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Microgravitational effects on the neurovestibular system and countermeasures to facilitate safe and effective adaptation to changes in gravity during future Mars explorations

A literature review

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Master thesis in medicine (MED-3950), June 2022
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Prologue

During our fourth and fifth year of medical school at the University of Tromsø, we write a master thesis. By doing so, I have learned and used systematically literature search to gathering information and present it as a complete thesis.

My interest in space started many years ago with subjects like astrophysics and the study of other planets that potentially could sustain life. After reading Terje Sæhle's article "Ingen måneferd uten romfartsmedisin" on space medicine in Tidsskriftet, I realized that I could combine my interest in space with my future profession, medicine, and write a thesis on this exciting topic. The environmental effects space has on the human physiology is fascinating, but hazardous with its reduced gravity, high amount of radiation, vacuum and extreme isolation. I found microgravity and the fact that many mechanisms in our body is gravity-dependent interesting and therefore decided to write about the neurovestibular system.

Luckily, I found a motivated and very inspiring thesis supervisor with the same interests as my own. Torsten Risør from the Institution for Community Medicine, University of Tromsø. To get some expertise on space medicine, I also reached out to Terje Sæhle, neurosurgeon, chief physician of the Norwegian Civil Aviation Authority and member of the ESA medical board, who agreed to assist as a co-supervisor.

I want to thank my thesis supervisor, Torsten Risør, and co-supervisor, Terje Sæhle, who has both been an invaluable help in guiding the writing process, motivating and giving great advice.

Inger Grøm Steinum

Palermo, 01.06.22

Innholdsfortegnelse

1 Abstract

1.1 Introduction

With the Artemis program National Aeronautics and Space Administration (NASA) plans to land humans on the moon to prepare for the next giant leap, Mars. In order to achieve this ambitious goal, lots of medical and physiological obstacles have to be overcome to ensure a safe voyage. A common but manageable issue with space travel has been neurovestibular dysfunction and altered sensorimotor functions, resulting in symptoms of space motion sickness (SMS) and spatial disorientation. With increasing spaceflight duration and adaptation to various gravities, this hurdle becomes more prominent and will require effective countermeasures.

1.2 Purpose of the study

The purpose of this study is to get a closer look at how microgravity affects the neurovestibular system, and to consider which countermeasures that can assist in a safe and effective adaptations to gravitational changes.

1.3 Material and method

By executing a systematical literature search through the databases PubMed and MEDLINE, articles were found and included in the thesis based on carefully selected criteria. The main search in PubMed resulted in 1780 articles, which first went through a filtration to exclude articles in other languages than English, published before 2011 and with no available abstract or full text. 132 articles' title and abstract were then reviewed for relevance based on the selection criteria. 94 articles were excluded, and the remaining 36 articles were read in full text. Of these, 19 articles were relevant and contributed to the purpose of the study, and therefore included in the thesis. To cover articles not found in PubMed, another search was carried out in MEDLINE, providing an additional 4 articles.

1.4 Results

Studies has shown that space motion sickness and spatial disorientation mainly affect astronauts during and right after gravitational transitioning. When being exposed to microgravity for longer durations, adaptation mechanisms are activated and leads to utricular deconditioning with synaptic plasticity and decreased ocular counter-roll reflex.

Susceptibility to space motion sickness seems to be higher in females, astronauts with a visual-depended orientation preference and increased otolith mass asymmetry.

Pharmaceuticals, especially scopolamine and promethazine, are widely used to prevent or to ease symptoms of SMS. The effect of these drugs is highly variating. Scopalamine has been found to be quite efficient in lower the symptoms, but has shown side effects of drowsiness, which could be counteracted by combining scopolamine with dextroamphetamine (ScopeDex).

Artificial gravity (AG) is suggested as a possible and effective countermeasure against vestibular deconditioning and intermittent exposures has been proven to be more tolerable. Virtual reality has been tested and showed promising results in modifying orientation preference to be less depended on visual cues. Galvanic vestibular stimulation is an analog creating similar altered vestibular inputs as microgravity and can be used in preflight adaptation training.

1.5 Conclusion

Microgravity can induce space motion sickness and spatial disorientation in astronauts, especially during gravitational transitioning. Long-duration exposure also leads to utricular deconditioning with synaptic plasticity and decreased ocular counter-roll reflex, which contributes to reentry symptoms.

Susceptibility to SMS variates and can be mapped with Motion Sickness Susceptibility Questionnaire, as well as vestibular and visual tests. Females seems to be more susceptible, due to their orientation preference being more visual-dependent. The sensory conflict, which leads to SMS, has been shown to increase in astronauts with marked otolith mass asymmetry.

Countermeasures include the use of pharmaceuticals, with individual and limited effect, and preflight training to aid adaptation through galvanic vestibular stimulations, virtual reality and artificial gravity.

There is a call for future research to develop countermeasures that are both effective and affordable.

2 Abbreviations

ISS – International Space Station
NASA - National Aeronautics and Space Administration
SMS – Space motion sickness
SANS – Spaceflight associated neuro-ocular syndrome
CNS – Central nervous system
VOR – Vestibular ocular reflex
OCR – Ocular counter roll
MeSH – Medical subject headings
SIC – Centrifugation-induced motion sickness
RPM – Rotations per minute
CC – Cross-coupled
AG – Artificial gravity
GVS – Galvanic vestibular stimulations
SV – Subjectiv verticle
SVV – Subjectiv visual verticle
MSSQ - Motion Sickness Susceptibility Questionnaire
EVA – Extravehicular activity

3 Introduction

In 1961 Russian cosmonaut Yuri Gagarin was the first human to orbit the Earth. Since then more than 560 people have followed him into space, and the number is expected to increase significantly (1). The International Space Station (ISS) is permanently manned with long-duration crews, commercial space travel is emerging and with the Artemis program, National Aeronautics and Space Administration (NASA) expects to land humans on the moon to prepare for the next giant leap, the Mars exploration (2).

To achieve their grand vision, there will be high demands on innovative engineering and development of technology, as well as medical and physiological knowledge (2). The environment in space differs from Earth with, among other things, reduced gravity, high amount of radiation, vacuum and extreme isolation. To ensure the safety of the crew and to possibly sustain life on Mars, it is important to understand how the environment affects the human physiology.

A common, but manageable issue with space travel has been neurovestibular dysfunction and altered sensorimotor functions, with following symptoms of space motion sickness and spatial disorientation (3). With increasing spaceflight duration and adaptation to various gravities, this hurdle becomes more prominent and will require effective countermeasures. By reviewing relevant literature, this thesis will enlighten and discuss this obstacle.

3.1 Spaceflight

We normally divide the different types of spaceflights into three categories depending on the altitude: suborbital, low Earth orbit and exploration class (Table 1) (1, 4).

Table 1: categories of spaceflights

Type of spaceflight	**Altitude**	**Duration**	**Example**

Suborbital	>100 km	A few minutes	Flights to the Kármán line
Low Earth orbit	200-400 km	From days to months	ISS
Exploration class	>400 km	Maybe years	Mars expedition

With these assorted types of spaceflights, comes different obstacles. Medical and environmental challenges changes according to the duration and trajectory of the flight (1).

3.2 Space physiology and microgravity

Near the surface of the Earth, objects in free fall have a constant gravitational acceleration of approximately 9,81 m/s^2 (denoted as "*g*"). The countereffect from the ground on which we stand, provides the feeling of weight and the downward pull and gravity vector our bodies are used to. Physiological processes such as cerebral blood perfusion, body fluid distribution, spatial orientation and stimulation of the musculoskeletal system are all affected by these gravitational gradients (5).

