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).

[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.