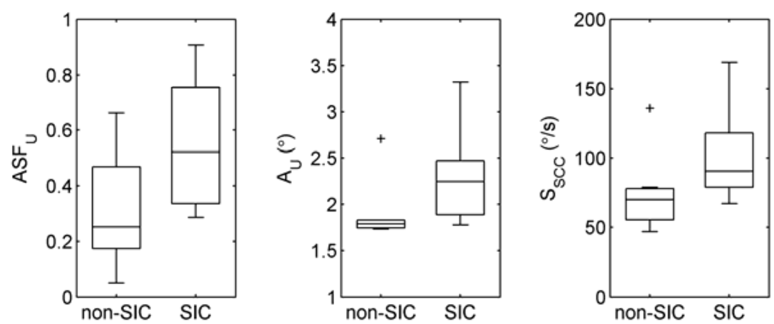

Figure 7.5: Box plots of the parameters that differed between the SIC-susceptible group and the non-susceptible group (p<.01): Utricular asymmetry factor (ASF_U) amplitude of the utricular response (A_u), and caloric responsiveness (S_{SCC}). Boxes represent the upper and lower quartile range, whiskers represent the extremes within 1.5 times the interquartile range. Outliers are indicated by the + sign.

Classification of subjects

Logistic regression analysis was performed to determine whether the subjects could be correctly classified as being SIC-susceptible or not. The regression model was of the form:

$$y = \frac{e^k}{(1+e^k)}, \text{ with } k = a_1 \cdot x_1 + a_2 \cdot x_2 + ... + a_n \cdot x_n + c \qquad (7.11)$$

where *y* ranges between 0 and 1, *x* denotes the different parameters, *a* denotes the regression coefficients, and *c* is a regression-contant. Although absolute otolith asymmetry differed significantly between the SIC-susceptible and the non-susceptible group, it had not enough discriminating power to classify all subjects correctly ($\chi^2(1)=3.4$, $p=.065$): the range of observed values overlapped (see also Figure 7.5) and consequently, four out of 12 subjects were misclassified. Including semicircular canal parameters in the model significantly improved classification. Because of the small number of subjects having a full data set on all parameters stepwise regression could not be performed. Instead, regression models were evaluated using different combinations of utricular (UC-test) and semicircular canal parameters (Caloric test). With a combination of utricular asymmetry (ASF_u), utricular responsiveness (A_U), semicircular canal asymmetry (LP_{SCC}) and semicircular canal responsiveness (S_{SCC}) a perfect classification of subjects could be obtained ($\chi^2(4)=15.2$, $p=.004$) Regression coefficients are shown in Table 7.3.

TABLE 7.3
Parameters of the logistic regression model

Parameter	Coefficient
A_u	206.5
ASF_u	371.1
S_{SCC}	1.7
LP_{SCC}	2672.4
Constant	–1133.4

DISCUSSION

The aim of the current study was to determine whether functional otolith asymmetries were related to SIC-susceptibility, as is suggested by the otolith-asymmetry hypothesis (Von Baumgarten & Thümler, 1979). The SIC-susceptible group indeed showed a higher level of utricular asymmetry than the non-susceptible group, which would be in favour of this hypothesis. Logistic regression analysis showed, however, that utricular asymmetry appears not to be the sole determinant of SIC-susceptibility. The finding that the SIC-susceptible group showed both a higher utricular gain and larger semicircular canal responsiveness to caloric stimulation suggests that the overall sensitivity of the vestibular system might also be contributing.

Prediction of SIC-susceptibility

Interestingly, combining the caloric test-parameters with the utricular test parameters in a single logistic regression model yielded perfect classification of the 12 subjects. This is a promising result, despite the fact that the data-set was too small to perform more advanced logistic regression techniques. It suggests that SIC-susceptibility can be predicted based on vestibular function parameters that address sensitivity and asymmetry of both the otolith and canal system. An important next step is to validate the model in a larger group of subjects. It is possible that a more accurate model can then be obtained using a different subset of parameters, possibly also including VOR-characteristics like gain and/or time constants. The current results, however, are already valuable in showing that utricular parameters alone are not sufficient to predict SIC-susceptibility.

The many attempts to predict SAS-susceptibility from susceptibility to other forms of motion sickness failed (e.g., Graybiel 1980; Oman et al., 1986; Homick et al., 1987) or did not specifically address SAS-susceptibility as measured in flight (Lin & Reschke, 1987; Cloutier & Watt, 2006). Given the correlation between susceptibility to SIC and to SAS, it is expected that a logistic model as proposed above can also be applied as a predictor for SAS in astronauts. In this thesis it was argued that sustained centrifugation was the only possible ground-based paradigm to assess SAS-susceptibility, but now the use of unilateral vestibular testing may thus be added as an assessment method. Also valuable in this respect are the findings of Harm and colleagues (1998), who found that astronauts who showed a visually dominated frame of reference (i.e., who were more field dependent) were more prone to SAS during space flight than astronauts who showed a body-centric frame of reference. It would be interesting to investigate whether this personal preference is also related to vestibular function or whether it could attribute to the prediction of SAS-susceptibility.

Static vs. dynamic Space Motion Sickness

The otolith-asymmetry hypothesis has always been related to a static form of SAS, that did not require motion to elicit the symptoms (Von Baumgarten & Thümler, 1979; Von Baumgarten et al., 1981; Von Baumgarten, 1987). Although it has occasionally been reported that SAS can be experienced during rest (Graybiel, 1980), it is generally accepted that head and body movements are a prerequisite for the symptoms to occur (e.g., Graybiel, 1980; Oman et al., 1986; Thornton et al., 1987). Importantly, this dynamic component is also a prerequisite for the generation of SIC: in none of the centrifuge studies SIC was observed when the subject remained motionless after centrifugation. In fact, head movements were used to classify an individual as SIC-susceptible or not. The finding that, next to utricular parameters, also semicircular canal parameters varied between the SIC-susceptible group and the non-susceptible group is in line with this dynamic character of SIC. It also is in line with the fact that both systems are involved in spatial orientation: integration of semicircular canal and otolith signals is required to obtain valid internal estimates of inertial acceleration and gravity, as was addressed in Chapter 1 and Chapter 6. Because the gravitational vertical plays a central role in the generation of motion sickness (Blest et al., 1998a), it is plausible that a disturbed interaction between the various parts of the vestibular system is involved in SIC and SAS.

Model to assess utricular asymmetry

The values obtained for the utricular parameters are partly dependent on the model used to fit the torsional position data in the angular acceleration phase of the test (Eq. 7.4). This model was based on the dynamics of the horizontal semicircular canal, given the resemblance between the torsional position response during yaw angular acceleration (i.e., with fixation) and the slow phase velocity of the horizontal nystagmus during angular acceleration (i.e., without fixation).

A semicircular canal basis for this torsional position response has also been suggested by Smith and colleagues (1995). They showed that the magnitude of this response is dependent on angular acceleration and is not related to the centripetal acceleration acting on the utricles, which makes a utricular origin unlikely. In agreement with this, the maximum net centripetal acceleration acting on the center of the head during angular acceleration was much smaller than during the translation phase of the UC-test, while the OCR-responses are of equal magnitude (i.e., compare max. Ψ_{SCC} with amplitude Ψ_U). In addition, the *tangential* acceleration acting on the utricles during yaw angular acceleration (≈0.0002G) is much smaller than the maximum centripetal acceleration of the translation phase (≈0.2G), indicating that the tangential stimulation of the utricles probably did not contribute to the response. Smith and colleagues also noted the correspondence of the torsional position response with the canal dynamics and suggested that the velocity-to-position integrator responsible for holding torsional eye position might receive input from the horizontal semicircular canal. However, the OCR-data show that the torsional position response and the horizontal velocity response are not equivalent. Both the mean adaptation time constant and the mean velocity storage time constant for the OCR-response are much larger than generally observed for the horizontal slow phase velocity (i.e., 15-20 sec.; see e.g., Brown & Wolfe, 1969; Fernandez & Goldberg, 1971; Malcolm & Melvill Jones 1970; Bos et al. 2002). Nevertheless, with the model of Eq. 7.4 a good description of the data was obtained within the temporal range of the measurement, and, more importantly, the utricular parameters could be estimated adequately. To elucidate the exact mechanism of the angular acceleration induced torsional position response, further research is required.

Conclusion

The mathematical model developed to assess utricular asymmetry yielded an adequate description of the data, by incorporating both angular acceleration induced torsion responses and the linear acceleration induced torsion responses. In line with the otolith asymmetry hypothesis, SIC susceptible subjects showed a higher level of utricular asymmetry than unsusceptible subjects, but a proper classification of subjects could only be obtained using both utricular and semicircular canal parameters. This illustrates that the whole vestibular system is involved in SIC and demonstrates the role of – complex – interactions between its parts.

