Research Report
Institute of Aerospace Medicine 2022

Preface

The Institute of Aerospace Medicine at the German Aerospace Center (DLR) comprises departments in Cologne and in Hamburg with an internationally unique research expertise and infrastructure. At DLR, our Institute serves as interface between sophisticated technology and life sciences research including biology, medicine, and psychology. We conduct our research in close collaboration with leading national and international research institutions and industry. The long-standing experience of the Institute in selecting and caring for pilots, air traffic controllers, and astronauts in particular directly after return to Earth provides a solid foundation guiding our research efforts. Mechanism-oriented human research, which is a particular strength of our Institute, is fostered by the state-of-the-art research infrastructure at the :envihab facility. Systematic ground-based studies in radiation, astro- and gravitational biology in dedicated simulation facilities are complemented by successful investigations in space. Our overarching goal is to conduct research that improves the human healthspan in space, in aeronautics, and on Earth. Knowledge and technologies generated at our Institute are transferred to applications that address important societal challenges and foster economic development.

We are proud to highlight some of our research activities in 2022, which addressed important medical, psychological, and biological issues in space, in aeronautics, and in traffic. One of the most fascinating projects is our contribution to the Artemis I mission: Our institute conducted the Matroshka AstroRad Radiation Experiment (MARE) in collaboration with international agencies and industry, which is an important landmark in astronautical space exploration. In the MARE experiment, the anthropomorphic female phantoms Helga and Zohar were flown in crew seats onboard the Orion capsule around the Moon and back to Earth loaded with sophisticated radiation detector technology. Zohar was equipped with a novel radiation protection vest. We hope that the knowledge gained in this experiment will help to address medical risks associated with exposure to space radiation. In 2022, we also continued the NASA Spaceflight-Associated Neuro-Ocular Syndrome Countermeasures head-down bed rest study (SANS-CM) at :envihab. The study will guide the development of preventive measures maintaining eye and brain health during long duration space travel. Furthermore, we conducted one-of-a-kind human studies on cardiac regeneration in patients following myocardial infarction, on how reduced oxygen conditions akin to conditions insight airplanes affect patients with complex cardiac malformations, and on mechanisms through which low oxygen levels affect circadian rhythms in human beings. The latter could have implications for persons affected by jetlag symptoms following air travel across time zones. The unique infrastructure of our :envihab also enabled a detailed study testing effects of simulated sonic booms on human sleep. We also welcomed ESA Astronauts Matthias Maurer and Samantha Cristoforetti after their missions on ISS at :envihab. Our biology program provided new insight in cellular responses to gravity changes and radiation exposure based on laboratory studies, experiments on various platforms including the drop tower in Bremen, DLR Mapheus sounding rockets and heavy ion accelerators. In 2022, Mapheus 9 and Mapheus 12 sounding rocket launches from the ESA ESRANGE facility in Kiruna Sweden yielding six minutes microgravity each permitted biology experiments with relevance for cancer research and measurements of gravity-dependent neuronal electrical activity using novel technology. Finally, we made great strides in applying bioregeneration technologies developed for space to dispose biological waste on Earth in a sustainable fashion.

We are very grateful for all the support from collaborators, funding agencies, and industry which made this research possible and look forward to tackle future challenges.

Jens Jordan, Head of the Institute of Aerospace Medicine, DLR

Ruth Hemmersbach, Acting Head of the Institute of Aerospace Medicine, DLR

Table of contents

Cardiovascular Aerospace Medicine

Cardiovascular Aerospace Medicine

Prof. Dr. med. Jens Tank (Head)

Dr. rer. nat. Darius Gerlach (Deputy)

The Department for Cardiovascular Aerospace Medicine investigates gene-environmental influences on the human cardiovascular system. We focus on real and simulated weightlessness, atmosphere conditions, nutrition, and exercise. The major aim is to elucidate mechanisms of cardiovascular structural and functional adaptation and how these responses are integrated by the autonomic nervous system.
Human space experiments are flanked by highly controlled terrestrial studies in healthy persons and in patients in close collaboration with leading university medical faculties. Combination of physiological or pharmacological challenges with high-fidelity human phenotyping and biomedical engineering is our particular strength. Moreover, we translate observations in patients with rare cardiovascular conditions and defined genetic variants to astronauts confronting spaceflight and vice versa. The ultimate goal is to improve diagnostics, cardiovascular countermeasures, and treatments in space, in aeronautics, and on Earth.

Teams

Advanced Functional Imaging (Dr. rer. nat. Darius Gerlach)

- Probing the brain-heart axis with brain and cardiac imaging
- Functional MRI assessment of the brainstem and hypothalamus, the centers of autonomic control
- Autonomic nervous system testing within the MRI scanner, for the characterization of functional and neuroplastic adaptations to immobilization, diseases, and life style
- Cardiac real-time MRI under extreme environments, including hypoxic condition and immobilization for the detection of cardiovascular deconditioning
- Unique combinations of cardio vascular challenges such as lower body negative pressure during real-time MRI and physiological monitoring
- Individual phenotyping with dynamic functional cardiovascular real-time MRI

Cardiovascular Control in Health and Disease (PD Dr. med Karsten Heußer)

- High fidelity cardiovascular phenotyping including direct measurements of muscle sympathetic nerve activity in healthy subjects and in patients with rare autonomic disorders as model for spaceflight conditions
- Inflight experiments (parabolic flights and ISS missions)
- Validation of certified non-invasive methods under extreme environment conditions
- Application and development of physiological and pharmacological methods and challenges, e.g. head-down tilt bed rest studies
- Determine the efficacy of drug therapy as well as nonmedical treatments including countermeasures and physical training
- Improving early detection cardiovascular disease in space and in terrestrial medicine

Proof of concept: A novel real-time magnetic resonance imaging approach to study orthostatic intolerance mechanisms in patients with hypermobile Ehlers-Danlos and postural tachycardia syndrome

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Background

Orthostatic intolerance often occurs in astronauts returning from long-term missions. Studies in patients with orthostatic intolerance can provide mechanistic insight and guide countermeasure development. Ehlers-Danlos syndrome, a congenital disorder of collagen synthesis, is often associated with orthostatic intolerance, particularly the postural tachycardia syndrome (POTS). POTS primarily affects young women, severely impairing their everyday life.[2] The condition is characterized by dizziness, nausea, malaise, and visual disturbances during the first ten minutes of standing in combination with tachycardia but without hypotension.[1] However, mechanisms causing POTS in these patients has yet to be elucidated. To study the hemodynamic mechanisms limiting orthostatic tolerance, we applied a novel approach combining real-time magnetic resonance imaging (MRI), physiological monitoring, and orthostatic testing with lower body negative pressure (LBNP). Our objectives were to first validate the approach in a patient with severe orthostatic hypotension and then apply the methodology to characterize orthostatic intolerance mechanisms in Ehlers-Danlos syndrome patients with POTS.

Material and Method

We recruited 9 women with hypermobile Ehlers-Danlos syndrome and POTS (33±7 years; 22.8±5.0 kg/m^2) and 5 matched healthy control persons (36±9 years; 24.1±2.8 kg/m^2). One patient with pure autonomic failure served as positive control. We performed real-time cardiac MRI without and during -30 mmHg LBNP with 33 ms temporal resolution to measure cardiac short axis, and quantitative blood flow in the aorta, pulmonary trunk, middle cerebral artery, and venous flow in the vena cava inferior (Figure 1). Additionally, we recorded brachial blood pressure, beat-to-beat finger arterial blood pressure, an electrocardiogram, and respiration.

Results

In the pure autonomic failure patient, blood pressure decreased from 118/74 to 58/35 mmHg with LBNP, whereas heart rate remained unchanged. With LBNP, left ventricular stroke volume decreased by 44.6 %, absolute middle cerebral artery flow by 37.6 %, and pulmonary trunk flow by 40 %.[3]

For the second part of the study, we compared Ehlers-Danlos syndrome POTS patients with matched control persons. LBNP increased heart rate by 24.4±10.3 bpm in patients and by 6.7±6.4 bpm in control persons ($p<0.01$ within, $p=0.005$ between groups). Systolic blood pressure did not change significantly in either group. Cardiac stroke volume decreased by 26.0±7.0 ml in patients and 22.0±11.3 ml in control persons. However, cardiac output responded similarly in both groups. Left ventricular mass index did not differ between groups (patients: 60.6 ±9.1 g/m^2; controls: 57.1 ±2.0 g/m2). During LBNP end systolic volume index was reduced by -5.3 ±3.2 ml/m^2 in patients and by -0.5 ±2.3 ml/m2 in controls ($p=0.017$) and changed differently between groups ($p=0.041$). End diastolic volume index reduced by -20.3 ±4.5 ml/m2 in patients and by -12.8 ±6.3 ml/m2 in control persons with LBNP ($p<0.01$), but were not different between groups. Aorta descendens blood flow was reduced in patients by -1.0 ±0.3 l/min and by 0.6 ±0.2 l/min in control persons ($p<0.01$) with LBNP. No direct difference between POTS and control subjects could be found, but reacted differently on LBNP. Venous blood flow