One of the most familiar aspects of space environment is weightlessness. In orbit, astronauts are weightless due to a state of free-fall around the Earth (6). The weightlessness is not absolute and is therefore often replaced by the term *microgravity* in scientific publications. In microgravity the gravity vector, to which our body is used to from Earth, is absent. This static sate affects the human physiology and makes it adapt to the new environment.

3.2.1 Early effects of microgravity environment

There are several physiological effects of microgravity with almost immediate clinical manifestation (5): 1) disturbance of the neurovestibular system, 2) loss of the gravity-induced hydrostatic pressure gradients leads to cephalad fluid shift and 3) anthropometry changes like body posture, stature and redistribution of fluids and muscle mass appears.

3.2.1.1 Space motion sickness

Space motion sickness (SMS) is a common and the most clinically significant neurosensory phenomenon in spaceflight and as many as 50-70% of first-time astronauts experience it within minutes to hours after entering microgravity (3, 5). Common symptoms are headache, drowsiness, nausea, sudden vomiting, dizziness and pallor, which can be disabling (7). The symptoms vary in degree, but about half of the astronauts experiencing SMS will have moderate to severe symptoms, which could highly affect their performance ability (8). The symptoms usually resolve after 3 days in microgravity and are on regular spaceflights, such as the ISS, accommodated for by limiting the astronauts' tasks the first days. In the event of a Mars exploration, there will be an increased pressure on the astronauts' ability to perform straight away. Severe symptoms of SMS will in that case compose a potentially huge risk for the crew and the mission (9). The corresponding syndrome that may occur upon return to gravity is termed reentry motion sickness (5).

3.2.2 Late effects of microgravity environment

Long-duration spaceflights, as the ISS program, gives us useful information about how the body reacts to space environment over time (5). One of the major concerns of prolonged exposure to microgravity is the fact that gravitational unloading causes deconditioning of the musculoskeletal system with bone demineralization and muscle atrophy (4). Other concerns are, among other things, neuro-ophthalmic changes collectively called Spaceflight Associated Neuro-ocular Syndrome (SANS), with attenuated baroreceptor responses, regulation of the immune system, changed haematopoiesis and alteration in lung volumes.

In addition to direct consequence of microgravity, but long-duration spaceflights, especially future Mars explorations, will also have significant psychological and psychosocial challenges (7). Long periods of high workload, exposure to possible life-threatening events, isolation and the stress of being confined with the same group of people, could lead to interpersonal conflicts, depression and limit the astronauts' motivation and performance. As these psycho-social conditions are known to cause symptoms as fatigue, disorientation, dizziness and other unspecific bodily sensations, they may complicate the assessment and need for countermeasures for the effects of microgravity.

3.3 The neurovestibular system

The vestibular system consists of two balance-sensing organs in the inner ear, the otolith organs and three semicircular canals (ductus semicirculares), which provide information about head positioning and movement, and helps with maintaining equilibrium (6). These functions are important for human performance and can be greatly reduced by the adverse effects of microgravity.

3.3.1 The otolith organs

The otolith organs, saccule and utricle, contains endolymph, hair cells connected to a small sensory area called the macula, an otolithic membrane filled with gelatinous substance and small calcium carbonate crystals called otoliths. The hair cells projects cilia with increasing length into the otolithic membrane (10). The longest cilium is called the kinocilium, while the smaller ones are called stereocilia. Because of the otolith's high density, they are more affected by gravity than the endolymph and the cilia. This causes deflection of the cilia in the direction of the gravitational pull. Deflection of the stereocilia towards the kinocilium causes depolarization, while deflection away from the kinocilium causes hyperpolarization (11). This gives the brain appropriate signals during linear acceleration (translation) and tilting of the head, which triggers postural control mechanisms to maintain equilibrium (10).

Since the otolith function depends on gravitoinertial forces, it will not work properly in space, giving rise to sensory conflict, which may manifest as space motion sickness (SMS), disturbances in sensorimotor functions and spatial disorientation (5). This could greatly reduce human task performance, and complete neurosensory adaptation may take weeks to achieve.

After a prolonged exposure to microgravity and adaptation to the new environment, the return of 1 G environment on Earth will frequently induce similar disturbances and impaired sensorimotor functions. These adverse effects may be of particular concern during future planetary missions and g transitions, for example from 1 G on Earth to microgravity to 0,38 G on Mars.

3.3.2 The semicircular ducts

Rotation of the head, angular acceleration, is detected by the semicircular ducts. The three ducts are oriented in three planes and are placed perpendicular to each other (11). The ducts are filled with endolymph and at the end of each duct there is an enlargement called the ampulla. In each ampulla there is a small crest of epithelial and hair cells called crista ampullaris. On top of the crista there is a gelatinous mass, the cupula, where hundreds of cilia from the hair cells are imbedded. Change in rotation of the head causes relative flow of the endolymph in the semicircular ducts. Because of the endolymph inertia, the fluid remains stationary while the ducts rotate. The fluid flows through the ampulla, shifting the cupula and bending the cilia. Depending on the direction the cilia bends, the hair cell will depolarize or hyperpolarize and appropriate signals are sent to the central nervous system through the vestibulocochlear nerve.

The semicircular canals are not gravity-dependent and will therefore function normally in microgravity.

3.3.3 Vestibular pathways

Most of the vestibular nerve fibers terminate in the brain stem in the vestibular nuclei, which are located approximately at the junction of the medulla and the pons (10, 11). The vestibular nuclei also receive afferents from other parts of the CNS, as the medulla spinalis, reticulum, mesencephalon and the cerebellum.

The efferent fibers from the vestibular nuclei is either 1) descending to the medulla spinalis and forms the vestibulospinal tract, which adjust muscle tonus in the antigravity muscles (extensor muscles) to maintain balance, 2) going to the lobus flocculonodularis in the cerebellum, 3) ascending through the fasciculus longitudinalis medialis, to the cranial nerve nuclei that are responsible for eye movements or 4) ascending all the way up to the thalamus and the cortex cerebri.