Chapter 8

General Discussion

In the previous chapters it was shown that sustained centrifugation is a valuable paradigm to mimic the symptoms of SAS on Earth. Motion sickness, one of the main symptoms of SAS, is the consequence of an inadequate disambiguation of tilt and translation, which requires neural integration of both semicircular canal and otolith signals. This is in line with the finding that dynamic head movements are essential in provoking SIC, and that SIC susceptibility was found to be related both to semicircular canal and otolith function parameters. It was furthermore demonstrated that sustained centrifugation also reduced the effect of gravity on orienting eye movements but that these changes were present in both SIC-susceptible and non-susceptible subjects. In this final chapter several mechanisms are discussed that may have contributed to these findings, and it is argued that a disturbed sensory integration likely forms a main contributor to many symptoms of SIC. It is furthermore argued that, although there are important differences between the two, SIC and SAS represent a similar form of motion sickness, making the paradigm of sustained centrifugation valuable for both applied and scientific purposes.

A persisting altered gravitational environment evokes a process of neuro-vestibular adaptation. This is observable after the transition from

Earth's gravity to the weightlessness condition of spaceflight, after the transition from weightlessness back to Earth's gravity, and, as was demonstrated in this thesis, also after a transition from hypergravity to Earth's gravity[12]. All these transitions have in common that the constant level of gravito-inertial acceleration has changed and this change has to be accounted for, as stated in the central tenet mentioned in the General Introduction (Chapter 1). Alternatively, it can be stated that the 1G condition we are familiar with on Earth is not essential for proper behavioural responses. Once adapted, this could have been any other level, including the singular state of 0G. The *necessity* to account for persistent changes in the gravity level can be inferred from disturbances in spatial orientation: the reports on visual or motion illusions that occur during movements of the head, on spatial disorientation, on motion sickness, and, when balance is at stake, on postural instability. All these items characterize that, right after such a change in the prevailing gravity level, the system's behaviour is inadequate for the new circumstances.

The experiments presented in the previous chapters explored different aspects of vestibular adaptation to altered gravitational states. Besides a limited number of observations obtained during and after space flight, the paradigm of sustained centrifugation was used to evoke adaptation on Earth. This final chapter starts with a summary of the most important findings of these experiments. Subsequently, various aspects that relate to the paradigm of sustained centrifugation will be addressed to answer the questions put forward in the introduction. First, what can be learned from these findings with regard to adaptation of the internal estimate of gravity (see Q.1), and second, whether sustained centrifugation evokes an adaptation process that is similar to adaptation to weightlessness (see Q.2).

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[12] Due to the confined space of the centrifuge gondola, we have not been able to demonstrate similar effects when *increasing* the gravitational load from 1G to hypergravity, but this is likely to result in similar effects.

SUMMARY OF THE MAIN FINDINGS

That sustained centrifugation is used as a general paradigm to study vestibular adaptation to altered gravity levels was prompted by the observation that it not only evoked symptoms similar to those of SAS, but that susceptibility to SIC and SAS were correlated as well. With new data on four astronauts presented in Chapter 2, the positive relationship between SIC and SAS susceptibility was further validated: the astronauts who were free from SAS during space flight were also free from symptoms of SIC after centrifugation, and the astronauts who experienced symptoms of SAS in space, also experienced SIC following centrifugation. This correlation is important, because susceptibility to SAS does not relate to susceptibility to other forms of (Earthly) motion sickness and it thus implies that a similar mechanism is triggered in SIC and in SAS. This makes sustained centrifugation a valuable tool in space research.

In Chapter 4 it was found that the severity of SIC-symptoms depended on both the magnitude of the gravito-inertial load and on the duration of the exposure. These factors interacted in a non-linear fashion, which could very well be described by a single exponential function depending on the gravitational load and exposure duration. The estimated time constant for adaptation (based on the 45 and 90 minute exposures) was about one hour, and this was also regarded being the minimal duration to provoke any symptoms of SIC. This experiment also demonstrated the clear distinction between susceptible and unsusceptible subjects in terms of motion sickness symptoms. Head movements changing the orientation of the head relative to gravity were indeed required to elicit symptoms of SIC after centrifugation, and the speed of the performed head movements affected symptom severity. Importantly, these data showed that true sickness susceptibility can therefore not be discerned by a misery rating only, but that the provocative stimulus, i.e. the head movements, should be taken into account as well. A head movement velocity adjusted misery rating was suggested, and proved to be valuable in discriminating true

SIC susceptible and unsusceptible subjects.

Although there was a clear distinction between subjects when it came to SIC susceptibility, this distinction was not found in the various vestibular tests. Centrifugation showed to change various vestibular parameters, but these changes were present in all subjects, independent of their susceptibility as classified by the head velocity adjusted misery ratings. The review presented in Chapter 3 demonstrated that most subjects subjected to centrifugation exhibited a deterioration of postural balance when no veridical visual information was available. No significant effects could be demonstrated in the perception of the subjective vertical during body tilt after centrifugation, but orienting eye movements (ocular counter rolling; Groen et al., 1996b) were found to be affected. This was underscored by the findings of the studies described in Chapters 5 and 6. After sustained centrifugation the counterpitch of Listing's plane during head tilt was decreased, and a backward change of LP-orientation was observed when the head was erect. It was suggested that the orientation of Listing's plane is determined by – at least – a head fixed *and* a space fixed reference (i.e., gravity). Interestingly, decreasing the influence of the latter component explained both the reduced counterpitch and the backward tilt of LP observed after centrifugation. Strikingly, a similar effect on orienting responses was demonstrated in Chapter 6, showing that sustained centrifugation reduced the reorientation of eye velocity towards gravity during optokinetic stimulation. Again, this could be explained by a reduction of the gravitational influence on the eyes' spatial behaviour. The importance of this observation is provided by the velocity storage mechanism which is said to be responsible for the integration of signals related to angular velocity and gravity, thus playing an important role in spatial orientation.

Because the experiments performed so far did not show differences between the responses of SIC-susceptible versus unsusceptible subjects, Chapter 7 sought for a way to separate the two groups on the basis of bilateral asymmetries in functioning of the organs of balance. Differences between the left and right otoliths were of particular interest, since these have been associated with SAS-susceptibility before. In the current experiments it was found that SIC susceptible subjects indeed showed a higher level of utricular asymmetry, and that both utricular sensitivity and the sensitivity of the horizontal semicircular canals were higher in this group. Utricular asymmetry alone, however, was not sufficient to classify the subjects into SIC susceptible and un-susceptible, but when both otolith *and* canal asymmetries were taken into account, the distinction could be made. This underscored the relevance of canal- otolith interaction in spatial orientation.

HOW TO EXPLAIN THE REDUCED INFLUENCE OF THE GRAVITATIONAL REFERENCE

The experiments on ocular responses learn that the transition to Earth's gravity after sustained exposure to hypergravity reduced the effect of the gravitational reference on the eyes' spatial behaviour. This holds for ocular counter rolling, the spatial orientation of Listing's plane, and the spatial orientation of eye velocity through the velocity storage mechanism. Explanations for this general finding can be sought at different levels in the processing chain, from the end organs to central brain centres. Because the responses under consideration are based on signals that differ in their level of 'centrality', the effects may also be caused by different mechanisms. Although otolith input is involved in all responses, ocular counterrolling, for example, is known to be a rather 'low-order' response, mainly based on the interaural component of the gravito-inetrtial acceleration (GIA, see e.g., Angelaki, 1998; MacDougall et al., 1999; Merfeld et al., 1996a; Miller & Graybiel, 1971; Moore et al., 2001; Teiwes et al., 1993). The orientation of Listing's plane, on the other hand, is based on the *gravity estimate* instead of the GIA (Hess and Angelaki, 1999), and is thus considered as a 'higher order' response, in that it requires more processing. Velocity storage may also represent a higher order, or central mechanism in that it is involved in sensory integration. Perceptual measures can in this respect be regarded as responses of the highest order in that they are affected by different sensory systems, as well as internal model estimates (see Chapter 1).

It is likely that sustained centrifugation induces changes at different levels, making it difficult to provide one conclusive solution. The following paragraphs address the pros and cons of several possible mechanisms possibly involved in vestibular adaptation. These mechanisms include:

- central versus peripheral adaptation,
- the reweighting of otolith cues,
- the importance of canal-otolith interaction
- the effect of temporal integration, and
- the hypothesized existence of an internal estimate of gravity.

Central vs. peripheral adaptation

The chain starts, of course, with the sensors: all ocular responses under consideration here are largely dependent on the amount of utricular stimulation during head tilt. This implicates that a reduction of the orienting response could be caused by a reduction of the peripheral utricular signal, due to a change in the stimulus-response relationship. This could be the consequence of response-adaptation during a persisting stimulus. However, several arguments plea against such a sensory adaptation process, as will be discussed below.

Fernàndez & Goldberg (1976) showed that a persisting linear acceleration as experienced during centrifugation alters the firing rate of the otolith neurons. At the onset of linear acceleration the primary vestibular neurons of squirrel monkeys showed an increasing firing rate, followed by a decreasing rate due to adaptation to the stimulus. This type of adaptation can be attributed to diverse mechanisms like decreases in synaptic gain, or changes in the sensitivity of a transduction process (Eatock et al., 1987). This is different from the adaptation that takes place at the level of the mechano-electrical transduction in hair cells (e.g., Eatock, 1987; Hudspeth & Gillespie, 1994; see also Hudspeth & Markin, 1994). Eatock and colleagues showed that when a bundle of hair cells is deflected from its resting position and held in that new orientation, a shift occurs in the operating point of the cell towards the new resting position. Thus, this process involves a shift of the stimulus-response curve towards the new operating point. With this kind of adaptation the hair cell is able to detect transient stimuli in the presence of large static backgrounds. These two kinds of sensory adaptation occur, however, on a too short time scale to explain adaptation to sustained centrifugation; tens of seconds and tens of milliseconds, respectively, where adaptation to hypergravity takes tens of minutes. If sensory adaptation occurs during centrifugation, it is to be expected that these effects have already disappeared at the time the vestibular responses were measured (i.e., 15 – 45 minutes after the stop of centrifugation).