Fig. 1a

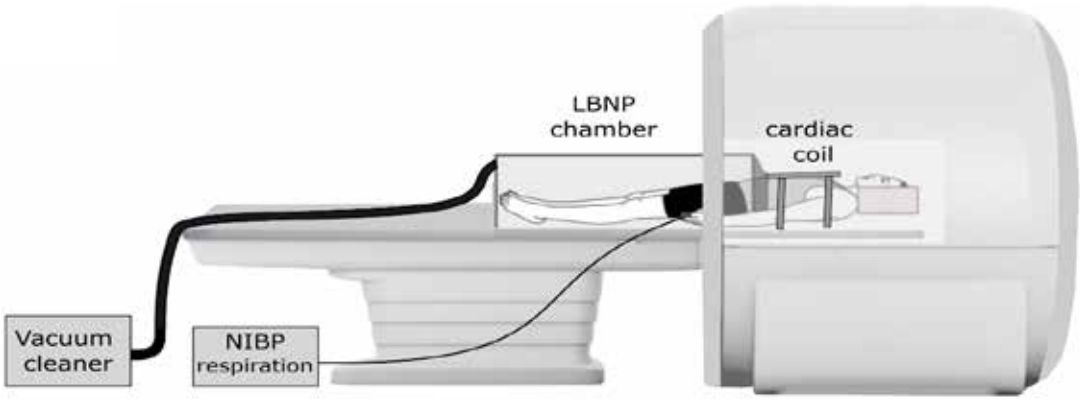

Fig. 1b

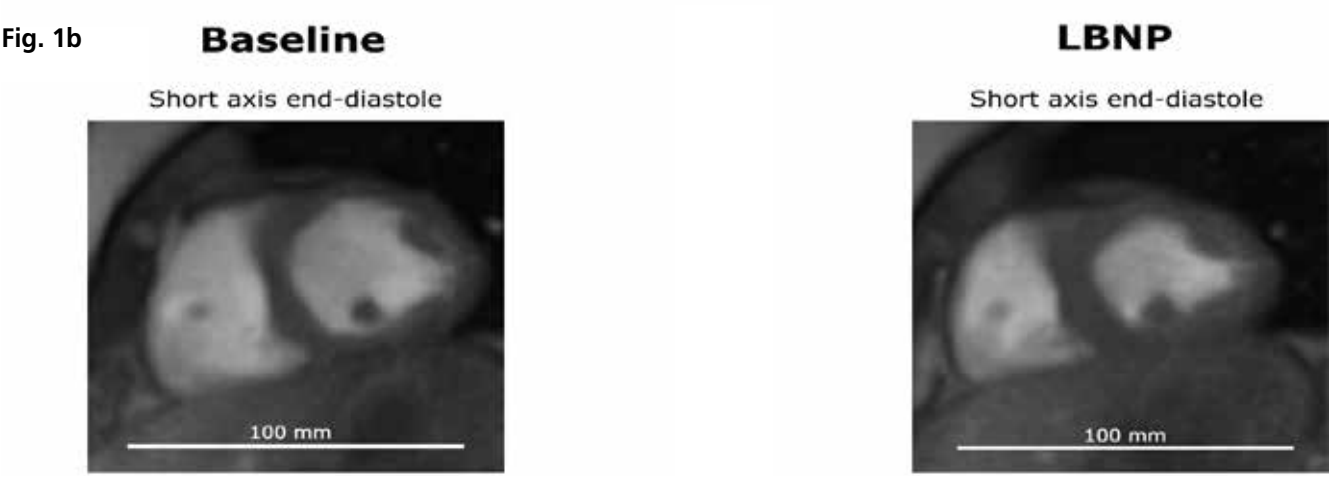

Fig. 1: Real-time magnetic resonance imaging during orthostatic challenge in humans a) Schematic drawing of the cardiac real-time MRI setup with lower body negative pressure (LBNP) and physiological monitoring including ECG, non-invasive beat-to-beat blood pressure, and respiration. b) Mid-ventricular MRI short axis view during diastole before (left) and during LBNP (right). Blood filling is visually reduced during LBNP.

trended to decrease in the inferior vena cava (p=0.059). Finally, right middle cerebral artery blood flow per pulse was reduced by -0.3 ±0.5 ml in patients and by -0.3 ±0.3 ml in control persons (p=0.42), however flow in l/min was unchanged. Interestingly, the left middle cerebral artery blood flow remained unchanged during LBNP.

Conclusion

Combination of real-time MRI and LBNP is a feasible approach to study hemodynamic mechanisms contributing to orthostatic intolerance in human beings be it in astronauts returning from space or in patients on Earth. The unobtrusive nature of the test, which does not require breath-holding or ECG triggering, and the ability to measure absolute vascular flow are distinct advantages. In this preliminary analysis, our Ehlers-Danlos syndrome patients with POTS did not show signs of cardiovascular deconditioning different from controls. Brain perfusion did not seem to be affected. More subjects are needed to determine contribution of cardiac structure, excess venous pooling, or reduced brain perfusion to orthostatic intolerance.

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Fontan circulation under moderate hypoxia insights from real-time cardiac MRI

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Background

In patients with Fontan circulation, the lungs are passively supplied with venous blood and the univentricular heart performs the function of the left ventricle. In other words, the Fontan circulation connects the large veins from the lower and upper body with the lung arteries bypassing the heart. Therefore, such patients are excellent models to study hypoxia influences on the cardiovascular system, which is relevant for aeronautics and space medicine alike. Hypoxia leads to vasoconstriction in pulmonary vessels and to systemic vasodilation which has an impact on cardiac output especially under physical load. Thus, the clinical recurrent question arises whether children and adults with Fontan circulation should expose themselves to prolonged hypoxia (≥ 12h) such as during airplane travel or travel to higher altitude. Our aim was to study how patients with Fontan circulation respond to moderate hypoxia of 15.1 % O_2 over 24 hours, which is equivalent to about 2400 m. Assessing the Fontan circulation is challenging with conventional imaging methods. Breathhold capacity is very limited in these patients, especially under hypoxic conditions. Cardiac real-time MRI offers rapid image acquisitions during spontaneous breathing, which allows new insights in the hemodynamics and the specific cardiac anatomy in these unique patients. Patients with univentricular hearts show large interindividual variability and conventional imaging techniques often fail to provide reliable data. Real-time MRI during free breathing can solve those problems but respiratory variability of hemodynamic parameters is an additional challenge. Thus, we aim to train an artificial intelligence network with pre-segmented images and to synchronize the obtained results with respiration.

Material and Method

We recruited 18 patients with Fontan circulation (9 women, 9 men; 24.8±6.3years; 23.0±3.6 kg/m^2) and performed real-time cardiac MRI in normoxia and in normobaric hypoxia (24 hours of 15.1 % O_2). We acquired conventional cine MRI (25 phases) during normoxia and real-time cardiac MRI (temporal resolution of 33 ms over 10 seconds) in the short axis during both, normoxia and hypoxia. We quantified blood flow in the ascending and descending aorta, the vena cava superior and inferior, in the Fontan tunnel and in the left and right pulmonal arteries with the same temporal resolution over 30 s each. We also recorded brachial blood pressure, beat-to-beat finger arterial blood pressure, ECG, and respiration. We analyzed real-time images with Cafur (Mevis Fraunhofer) and obtained mean values over the acquired time periods. We analyzed cine images using Circle CVI42 software. We used expert annotations of cardiac short axis images of the univentricular hearts to teach the U-net [1] based AI for segmentation. In addition, we compared the automatic detection of systole, diastole, inspiration and exspiration with corresponding time points in the physiological recordings.

Results

Hypoxia increased heart rate from 65 ±13 bpm to 74 ±13 bpm ($p<0.001$) while systolic blood pressure remained unchanged (normoxia: 110 ±10 mmHg, hypoxia: 111 ±11 mmHg), however, diastolic blood pressure increased from 59 ±8 mmHg to: 63 ±9 mmHg ($p=0.011$). Stroke volume decreased from 58±17 ml to 54±15 ml measured in the ascending Aorta ($p=0.005$). Cardiac output remained unchanged due to increased heart rate. Left pulmonary artery flow increased from 1.55±0.36 l/min to 1.80 ±0.49 l/min ($p=0.015$). Flow in the right pulmonary artery was 1.23±0.51 l/min during normoxia and 1.13±0.52 l/min ($p=0.305$) in hypoxia. The difference between pulmonary blood flow (RPA plus LPA) and systemic blood flow (cardiac output) did not change during hypoxia compared to normoxia. Blood flow per heart beat decreased in the descending aorta (34.4±13.4 ml vs. 30.5±11.3 ml, $p=0.027$), right pulmonary artery (19.7±8.6 ml vs. 15.9±7.9 ml, $p=0.021$) and in the Fontan tunnel (35.5±12.6 ml vs. 32.7±12.5 ml, $p=0.038$).

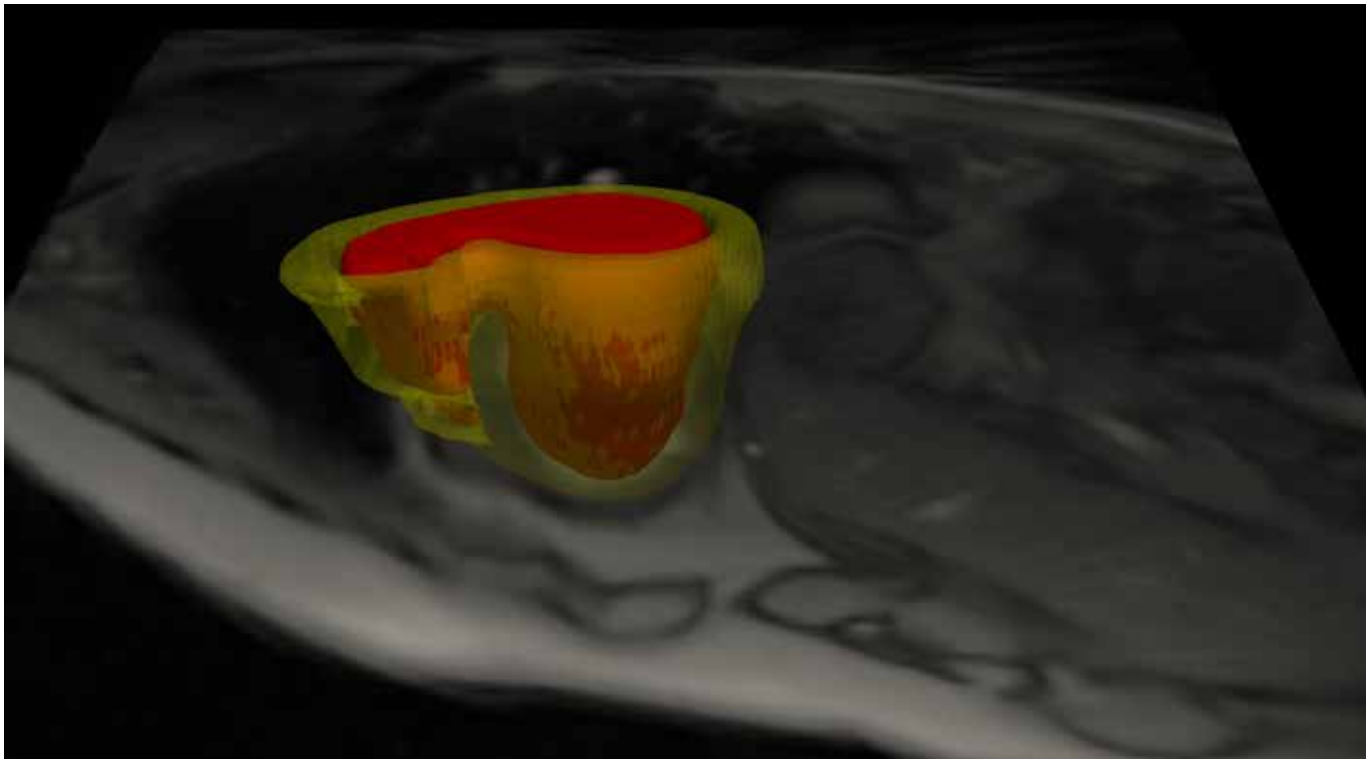

Fig. 1: Fontan circulation with hypoplastic right heart was acquired with cardiac real-time MRI during spontaneous breathing. The cardiac short axis slices were segmented with artificial intelligence (red: blood pool and yellow: myocardial volume) sorted automatically for their cardiac and respiratory phase to create and 3D stack representing end-diastolic and end-expiratory phase. The result shows the blood pool and heart muscle. The 3D model shows the end-diastole and end expiration.