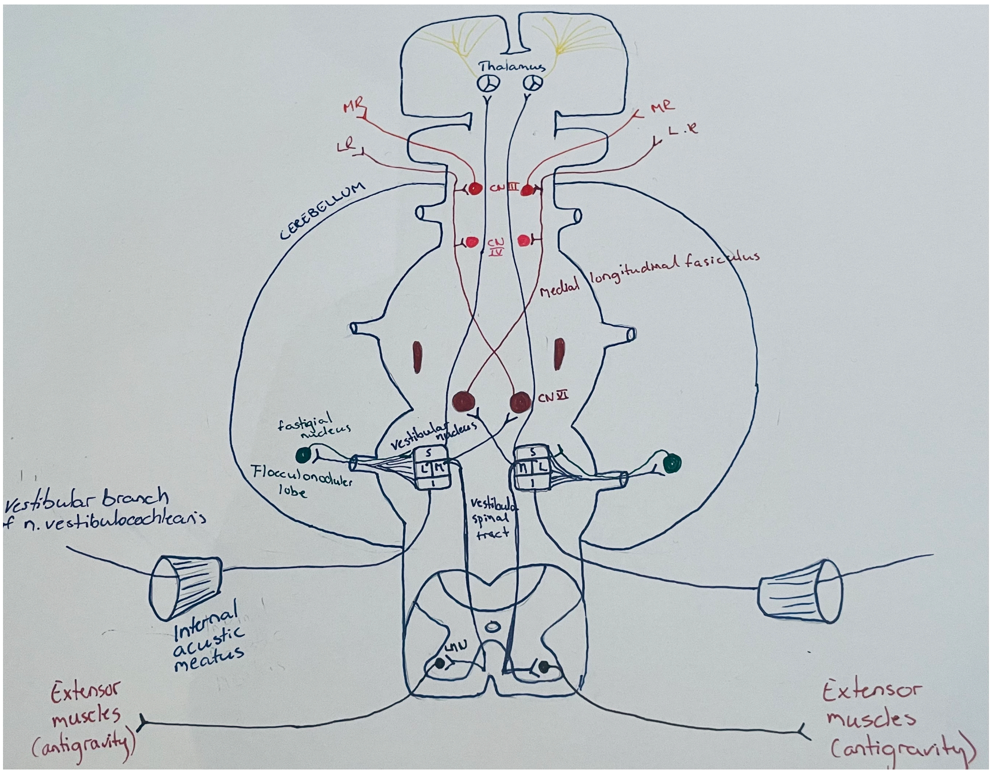


Fig. 1: *illustration of the vestibular pathways*

3.3.4 The vestibular ocular reflex

The vestibular ocular reflex (VOR) makes it possible to maintain gaze while rotating the head, by generating a opposite, compensatory movement of the eyes (5). As mentioned earlier, action potentials created by angular acceleration goes from the hair cells in the semicircular ducts through the vestibulocochlear nerve to the vestibular nuclei in the brain stem. By turning your head to the right, the hair cells of the right semicircular duct will depolarize and send stimulating signals to the right vestibular nucleus. Efferent fibers will then ascend to the contralateral abducens nucleus, which innervates m. rectus lateralis and abducts the left eye. From the abducens nuclei nerve fibers goes through the fasciculus longitudinalis medialis to the contralateral oculomotor nucleus. Among others, n. oculomotorius, innervate mm. rectus medialis and contraction of these muscles makes the eyes adduct. Head rotation to the right will therefore provoke a rapid eye movement to the left to maintain gaze.

3.3.5 Ocular counter roll reflex

As the VOR maintains the gaze during head rotation, the ocular counter roll (OCR) reflex stabilizes the gaze during static head tilt (12). While the angular acceleration in head rotation stimulates the hair cells in the semicircular ducts, the utricle responds to head tilting and gives appropriate signals through the utricular afferents to the vestibular nuclei in the medulla (13). From there on the pathway ascends through the fasciculus longitudinalis medialis, to the cranial nerve nuclei that are responsible for eye movements. Instead of stimulating or inhibiting the mm. rectus medialis and lateralis as the VOR does, the OCR reflex acts on the mm. rectus inferior and superior and mm. obliquus superior making the eyes either elevate and incycloduct or depress and excycloduct in response to the direction of the head tilt.

3.3.6 Spatial orientation

Spatial orientation is our ability to sense our body’s disposition in relation to our visual surroundings and the force of gravity (10). On Earth these frames of references provide dependable information about positional awareness and motion control. Movements will shift the visual images of our surroundings on the retina, giving the CNS information about the body’s position. Even without a functional vestibular apparatus, the visual cues will provide sufficient equilibrium if the eyes are open (11).

The otolith organs and semicircular canal detects linear and angular acceleration and thereby gives the CNS information about the head’s position related to gravity, joint proprioceptors in the neck registers the orientation of the head in respect to the body and tactile receptors respond to mechanical stimulation (5, 10). These gravity-dependent cues are a fundamental part in spatial orientation, and in weightlessness the astronaut’s sight will initially be the main sensory frame of reference (14).

4 Purpose of the study

Neurovestibular dysfunction and altered sensorimotor functions, and its manifestations as space motion sickness and spatial disorientation, are challenges that needs to be overcome to ensure safe explorations to the moon and Mars, where the astronauts will be exposed to profoundly difficult tasks and various gravitational environments. As the brief outline of the neurovestibular system above indicates, there is a complex physiological dynamic to consider, which makes the development of countermeasures an equally complex endeavor. Thus, we must take a holistic approach. This is some ways may contrast with many medical interventions that focus on only one physiological mechanism or only one diagnostic category. Here, there is a need to take the whole system into consideration and understand this in the context of future space travel.

The purpose of this study then is to get a closer look at how microgravity affects the neurovestibular system, and to consider which countermeasures that can assist in a safe and effective adaptation to gravitational changes.

5 Material and method

5.1 Study design and search strategy

By reviewing literature found through the databases PubMed and MEDLINE, this thesis will give an overview of former research and give recommendations for future research.

5.1.1 PubMed

To find relevant literature, a primary search in PubMed using suitable MeSH terms (Medical Subject Headings) was carried out. Since many relevant search words were not included in the MeSH terms and because of the time delay on newly published articles receiving their terms, titles were also added to the search. By doing this, more articles were covered by the main search. The terms and titles were divided into three groups based on focus:

- Space
- Neurovestibular system and related conditions
- Countermeasures

In each group, the terms are combined with the operator OR. Since the focus of the study is divided into two parts: (1) the effects microgravity has on the neurovestibular system and (2) countermeasures, all three groups are combined with the operator AND, as well as “Space” and “Neurovestibular system and related conditions” in the same way, before they were all combined with OR as illustrated below.

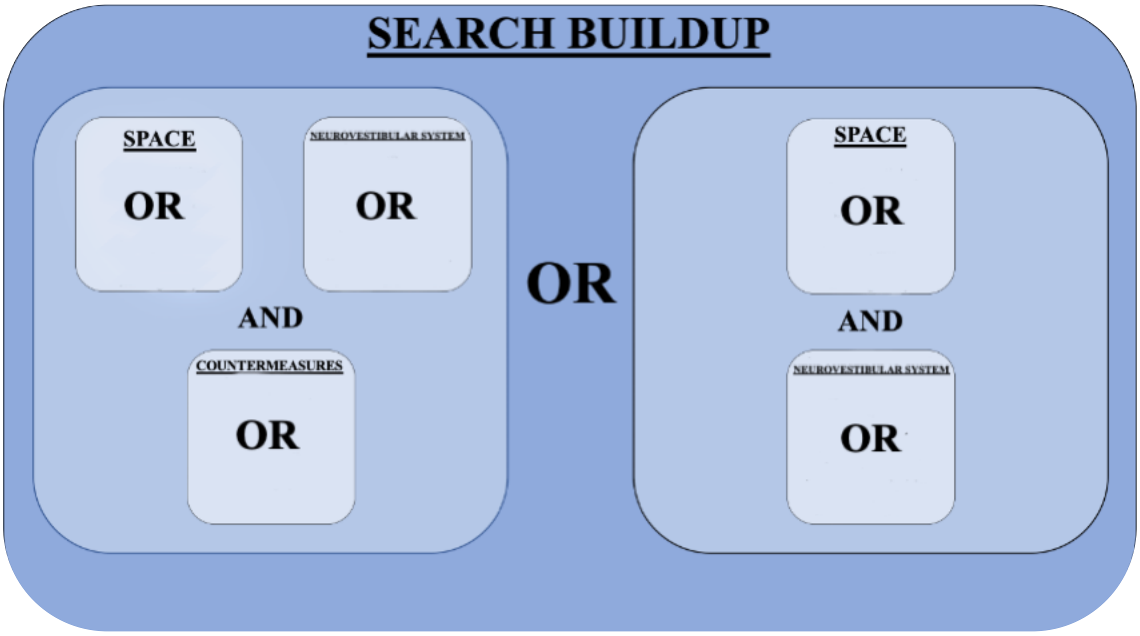
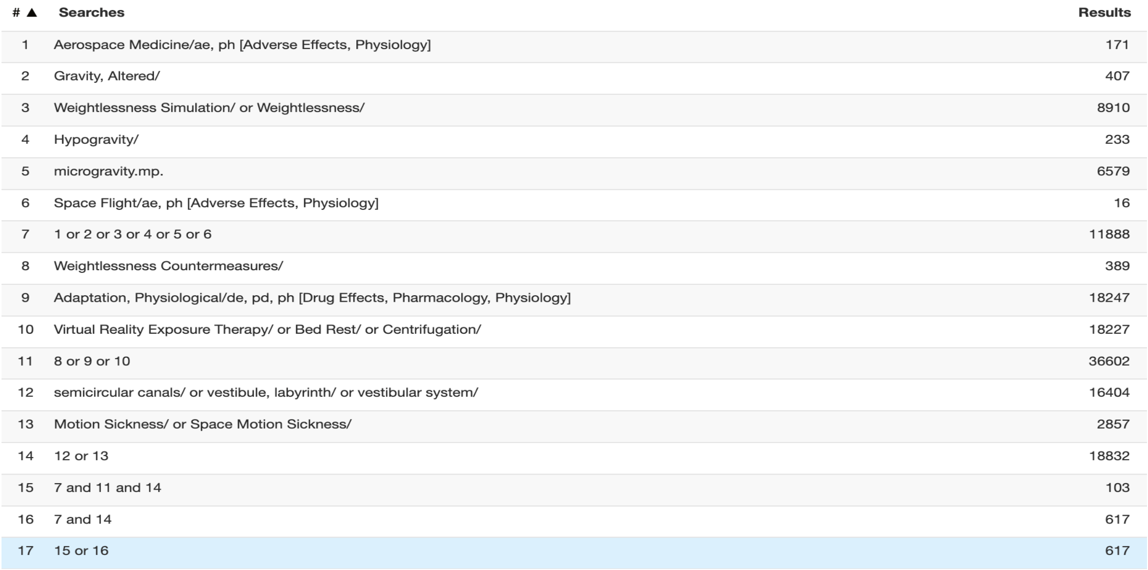