A second argument against adaptation at the level of the end organ is that the observed effects were not restricted to the direction of the gravitational stimulus. Both SIC and a deterioration of postural balance were observed after G_x, G_y, and G_z stimulation (Albery & Martin, 1996; Bles & De Graaf, 1993). Furthermore, effects on ocular counter rolling (Groen et al., 1996b) and the spatial orientation of velocity storage (Chapter 6) both were measured in the roll plane, which is perpendicular to the applied G_x stimulus. The fact that the effects of sustained centrifugation were found to be independent of the direction of gravitational stimulation suggests that adaptation takes place at a higher level, thus pointing to a central origin. This is also indicated by the findings of Kaufmann and colleagues (1991; 1992) who measured brainstem activity in rats that were centrifuged at 2G for 90 minutes. As in the current thesis, Kaufman c.s. suggested that a sustained change in gravito-inertial acceleration requires the establishment of a new reference for sensory integration, and their study aimed at identifying the brainstem nuclei that would take part in 're-establishing an inertial reference' (Kaufman et al., 1992). To this end, brainstem activity during centrifugation was identified using Fos immunohistochemistry. In this technique, the presence of labelled Fos in the nuclei of neurons is considered to be a marker for sites of cellular adaptation (Herschman, 1989). The centrifugation protocol was similar to the one used in the current human centrifuge studies, in that the rats were restrained and not moving freely in the 2G environment. The data is interesting because it indicated that, apart from some traditional brainstem (oculomotor and vestibular) nuclei, also some novel brainstem area's responded to sustained centrifugation, including vestibulo-olivo-cerebellar pathways. This activity was not present in hemilabyrinthectomized animals, illustrating its dependence on an intact labyrinth (Kaufman et al., 1993). Later results in gerbils also suggested that the inferior olive is, as part of an otolith-olivo-cerebellar pathway, involved in regulating adaptation to novel inertial backgrounds (Marschburn et al., 1997). These pathways are particularly interesting, as the inferior olive projects to the nodulus and the uvula, which are important for spatial orientation of velocity storage (Cohen et al., 2002, Wearne et al., 1998). Thus, these examples illustrate that changes in *central pathways* can occur during centrifugation, without the necessity of any active interaction with the environment (as was also the case in the human centrifuge studies described in the preceding chapters). That Kaufman et al. (1991; 1992; 1993) predominantly applied utricular stimulation, whereas Marschburn c.s (1997) studied the effects of saccular stimulation suggests that the direction of the applied acceleration is not of major importance, but that it is the magnitude of the gravito-inertial acceleration that is essential. This is in accordance with the findings described in this thesis.

Reweighting of otolith cues

Instead of a reduction of the otolith signal *itself* (that is, the peripheral signal) the general decrease of ocular orienting responses may be due to a central reduction of the otolith *contribution* in spatial orientation. The final estimate of the body state is determined by various integrated signals, where the *weight* assigned to the otolith cues may be reduced in favour of other contributors. These include the visual and somatosensory systems and possibly also the ideotropic vector (i.e., the tendency to take the longitudinal body axis as a reference of verticality c.f. Mittelstaedt, 1983). Increasing the contribution of the latter may reflect a shift towards a more body centered frame of reference. The weight that is assigned to each input is generally associated with the reliability of the signal, in that reliable signals are assigned the largest weight (see also Borah et al., 1979). Illustrative in this respect is the fact that subjects who were exposed to sustained G_x, G_y, and G_z centrifugation were able to maintain postural balance when – reliable – visual information was available, but that balance deteriorated when they had to rely more on otolith cues (Albery & Martin, 1996; Bles & De Graaf, 1993). Assigning a reduced weight to the less reliable otolith cues is likely to affect also otolith mediated ocular responses. To validate this possibility further experiments would be required taking visual-vestibular, somatosensory-vestibular, and visual-somatosensory interactions explicitly into account.

Disturbed sensory integration: canal-otolith interaction

A next step in the processing chain concerns sensory integration: the combining of all signals into single estimates of the body state. Resolving the tilt/translation ambiguity is the most relevant process in this respect, where otolith signals are integrated with angular velocity information to obtain a vestibular estimate of **a** (inertial acceleration) and **g** (gravity). As stated in Eq. 1.2, this process entails the temporal integration of angular velocity signals, which is associated with the velocity storage integrator (Green & Angelaki, 2003; 2004). Because velocity storage depends on an intact nodulus and uvula (Angelaki & Hess, 1995; Cohen et al., 2002; Wearne et al., 1998), it is interesting that the results of Kaufman and colleagues (Kaufman et al., 1991; 1992; 1993; Marschburn et al., 1997) showed that brainstem nuclei projecting onto these areas are affected during sustained centrifugation. In addition, structural changes in the rat's nodulus have been observed during space flight (Holstein et al., 1999).

Changes in the velocity storage pathways could affect the ability to separate tilt from translation, for instance by a reduced coupling between angular velocity and otolith signals. If this interaction would be disturbed, the estimate of gravity during dynamic head tilts may be inaccurate or less reliable, leading to inappropriate responses. This was shown by Green & Angelaki (2003), who developed a neuronal model describing the generation of horizontal eye movements during tilt and translation, as observed in monkeys. An illustrative example is the situation where lateral translation and lateral tilt were applied simultaneously, in a way that the interaural stimulation caused by translation is cancelled by the interaural stimulation caused by head tilt. Thus, this paradigm, denoted by Tilt – Translation, yielded a zero net utricular stimulation. Interestingly, during this paradigm with absent utricular stimulation compensatory horizontal eye movements were observed that thus have to originate from integrated semicircular canal cues (Angelaki et al, 1999; Green & Angelaki, 2003). Model simulations using the model described by Green & Angelaki, (2003), showed that the coupling between otolith and semicircular canal pathways was essential for these compensatory eye movements to occur. Decreasing the coupling gain to zero diminished the eye movenments, leading to an inappropriate response. The role of the semicircular canals in generating these horizontal eye movement in absence of utricular stimulation is underscored by the finding that this response is absent after canal plugging (Angelaki et al., 1999).

The model by Green & Angelaki (2003) also predicted the prolongation of the horizontal aVOR time constant during constant velocity rotation when the canal-otolith coupling is intact. This time constant decreased to the cupular time constant when the coupling was absent. The reduced aVOR time constant found after sustained centrifugation (Groen, 1997) can, thus, as well be explained by a decreased coupling gain. Unfortunately the model does not (yet) account for the spatial orientation of velocity storage, but it seems plausible that a decreased coupling between semicircular and otolith signals would also reduce the reorientation of the eye velocity vector towards gravity. This hypothesis awaits verification.

Another appealing aspect of this reduced integration between otolith and semicircular canal signals (i.e., angular velocity signals) is that it also affects the estimate of gravity during angular movements (Eq. 1.2). As was already put forward in Chapter 6, this is in line with the finding that mid-frequency head movements (where the semicircular canals contribute to the perception of angular velocity) provoke motion sickness in susceptible subjects. This makes a disturbed sensory integration a plausible cause for the effects of sustained centrifugation. Moreover, this would also be in line with the observation made in Chapter 7 that a distinction between SIC susceptibility could be made on the basis of combined otolith and canal parameters.

In conclusion, a disturbed interaction between semicircular canal and otolith signals leads an inappropriate disambiguation of tilt and translation. This then, affects compensatory eye movements during these movements, and also the velocity storage parameters as they have been experimentally observed. It furthermore provides an explanantion for the provocativeness of orienting head movements in SIC.

Temporal integration

As touched upon in the previous paragraphs, temporal integration plays an important role in resolving the tilt translation ambiguity. It remains an intriguing question whether this integration process itself is affected during sustained centrifugation. A deteriorated ability to temporally integrate signals would have similar effects on the velocity storage time constant and on compensatory eye movements. It could also relate to the symptoms of oscillopsia that many subjects experienced during head movements, following sustained centrifugation. The data presented in this thesis is, however, not suitable to investigate the hypothesized role of temporal integration in SIC. Yet, there are some findings in the literature that suggest that otolith signals do affect temporal integration, and these will be discussed shortly.

The perception of angular velocity during constant velocity rotation, for example, is prolonged when subjects are rotated eccentrically, as opposed to on-axis rotation (Mittelstaedt & Mittelstaedt, 1996). Likewise are the duration and intensity of perceived tumbling during Coriolis (cross-coupled) stimulation augmented during the 2G phase of parabolic flight, and eliminated during the 0G-phase (DiZio et al., 1987). In more recent parabolic flight experiments DiZio and colleagues showed that subjects who were oriented supine and tilted about their yaw axis were able to indicate perceived displacement during the 1G and 1.8G phases, but during the 0G phase the sense of angular displacement was lost (see Lackner & DiZio, 2005). Pointing experiments during space flight also indicated that the integration of angular velocity signals was disturbed (Clément et al., 1987; Glasauer & Mittelstaedt, 1998). These findings suggest that otolith stimulation is required to enable central integration of (angular) velocity signals, which makes this an interesting parameter to investigate in future research. A first step to investigate these issues further is to measure the effect of sustained centrifugation on the perception of travelled distance (both angular and linear) and its interaction with gravity.