Conclusion

Patients with Fontan circulation exposed to moderate hypoxia over 24 hours did not show clinically relevant changes in pulmonary or systemic flow. Moreover, shunt volume remained unchanged during moderate hypoxia. These findings suggest that patients with Fontan circulation should not be generally excluded from airplane travel. However, further analysis of possible subgroups may be needed. Given the utility of cresponses, we will use the methodology in future studies to assess diastolic filling during deep breathing maneuvers and under different cardiac loading conditions to differentiate functional capabilities of individual Fontan circulations.

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Functional connectivity changes in hypothalamic nuclei following a glucose challenge: a single subject fMRI study

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Background

Brainstem and hypothalamus have a crucial role in adjusting human physiology in the face of altered environmental conditions be it in space, in aeronautics, or on Earth. Altered energy balance promotes Obesity and overweight, serious health problems worldwide, but may also challenge metabolic health during space missions. Indeed, obesity is a major risk factor for cardiovascular diseases, type 2 diabetes mellitus, sleep apnea, musculoskeletal disorders, along with some cancers [1]. Although the final cause for obesity is an imbalance between energy intake and expenditure, the underlying causes include dysfunctions in several organs like the pancreas, liver, and adipose tissue. The brain is also imperative for regulating energy homeostasis, since it controls satiety, as well as metabolism.

Glucose homeostasis plays an important role in acute energy regulation. Plasma glucose levels are sensed not only in the periphery like the tongue, pancreas, intestine, carotid bodies, or the portal vein; but also by glucose-sensing neurons within the central nervous system. These neurons are mainly located in the hypothalamus and in the brainstem, and are known to be involved in energy homeostasis through the control of feeding, as well as through efferent autonomic regulation, including pancreatic, hepatic and thermal modulation [2].

Traditionally, the hypothalamus has been a difficult region to study in humans due to its small size and location deep within the brain. However, recent advances in functional magnetic resonance imaging (fMRI) permit to capture hypothalamic activity changes in groups of subjects. To avoid averaging over different subjects, we limited our study to only one subject and increased the power by repeating a glucose challenge multiple times.

Methods

We conducted ten oral glucose tolerance tests at different days in the same healthy man (56 years, 64 kg, 1.77 m), while acquiring functional images before, and 10 and 45 minutes after glucose ingestion. Moreover, we measured plasma glucose and insulin levels at seven time points. Functional connectivity changes were calculated using independent component analysis followed by a dual regression using an F-test and post-hoc two-sample t-tests.

Results

Plasma glucose (147.5 ± 8.4 mg/dl) peaked 30 minutes after glucose intake followed by an insulin maximum 15 minutes thereafter (45.7 ± 7.0 mU/l), as expected from previous experiments. Moreover, we observed significant intrinsic functional connectivity increases 45 minutes after glucose intake in the arcuate, paraventricular, and dorsomedial nuclei, as well as in the posterior hypothalamic area, median eminence, and mamillary bodies. Furthermore, the mamillary bodies increased their functional connectivity to the ventromedial nucleus.

Discussion

This single subject fMRI study combined data-driven parcellation with functional connectivity analysis during a glucose challenge to investigate acute hypothalamic energy regulation. During these challenges, plasma glucose and insulin levels followed the expected time courses [3]. We could visualize six out of the seven most important hypothalamic regions for energy homeostasis. Our results, which are consistent with previous animal experiments [4], show that fMRI can capture individual connectivity changes in specific hypothalamic nuclei during a glucose challenge. The methodology holds promise in delineating the role of hypothalamic and brainstem mechanisms in patients with cardiometabolic disease

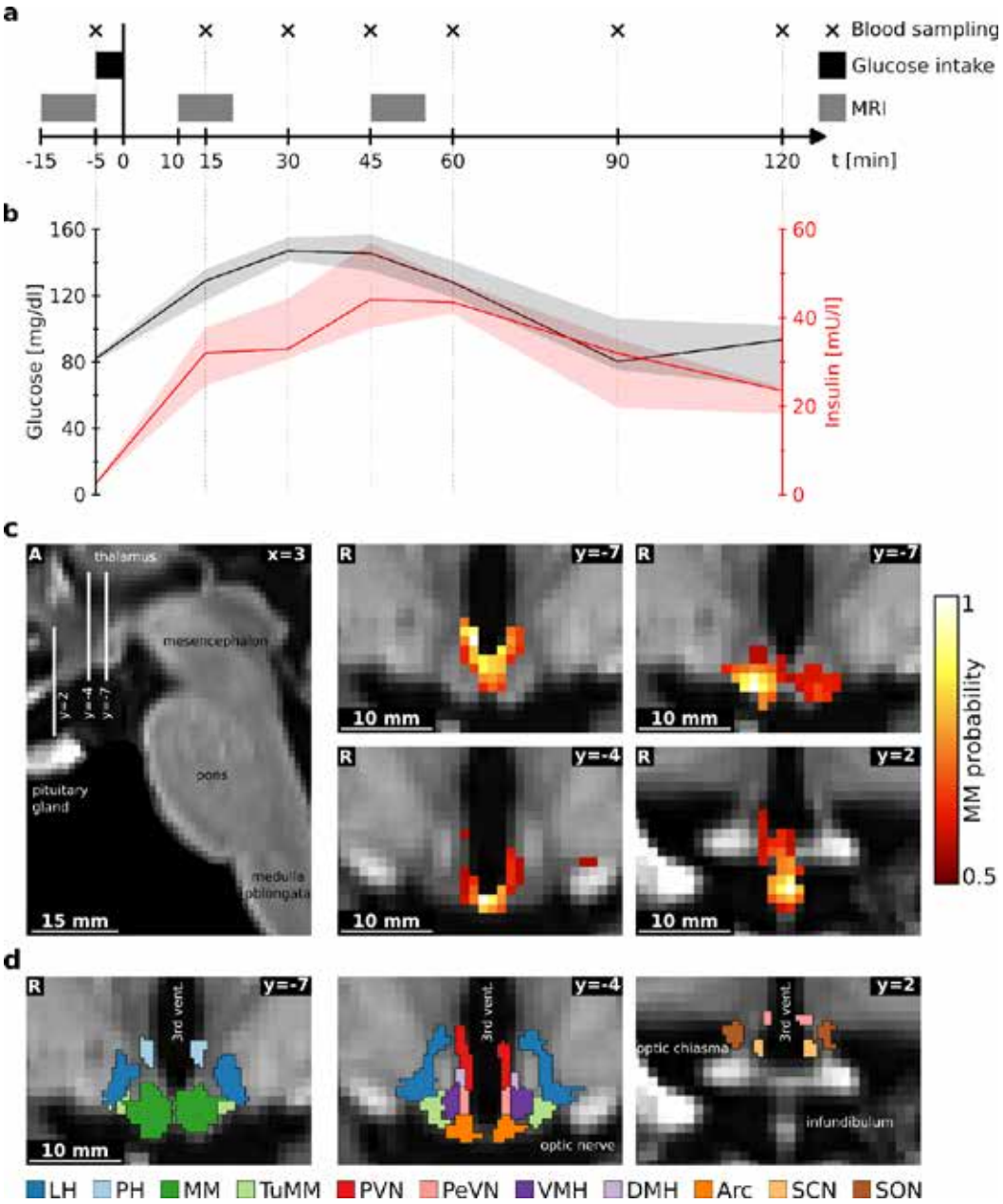

Fig. 1: (a) Study design. (b) Measured plasma glucose and insulin levels (median and range). (c) Regions showing functional connectivity changes 45 minutes after glucose ingestion. The independent components are depicted as mixture model thresholded probability maps. (d) Hypothalamic regions from the atlas of Neudorfer et al. (2020) [5]. All images are in MNI standard space. Abbreviations: Arc - arcuate nucleus; DMH - dorsomedial hypothalamic nucleus; LH - lateral hypothalamic area; MM - mamillary bodies; PeVN - periventricular nucleus; PH - posterior hypothalamic area; PVN - paraventricular nucleus; SCN - suprachiasmatic nucleus; SON - supraoptic nucleus; TuMM - tuberomamillary nucleus; vent. - ventricle; VMH - ventromedial hypothalamic nucleus.

and in human beings exposed to harsh environmental conditions relevant to aerospace medicine.

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Effects of six hours daily lower body negative pressure on orthostatic tolerance and cardiac performance during 30 days strict head-down tilt bedrest

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Introduction

Orthostatic intolerance commonly occurs in astronauts returning to earth. Head-down tilt bedreR), which models cardiovascular adaptation to weightlessness, decreases orthostatic tolerance by 34-60% in zhe absence oy countermeasures. We hypothesized that daily six hours lower-body-negative-pressure (LBNP, -25 mmHg) ameliorates orthostatic tolerance and central hemodynamic parameters during head-down tilt bedrest.

Methods

We submitted 23 healthy persons (12 women, 34.5±9 years, 23.9±2.8 kg/m^2) to 30 days of strict head-down tilt bedrest (NASA SANS-CM study at the DLR :envihab). Participants were assigned to sx6 hours upright seating (positive control, n=11) or -25 mmHg LBNP (n=12) per day. Orthostatic tolerance was assessed five days before and after head-down tilt bedreBR with tilt table testing (HUT) over 15 minutes 80 degrees followed by incremental LBNP (-10 mmHg for 3 minutes) until presyncope. We assessed mean arterial blood pressure durile HUT every two minutes by upper arm blood pressure measurements and heart rate by 3-lead ECG. We measured left ventricular outflow tract diameter (LVOT) and LVOT- stroke volume by pulsed wave doppler echocardiography during 15 min of 80° head-up tilt testing (HUT) with incremental LBNP until presyncope before and after head-down tilt bedreBR. We determined plasma volume with CO-rebreathing two days before and at head-down tilt bedrest day 27.

Results

With head-down tilt bedrest, orthostatic tolerance decreased 289±89 s (-23%) in the seated and 284±95 s (-22%) in the LBNP group (p<0.001 vs. baseline, p=0.986 between groups). Plasma volume decreased 569±114 ml in the seated and 604±104 ml in the LBNP group (p<0.001 vs. baseline, p=0.813 between groups). Heart rate increased with bed rest (p>0.001) and during tilt table testing. Mean arterial blood pressure remained unchanged after bed rest and during HUT. While supine stroke volume was decreased after head-down tilt bedrest (p<0.001 vs. baseline, p=0.874 between groups), both groups showed similar reductions in upright stroke volume following head-down tilt bedrest. However, stroke volume at presyncope did not change with head-down tilt bedrest.

Conclusions

Six hours daily moderate intensity LBNP or seating did not fully attenuate orthostatic intolerance, plasma volume loss, or cardiovascular deconditioning during 30 days head-down tilt bedrest. However, both interventions better maintained orthostatic tolerance compared with previous 30-60 days head-down tilt bedrest studies without countermeasures.

