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 (SMS) 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).

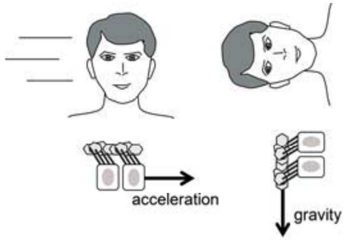

Figure 1.1: Schematic representation of the utricular hair cells with otoconia. Both translation (left) and tilt (right) can induce an equal response of the hair cells.

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):

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

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.

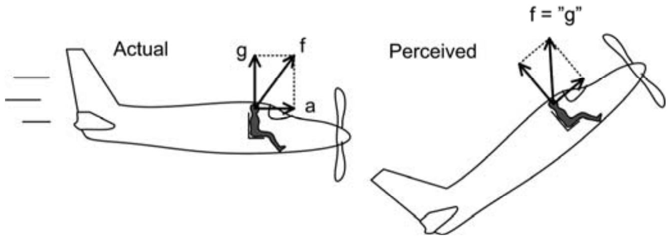

*Figure 1.2: In the somatogravic illusion the total gravito-inertial acceleration **f** is, erroneously, interpreted as gravity, thus inducing a sense of tilt.*

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.

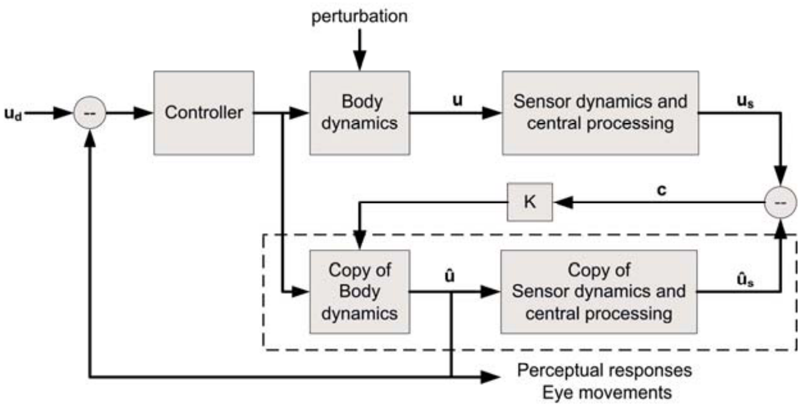

*Figure 1.3: Observer model for spatial orientation. The observer or 'internal model' is indicated by the dashed box. It is proposed that perceptual and ocular responses are derived from an internal estimate of the body state ($\hat{\mathbf{u}}$) instead of sensory output ($\mathbf{u}_s$). The sensory estimates of the body state ($\mathbf{u}_s$) are compared with sensory estimates of the expected body state ($\hat{\mathbf{u}}_s$) 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 to reorient 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.