The effect of otolith cues on temporal integration may also relate to the perception of time, or the internal time reference that is used for integration (Ockels, 1987, 1988). Israël and colleagues (2004) performed experiments on linear motion perception and found evidence for the hypothesis that linear acceleration affects time perception. Semjen and colleagues (1998) performed a timing experiment in space and concluded that the ‘internal time keeper’ (Wing & Kristoffersen, 1973) might be affected by microgravity.

Some pilot experiments were also performed during the centrifuge runs described in this thesis to investigate whether time perception was altered during centrifugation. Subjects listened to a regular sequence of beeps, and were to adjust the inter-beep interval to 1 Hz. In a first experiment a slight (non-significant) increase in the inter-beep interval was observed during the course of a 60 min. centrifuge run, but this trend was not observed in a later experiment during a 90 min. centrifuge run. Another pilot experiment assessed the subjects' ability to integrate visual motion. Subjects were to predict the position of a visual target (moving along a circular path) after the target had disappeared behind an imaginary occluder (Vaina & Giulianini, 2004). The accuracy of the predictions was psychophysically measured using a forced choice paradigm. However, no effects of sustained centrifugation on this task could be demonstrated. Because of the lack of any significant effects in this respect, these experiments were not continued.

Internal model of gravity

Even more central than otolith reweighting and changes in the sensory integration process is the aspect of expectation, or in other words, the internal representation of gravity. Two examples, described below, will illustrate that it seems plausible to assume that the 1G gravity vector, which is omnipresent during our life on Earth, is embedded somewhere in our nervous system. Particular responses, like tilt perception, seem to be scaled to this internal estimate rather than to a 'sensed' gravity vector. A change in the internal gravitational reference induced by sustained centrifugation was therefore expected to affect tilt perception. The available data on tilt perception, however, did not provide evidence for such a change. As will be discussed below, this might imply that embedding a new gravitational reference in our system requires active interaction with the environment.

The first example illustrating the possible existence of an internal representation of gravity concerns a model for static spatial orientation (Bortolami et al., 2006). Based on earlier observations of Correia (Correia et al., 1968), Bortolami c.s. assumed that the utricular stimulation during static tilt normally is interpreted as being caused by a 1G vector, irrespective of the real magnitude of the gravity vector. Such an assumption would lead to an erroneous perception of tilt in a 2G-environment, where a particular tilt induces a larger interaural stimulation of the utricles than would have been the case in a 1G environment. Interestingly, the Bortolami-model adequately predicted these errors in tilt perception, observed during the 2G phase of parabolic flight. This suggests that tilt perception is mediated by an internal gravity reference (i.e., 1G), rather than by the sensed magnitude of the GIA (i.e., 2G).

Also related to this issue are the findings of Clément and colleagues (2001), who measured roll tilt perception during eccentric rotation on a short-arm centrifuge during the Neurolab space mission. On Earth, a 1G interaural acceleration induced a 45º roll tilt of the GIA, which was also perceived as such. In space this stimulus resulted in a 90º GIA tilt, which was perceived as such only after a few days in weightlessness. Early in flight, the perceived tilt was similar to the tilt perception on Earth (i.e., perceived tilt of about 45°). The authors sought an explanation for these findings in the contribution of the ideotropic vector (Mittelstaedt, 1983). They argued that the weight of this vector was increased early in flight, resulting in an underestimation of GIA-tilt, and slowly decreased over the course of the flight, resulting in a more veridical tilt perception. What could also have contributed to these results, which was not mentioned by these authors, is the 'Earthly' internal model, or expectation pattern. On Earth, the interaural stimulus was always combined with a 1G vector, resulting in a 45º GIA tilt, so this expectation may have been maintained early in flight. That tilt perception changed later in flight suggests that then the internal model had been adequately updated, a process typically taking days.

Following this reasoning, centrifugation could induce an updating of the gravitational reference towards the new value of 3G. This would then reduce the magnitude of responses that are mediated through this gravitational reference, such as perceived tilt. The data on subjective vertical measurements, however, do not provide evidence for this hypothesis. The tilt settings showed a large inter- and intra subject variability, indicating either that the effect is absent, or that the test was not sensitive enough to detect relatively small changes. Alternatively, the absence of active interaction with the environment could be responsible for the lack of effects. During the Neurolab mission, for example, it took a few days for the new model to build up, during which the astronauts interacted actively with their environment. Although during centrifugation the body is continuously exposed to an increased linear acceleration, active interaction with the environment is absent. Although this stimulus is sufficient to induce adaptive changes in various brain centres (see the work of Kaufman and colleagues discussed above), it may be too static to update behavioural response patterns.

SIC VS. VESTIBULAR RESPONSES AND OTHER FORMS OF MOTION SICKNESS

One striking observation revealed by the experiments described in this thesis is that the effect of sustained centrifugation on SIC (i.e., symptoms of motion sickness) were very different from the effects on ocular responses. First, the different centrifuge conditions (varying G-load and duration) induced large differences in symptom severity within subjects (see Chapter 4), whereas only minor (non-significant) differences were observed in ocular responses (Chapters 5 and 6). And second, there was a marked distinction *between* subjects when it comes to SIC, whereas no such distinction could be demonstrated for the ocular responses. Furthermore, postural instability also lacked a correlation with SIC susceptibility (Bles & De Graaf, 1993), whereas a correlation was anticipated.

One explanation for this apparent paradox is that SIC is governed by a different mechanism than the behavioural and ocular measures. This, however, does not seem to be plausible because the estimate of gravity is a factor that is strongly linked to both motion sickness and vestibular responses. Alternatively, motion sickness dynamics may contribute to the differences between both categories of responses. These are the dynamics between the sensory conflict signal (i.e., the difference between the sensory and expected output, see Chapter 1) and the eventual symptoms of motion sickness, being highly nonlinear. Oman (1982; 1990) modeled these dynamics using two interacting parallel paths, respectively with 'slow' and 'fast' low pass dynamics, a nausea threshold and a power law element (see Bos & Bles 1998 for a slightly different approach). Nausea thus only appears as the accumulated conflict exceeds the threshold, which, apparently, was only the case in the more strenuous centrifuge conditions. The fact that effects on ocular responses were already visible after 45 min. of centrifugation at 2G indicates that the system then already is in a disturbed state, with a general down-scaling of orientation responses as a result.

The large variability in motion sickness susceptibility between individuals is accounted for in the models by assumning individual differences in gains (weights) and thresholds. One's susceptibility may, however, vary between differents kinds of motion, since the correlation between susceptibility to different types of motion sickness (e.g., sickness induced by linear oscillation vs. Coriolis stimulation) is generally low (see Golding, 1998, Kennedy et al., 1989; Reason & Brandt, 1975). Individuals susceptible to one form of motion sickness may turn to be insusceptible for another form of motion sickness. In that sense, space motion sickness or SIC are not different from other forms of motion sickness. Moreover, from this point of view the term 'motion sickness susceptibility' seems to be too generic. Motion sickness may thus result from different types of conflicts and susceptibility may differ per type of conflict. What determines one's susceptibility to a certain type of motion sickness may depend on various factors, like vestibular function, motion history and perceptual style (see e.g. Kennedy et al., 1989; Reason & Brandt, 1975). For example, velocity storage parameters have been shown to be correlated with susceptibility to motion sickness through Coriolis stimulation (Dai et al., 2003; 2007) and off-vertical axis rotation (Bos et al., 2002), but were not found to be indicative for SIC susceptibility (see Groen, 1997, and Chapter 6). Related to this is the observation that SIC in rats (i.e., motion sickness following a 120 min. exposure to 2G) is not reduced after lesions of the vestibulo-cerebellum, including the velocity storage centers (Uno et al., 2000). Instead of depending on velocity storage parameters, the experiment described in Chapter 7 showed that SIC susceptibility was correlated with bilateral asymmetries within, and sensitivity of the vestibular system. This would then indicate that, if SIC and SAS represent a response to a similar type of conflict, these parameters can also be used as indicators for SAS susceptibility. This knowledge may, in turn, be useful for pharmaceutical countermeasures against SAS. That perceptual style may also contribute to SAS susceptibility is suggested by the findings of Harm and colleagues (1998), who showed that astronauts who relied on the visual scene for spatial orientation were more prone to SAS than astronauts who adopted a body-centred frame of reference. It would be interesting to investigate whether this also applies to SIC-susceptibility.

SIC and SAS: A general adaptation mechanism?