***Fig.** 2: simplified illustration of the search buildup. For fully detailed main search, see appendix A.*

To limit the search, filters were applied in PubMed to rule out articles written before 2011 and articles with no full text available in English. The remaining articles were read and included/excluded based on the selection criteria described in 5.2.

5.1.2 MEDLINE

To cover articles not found in PubMed, an additional search was carried out in MEDLINE. The same search buildup and filters were used, but with some variations due to different available subject headings.



# ▲	Searches	Results
1	Aerospace Medicine/ae, ph [Adverse Effects, Physiology]	171
2	Gravity, Altered/	407
3	Weightlessness Simulation/ or Weightlessness/	8910
4	Hypogravity/	233
5	microgravity.mp.	6579
6	Space Flight/ae, ph [Adverse Effects, Physiology]	16
7	1 or 2 or 3 or 4 or 5 or 6	11888
8	Weightlessness Countermeasures/	389
9	Adaptation, Physiological/de, pd, ph [Drug Effects, Pharmacology, Physiology]	18247
10	Virtual Reality Exposure Therapy/ or Bed Rest/ or Centrifugation/	18227
11	8 or 9 or 10	36602
12	semicircular canals/ or vestibule, labyrinth/ or vestibular system/	16404
13	Motion Sickness/ or Space Motion Sickness/	2857
14	12 or 13	18832
15	7 and 11 and 14	103
16	7 and 14	617
17	15 or 16	617

Fig. 3: *Additional search in MEDLINE.*

5.2 Criteria of selection

5.2.1 Criteria of inclusion

Studies that met the following criteria were included in the study:

- Published the last 10 years
- Relevance to the study:
  - Articles that describe the connection between microgravity and vestibular dysfunction
  - Articles that discusses countermeasures for vestibular dysfunction in space

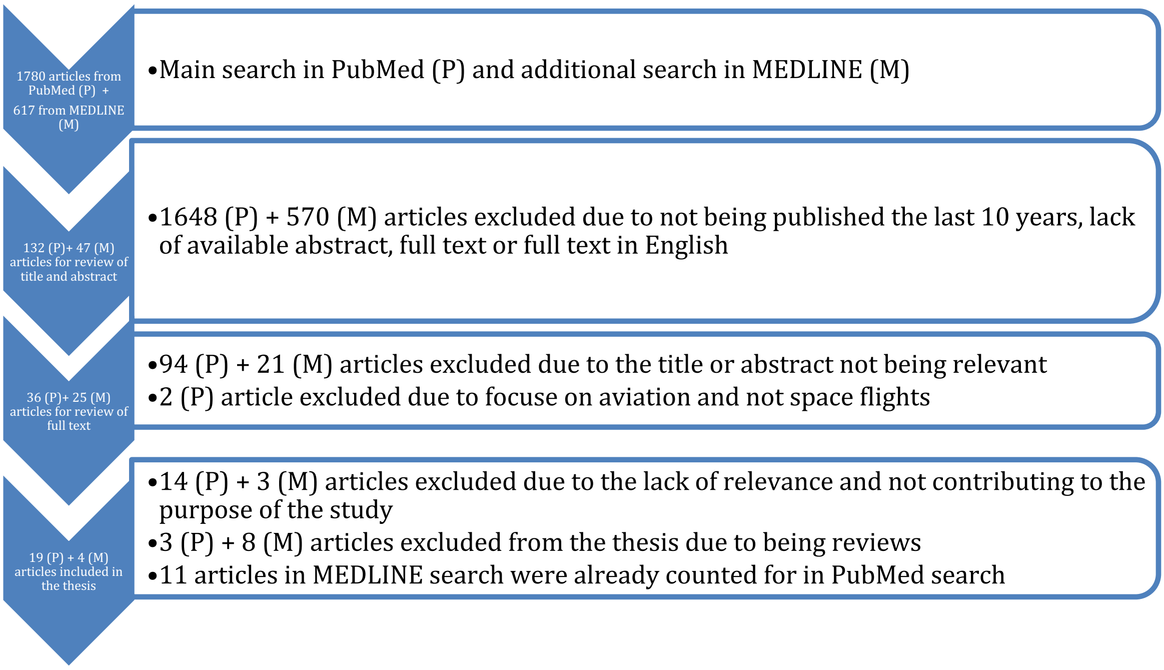
5.2.2 Criteria of exclusion

Studies that met the following criteria will be excluded from the study:

- Full text not available
- Full text not available in English
- Abstract not available
- Published earlier than 2011
- Articles that specifically focuses on aviation and not space flights
- Articles that focus on sub-orbital commercial flights

- Reviews

  - One review was included due to the coverage of pharmaceutical approach to SMS



- Main search in PubMed (P) and additional search in MEDLINE (M)
- 1648 (P) + 570 (M) articles excluded due to not being published the last 10 years, lack of available abstract, full text or full text in English
- 94 (P) + 21 (M) articles excluded due to the title or abstract not being relevant
- 2 (P) article excluded due to focuse on aviation and not space flights
- 14 (P) + 3 (M) articles excluded due to the lack of relevance and not contributing to the purpose of the study
- 3 (P) + 8 (M) articles excluded from the thesis due to being reviews
- 11 articles in MEDLINE search were already counted for in PubMed search

Fig. 4*: illustration of the exclusion process*

As illustrated in Fig. 4, the main search in PubMed resulted in 1780 articles, which first went through a filtration to exclude articles in other languages than English, published before 2011 and with no available abstract or full text. 132 articles' title and abstract were then reviewed for relevance based on the selection criteria. 94 articles were excluded, and the remaining 36 articles were read in full text. Of these, 19 articles were relevant and contributed to the purpose of the study, and therefore included in the thesis. To cover articles not found in PubMed, another search was carried out in MEDLINE, providing an additional 4 articles. For complete overview of included articles see Appendix B.