Funding

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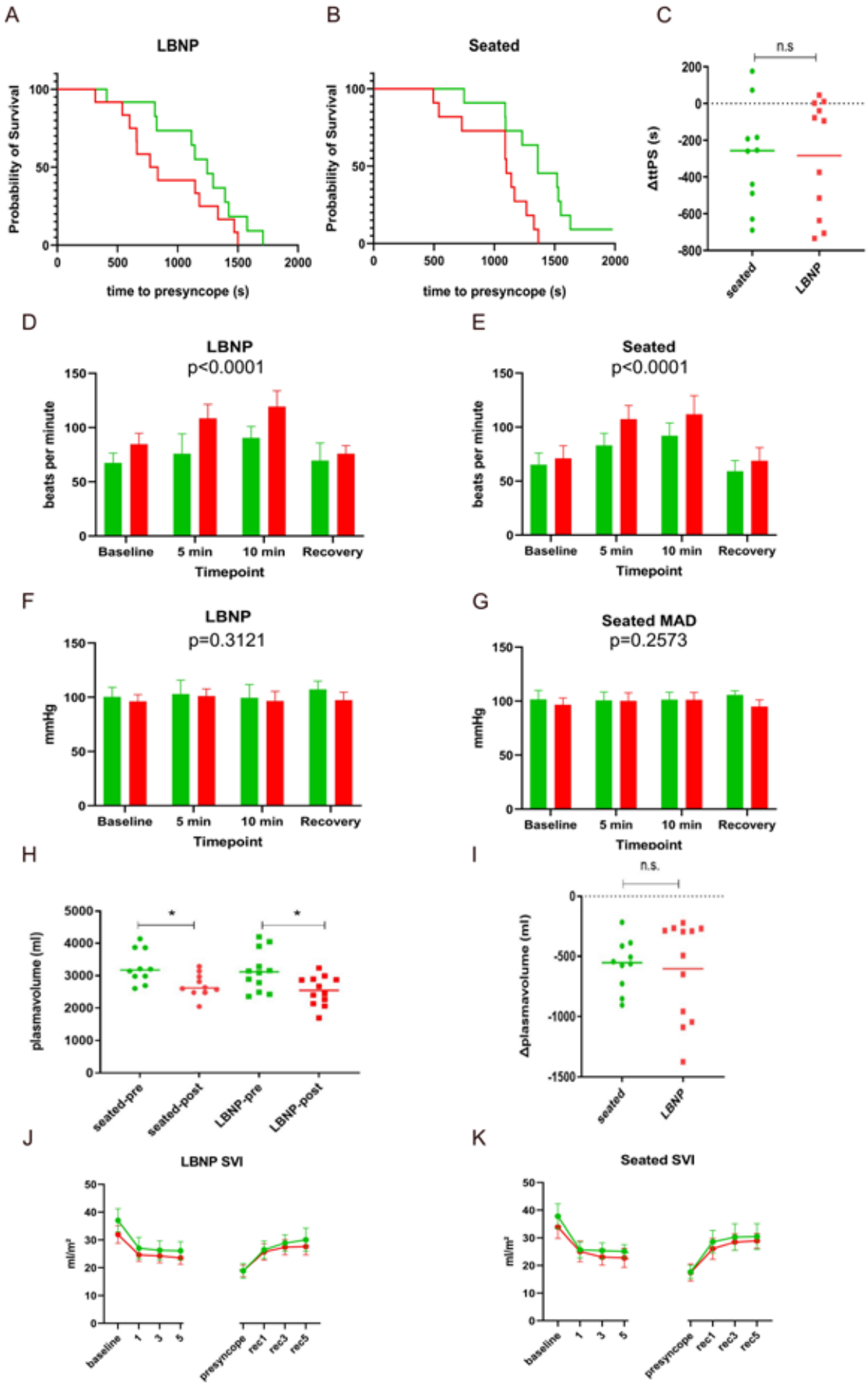

Fig. 1: Orthostatic tolerance and hemodynamic parameters were assessed in 80° head-up tilt table testing with incremental lower body negative pressure 5 days before and immediately after 30 days of head-down tilt bed rest. Time to presyncope, a surrogate for orthostatic tolerance, decreased following bedrest in both groups (p<0.0001, linear mixed elements model, A-C).
Resting heart rate was elevated following bed rest and showed a steeper increase in early 80° upright standing (D,E), whereas mean arterial blood pressure was unchanged in both groups (F,G).
Plasma volume decreased in both groups, but there was evidence for large interindividual differences (H,I).
Left ventricular stroke volume index, measures by transthoracic echocardiography, was reduced following bed rest (p<0.0001) and did not differ at presyncope before and after bedrest (J,K).
Green: before bedrest, red: after bedrest

Feasibility and safety of hypoxic exposure in patients after myocardial infarction – aiming a translation of myocardial regeneration through hypoxia from mice to human

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Background

In mice with myocardial infarction, extreme normobaric hypoxia induced sustained improvements of left ventricular contractility by myocardial regeneration. We conducted a proof-of-concept study to test a possible translation of this finding from mice into patients after myocardial infarction, which were selected following a safety and feasibility study.

Methods

We conducted the study in the :envihab facility at DLR in Cologne. Three patients who experienced an anterior myocardial infarction 10 to 4 years earlier, but were fully revascularized, revealed reduced to preserved left ventricular ejection fraction (ejection fraction 41-58%), otherwise healthy, physically fit, and one healthy age-matched control (age 55-64 years) participated. Following slowly progressive hypoxia acclimatization, we maintained FiO2 around 9.8±0.6% for two weeks. The amount of viable myocardium in milliliter was measured by 18F labeled D-glucose positron emission tomography/MRI and changes in the structure of myocardial scar were further addressed by MRI with contrast medium (Gadolinium).

We measured the amount of viable myocardium by 18F labeled D-glucose positron emission tomography/MRI and assessed changes in the architecture of the myocardial scar by MRI with contrast medium (Gadolinium) in normoxic baseline, last day of hypoxic exposure and 30 days after completion of the stationary study phase. Left ventricular contractility was measured in transthoracic echocardiography and cardiac MRI by determining stroke volume and ejection fraction, whereas both values were adjusted in regional changes by application of the 17 segments model of the American heart association in strain analysis.

To address cellular responses to hypoxia, we estimated hypoxia-inducible factor expressed in nucleated blood cells, DNA-repair capacity in PBMC after induction of double-strand breaks by radiation, changes in metabolomics of cardiomyocytes and expression of microRNAs that were closely linked to myocardial regeneration in cell and animal studies.

Results

All participants experienced alveolar hypoxia of about 35 mmHg pO2 without severe acute mountain sickness symptoms and completed the study. Participants never experienced angina pectoris and daily 12-lead resting ECG readings revealed no signs of acute ischemic events. High-sensitive troponin remained in 99th percent reference range and NTproBNP tended to decrease in patients. Hypoxic exposure induced pulmonary hypertension, which rapidly abated in

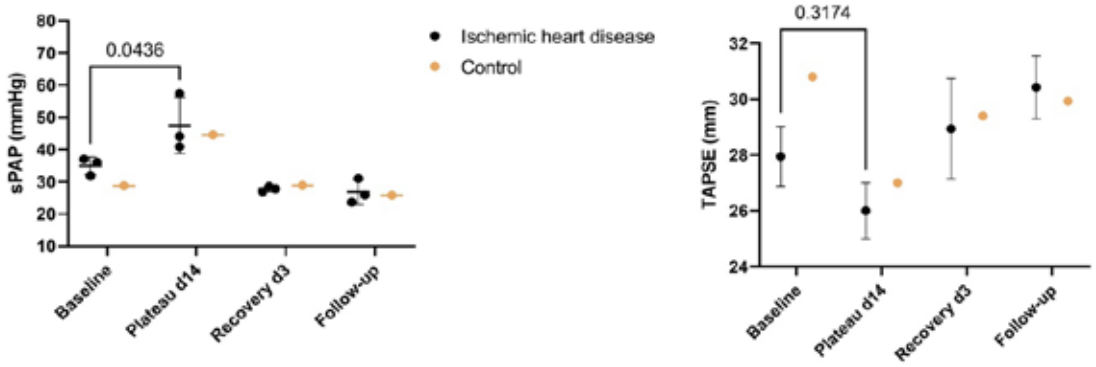

Fig. 1: Systolic pulmonary artery pressure (sPAP) increased while hypoxic exposure due to increased right ventricular afterload mediated by hypoxic vasoconstriction of the pulmonary artery. We observed a normalization in patients and control in normoxic recovery. The induction of pulmonary hypertension did not lead to an impairment of longitudinal right ventricular function measured by tricuspid annular plane systolic excursion.

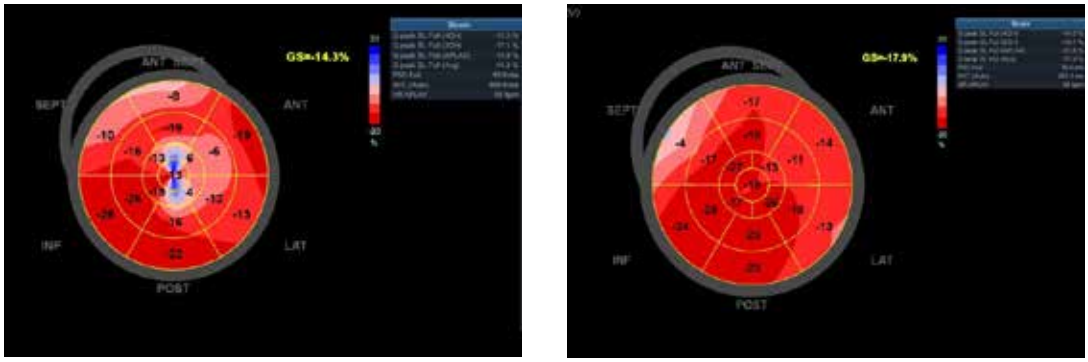

Fig. 2: Comparison of left ventricular global longitudinal strain (LVGLS) analysis of one subject in baseline (left panel) and 30 days follow-up (right panel). Hypoxic exposure induced a sustained improvement of LVGLS 30 days after hypoxic exposure.