In the previous sections it was argued that sustained centrifugation most likely does not alter the magnitude of the internal estimate of gravity, but that it may affect its reliability. This brings us to the final question addressed in this thesis: can SIC and SAS be regarded as consequences of one general adaptation process? The fact that susceptibility to these two forms of motion sickness are correlated, suggests that SIC and SAS do indeed represent the same kind of motion sickness, i.e., a response to an altered gravitational environment. Various responses to spaceflight seem similar to those of sustained centrifugation, although microgravity remains inevitably unique for the complete absence of a gravitational reference instead of a change in magnitude. To say that sustained centrifugation therefore induces an adaptation process similar to adaptation to weightlessness might therefore be somewhat too simple. Adaptation to weightlessness entails a process of adapting to novel response patterns incorporating the absence of gravity, specifically the patterns that accompany movements. This, of course, is absent in the centrifuge paradigm. Another difference is the time scale: it takes a few days to get fully adapted to weightlessness, whereas Chapter 4 showed an adaptation time constant of 1 hour for the centrifuge paradigm. That makes it difficult to compare the effects of spaceflight directly with the effects of sustained centrifugation. The later in the flight the responses are recorded, the more they reflect appropriate adaptation to the novel environment. After sustained centrifugation, on the other hand, the system 'only' is disturbed, without establishing these novel response patterns. Responses measured following centrifugation may therefore only be a reflection of this disturbed state, rather than of adaptation to a novel force environment. Yet, this would be in line with assuming an internal model. As said in the General Introduction (Chapter 1), it can be assumed that the internal model is only updated when a conflict lasts for several hours as is generally observed when wearing new glasses, when habituating to novel motion environments, when habituating to vestibular diseases, and hence also when habituating to the condition of weightlessness. The time constant found in Chapter 4 may therefore represent a fundamentally different process (i.e., that of perturbation) as compared to the updating process of the internal model (i.e., that of habituation).

PRACTICAL IMPLICATIONS

Having said this, the fact that SIC and SAS do represent a similar type of motion sickness per se does make sustained centrifugation a valuable and powerful tool. One suggested implication may be the use for astronaut selection. This, however, should be treated with care. One person being more susceptible than another *initially*, may prove to be less susceptible after *repeated* exposures. Such an ability to adapt has already been shown for cross-coupled coriolis stimulation. This stimulation generally causes motion illusions, motion sickness and inappropriate eye movements, but several studies showed that repetitive exposure leads to a decrease in all measures, that persisted over days (e.g., Anedot et al., 2005; Brown et al., 2002; Dai et al., 2003; Hecht et al., 2002; Jarchow & Young, 2007;

Young et al., 2001; 2003). This is indicative for the adaptive properties of the vestibular system, which could also apply to sustained centrifugation. Therefore the issue of *training* seems to be the most promising application. This is relevant because artificial gravity becomes indispensible during longer space missions, and short arm centrifuges currently seem the most practical way to obtain this – at least from a constructional point of view. The use of short arm centrifugation, however, implies that the centrifugation should be intermittent. When the head is positioned eccentrically, this will induce a gravity transition each time the astronaut gets off the centrifuge. Here too, the present study may prove to be valuable, because the time constant for the perturbation process was shown to be about 1 hour, why short-arm centrifugation of less than half an hour may be assumed not to be provocative with respect to vestibular adaptation.

Re-entering the Earth's gravity field or a planet's gravity field will induce similar gravity transitions as observed after centrifugation. (Re)-entry to a planet's gravity field belongs to the most crucial phases in any space mission, where SAS and spatial disorientation are a serious threat. Here too, training using the SIC paradigm may be a valuable tool in counteracting the negative vestibular effects on (re)-entry.

Another aspect concerns the use of anti motion sickness medication in space. One of the most popular drugs is scopolamine, a drug that is also frequently used against typical Earthly motion sickness symptoms. However, as further substantiated in this thesis, susceptibility to Earthly motion sickness and to space sickness may be very different, why drugs could (or even should) be different too. Here the SIC paradigm offers a unique opportunity to study the effect of medication specifically counteracting the negative effects of space sickness.

The observation that sickness symptoms are affected by the amount of head movements made, led to a new measure for sickness severity: the head velocity adjusted misery rating (CMISC). This observation and this new measure are not only valuable with respect to space related studies as currently presented, but also regarding any kind of Earthly sickness. In any study on motion sickness, head movements should either be controlled for or recorded head movements taken into account.

Though not applicable yet, the insights obtained in the current study do, however, contribute to the general knowledge on motion perception and misperception in general, and this is certainly related to the incapacitating effects of diseases such as Ménière's disease, vestibular neuritis, and other forms of vertigo and oscillopsia. The benefit these patients may, on the long term, profit from space research would be valuable reward, making the investments even more worth it.

CONCLUSIONS

The work presented in this thesis made a reasonable case for concluding that sustained centrifugation induces a *central* vestibular adaptation process that leads to inappropriate behavioural responses after the transition back to Earth's gravity. Most likely this is due to an inadequate disambiguation of tilt and translation, resulting in disturbances of spatial orientation in most subjects, but in motion sickness in susceptible subjects only. A disturbed sensory integration of otolith and semicircular canal signals has been identified as a major contributor to the inappropriate behavioural responses. The finding that orienting head movements are required to trigger the symptoms of SIC, and that both otolith and semicircular canal parameters are related to SIC susceptibility add to this conclusion. The role of gravity in this kind of vestibular adaptation is further underscored by the experiments on vestibulo-ocular responses.

In addition, it is concluded that, although adaptation to weightlessness remains inevitably different from the adaptation process induced by sustained centrifugation, SIC and SAS represent the same form of motion sickness. Up to this date, SIC is therefore *the only* way to mimic SAS on Earth. It was demonstrated that the adaptation process during centrifugation could well be described by a single exponential function depending on G-level and exposure duration, with a time constant of about 1 hour. This has practical implications for the application of artificial gravity during space missions. In the future, the centrifuge paradigm may be used to elaborate further on the mechanisms underlying SIC and SAS; to (among other things) search for ways of training astronauts in advance of their space missions; and to study the effectiveness of anti motion sickness medication specifically regarding SAS.

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Summary

Vestibular adaptation to an altered gravitational environment: Consequences for spatial orientation

Earth's gravity is an omnipresent factor in human life and provides a strong reference for spatial orientation. It is in an altered gravitational environment, like in space, that we come to appreciate the fact that we, humans are 'Earth-like' (Ockels, 1988). This thesis is about adaptation to an altered gravitational environment, and its consequences for spatial orientation.

The organs of balance play a vital role in spatial orientation and the perception of gravity. Or actually, the perception of the *gravitational acceleration*. The organs are located in the inner ear and consist of the *semicircular canals*, sensitive to angular velocity, and the *otoliths*, sensitive to liner acceleration. This is the gravitational acceleration, but also the linear acceleration due to self-motion (inertia). However, as holds for any linear accelerometer, the otolith cannot distinguish between these two sources (Einstein's Equivalence principle). Nevertheless, an adequate estimate of the magnitude and direction of the gravitational acceleration and the inertial acceleration is essential, for instance for the control of postural balance. Fortunately, the central nervous system is able to make the distinction by using, among other sources, information from the semicircular canals. As is shown in this thesis, it is this process that is disturbed in an altered gravitational state.

A clear example of our dependence on gravity is provided by human space flight. In about 50-70% of the astronauts, adaptation to

weightlessness is accompanied by symptoms of the Space Adaptation Syndrome (SAS): disorientation, illusions of self and surround motion, dizziness and motion sickness. Symptoms are mainly triggered by head movements. In two or three days time the system generally adapts to the new environment and symptoms disappear, but they may re-appear upon return to Earth. In addition to these symptoms of SAS, many astronauts then also have problems with their postural stability.

The occurrence of Earth sickness indicates that it is not the microgravity condition per se that induces these symptoms of SAS. This is also shown by the findings of earlier studies that the symptoms of SAS can be experienced after sustained exposure to a *higher* constant linear acceleration in a human centrifuge (≥60 min at a level of three times Earth's gravity, 3G). During centrifugation, the system gets adapted to the new gravitational load, and thus becomes maladapted to Earth's gravity *after* centrifugation. Typically, after centrifugation about 50% of the subjects experiences SAS-like symptoms, including postural instability. This is now referred to as Sickness Induced by Centrifugation, or SIC. Symptoms are – again – provoked by head movements and may last for several hours.

The similarities between SIC and SAS suggest a general mechanism of adaptation to altered gravitational environments. This makes sustained centrifugation a valuable ground-based research tool. Previously several experiments have been performed trying to identify the mechanism underlying SIC, and thereby SAS. Although this resulted in many interesting findings, the exact mechanism is still not entirely understood. In this thesis the paradigm of sustained centrifugation is used to continue this research and investigate 1) whether sustained centrifugation can be characterized by a similar adaptation process as adaptation to microgravity, and 2) how sustained centrifugation affects the internal estimate of gravity.