6 Results

As mentioned in the introduction, the otolith function is gravity-dependent and the lack of gravitoinertial forces will lead to sensory conflict which may manifests as space motion sickness (SMS), disturbances in sensorimotor functions and spatial disorientation, where SMS is most clinically prominent (3, 5). The majority of the articles describes different aspects of SMS; susceptibility, triggering factors and consequences, as well as mitigating and preventing elements.

6.1 Space motion sickness (SMS)

SMS is a common obstacle for astronauts, especially during their first flight, where up to 70% of crewmembers experience symptoms of variable severity (15, 16). A case study was conducted of a first flight astronaut on a 7-days mission who experienced severe motion sickness (15). During preflight visual- and vestibular tests, the astronaut showed average susceptibility to motion sickness. After entering microgravity, he experienced rapidly increasing symptoms including oscillopsia, extreme nausea and highly frequent vomiting, which totally incapacitated him. The symptoms were aggravated by any kind of movement and 50 mg Phenergan intramuscular only eased the malaise a bit. Disorientation, drowsiness, concentration impairment and emesis continued for five days, highly affecting his ability to contribute to the mission.

6.1.1 Susceptibility

The knowledge of what makes an astronaut susceptible for SMS could be used in both preflight training and in selecting suitable candidates for future Mars explorations, while understanding what triggers and worsen the symptoms could decrease the incidence and severity of SMS (15, 16). Several of the articles discussed different factors that makes the astronauts more susceptible, including orientation preference, the theory of otolith asymmetry and gender (15, 16, 18, 19).

6.1.1.1 Orientation preference

Chen et al. (8) used a virtual reality environment to stimulate SMS symptoms and examined the relationship between orientation preference and motion sickness. Their perceptual upright was used to measure their orientation preference and the results suggested that the subjects that were more dependent on visual cues to judge the orientation of perceptual upright, were more susceptible to visually induced motion sickness.

6.1.1.2 Otolith asymmetry

Asymmetry between the left and right otolith organs has been suggested as one of the contributors to space motion sickness susceptibility. By unilateral centrifugation, Nooij et al. (18) investigated whether subjects susceptible to centrifugation-induced motion sickness (SIC) had a higher level of utricular asymmetry compared to non-susceptible subjects. The results were only marginally significant. The SIC-susceptible subjects also showed slightly higher values on semicircular canal parameters, which support a possible combinational explanation rather than the otolith asymmetry theory as the sole determinant in SIC.

Clark and Schönfeld (19) also used unilateral centrifugation to study otolith asymmetry and adaptive modification of the otolith system. The results showed an increase in asymmetry both in utriculo-ocular response and in estimation of subjective visual vertical after reentry, which returned to baseline values after 5-8 days. The findings also indicates that one utricle recovers more rapidly than the other.

6.1.1.3 Gender

Chen et al. (8) found in their study that the motion sickness severity score was observed to be generally higher in the 9 female participants (71,0) than in the 23 males (46,0), which suggests that females are more susceptible to motion sickness than men. The reason for this has not been concluded, but it is possible that women are more dependent on visual cues for orientation, and therefore more susceptible.

6.1.2 Motion control and performance

During a short-radius centrifugation in the dark, the subjects in a study conducted by Rosenberg et al. (20), attempted to null out random roll-tilt motions with a joystick, showing a significant decrement in manual control and performance in 0,5 G than in 1,0 G and 1,33 G.

Clément and Wood's study (21) showed alterations in motion perception in 11 astronauts after two weeks on board the Space Shuttle. During static tilt stimuli on the day of landing, they showed an overestimation of roll tilt perception and an overall increased motion sensitivity. These findings normalized within 1-2 days. The subjects also experienced an increasing sense of linear acceleration, postflight compared to preflight when exposed to dynamic linear acceleration stimuli along the X- and Y-axes. These changes persisted longer than the alteration of static perception, especially in the pitch plane.

Using a centrifuge to create a hypogravity analog and subjective visual tasks, Galvan-Garza et al. (22). measured orientation perception in 0,5 G in nine subjects. The subjects initially underestimated the roll tilts, but showed adaptation and improved results after receiving static visual feedback. Similar results were portraited in a case study (23) on roll tilt perception during parabolic flight. The subject, which was exposed to 0,165 G and 0,38 G (corresponding to lunar and Martian gravity) underestimated roll tilt by approximately 40%.

6.2 Other effects of microgravity on the neurovestibular system

Microgravity has been shown to inflict temporary physiological changes in the neurovestibular system (9, 24).

6.2.1 Ocular counter roll (OCR) reflex

Since stimulation of the utricles are gravity-depended, microgravity will also affect the OCR reflex. By comparing the OCR reflex during head tilt in astronauts before, during and immediately after a short-duration spaceflight as well as before and after a long-duration spaceflight, Reschke et al. (12) found that the OCR were absent in microgravity and the time it took before it returned to normal depended on the duration of the flight. After a 4-6 days space shuttle flight it returned within just two hours, but after 4-9 months of ISS flight, the OCR amplitude was reduced relative to preflight values for four days.

Hallgren et al. (16) also found a statistically significant decrease of OCR in their study of 13 astronauts returning from a 6-month stay in the ISS. Similar results were found in 19 of 25 astronauts also returning from a spaceflight of 6 months (17). In both studies the measured OCR response had normalized 9-10 days after reentry compared to preflight.

6.2.2 Synaptic plasticity

By using immunohistochemical methods on the utricles of mice after two weeks in space, Sultemeier et al. (24) discovered a microgravity-induced reduction in synaptic density in the medial extrastriola of the utricle. Static unloading of the utricular epithelium diminishes the sensory transduction activity, resulting in a reduction in synapses. While this study focused on adaptive plasticity in the utricles, Hupfeld et al. (9) used fMRI on 15 astronauts to measure brain activity in response to vestibular stimulation, before and after spaceflight. The results showed a widespread decreased somatosensory and visual cortical deactivation, suggesting that microgravity-induced alterations in vestibular signaling causes compensatory and adaptive changes by down-regulating the vestibular inputs and up-regulating other sensory processing regions.

6.3 Countermeasures

To prevent severe adverse effects of microgravity on the neurovestibular system, possible countermeasures should be identified and incorporated.

6.3.1 Pharmaceuticals

In today's space flights the use of pharmaceuticals to lower or diminish symptoms of SMS are widespread (25). Scopalamine, a selective vestibular suppressor, and promethazine, a global vestibular suppressor, are the most used pharmaceuticals. A well-known side effect of scopalamine is drowsiness, which is unfortunate due to reduction of astronaut's performance ability. This could be counteracted by adding 5-10 mg amphetamine. The administration method has also been discussed and tested, since microgravity has a negative impact on oral bioavailability of pharmaceuticals. Both intramuscular and oral administration is widely used, but it's been suggested that intranasal scopolamine can be a favorable method of administration due to bypassing of first passage metabolism.

Data from the Neurolab study (26) showed that a combination of promethazine and dextro-amphetamine significantly altered the level of utricular asymmetry.

6.3.2 Orientation preference

Using virtual reality where 24 subjects were repeatedly exposed to a rotating visual scene, Chen et al. (27) tested whether orientation preferences are modifiable. 20 of the subjects became less susceptible and symptoms score were reduced by 40%. 16/24 became less dependent on visual cues.

6.3.3 Artificial gravity

Artificial gravity (AG) is suggested as a possible and effective countermeasure against vestibular deconditioning (26, 28, 29). By using short-arm human centrifugation, which spins at a rate of 15-30 rotations per minute (RPM), AG can be generated in analog space flight conditions on Earth.