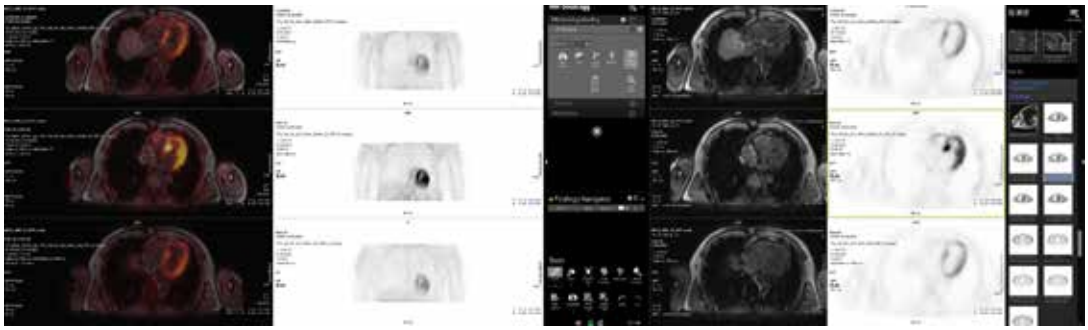

Fig. 3: Cardiac PET-MRI imaging in one subject 30 days following hypoxic exposure (upper panel), last day of hypoxia under 9,5% fraction of inspired oxygen (centred panel), and at baseline (lower panel).

recovery (figure 1), whereas right ventricular contractility appeared to be maintained over the whole protocol (figure 2). Analysis of various cellular markers as well as imaging are ongoing. An example of cardiac PET-MRI is given in figure 3.

Conclusion

Fourteen days of normobaric hypoxia <10% O2 is feasible in physically fit patients following an individualized acclimatization profile after myocardial infarction. Follow-up measurements at 3, 6 and 12 months and analysis of obtained data are ongoing and will provide insight into the potential of sustained hypoxia in inducing myocardial regeneration in adults.

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Sleep and Human Factors Research

Sleep and Human Factors Research

Prof. Dr. sc. nat. Daniel Aeschbach (Head)

PD Dr. med. Eva-Maria Elmenhorst (Deputy)

Our mission is to maintain optimal human performance, sleep, and wellbeing for operators working under the specific challenges and risks of a mobile 24-hour society. Shift work is highly prevalent in operators working in the field of aeronautics, space, and transport exposing a large number of persons to its negative short-term (cognitive decline) and long-term (health) consequences. We apply our highly advanced and controlled laboratory environment to systematically study how homeostatic and circadian processes regulate cognitive performance as well as the quality, duration, and timing of sleep and how they are impacted by disturbances like acute and chronic sleep loss or circadian misalignment. In a unique combination of molecular neuroimaging and behavioral research, we strive to uncover mechanistic pathways that help us understand why some individuals show stronger cognitive decline and negative health consequences due to sleep loss than others.

Our society's need for mobility is in conflict with local residents' need for undisturbed recreation and sleep. In order to ease this conflict, we investigate how sleep, cognitive performance, and annoyance are affected by air, rail, and road traffic noise, and share protection concepts with stakeholders. Aircrews and astronauts work and sleep under conditions of hypobaric hypoxia or hypercapnia. Thus, we have a specific interest in studying systematically in the lab or inflight how barometric and atmospheric alterations affect performance, sleep and well-being. Digital health expertise provides medical support for patients and research through remote applications.

Working Group

Performance and Sleep (PD Dr. med. Eva-Maria Elmenhorst)

- Effects of sleep loss, irregular timing of sleep, adverse work hours, and workload
- Effectiveness of flight time limitations
- Effect of environmental conditions (e.g. hypoxia)
- Neuromolecular mechanisms conveying individual (trait) vulnerabilities
- Developing individualized countermeasures

Teams

Noise Effects Research (Prof. Dr. sc. nat. Daniel Aeschbach)

- Effects of transport noise on sleep, performance, annoyance, and cardiometabolic health
- Exposure-response relationships and physiologically based noise protection concepts
- Defining vulnerable groups (e.g. children, older individuals)

Digital Health (Dr. med. Markus Lindlar)

- Developing and evaluating biomedical systems and care concepts

Effects of train type, rolling speed, and brake system on perceived pleasantness of railway noise

Sarah Weidenfeld[1,2], Marie-Therese Schmitz[3], Sandra Sanok[1], Arne Henning[4], Daniel Aeschbach[1,5], Eva-Maria Elmenhorst[1,2]

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In Germany, a new railway noise abatement law prohibits the operation of freight train wagons with gray cast iron (GCI)-brake blocks since they do not meet the certification criteria for noise emission (Schienenlärmschutzgesetz - SchlärmG, 2017). The GCI-braking systems are gradually substituted by composite braking systems, the so-called LL-blocks that cause less noise. We intended to examine how sounds of freight wagons with the conventional GCI-brake system and the LL-brake system are rated in comparison to each other and to disk-braked ICEs with regard to their pleasantness. Furthermore, the impact of an uneven wheel surface - the so-called wheel flat -, different speeds as well as differences in train composition and sequence of wagons equipped with GCI and LL-brakes within a train was tested.

The DLR Institute of Aerodynamics and Flow Technology synthesized thirteen different railway sounds (Table 1). Using the method of full paired comparison (FPC), we conducted a laboratory study with 44 participants. Immediately after the consecutive acoustic presentation of two sounds via binaural headphones, participants were requested to state which of the presented sounds they perceived as more pleasant. Three preference rankings were derived that were based on a metric scale according to the Bradley-Terry-Luce model (BTL; Bradley & Terry, 1952). The 95% confidence intervals (CI) were determined to evaluate whether the difference between the scale values were of statistical importance. When the 95% CI of two stimuli overlap, we defined the difference as non-significant.

The resulting ranking showed that freight trains equipped with LL-brakes were generally

Table 1: Acronyms of different train types/ compositions. L = LL-composite brake; G = gray cast iron brake; ICE = Intercity-Express; number before L or G = number of wagons; number after L, G, or ICE = speed.

Label	Train type	Wagon composition	Speed in km/h
L80	Freight train	100% LL	80
L100	Freight train	100% LL	100
L120	Freight train	100% LL	120
G80	Freight train	100% GCI	80
G100	Freight train	100% GCI	100
G120	Freight train	100% GCI	120
ICE100	High-speed passenger train	100% disk brakes	100
ICE180	High-speed passenger train	100% disk brakes	180
Lflats	Freight train	100% LL with wheel flats	100
5LG4L	Freight train	90% LL and 10% GCI	100
LG	Freight train	50% LL and 50% GCI, alternating	100
5G5L	Freight train	First five wagons with LL and following five wagons with GCI	100

preferred to trains equipped with GCI-brakes (Fig. 1), irrespective of their speed. A slow pass-by of a freight train with LL-brakes was judged as more pleasant than pass-bys by such a train at higher speeds (80 km/h > 100 km/h and 120km/h).

Participants rated the pass-by of a high-speed train at 100 km/h (ICE100) as more pleasant than those of freight trains equipped with LL- and GCI-brakes at the same speed (L100, G100), respectively (Fig. 2). The pass-by of the freight train with wheel flats caused by LL-brakes (Lflats) was preferred to the pass-by of the train equipped with GCI-brakes. The ICE100 turned out to be the most preferred sound.

The exploration of different freight train compositions revealed that the more wagons of a train were equipped with LL-brakes the more pleasant the sound was rated (Fig. 3): 100% equipped with LL-brakes > 90% LL-brakes and 10% GCI-brakes (5LG4L) > 50% LL-brakes and 50% GCI-brakes (LG, 5G5L, 5L5G).

The results confirmed that freight trains with a retrofitted brake system were preferred to those with a conventional system, irrespective of rolling speed. The more wagons of a train were retrofitted, the more pleasant the sound was rated. Since long-term exposure to unpleasant railway sounds may increase the number of highly annoyed residents near railway tracks, the preference ranking is an important tool for providing recommendations to railway operators and policy makers. Our findings support the ban of freight train wagons with conventional braking systems.

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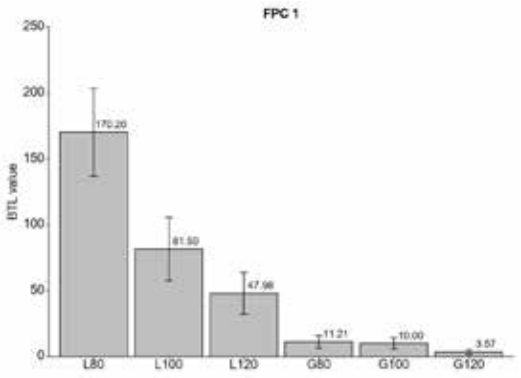

Fig. 1: Pleasantness of noises of freight trains with different speed and brake systems. Six stimuli of full paired comparison (FPC) 1, including 660 judgements. 95% confidence intervals (CI) are shown by error bars. See Table 1 for explanation of acronyms.

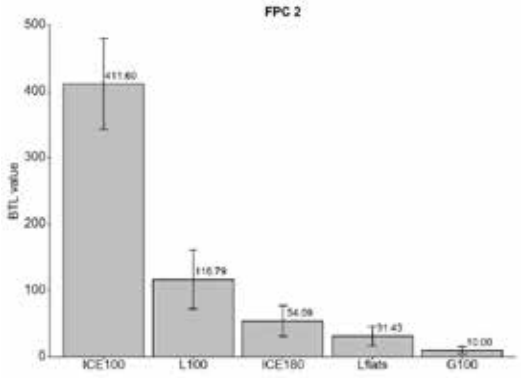

Fig. 2: Pleasantness of noises of different types of trains, speed and brake systems. Five stimuli of full paired comparison (FPC) 2 based on 440 judgments. 95% confidence intervals (CI) are shown by error bars. See Table 1 for acronyms.

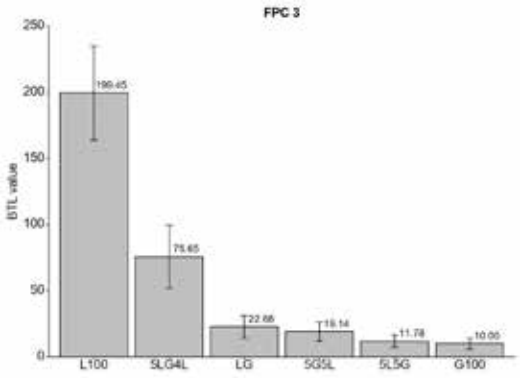

Fig. 3: Pleasantness of noises of trains with different mixtures of brake systems. Six stimuli of full paired comparison (FPC) 3 including 660 judgements. 95% confidence intervals (CI) are shown by error bars. See Fig.1 for acronyms.

Sleep loss and collaboration: how sleepiness affects team communication in control rooms

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Institute of Aerospace Medicine, German Aerospace Center (DLR), Cologne, Germany

In our previously reported study we found that team performance in a simulated control room setting deteriorated under sleep loss, but depending on type of task and mode of teamwork even improved [1,2]. In addition, we analyzed how team members verbally communicated during collaboration 1) to explore how communication is affected by sleepiness and 2) to elucidate the process that may have led to the observed outcomes, since team communication is associated with team performance [3].