Chapter 2 addresses the correspondence between SIC and SAS. A strong indicator for the existence of a general adaptation mechanism to altered gravity levels is the finding that *susceptibility* to SIC and SAS are correlated: astronauts who experience SAS during spaceflight also experience SIC after sustained centrifugation. This is an interesting finding, because susceptibility to SAS is *not* related to susceptibility to other forms of 'Earthly' motion sickness. Before the start of this PhD-research this relationship between SIC and SAS susceptibility was established in eight astronauts. In those studies symptoms of SIC were evoked by a head movement protocol after sustained centrifugation (60 min at 3G). Susceptibility to SAS was, however, not measured during space flight but afterwards, based on the astronauts' recollection of symptoms experienced during daily behaviour. Within the framework of this thesis a new study was performed in four astronauts, where a similar head movement protocol was used to assess SIC-susceptibility after sustained centrifugation and SAS susceptibility during flight. This enabled a more detailed comparison of SIC and SAS. This data showed that the two astronauts susceptible to SAS in flight were also suffering from symptoms of SIC after centrifugation and vice versa. Although the head movements appeared more provocative in space than following centrifugation, the susceptible astronauts had higher levels of motion sickness and showed altered movement behaviour (e.g. robot-like movements). These findings support the earlier found correlation between SIC and SAS susceptibility. This indicates that the transition from 1G to weightlessness induces the same symptoms as the transition from 3G to 1G, suggesting that the same mechanism is being triggered.

Chapter 3 provides a summary of previous research on the effects of sustained centrifugation on various responses, complemented with new data. These data stress the role of gravity and the vestibular system in SIC. The neural estimate of gravity is known to be essential in the development of motion sickness, which is one of the major symptoms of SIC. In line with this, after centrifugation only those head movements are provocative that change the orientation of the head relative to gravity (i.e., head tilt), irrespective of the position of the body. Static head tilt is, however, not provocative. The symptoms of nausea depend furthermore on the amount and the speed of the head movements. Most subjects show a deterioration of postural stability following centrifugation, indicating a change in the estimate of the gravitational vertical. Perceptual measures of the gravitational vertical (i.e., indication of the perceived vertical during body tilt) were, however, not found to be affected. On the other hand, vestibular mediated eye movement responses did show clear effects, which led to further investigation of such responses. This is described in Chapters 5 and 6.

Chapter 4 addresses the nature of the gravitational stimulus that is required to induce the adaptation process, by investigating the interaction between gravitational load and exposure duration on the generation of SIC. To this end, 12 non-astronaut subjects were each exposed to four different centrifuge conditions: centrifugation during 45 and 90 minutes, at a level of 2G and 3G. Before and repeatedly after centrifugation subjects performed a standardized head movement protocol to evoke SIC, while their head movement characteristics were measured. Because nauseated subjects generally tend to minimize their head movements in order to reduce the evoked nausea, sickness scores were corrected for the head movement characteristics. This provided a more reliable comparison between the effects of the different centrifuge conditions. In this way a significant difference between the scores of the non-susceptible group and the SIC-susceptible group was found. In the latter, both the duration and the G-level affected the symptom scores, with the 90min exposure to 3G having the largest effects. These effects were modeled by an exponential model with a time constant of about 1 hr, giving an indication for the minimal exposure duration to induce any effects. This is not only useful information for future research on SIC, but can also be used in the development of protocols using intermittent centrifugation aboard the space station (‘Artificial Gravity’). Centrifugation is then often used as a countermeasure against physiological deconditioning (e.g. bone loss), but unwanted side effects, like motion sickness, should be prevented. The results of this study show that motion sickness occurring after centrifugation is prevented when the duration of centrifugation remains limited.

In the search for physiological parameters reflecting the vestibular adaptation process, Chapter 5 investigates the effect of sustained centrifugation on three dimensional (3D) eye position, which is dependent on gravity. With the head stationary, the 3D eye position is subject to Listing’s law, which specifies the amount of ocular torsion (i.e., rotation about the line of sight) that is present in each gaze direction. This relationship is expressed by the orientation of the so-called *Listing’s plane*. Interestingly, Listing’s plane orients towards gravity during forward and backward head tilt. This can be interpreted as an attempt to maintain an invariant eye position in space during movements of the head. Using the same 12 subjects and centrifuge conditions as described above, the orientation of Listing’s plane was determined before and after centrifugation, in different head orientations. After sustained centrifugation changes in the orientation of Listing’s plane were found that were in accordance with *a reduced effect of gravity* on 3D eye position.

A second experiment on eye movement responses is described in Chapter 6, focusing on the spatial behaviour of the eye during visual stimulation (optokinetic nystagmus). When viewing a moving pattern rotating about the longitudinal axis of the head, but with the head tilted to the side, the eye orients towards gravity: it rotates about an axis that is somewhere between the rotation axis of the stimulus and gravity. This orienting response was measured in all 12 subjects, and was found to be reduced after sustained centrifugation. This is interesting because the neural network that is responsible for spatial behaviour (the so-called *velocity storage mechanism*) is involved in the integration of angular velocity signals and linear acceleration signals. As mentioned above, this integration is essential to obtain an adequate estimate of self motion (i.e., translation) and gravity (i.e. tilt) during natural movements, in particular during head tilt (i.e., angular head motion about off-vertical axes). Interestingly, SIC arises exactly during these movements! The reduced orienting responses found after centrifugation may therefore reflect a deteriorated ability to adequately integrate the sensory signals representing angular velocity and linear acceleration, This, in turn, may be related to the problems with spatial orientation that have been observed following gravity transitions and provides a good indication for a possible cause for these effects.

Chapter 7 addresses possible determinants of SIC-susceptibility, since not everyone experiences SIC after sustained centrifugation. It has been suggested that a functional asymmetry between the right and left otoliths contributes to SAS-susceptibility in astronauts. This is known as the *otolith-asymmetry hypothesis*. However, an adequate paradigm to investigate this hypothesis by stimulating only one of the two otoliths was lacking at that time. With the development of a new vestibular test enabling one-sided otolith stimulation, called *unilateral centrifugation*, the relationship between SIC-susceptibility and otolith asymmetry could be assessed in more detail. To that end unilateral otolith function was measured in 15 subjects with known susceptibility to SIC. Also the unilateral function of the semicircular canals was measured. SIC susceptible subjects appeared to have a higher degree of otolith asymmetry, otolith sensitivity, and semicircular canal sensitivity. Otolith asymmetry alone did not have enough discriminative power to classify the subjects as susceptible or not, but such a classification could be made when various otolith and semicircular canal parameters were combined. This illustrates that the whole vestibular system is involved in SIC and demonstrates the role of – complex – interactions between its parts.

The results of the experiments presented in this thesis thus contribute to our understanding of the effects of sustained centrifugation, and demonstrate the relationship between SIC and SAS. That SIC and SAS represent a similar form of motion sickness, and that SAS can be silulated on Earth makes sustained centrifugation a valuable tool. Not only for scientific but also for applied purposes. It may be used as a paradigm to train astronauts to deal with the gravity transitions occuring during space flight (e.g., during launch and landing). And ground-based simulation of SAS also offers a way to test pharmaceutical countermeasures against these forms of motion sickness, which is cheaper than testing them in actual flight. Such studies may contribute to an increased safety in manned space flight, where motion sickness and spatial disorientation still form serious threats.

Suzanne A. E. Nooij

Samenvatting (Dutch summary)

Aanpassing van het evenwichtssysteem aan een ander zwaartekrachtsniveau: Consequenties voor ruimtelijke oriëntatie

De alomtegenwoordige zwaartekracht vorm een belangrijke referentie voor onze ruimtelijke oriëntatie ("Hoe beweeg ik en hoe ben ik georiënteerd; hoe val ik niet om?"). Pas bij blootstelling aan een ander zwaartekrachtsniveau, zoals bijvoorbeeld in de ruimte, beseffen we hoezeer we 'aardse wezens' zijn (Ockels 1988). Dit proefschrift gaat over het aanpassen aan zo'n ander zwaartekrachtsniveau en over de consequenties die dat heeft voor ruimtelijke oriëntatie.

Het evenwichtsorgaan speelt een belangrijke rol bij ruimtelijke oriëntatie en het waarnemen van de zwaartekracht. Of beter gezegd, bij het bepalen van de *valversnelling* (g=9.81 m/s^2, ofwel 1G). Het evenwichtsorgaan zit in het binnenoor en bestaat uit de *halfcirkelvormige kanalen*, gevoelig voor rotatie, en de *otolieten*, gevoelig voor lineaire versnellingen. Dit kan de valversnelling zijn, maar ook de versnelling die we zelf genereren door te bewegen (inertie). Echter, voor een otoliet geldt net als voor iedere versnellingsmeter, dat hij zelf geen onderscheid kan maken tussen die twee soorten versnellingen (Einsteins gelijkheidsprincipe). Maar het maken een goede schatting van de grootte en richting van de valversnelling en van de versnelling als gevolg van bewegingen is wel noodzakelijk, bijvoorbeeld voor de controle van ons houdingsevenwicht. Gelukkig is ons brein wel in staat dit onderscheid te maken door, onder andere, gebruik te maken van informatie over rotatie uit bijvoorbeeld de halfcirkelvormige kanalen. Zoals aannemelijk zal worden gemaakt in dit proefschrift, is het juist dit proces dat verstoord is in een andere zwaartekrachtsomgeving.

Een sprekend voorbeeld van onze afhankelijkheid van de zwaartekracht is de bemande ruimtevaart. Aanpassing aan gewichtsloosheid gaat in 50-70% van de astronauten gepaard met symptomen van het *Space Adaptation Syndrome* (SAS): desoriëntatie, visuele illusies, bewegingsillusies en bewegingsziekte (d.w.z. misselijkheid). Deze symptomen worden vooral opgewekt door het maken van hoofdbewegingen. In twee tot drie dagen is het systeem aangepast en verdwijnen de symptomen, maar bij de terugkeer naar de aarde kunnen ze weer terugkomen (genaamd *Earth-sickness*). Ook hebben veel astronauten dan moeite met het bewaren van hun evenwicht.