Tolerability to AG has been an issue due to cross-coupled (CC) illusion, a disorientating sensation of tilt provoked by the high spin rates (30). Through two individual studies, Bretl et al. (30, 31) assessed the tolerability of both a personalized and a standardized protocol for acclimating astronauts to the cross-coupled illusion. Both protocols involved spinning the subjects while they performed roll head tilts to induce CC-illusion. In the personalized protocol the spin rate was incremented till CC-illusion was reached, while in the standardized protocol they used the median stimulus sequence from the personalized protocol, and incrementing the spin rate after every session, independent of the subjects reported CC-illusion or not. Both studies showed acclimation to CC-illusion, making it possible to increase spin rate from 1,8 RPM to 17,7 RPM (personalized) and 11,8 RPM (standardized).

During a five-day bed rest study organized by ESA, Clément et al. (28). exposed 10 healthy subjects to short-radius centrifugation during a 6° head-down tilt bed rest. They compared the use of intermittent and continuous centrifugation. The results showed that six 5-min 1 G centrifugations with 3 min of rest (AG1) were tolerated better and induced less neurovestibular symptoms than one continuous 30-min 1 G centrifugation (AG2). A 80° head-up tilt test was performed immediately after the 5 days of bed rest. While seven and six subjects reported symptoms when AG1 and AG2 were used, all of the subjects reported symptoms when no countermeasure was used. The severity of the symptoms, measured with Readaptation Symptom Severity (RSS) scores, were also reduced after centrifugation (62% for AG1 and 49% for AG2).

The AGBRESA study (29), which also compared the tolerability of 30 min (6x5 min) intermittent with 30 min of continuous short-arm centrifugation of 1 G, found similar results during their 60 days 6° head-down tilt bed rest.

Comparing data from the Neurolab study, Buytaert et al. (26) investigated whether artificial gravity could be used as an adequate countermeasure for deconditioning of the ocular counter-roll reflex and the vestibulospinal reflex. On a 16 days mission, the subjects were exposed to intermittent periods of in-flight centrifugation on a specially designed rotatory chair. The results were promising, showing that none of the astronauts had a postflight decrease in OCR.

6.3.4 Other post-flight analogues

Trying to replicate the postflight sensorimotor experience, Dilda et al. (32) developed a technique for disrupting vestibular input by galvanic vestibular stimulations (GVS). The results showed that by passing small electrical currents between mastoidal surface electrodes, postflight imbalance, impaired manual control and reduced visual acuity were replicated.

7 Discussion

On an exploration to Mars the astronauts will experience several gravity changes. After entering microgravity and spending several months there, they will land on Mars and be exposed to 0,38 G.The periods during and soon after G-transitions holds the greatest risk of impairment from neurovestibular dysfunction (3). As mentioned earlier, the most clinically significant aspect of this impairment is the development of space motion sickness.

7.1 Etiology of space motion sickness

7.1.1 Sensory conflict theory

Reason and Brand (33) presents in their book on motion sickness, a sensory conflict theory which originates from the assumption that human orientation in three-dimensional space, under terrestrial gravity, is based on at least four sensory inputs (otolith organs; semicircular canals; visual system; and touch, pressure and somatosensory systems). Environmental alterations can result in a mismatch between sensory input and previously stored neural patterns, and thereby cause motion sickness. This theory is widely accepted as a plausible explanation for SMS, but it lacks the power to predict what kind of sensory conflict that will lead to symptoms (34).

7.1.2 Subjective vertical conflict theory

Bles et al. proposed a theory that most types of motion sickness could be explained due to the mismatch between the internal representation of the vertical, the subjective vertical (SV) and the sensed vertical (35). SV is our own, subjective perception of our position and orientation (34). It is determined by our visual surroundings, sensory cues of gravity and the longitudinal axis of the body (idiotropic cue). In microgravity, where the gravitational reference of verticality is absent, the sensed vertical does not match the expected SV and gives rise to a conflict with spatial disorientation and following space motion sickness (34, 35).

Most humans use allocentric references to identify what is up and down and are therefore more dependent on visual cues from the surroundings (3). Chen et al. (8) investigated the correlation between orientation preferences and susceptibility to space motion sickness. Being more dependent on visual cues, seems to increase this sensory conflict and trigger SMS. In absence of visual cues and struggles of switching to other references, the astronauts may experience loss of orientation (3). The other main frame of reference, the idiotropic reference, does not allow as much disorientation due to the perception of SV being aligned with the head-foot axis.

7.1.3 Otolith mass asymmetry hypothesis

According to the otolith mass asymmetry hypothesis, natural differences in mass between the left and right otolithic organs leads to asymmetric output signals (3). On Earth this asymmetry is compensated by the CNS, but may contribute to sensory conflict in microgravity. By measuring the vestibular ocular reflex (VOR), the asymmetry can be investigated. After putting subjects through unilateral centrifugation, Clark and Schönfeld (19) saw an increase in VOR asymmetry which normalized after 5-8 days, which supports the theory of otolith asymmetry and indicates adaptive changes in neural integration of the inputs from the labyrinths. The increased response of the reflex soon after reentering Earth's gravity, also demonstrates a probable overall gain of otolith sensitivity in microgravity.

Even though several studies have shown similar results (18, 19), Nooij et al. (18) also found overlapping results of utricular asymmetry in subjects susceptible to centrifugation-induced motion sickness (SIC) and non-susceptible subjects, which makes it seem like utricular asymmetry alone cannot provide a sufficient explanation to SIC/SMS susceptibility. The SIC-susceptible subjects also showed slightly higher values on semicircular canal parameters, suggesting a combinational explanation for increased susceptibility involving both the otolithic organs and the semicircular canals. These are preliminary results and requires more research, but it could explain why the subjects experiencing SIC were triggered by dynamic head tilts, a stimulus that also activates the semicircular canals.

7.1.4 Susceptibility

There are some factors which have shown to increases the susceptibility to SMS and worsen the symptoms (8, 12, 16, 17, 18, 19). Identifying and studying these factors could aid in finding suitable candidates for Mars explorations and to develop countermeasures to prevent SMS.

An astronaut's susceptibility to space motion sickness is mapped by vestibular and visual tests and a Motion Sickness Susceptibility Questionnaire (MSSQ), also called motion history questionnaires (15, 36). The questionnaires are cheap and easy to execute, contains questions concerning experience of travel and motion sickness in childhood and the last 10 years of adulthood, and are therefore a useful tool for predicting SMS as well as terrestrial motion sickness (36). first-time astronaut portraited in the case study about severe motion sickness (15) had struggled with motion sickness as a child and showed average susceptibility during preflight tests. This was not counted for while selecting this candidate for a 7-day spaceflight and possible contributed to the incapacitating symptoms of space motion sickness, which enabled him from participating in the planned mission tasks. He also had severe symptoms of reentry motion sickness for several days after returning to Earth, which also may pose a risk if he or a similar astronaut would enter Martian gravity.

With findings of higher motion sickness severity score in female participants than in males during VR-induced motion sickness, Chen et al. (8) suggests that women are more susceptible to motion sickness. The reason for this has not been concluded, but it is possible that women are more dependent on visual cues for orientation, and therefore more susceptible. This was investigated by Barnett-Cowan et al. (37) by comparing the subjective visual vertical (SVV) and the perceptual upright. In the upright position, females' SVV was more affected by visual cues then men, and the findings were explained by difference in sensory processing mechanisms in brains of females and males during task performance.

7.2 Motion control and performance

Sensory input, motion cues and precision are crucial factors in an astronaut's ability to perform. As illustrated in Rosenberg et al. study (20) vestibular perceptual thresholds are related to performance in manual control tasks. Their findings showed a significant reduction in manual control and performance in 0,5 G compared to 1,0 G. In subjective visual tasks in microgravity created by both analogs and parabolic flights, subjects seem to underestimate roll tilts (22, 23). Astronauts tested after returning to Earth for space, showed the opposite with overestimation of roll tilt and an overall increased motion sensitivity (21).

