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 linear 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 this 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.

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