Dat gewichtsloosheid geen strikte voorwaarde is voor het ontstaan van deze symptomen, is af te leiden uit het feit dat SAS ook wordt opgewekt door langdurige (in de orde van een uur of langer) blootstelling aan een hoger ‘zwaartekrachtsniveau’ in een personen-centrifuge. *Tijdens* het centrifugeren past het lichaam zich aan aan de nieuwe omstandigheden, zodat het *na* het centrifugeren niet meer optimaal kan functioneren onder normale 1G-omstandigheden. Ongeveer de helft van de proefpersonen heeft na langdurig centrifugeren last van dezelfde symptomen als SAS, inclusief de balansproblemen. We noemen dit *Sickness Induced by Centrifugation* (SIC). De symptomen van SIC worden – ook weer – opgewekt door hoofdbewegingen en kunnen enkele uren aanhouden.

De overeenkomsten tussen SIC en SAS suggereren dat er een algemeen principe is voor het aanpassen aan een ander zwaartekrachts-niveau. Dit maakt langdurig centrifugeren tot een waardevol onderzoeks-paradigma. In het verleden is er al veel onderzoek gedaan naar het mechanisme dat ten grondslag ligt aan SIC (en dus ook aan SAS). Hoewel dit veel waardevolle bevindingen heeft opgeleverd bleef het exacte mechanisme nog onduidelijk. In dit proefschrift wordt het paradigma van langdurig centrifugeren gebruikt om te onderzoeken of dit enerzijds leidt tot eenzelfde aanpassingsproces als aanpassing aan gewichtsloosheid en anderzijds of langdurig centrifugeren onze schatting van de zwaartekracht beïnvloedt.

Hoofdstuk 2 gaat in op de relatie tussen SIC en SAS. Een goede indicator voor een algemeen adaptatie-principe is het feit dat gevoeligheid voor SIC en SAS gecorreleerd is: de astronauten die last hebben van SAS tijdens hun ruimtevlucht zijn ook degenen die last van SIC na centrifugeren. Dit is een belangrijke bevinding omdat gevoeligheid voor SAS *niet* samenhangt met gevoeligheid voor andere vormen van bewegingsziekte. In eerdere studies is de relatie tussen SIC- en SAS-gevoeligheid bepaald bij acht astronauten. In die studies werden symptomen van SIC opgewekt door het maken van hoofdbewegingen *na* langdurig centrifugeren (60 minuten op een niveau van drie keer de aardse valversnelling, 3G). De gevoeligheid voor SAS werd echter niet tijdens maar na de ruimtevlucht bepaald, op basis van herinnering ('welke symptomen heb ik ervaren tijdens mijn ruimtevlucht?'). In het kader van dit proefschrift is er een nieuwe studie uitgevoerd, bij vier astronauten, waarin een zelfde hoofdbewegings-protocol werd gebruikt om SAS-gevoeligheid te bepalen tijdens de vlucht en SIC gevoeligheid na langdurig centrifugeren. Dit geeft een meer gedetailleerde vergelijking van SIC en SAS. De resultaten bevestigen dat de astronauten die last hadden van SAS ook last hadden van SIC en vice versa. Hoewel de hoofdbewegingen tijdens de ruimtevlucht tot meer bewegingsziekte leidden, onderscheidden de SIC-gevoelige astronauten zich van de anderen door een hogere misselijkheidsscore en een andere manier van bewegen (meer robot-achtig). Dit geeft aan dat de overgang van 1G naar gewichtsloosheid dezelfde symtpomen opwekt als de overgang van 3G naar 1G en dat het inderdaad waarschijnlijk is dat eenzelfde mechanisme hieraan ten grondslag ligt.

Hoofdstuk 3 geeft een overzicht van het belangrijkste werk dat eerder gedaan is over de effecten van langdurig centrifugeren, aangevuld met enkele nieuwe resultaten. Deze studies onderstrepen de rol van de zwaartekracht en het evenwichtssysteem in SIC. De schatting van de zwaartekracht speelt een belangrijke rol in het ontstaan van bewegingsziekte en is dus ook belangrijk in het ontstaan van SIC. Inderdaad is gevonden dat, na centrifugeren, alleen die hoofdbewegingen misselijkmakend zijn die de stand van het hoofd ten opzichte van de zwaartekracht veranderen (hoofdkanteling). De mate van bewegingsziekte is verder afhankelijk van het aantal hoofdbewegingen en van de hoofdbewegingssnelheid. Verder staan veel proefpersonen minder stabiel na centrifugeren, wat mogelijk duidt op een verkeerde inschatting van de zwaartekracht ten opzichte van het lichaam. Echter, proefpersonen zijn na centrifugeren nog goed in staat de richting van de zwaartekracht aan te geven tijdens (statische) lichaamskanteling. Daarentegen zijn er wel effecten gevonden van langdurig centrifugeren op verschillende oogbewegingen die gestuurd worden door het evenwichtssysteem. Dit gaf aanleiding om het effect op oogbewegingen nader te onderzoeken, wat beschreven wordt in Hoofdstuk 5 en 6.

Hoofdstuk 4 gaat in op de centrifuge-stimulus die nodig is om het aanpassingsproces op gang te brengen. Er werd gekeken naar de invloed van G-belasting en duur van centrifugeren op het onstaan van SIC. Twaalf proefpersonen (geen astronauten) ondergingen vier verschillende centrifuge-condities, te weten 45 en 90 minuten op een niveau van 2G en 3G. Voor en enige malen na het centrifugeren voerden deze proefpersonen een hoofdbewegings-protocol uit om SIC op te wekken. Hun hoofdbewegingssnelheid werd daarbij geregistreerd. Omdat SIC-gevoelige proefpersonen de neiging hebben om hun hoofdbewegingen langzamer uit te voeren in een poging misselijkheid te reduceren, werden de misselijkheidscores gecorrigeerd voor hoofdbewegingssnelheid. Hierdoor konden de effecten van de vier centrifuge-condities beter vergeleken worden. Op deze manier werd een groot verschil gevonden in de misselijkheidscores van de proefpersonen die gevoelig waren voor SIC en van degenen die ongevoelig waren voor SIC. In de eerste groep had zowel de G-lading als de duur een significant effect op de misselijkheidsscores, waarbij de hoogste scores werden gemeten na een belasting van 90 minuten op 3G. Deze effecten werden gemodelleerd door een exponentiële functie met een tijdsconstante van ongeveer 1 uur, wat een indicatie geeft voor de minimale duur van centrifugeren om SIC op te wekken. Dit is niet alleen waardevolle informatie voor verder onderzoek naar SIC, maar is ook relevant voor het ontwikkelen van centrifuge protocollen ten behoeve van 'kunstmatige zwaartekracht' tijdens een ruimtereis. Centrifugeren wordt dan vaak gebruikt als maatregel tegen de achteruitgang van de fysieke gezondheid van de astronaut (bijv. verlies van bot- en spiermassa), maar ook moet voorkomen worden dat dit ongewenste bij-effecten heeft, zoals misselijkheid. De resultaten van deze studie laten zien dat wanneer de duur van centrifugeren beperkt blijft, het optreden van bewegingsziekte na centrifugeren kan worden voorkomen.

Om meer inzicht te krijgen in het onderliggende mechanisme van SIC wordt in Hoofdstuk 5 een studie beschreven die kijkt naar het effect van zwaartekracht op de positie van de ogen in het hoofd. Wanneer het hoofd stilgehouden wordt, wordt de drie-dimensionale oogpositie beschreven door de Wet van Listing. Deze wet zegt dat de hoeveelheid oogtorsie (rotatiestand van het oog om de as door de pupil) afhangt van de kijkrichting. De relatie tussen oogtorsie en kijkrichting wordt weergegeven door het zogenaamde *Listing's Vlak*. De oriëntatie van dit vlak in het hoofd richt zich naar de zwaartekracht tijdens voor- of achteroverkanteling van het hoofd. Dit betekent dat het oog *als het ware* een aard-vaste positie wil innemen, ongeacht de stand van het hoofd in de ruimte. In dezelfde 12 proefpersonen is zowel voor als na langdurig centrifugeren de oriëntatie van dit Listing's Vlak bepaald, in verschillende standen van het hoofd. De effecten die gevonden werden duiden op een *verminderde invloed van de zwaartekracht* op de stand van het oog in het hoofd na het centrifugeren.