Sixty-six healthy volunteers (32 females, mean age 26 ± 5 years SD) participated in a sleep laboratory study for 5 consecutive days. Working in groups of three members they performed collaborative tasks based on a synthetic task environment simulating work in a control room (ConCenT: Control Center Task Environment [5]). These included monitoring for system failures requiring sustained attention (monitoring task) and identifying the cause of system failures by logical reasoning (diagnosis task). The terminals were interconnected and the team members communicated via intercom. In a cooperative condition, team members had common goals acting in favor for the team. In a competitive condition, however, they had conflicting goals since they were instructed to focus on their own performance. Both team conditions were applied once following 19 h of wakefulness (sleep deprivation condition) during the circadian low (02:00 h - 07:00 h) and once between 08:00 h and 13:00 h following 8 h of scheduled sleep and 1 h awake (baseline condition). Recorded audio files of the verbal communication were transcribed into text files and categorized focusing on information relevant for task completion. For the monitoring task, the frequency and type of task-related shared information (e.g. observation or conclusion) were rated. For the diagnosis task, the frequency of task-related shared conclusions / solutions and their correctness were evaluated. General supportive communication (e.g. motivating comments) was rated for both tasks. We used mixed models and repeated measures correlations to examine how team communication changed with sleepiness in the different team situations and how these changes were associated with performance.

In the monitoring task, the frequency of shared information (Figure 1) increased dur-

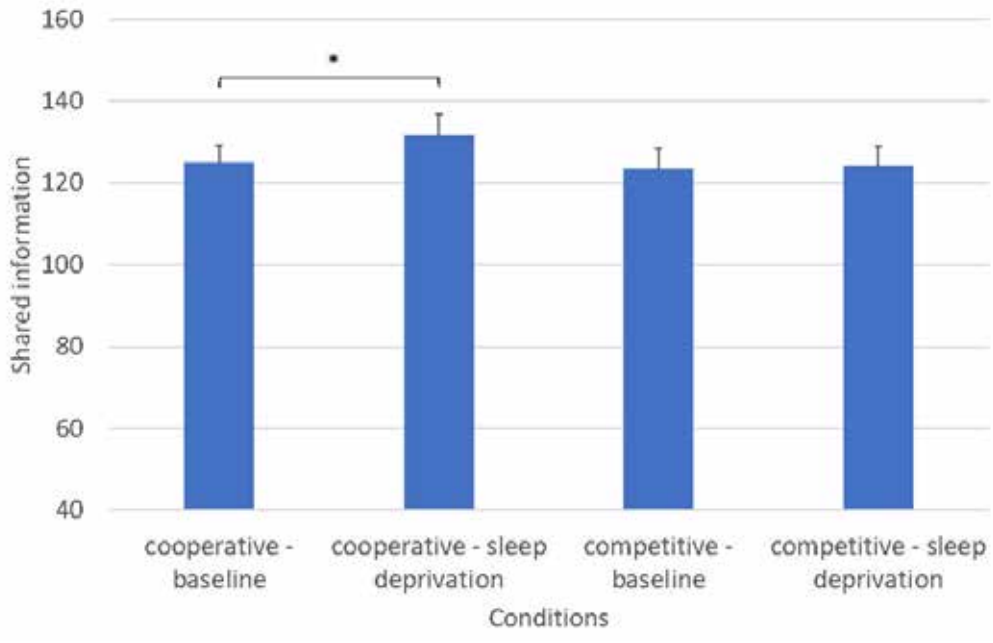

Fig. 1: Task-relevant shared information depending on team and sleep condition in the monitoring task (means and standard errors for each condition)

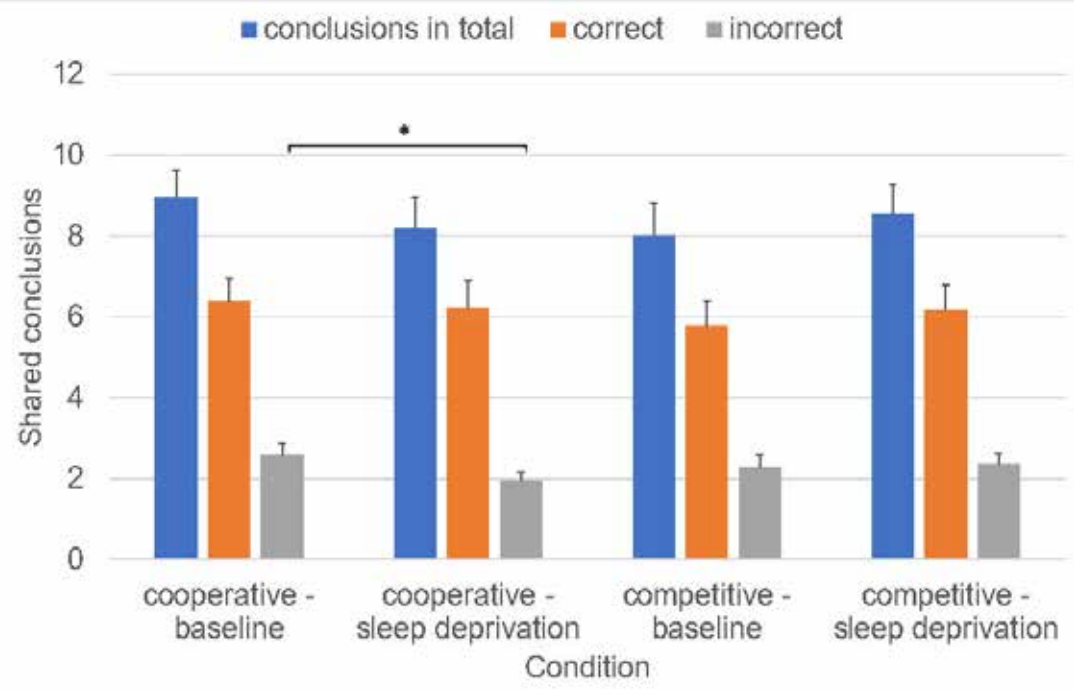

Fig. 2: Shared conclusions (in total, correct, and incorrect) depending on team and sleep condition in the diagnosis task (means and standard errors for each condition)

ing sleep deprivation compared to baseline ($p < .05$) and was correlated with faster reaction times ($r = -.155$, $p < .05$). In the diagnosis task, participants shared less incorrect information (Figure 2) during sleep deprivation than during baseline ($p = .01$) which was associated with higher accuracy ($r = -.45$, $p < .001$). These differences, however, emerged only in the cooperative condition, but not in the competitive condition. In both team conditions, more motivating comments were observed during sleep deprivation than during baseline in the monitoring task (both $p < .05$). Our results show, that communication between team members can change under fatigue induced by sleep deprivation. General, motivating communication increased under sleepiness in both team conditions. But, the team adapted task-related communication only when collaborating in a cooperative manner and not during competitive collaboration. Depending on the specific task, team members shared more relevant information or communicated more effectively by avoiding incorrect information. The association between these communication changes and performance indicates support processes leading to the compensation of negative effects of fatigue on performance. The effects of sleep loss on communication behavior seem therefore rather an adaptation than an impairment due to sleep loss. Thus, cooperative collaboration in occupational settings like control rooms may be protective against some of the negative effects of sleep loss on performance.

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Resetting of the circadian rhythm of melatonin by exposure to moderate hypoxia in humans

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Research in rodents revealed daily rhythms in tissue oxygen levels and indicated that modulation of oxygen levels – via activation of hypoxia inducible factor 1α (HIF-1α) – may be a resetting cue for circadian clocks. Understanding the link between circadian and hypoxia-sensing pathways may provide insight into novel therapies for jet lag and other circadian disorders. In order to study the possible phase shifting properties of hypoxia in regard to jet lag therapy or its potential for preventing/treating of circadian rhythm disorders, a study design free from any external time cue is essential. In a dim light environment, we studied the effects of late-evening exposure to moderate hypoxia on the timing of the circadian melatonin rhythm in humans.

We designed a randomised, single-blind, crossover study. Twenty-two healthy adults (12 women; mean age ± SD: 25.2 ± 2.7 years) followed a fixed 8-h sleep schedule prior to and during two 4-day laboratory visits during each of which the circadian rhythm of melatonin was measured twice, once before and once after treatment (Fig 1.). During treatment, oxygen concentration in the atmosphere was lowered to 15% for 6.5 h, centred at 23:00 h (normobaric hypoxia; corresponding to an altitude of 2438 m). No change in oxygen was applied during the control condition. Dim light melatonin onset (DLMO) was derived on days before and after treatment

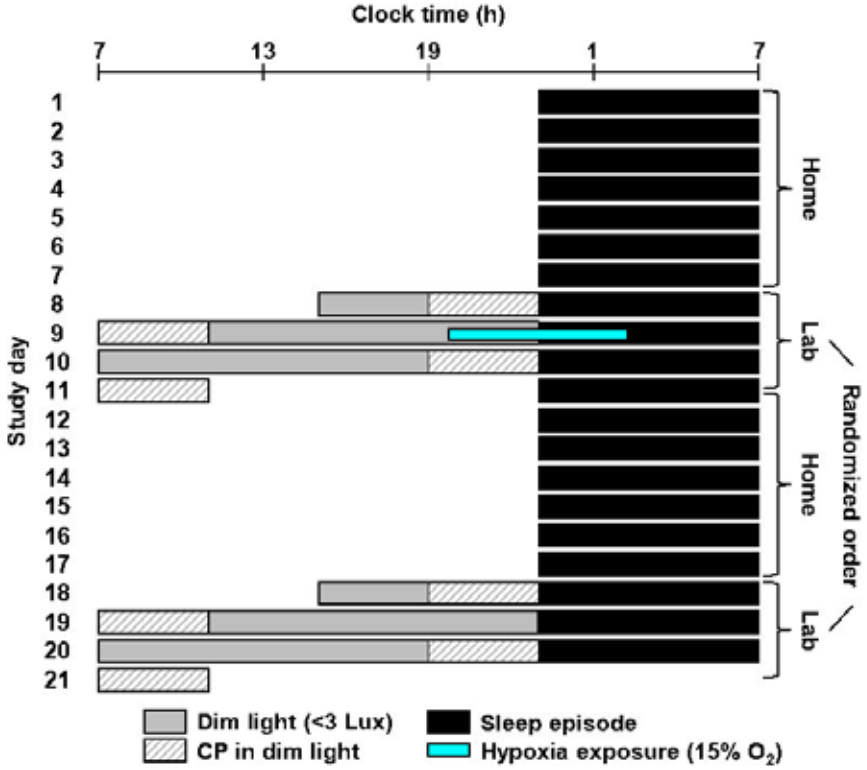

Fig. 1: Raster plot of the 21-d study protocol. Black bars indicate the 23:00 – 07:00 h sleep episode in darkness. Gray bars denote dim room light (<3 lux in the angle of gaze; Materials and Methods). Striped bars show the constant posture (CP) procedures. Participants were randomized to the order of atmospheric condition.