The worsening of performance in microgravity, shows a potential large risk for the astronauts performing profoundly difficult tasks as piloting and landing spacecrafts, extravehicular activity (EVA) and remotely controlling devices during future Moon- and Mars explorations (9, 21). All these tasks require a fully functional sensorimotor system.

7.3 Other effects of microgravity on the neurovestibular system

7.3.1 Ocular counter roll reflex

Seen in several studies (12, 16, 17, 26) long-term exposure to microgravity reduces the OCR amplitude. The OCR reflex is an otolith-mediated vestibular response, which stabilizes gaze during static head tilt (12). It is gravity-dependent and therefore absent in microgravity. In absence of gravitational input, it seems like this response adapts over time through an otolith deconditioning (17). This adaptive modification of the otolith system results in decreased stabilization of gaze during head tilt and following disorientation, posing an issue when reentering gravity. The amplitude normalizes within 4-10 days, depending on the flight duration, which show that the changes are temporary (12, 16, 17).

7.3.2 Synaptic plasticity

Shown in Hupfeld et al. (9) study on brain activity in response to vestibular stimulation, before and after spaceflight, showed increased activity in areas responsible for processing somatosensory and visual inputs, while the vestibular inputs were downregulated, a sign of synaptic plasticity and reduction of unused synapses. Similar adaptation was seen in the utricles of mice after two weeks in space (24). By inducing disrupting vestibular input, galvanic vestibular stimulations (see 6.3.4), also leads to synaptic plasticity in the cerebellum (38).

These indications of synaptic plasticity could be exploited in preflight training to improve adaptability and thereby assist in postflight recovery.

7.4 Countermeasures

7.4.1 Pharmaceuticals

About one-third of astronauts has reported using pharmaceuticals against SMS, both prophylactically and inflight (7). Many different drugs have been tested against space motion sickness, but with variating and individual effectiveness (3, 25). The administration method has also been discussed and tested, since microgravity has a negative impact on oral bioavailability of pharmaceuticals. It has been suggested that intranasal scopolamine can be a favorable method of administration due to bypassing of first passage metabolism, but oral, especially for prophylactic purposes, and intramuscular administration is most common (7, 25).

As described in Russomano et al. review of SMS (25), scopolamine, an anticholinergic, has been found to be quite efficient in lower the symptoms, but has shown side effects of drowsiness, which can, at worst, result in devastating consequences for the affected astronaut and the rest of the crew. Although this could be counteracted by combining scopolamine with dextroamphetamine (ScopeDex), reports show that it only prevents development of symptoms in a few cases (7). Another combination has therefore been tested, 25 mg of promethazine and 5 mg dextroamphetamine (PhenDex), as prophylaxis. Data from the Neurolab study (26) showed that a PhenDex significantly altered the level of utricular asymmetry, which would lower the reduces the sensory conflict and thereby minimizing SMS symptoms.

In the case study on severe SMS (15), the astronaut did not have a satisfactory effect of the pharmaceuticals and kept on vomiting, even after 50 mg Phenargan (promethazine) intramuscular. This shows the limitations of pharmaceuticals, but it stills plays an important part in easing symptoms of SMS and could in the future be a supplement to other countermeasures, for example artificial gravity (7).

7.4.2 Preflight training

To prevent or minimize symptoms of SMS, preflight adaptation training and vestibular training has been used (3) The theory is that by exposing the astronauts to similar conflicting sensory inputs as in microgravity, they will either adapt through sensory compensation, reinterpretation and rearranging of the sensory stimuli, or learn and store appropriate responses to different sensory stimulus conditions.

7.4.2.1 Virtual reality

By using virtual reality, the astronaut’s orientation preferences could be manipulated into being less visual-dependent and thereby reduce susceptibility for SMS (27). By decreasing the dependency on a single sensory source, the ability to adapt to microgravity and it’s altered sensory environment would be enhanced (3).

7.4.2.2 Artificial gravity

Artificial gravity (AG) has been suggested as a countermeasure against neurovestibular dysfunction, as well as cardiovascular deconditioning, bone loss and weakening of the muscles (39). AG can be produced using a short-arm human centrifuge, which spins at a rate of 15-30 rotations per minute (RPM). In bed rest studies where subjects were exposed to short-radius centrifugation during 6° head-down tilt bed rest, Clément et al. (28) and Arz et al. (29) compared the effect and tolerability of intermittent and continuous centrifugation. Both showing that AG reduces severity of readaptation symptoms, and that intermittent centrifugation was better tolerated.

The disorientating cross-coupled (CC) illusions, which often occurs with high spin rates, has reduced the tolerability of AG and protocols for acclimating the astronauts to increasingly higher spin rates have been tested with promising results (30, 31).

7.4.2.3 Galvanic vestibular stimulations

Trying to replicate the postflight sensorimotor experience, Dilda et al. (32) developed a technique for disrupting vestibular input by galvanic vestibular stimulations (GVS). The results showed that by passing small electrical currents between mastoidal surface electrodes, postflight imbalance, impaired manual control and reduced visual acuity were replicated. This makes it possible to study the human vestibular cortex, spatial orientation, postural control and locomotion and the method has been validated by using the NASA Ames Vertical Motion Simulator (40). It has been suggested as a possible tool to prepare astronauts for long-duration explorations by exposing them to repeated GVS (41). This has shown promising results in adaptation by upregulating extra-vestibular sensory inputs in the cerebellum, such as somatosensation and vision, and thereby reducing the severity of reentry impairment.

7.4.3 Inflight countermeasures

7.4.3.1 Orientation

To minimize this sensory conflict, the interior of the ISS is designed with orientation aids to give a sense of what is up and down (42). By using different color shades, where the ceiling or “up” is in lighter shades, while the floor or “down” is in darker, deep-colored paint, the astronauts are given a cue of “local vertical”. This together with labels, lights near exits, tunnels and emergency paths, and symbols and markings help the astronauts stay oriented, but is not a satisfactory countermeasure, and the knowledge of orientation preference should be used both in preflight training and in selecting suitable candidates for future Mars explorations.

7.4.3.2 Artificial gravity

AG has also been tested in-flight as a countermeasure for deconditioning of the ocular counter-roll reflex. The study showed promising results with no detected postflight OCR decrease in any of the participants.

AG on Earth can, as mentioned, be produced by short-radius centrifugation. Inflight, AG could be used in a larger scale during long-duration spaceflights. By rotating the entire spacecraft, or the more affordable solution: one part of it, it may generate a centrifugal force of approximately 1 G (3). For this to be realized, further research on tolerability and optimal radius and rotation rates must be conducted, as well as investigation of the transition between AG, microgravity and Martian gravity (3, 28, 29).

7.4.4 Selection criteria

As discussed earlier, there are some clear factors that increases the risk of space motion sickness and spatial disorientation. Should the knowledge about these factors and susceptibility be counted for when selecting astronauts for lunar and Mars explorations? With the knowledge of the astronauts' orientation preferences, candidates that mainly use idiotropic reference, and therefore less susceptible to SMS, could be prioritized.

7.5 Future research

There is limited research on astronauts and the neurovestibular system's adaptation to microgravity. Microgravity is not easily replicated and analogs such as short-arm centrifuge are more compatible with studies of hypergravity (43). Head-down tilt bed rest is widely used, especially for longer studies. Head-out water immersion, where the buoyancy gives a replication of "supportlessness" rather than "weightlessness", is also used, but has obvious limitations (44). Parabolic flights, such as in Clark and Young's case study (23) inflicts real microgravity on the subjects, but just for 20-25 seconds at a time, limiting the opportunity of study.