Een tweede experiment over oogbewegingen wordt beschreven in Hoofdstuk 6 en gaat over het spatiële gedrag van het oog tijdens visuele stimulatie (optokinetische nystagmus). Als iemand het hoofd zijwaarts kantelt en in die positie kijkt naar een strepenpatroon dat beweegt van het linker- naar het rechteroor, volgt het oog niet alleen de strepen, maar heeft het ook de neiging om in het aard-horizontale vlak bewegen. De uiteindelijke oogbeweging ligt hier ergens tussen in. Dit betekent dat de as waarom het oog draait zich gedeeltelijk richt naar de zwaartekracht. Deze oogbeweging is ook gemeten in de 12 proefpersonen en er werd gevonden dat dit effect – het richten van de oogbeweging naar de zwaartekracht – verminderd is na langdurig centrifugeren. Dit is interessant omdat het neurale netwerk dat verantwoordelijk is voor dit gedrag (het zogenaamde *velocity storage* mechanisme) betrokken is bij het integreren van zintuigelijke signalen over rotatie en lineaire versnelling. Zoals eerder gezegd is deze interactie ook belangrijk voor het goed schatten van de zwaartekracht, vooral tijdens dynamische hoofdkanteling (d.w.z. rotatie rond een niet-verticale as). Interessant genoeg zijn dat nou juist ook de bewegingen die SIC opwekken! De gevonden vermindering van het spatiële gedrag van het oog kan dus duiden op een verminderd vermogen om rotatie-informatie met informatie over lineaire versnelling te integreren. Dit kan, op zijn beurt, weer bijdragen aan de verstoorde ruimtelijke oriëntatie die optreedt na centrifugeren en vormt zo een goede indicatie voor een mogelijke oorzaak hiervan.

Hoofdstuk 7 gaat in op de vraag waardoor iemands gevoeligheid voor SIC bepaald wordt. Immers, niet iedereen ervaart de symptomen van SIC na centrifugeren. Eerder is gesuggereerd dat een verschil in de werking van de linker en rechter otoliet bijdraagt aan SAS-gevoeligheid in astronauten. Dit zou dus ook moeten gelden voor SIC. Het was destijds echter niet goed mogelijk om deze zogenaamde *otoliet-asymmetrie hypothese* verder te onderzoeken omdat er geen technieken bestonden om slechts één van beide otolieten te stimuleren. Met de komst van een nieuwe test, *unilateraal centrifugeren,* is het wel mogelijk om eenzijdige otoliet-functie te meten. Met behulp van deze test is gekeken of er een relatie bestaat tussen otoliet-asymmetrie en SIC-gevoeligheid. Hiervoor is bij 15 proefpersonen van wie SIC-gevoeligheid al eerder was bepaald de eenzijdige otoliet functie gemeten, alsmede de functie van de halfcirkelvormige kanalen (kortweg: kanalen). De personen die SIC-gevoelig waren bleken een grotere otoliet-asymmetrie te hebben, en ook een grotere gevoeligheid van zowel het otoliet- als kanaalsysteem. De proefpersonen konden niet geclassificeerd worden als SIC-gevoelig of niet-gevoelig op basis van otoliet-asymmetrie alleen, maar wel op basis van een combinatie van verschillende otoliet- en kanaal parameters. Dit laat zien dat het *hele* evenwichtsorgaan betrokken is bij SIC en dat het bij het ontstaan van SIC vermoedelijk gaat om de – complexe – interacties tussen de verschillende delen.

De resultaten van de bovengenoemde experimenten hebben bijgedragen aan het begrijpen van de effecten van langdurig centrifugeren en laten zien dat er een relatie is tussen SIC en SAS. Dat SIC en SAS eenzelfde vorm van bewegingsziekte representeren, en SAS dus op aarde nagebootst kan worden, maakt langdurig centrifugeren tot een waardevol paradigma. Niet alleen voor wetenschappelijke, maar zeker ook voor toegepaste doeleinden. Zo kan het toegepast worden als middel om astronauten te trainen om te gaan met de overgangen in zwaartekrachtsniveau die plaatsvinden tijdens een ruimtevlucht. Een andere belangrijke toepassing vormt het testen van medicatie tegen deze vormen van bewegingsziekte. Dergelijke studies kunnen bijdragen aan een verhoogde veiligheid tijdens bemande ruimtereizen waar bewegingsziekte en ruimtelijke (des)oriëntatie nog steeds een reëel probleem vormen.

Suzanne A. E. Nooij

Acknowledgements

Iieuuuw-psssss-iieuuuw-pssss...... If there is anything that I won't forget after finishing this thesis, it is the sound of the spinning centrifuge. Taken all runs together, the experiments described in thesis account for 4200 minutes of spinning, equal to almost 10.000 revolutions. Quite a bit! I think that the centrifuge operators, the medical staff supervising the experiments, and the subjects all wondered why the centrifugation had to be *sustained* ……. It always was exiting to see how subjects came out of the centrifuge and started moving about. First reactions ranged from "cool, what a weird feeling, I want to do it again" to something like "Aaaaaah, everything I do makes me sick, I'll never do this again!" That, exactly, is the unpredictable aspect of sustained centrifugation. Beforehand you do not know how someone is going to react, and when you do know it afterwards, the harm has already been done. Then the only remedy is to wait….Nevertheless, I never had trouble finding subjects for my experiments and even some of the susceptible ones kept coming back. So thanks to all my subjects, for their patience and endurance. Furthermore, I would like to thank the personnel of the Centre for Man in Aviation, for letting me use their centrifuge and for supervising the centrifuge runs. Special thanks goes to Amanda Moerman, Hans Wittenberg, Jason van de Burgt and Ted Meeuwsen, who were closely involved in all experiments.

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Given the direct relation between this thesis and human space flight I am more than proud that both of my "Promotoren" are former astronauts: Wubbo Ockels and Larry Young. Wubbo, because of our different backgrounds it was not always easy to get to the same grain of analysis during our discussions, but nevertheless, these discussions were of great value to me. I enjoyed listening to you ideas about space and time. They are indeed fascinating and I would love to dance one time in your hypergravity disco-show. Larry, thank you for comments on the first draft of this thesis, and for enjoyable discussions on internal models and spinning space crafts.

I reserve the last paragraph for the person who was involved the most in this thesis: my TNO-supervisor Jelte Bos. Jelte, it was a pleasure working with you and I appreciate the time and effort you put in me. For me you were a perfect supervisor. You kept me on track when I was lost and you learned me, among many other things, to take a minute to enjoy the milestones before attacking the next problem. There is only one thing that you failed upon: you never got me off my *bukfiets*….

Curriculum Vitae

Suzanne Nooij was born on May 7th 1976 in Ede, The Netherlands. After finishing secondary school (VWO) at the Chr. Streeklyceum in Ede in 1994, she obtained a degree in Human Kinetic Technology at The Hague University (Haagse Hogeschool) in 1998, where she graduated cum laude. During this period she visited the lab of Prof. David Browdy at Liverpool University (United Kindom), and performed an MRI study on the relation between structure and function of the human foot. In 1998 she continuated her education at the faculty of Human Movement Science of the Vrije Universiteit Amsterdam, where she followed a specialization program in movement coordination. She received a MSc. degree in 2002 and graduated cum laude. During this period she performed research at the TNO Human Factors institute in Soesterberg (The Netherlands), on the effect of ship motion and ship listing on movement behaviour. This was within the research group Equilibrium and Orientation, where she worked together with Dr. Willem Bles. The research for her MSc thesis was completed at the Vrije Universiteit in collaboration with Dr. Lieke Peper, and involved an investigation into rhythmic interlimb coordination. In 2002 she returned to the Equilibrium and Orientation research group at TNO Human Factors, where she performed the research described in this thesis to obtain a PhD-degree. Here she worked in close collaboration with Dr. Jelte Bos until 2008. During this period she performed research on eye movements, motion sickness, spatial orientation, and vestibular adaptation. She also visited the vestibular labs of Prof. Andrew Clarke in Berlin (Germany), of Dr. Thomas Haslwanter in Linz (Austria), and Prof. Floris Wuyts in Antwerp (Belgium).

List of publications

The work presented in this thesis is based on the following manuscripts:

Chapter 2 and 3:

- Nooij SAE, Bos JE, Groen EL, Bles W, Ockels WJ: Space sickness on Earth. Accepted for publication in Microgravity, Science & Technology
- Nooij SAE, Bos JE, Groen EL, Bles W (2006) Validating the SIC-SAS paradigm during the Delta Mossion: Motion perception and new vestibular function tests. *TNO report, TNO Human Factors, Soesterberg, the Netherlands* TNO-DV3 2005 IN018.

Chapter 4

- Nooij SAE, Bos JE: Sickness induced by head movements after different centrifugal Gx loads and durations. Accepted for publication in Journal of Vestibular Research

Chapter 5

- Nooij SAE, Bos JE, Groen EL: Orientation of Listing's plane after hypergravity exposure in humans. Submitted.

Chapter 6

- Nooij SAE, Bos JE, Groen EL: Velocity storage activity is affected after sustained centrifugation: a relationship with spatial disorientation. Submitted.

Chapter 7

- Wuyts FL, Nooij SAE, Vanspauwen R, Neyt X: A new method for analyzing utricular asymmetries. Manuscript in preparation.
- Nooij SAE, Vanspauwen R, Bos JE, Wuyts FL: Do vestibular asymmetries contribute to sickness induced by sustained centrifugation? Manuscript in preparation.

Other manuscripts on related topics:

- Bos JE, Groen EL, Nooij SAE. (2004) Further thoughts on and calculations by spatial orientation and motion sickness modelling. *TNO Report, TNO Human Factors, Soesterberg, Netherlands* TM-04-I005.
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