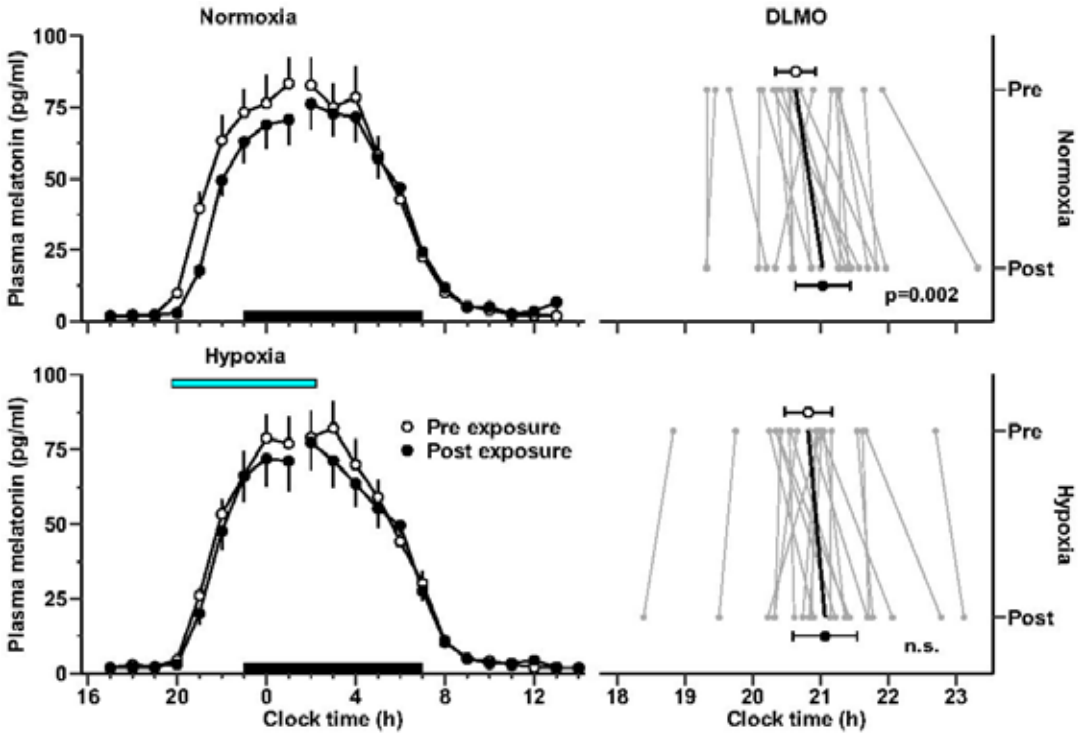

Fig. 2: (Left) Mean (SEM) hourly levels of plasma melatonin before and after normoxia or hypoxia conditions. The black bar denotes the scheduled sleep episode. The blue bar denotes the scheduled hypoxia exposure.
(Right) Individual time points of the dim light melatonin onset (DLMO) and group averages (95% CI) are shown.

through hourly blood sampling in constant posture. The shift in DLMO was compared between the hypoxia and control condition. Blood oxygenation was measured with a finger pulse oximeter throughout the night of exposure. Transcription of HIF1α and target genes was determined in whole blood samples before and during hypoxia exposure.

Exposure to hypoxia lowered blood oxygenation such that values were lowest during the interval that overlapped with the sleep episode (23:00 – 02:15 h; mean, 95% CI: 86.4, 85.2-87.7 %). Late-evening hypoxia exposure induced a phase advance of DLMO (mean, 95% CI) of 9, 1-16 min (n=21; p<0.020, Wilcoxon; corrected for circadian drift during control; Figs. 2 and 3). No changes were observed in HIF-1α related transcription.

We conclude that evening exposure to hypoxia phase-advances the circadian rhythm of melatonin on average by ~9 min. This is the first evidence that hypoxia may act as zeitgeber for the human circadian system. This effect does not appear to be mediated through changes at the level of HIF-1α transcription. While the observed phase-shifting effect of hypoxia was small, its magnitude is such that circadian entrainment to a 24-h cycle appears to be possible.

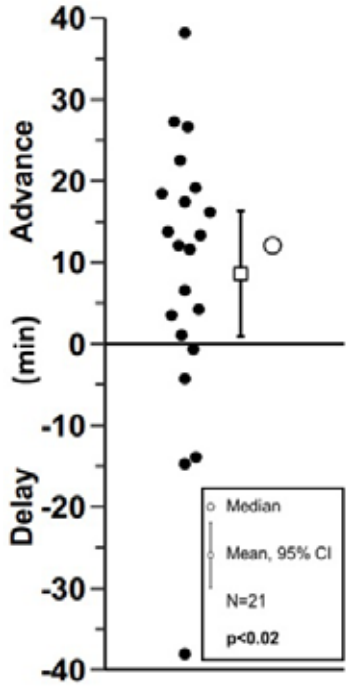

Fig. 3: Hypoxia-induced change in DLMO (min). Closed symbols represent individual subjects.

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Clinical Aerospace Medicine

Clinical Aerospace Medicine

Dr. med. Claudia Stern (Head)

Dr. med. Martin Trammer (Deputy)

The Department of Clinical Aerospace Medicine is responsible for medical qualification and individual health prevention strategies in aviation, spaceflight, and other occupational settings. We primarily target private and professional pilots, aircrew members, astronauts as well as personnel in the other areas of aerospace, air traffic control and transportation. Additionally, we apply our experience in medical qualification examinations supporting the Institute's departments in selecting test subjects for various clinical and physiological trials.

Our aim is to maintain flight safety as part of the flight medicine community. One key factor for flight safety is a healthy and well-trained cockpit and cabin crew. One centerpiece of this process is the medical qualification examination according to national and international requirements. In addition, we care for other operators with different responsibilities and tasks contributing to flight safety including air traffic controllers, airplane technicians, mechanics, and ramp agents. Indeed, flying and non-flying tasks are equally important to maintain flight safety in aviation. We translate our findings to other occupational settings like spaceflight, terrestrial medicine, scientific research, traffic, and transportation among others.

We serve as the occupational health service for DLR sites in the western region (> 3000 employees), all new DLR Institutes without an occupational health service and the residencies abroad (Brussels, Paris, Tokyo and Washington D.C.). We are certified for medical specialist training in occupational health and are responsible for all hygiene related topics.

Our overall goal is to support aerospace safety and maintain the health of aerospace personnel during their working life time. To attain this goal, we closely collaborate with the Institute's research departments to foster the translation of science to applications in aerospace medicine.

The scientific emphasis focuses on research of numerous eye changes in astronauts in the scope of the Spaceflight associated Neuro-ocular Syndrome (SANS).

Teams

Aeromedical Center (Dr. med. Martin Trammer)

- Examination and certification of aviation personnel, certified physician for patient information due to the federal genome diagnostic act of electrodes (Gendiagnostikgesetz GenDG)

Aerospace Ophthalmology (Dr. med. Claudia Stern)

- Ophthalmological research and examinations of astronauts, aviation personnel and test subjects

Occupational Medicine (Peter Tuschy)

- Prevention and managing health of DLR staff and test subjects, medical specialist
- training in occupational medicine
- responsible physician for hygiene related topics
- certified physician for patient information due to the federal genome diagnostic act (Gendiagnostikgesetz GenDG)

Retinal Diagnostics: An International Space Station technology demonstration

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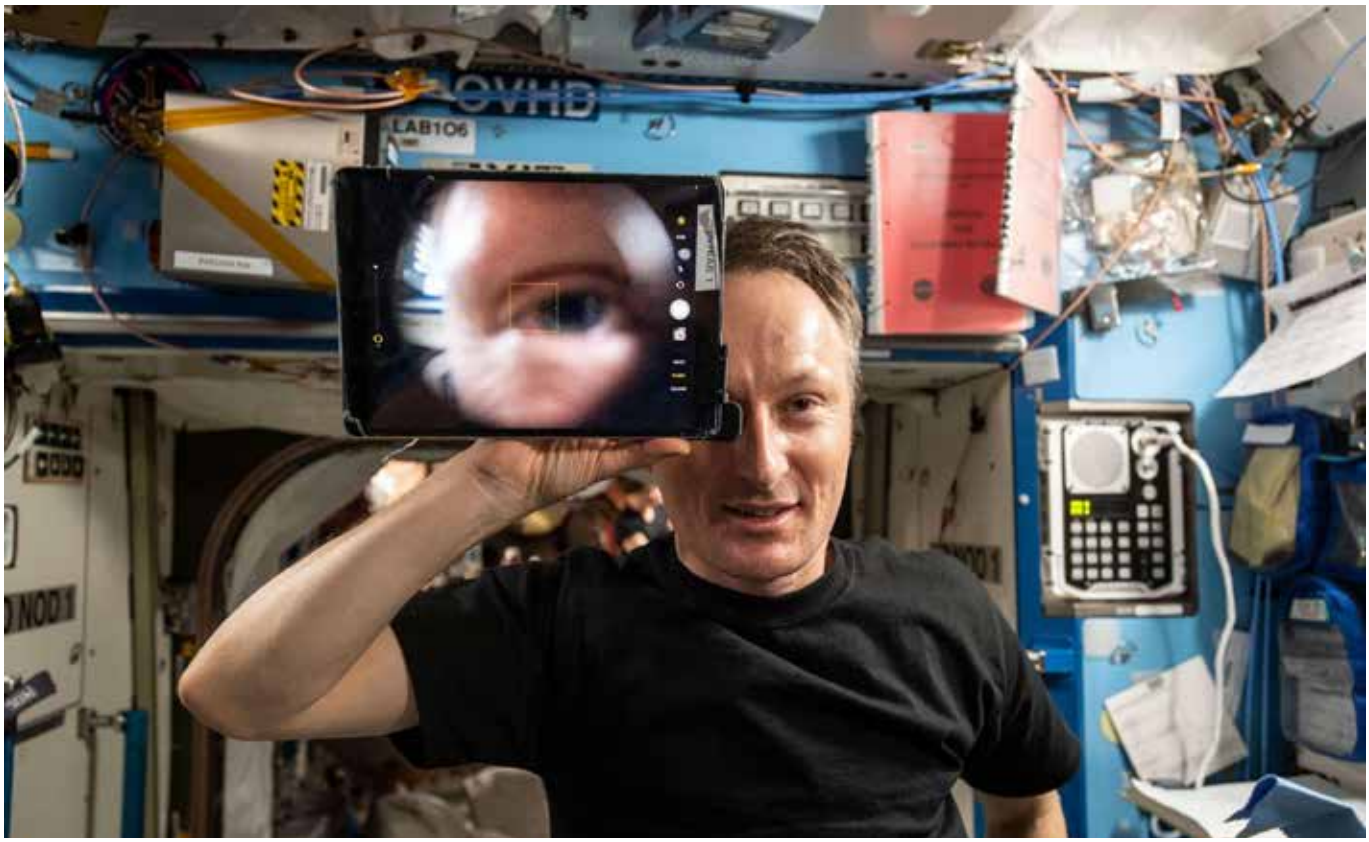

Fig. 1: Retinal Diagnostics ISS Technology Demonstration. Image credit: ESA/DLR

Background

To test the use of mobile fundoscopy in space, we conducted an International Space Station (ISS) technology demonstration experiment during European Space Agency (ESA) Astronaut Matthias Maurer's Cosmic Kiss Mission. Together with our partners at the European Astronaut Center (EAC), we developed, launched, and tested a small, lightweight mobile device aboard ISS during Increment 66 (see Figure 1) [1].