Dixon and Clark (45) suggest using their novel neurovestibular analogue, a wheelchair head-immobilization paradigm (WHIP), which was tested on nine subjects and successfully replicated the spatial orientation sensory cues experienced by astronauts in microgravity. By successfully doing so, topics that are difficult to address in a spaceflight study, could possibly be tested with the WHIP and provide sufficient statistical data before proceeding with operational spaceflight studies.

Future research on effective and affordable countermeasures as well as microgravity analogues is needed in advance of the Artemis Program and the expedition to Mars.

7.6 Strengths and weaknesses

This thesis gives an overview of the affects microgravity has on the neurovestibular system and which countermeasures that could be implemented to facilitate safe space travel. Included in this overview are relevant literature published the last 10 years. Several informative studies were conducted and published before this and has therefore not been included. The same goes for the many articles that are just published in Russian. This may affect the content and quality of this thesis. Even though this thesis covers many of the challenges and countermeasures, it gives a superficial overview of a very large topic. There are also some areas, including the development of postflight orthostatic intolerance, that purposely were not included, which makes the thesis less thorough.

8 Conclusion

In order to conduct future Mars explorations in a safely matter, there are many obstacles to overcome. This thesis has focused on the neurovestibular challenges, mainly space motion sickness and spatial disorientation, which primarily happens during and soon after gravitational transitions, and can in severe cases be disabling for the exposed astronaut and give rise to dangerous situations for the crew and the mission. Long-duration exposure to microgravity also leads to utricular deconditioning with synaptic plasticity and decreased ocular counter-roll reflex, which contributes to reentry symptoms.

Susceptibility to SMS can be mapped with Motion Sickness Susceptibility Questionnaire, vestibular and visual tests, as well as other factors like gender; where females show a higher incidence than men, orientations preference; where visual-depended subjects are more susceptible, and otolith asymmetry; where increased mass differences between the left and right otolithic organs leads to more sensory conflict.

Even though pharmaceuticals have variating and limited effect, it still has an important place in easing symptoms, and could be combined with AG for maximal effect. Preflight training with galvanic vestibular stimulations, virtual reality and AG could also be further evolved to enhance adaptation of the neurovestibular system in advance of microgravity exposure and aid both inflight and during reentry to Earth’s gravity.

There is a call for future research to develop countermeasures that are both effective and affordable.

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10 Supplementary data

Appendix A: Complete main search in PubMed

((((((((((((((((apparatus, vestibular[MeSH Terms]) OR (vestibular disease[MeSH Terms])) OR (vestibular diseases[MeSH Terms])) OR (motion sickness[MeSH Terms])) OR (motion sickness, space[MeSH Terms])) OR (space motion sickness[MeSH Terms])) OR (rotation[MeSH Terms])) OR (adaptation syndrome, space[MeSH Terms])) OR (space adaptation syndrome[MeSH Terms])) OR (syndrome, space adaptation[MeSH Terms])) OR (vertigo[MeSH Terms])) OR (vestibule, labyrinth[MeSH Terms])) OR (vestibule aqueducts[MeSH Terms])) OR (neurovestibular[Title])) OR (readaptation syndrome[Title])) AND (((((((((((((space medicine[MeSH Terms]) OR (space flight[MeSH Terms])) OR (space flights[MeSH Terms])) OR (gravity, altered[MeSH Terms])) OR (microgravity[MeSH Terms])) OR (weightlessness[MeSH Terms])) OR (zero gravity[MeSH Terms])) OR (gravity, zero[MeSH Terms])) OR (weightlessness[Title])) OR (fractional gravity[Title])) OR (0G[Title])) OR (microG[Title])) OR (gravitational transitions[Title]))) OR (((((((((((((((space medicine[MeSH Terms]) OR (space flight[MeSH Terms])) OR (space flights[MeSH Terms])) OR (gravity, altered[MeSH Terms])) OR (microgravity[MeSH Terms])) OR (weightlessness[MeSH Terms])) OR (zero gravity[MeSH Terms])) OR (gravity, zero[MeSH Terms])) OR (weightlessness[Title])) OR (fractional gravity[Title])) OR (0G[Title])) OR (microG[Title])) OR (gravitational transitions[Title])) AND ((((((((countermeasure, weightlessness[MeSH Terms]) OR (countermeasures, weightlessness[MeSH Terms])) OR (weightlessness countermeasure[MeSH Terms])) OR (weightlessness countermeasures[MeSH Terms])) OR (adaptation, physiological[MeSH Terms])) OR (adaptation, physiologic[MeSH Terms])) OR (space adaptation[Title])) OR (readaptation[Title]))) AND (((((((((((((((apparatus, vestibular[MeSH Terms]) OR (vestibular disease[MeSH Terms])) OR (vestibular diseases[MeSH Terms])) OR (motion sickness[MeSH Terms])) OR (motion sickness, space[MeSH Terms])) OR (space motion sickness[MeSH Terms])) OR (rotation[MeSH Terms])) OR (adaptation syndrome, space[MeSH Terms])) OR (space adaptation syndrome[MeSH Terms])) OR (syndrome, space adaptation[MeSH Terms])) OR (vertigo[MeSH Terms])) OR (vestibule, labyrinth[MeSH Terms])) OR (vestibule aqueducts[MeSH Terms])) OR (neurovestibular[Title])) OR (readaptation syndrome[Title])))

Appendix B:

Article	**Published**	**Database**	**Authors**
Space motion sickness: a common neurovestibular dysfunction in microgravity	2019	PubMed	Russomano, T. da Rosa, M. dos Santos, M.
Sensorimotor impairment from a new analog of spaceflight-altered neurovestibular cues	2020	PubMed	Dixon, J. Clark, T.
Human manual control precision depends on vestibular sensory precision and gravitational magnitude	2018	PubMed	Rosenberg, M. Galvan-Garza, R. Clark, T. Sherwood, D. Young, L. Karmali, F.
Rocking and rolling – perception of ambiguous motion after returning from space	2014	PubMed	Clément, G. Wood, S.
Effects of five day of bed rest with intermittent centrifugation on neurovestibular function	2015	PubMed	Clément, G. Bareille, M. Goel, R. Linnarsson, D. Mulder, E. Paloski, W. Rittweger, J. Wuyts, F. Zange, J.
Tolerability of daily intermittent or continuous short-arm centrifugation	2020	PubMed	Arz, M. Frett, T. Petrat, G.

during 60- day 6 degree head down bed rest (AGBRESA study)			Ogoh, S. Noppe, A. Mulder, E. Jordan, J. Pustowalow, W. Tegtbur, U. Green, D.
Quantitative orientation preference and susceptibility to space moton sickness simulated in a virtual reality environment	2015	PubMed	Chen, W. Chao, J. Chen, X. Wang, J. Tan, C.
Ocular counter rolling in astronauts after short- and long duration spaceflights	2018	PubMed	Reschke, M. Wood, S. Clément, G.
Decreased otolith-mediated vestibular response in 25 astronauts induced by long-duration spaceflight	2016	PubMed	Hallgren, E. Kornilova, L. Fransen, E. Glukikh, D. Moore, S. Clément, G. Van Ombergen, A. MacDougall, H. Naumov, I. Wayts, F.
Modification of unilateral otolith responses following spaceflight	2015	PubMed	Clarke, A. Schönfeld, U.
Spaceflight-induced synaptic modifications within hair cells of the mammalian utricle	2017	PubMed	Sultemeier, D. Choy, K.

			Schweizer, F. Hoffman, L.
A re-investigation of the role of utricular asymmetries in space motion sickness	2011	PubMed	Nooij, S. Vanspauwen, R. Bos, J. Wuyts, F.
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