This technology demonstration confirmed the feasibility of using lightweight, small footprint devices in a microgravity environment to detect and mitigate against the eye pathologies that astronauts experience, collectively termed Spaceflight Associated Neuro-ocular Syndrome (SANS)) [2]. Parallel Mars analog ground studies, conducted in partnership with Austrian Space Forum (OeWF) and LunAres, confirmed the feasibility of using this technology in isolated, confined, extreme (ICE) Mars analog environments (see Figure 2) [3].

Current status

Conclusion of this technology demonstration in Mars analog environments and aboard ISS has advanced the Technology Readiness Level (TRL) to 7, as defined by the National Aeronautics and Space Administration (NASA) [4]. We are working with our EAC partners to iterate upon our product design, to enable the potential for use during the Artemis program, for future commercial use on Earth and in space, and to enable future human-in-the-loop (HITL) testing to advance the TRL from 7 to 9 [5].

Fig. 2: OeWF Mars analog environment. Image credit: OeWF/Florian Voggeneder

Additionally, we are using the data collected from these experiments and our clinical partners to train machine learning models to aid future crew members in disease detection. This includes anonymized images from clinical cases of optic disc edema and medical monitoring of bed rest cases during the NASA/DLR SANS Countermeasure Study, occurring from 2021-2023 at the DLR Institute of Aerospace Medicine :envihab facility. Together, these technologies may serve to support clinicians and crew members conducting remote medical operational activities in space and on Earth, in support of United Nations Sustainable Development Goal 3: Good Health and Wellbeing [6].

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European astronaut selection

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Fig. 1: The selected Career Astronauts of the last European Astronaut Selection in 2008/2009. Image credit: ESA

In 2009, we performed the medical part of the European Astronaut Selection together with MEDES in Toulouse. 8413 Europeans applied, 15,5% were women. Finally, Samantha Christoforetti, Alexander Gerst, Andreas Mogensen, Luca Parmitano, Timothy Peake and Thomas Pesquet were nominated as European astronauts, Matthias Maurer followed a few years later.

In 2021, the European Space Agency published an astronaut vacancy note for four to six career astronauts and additional reserve astronauts. For the first time, persons with disabilities such as a lower limb deficiency and/or statures below 130 cm were encouraged to apply.

22.589 Europeans applied to become an astronaut, this time the number of female applicants increased to 24 percent. 257 persons applied to the parastronaut section. 7137 applications came out of France, followed by 3700 German applications, 28% of them being female. In terms of the number of applications per million inhabitants, Luxemburg is leading with 103,834, followed by France, and Belgium.

ESA is seeking professionals with at least a master's degree and a minimum of three years of working experience in Medicine, Engineering, Mathematics, Natural, or Computer Sciences or a test pilot degree, who stay calm under pressure and are willing to participate in life sciences experiments.

The applicants needed to submit an EASA class 2 medical for private pilots and should be in good health and must have a visual acuity in both eyes of at least 100% with correction, if needed. They must be free from any dependency on tobacco, alcohol, drugs and any psychiatric disorder. Following a comprehensive screening phase 1361 applicants, of whom 530 were female, entered the first psychological phase and conducted basic knowledge, cognitive per-

Fig. 2: Selected candidates of the ESA astronaut class of 2022. Image credit: ESA

formance tests, and personality questionnaires. About 400 applicants were selected for further psychological examinations, finally less than 100 applicants were invited to the medical selection phase and additional interviews, which took place in Cologne and Toulouse from May to September 2022. The applicants stayed with us for a week and were examined in the field of anthropometry, dentistry, dermatology, gynecology, internal medicine, neurology, ophthalmology, orthopedics, otolaryngology, psychiatry, radiology and urology.
The standard medical requirements are set by all Space Agencies that are represented on the International Space Station (CSA, ESA, JAXA, NASA and Roscosmos). They reflect the necessity of career astronauts having a medical precondition that allows to perform training successfully and to participate in space missions without endangering her or himself, other international astronauts or the mission itself.)
We are looking forward to examining the new class of astronauts in the future.

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Fig. 3: Arrival of ESA astronaut Matthias Maurer at Cologne/Bonn Airport

Muscle and Bone Metabolism

Muscle and Bone Metabolism

Prof. Dr. med. Jörn Rittweger (Head)

Prof. Dr. rer. nat. Dominik Pesta (Deputy)

Humans have evolved as a species that is uniquely capable of enduring physical performances. Long periods of physical inactivity, conversely, lead to deconditioning, to untoward metabolic consequences, and to compromised health. The Muscle and Bone Metabolism department therefore examines the effects of physical activity, and of the lack thereof in the context of mission-related environmental conditions, such as microgravity, atmospheric challenges, nutrition, circadian disruption and radiation. Genetic predisposition and the ageing process are taken into account as well.

Our ultimate goals are to screen for immobilization-related musculoskeletal disorders, to prevent them where possible and to rehabilitate them where needed. To this purpose, we aim to define valid muscle test protocols, to develop efficient measures to counteract muscle atrophy, bone loss and metabolic derailment in space and on Earth. We aim at these goals in a rational approach that ranges from cellular to organismic levels.

Researching the biomechanics and mechanophysiology of muscles and bones are a prerequisite to understand the physiological effects of muscle contractions and exercise. This is seconded by research into skeletal muscle's metabolism and its systemic interactions. Combining this knowledge with genetic model systems allows us to develop exercise and other countermeasures that are purpose-optimized for space and specific Earth-based applications.

Working Group

Translational Metabolism Research (Prof. Dr. rer. nat. Dominik Pesta)

- Metabolic studies, euglycemic hyperinsulinemic clamp testing, biosample management
- Evaluation of artificial gravity achieved through short-arm centrifugation alone or in combnation with physical training or virtual reality applications as potential counter-measure for health issues during space travel

Teams

Mechano-Physiology (Prof. Dr. med. Jörn Rittweger)

- Biomechanical testing, biomechanical modeling, technology development, data management

Training and Countermeasures (PD Dr. rer. nat. Jochen Zange)

- Exercise training studies, musculoskeletal imaging, exercise countermeasure development

Effects of sleep deprivation on performance in a manual spacecraft docking task

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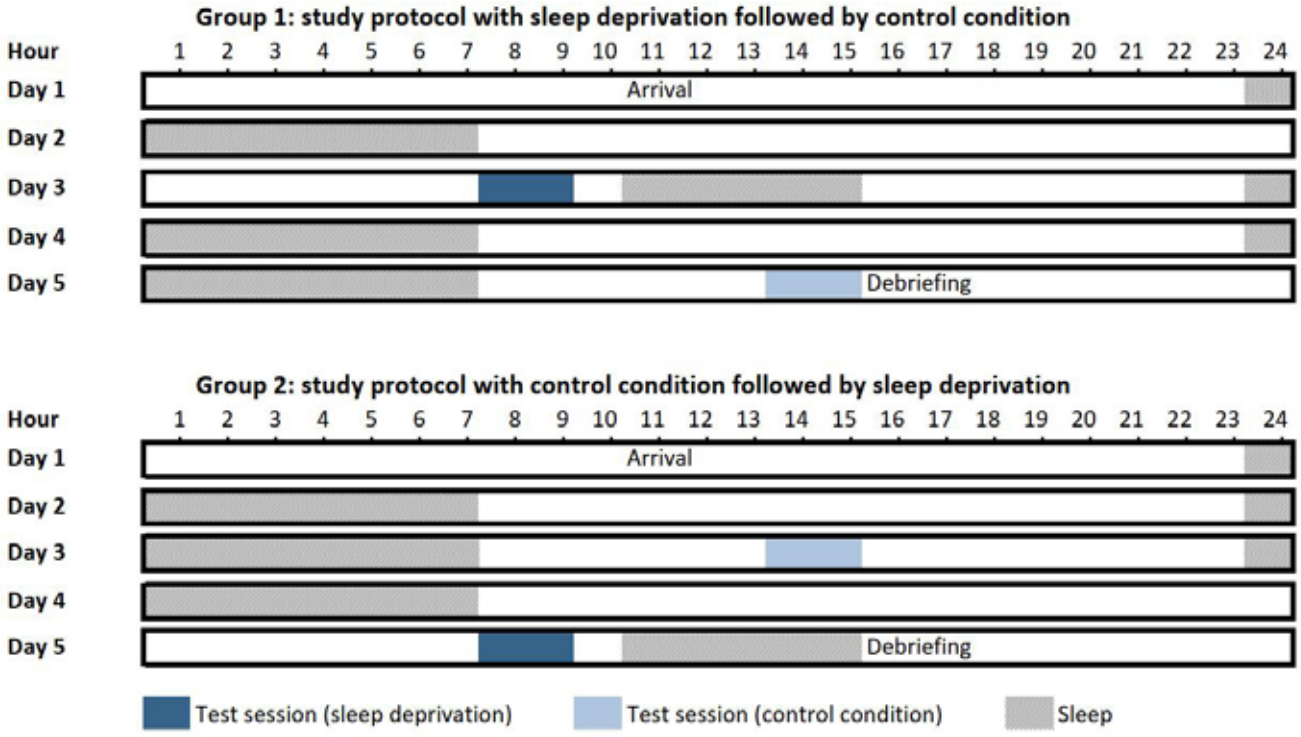

Fig. 1: Repeated measures cross-over design of the sleep deprivation study

Background

Sleep deprivation and disruption of circadian rhythm are highly prevalent in shift workers on Earth and also in astronauts. Stressors associated with space flight, e.g. altered light-dark cycle, high workload, and noise, interfere with sufficient and restful sleep. Resulting sleepiness might deteriorate performance, facilitate accidents, and jeopardize space missions. There is a tight link between sleep deprivation and impaired cognitive performance in laboratory tasks. Especially sustained attention has been shown to be vulnerable to sleep loss. However, research on more complex operational performance is still scarce. A high level of sustained attention is crucial for many operational tasks, but individuals might be motivated to apply additional effort to compensate performance decrements when the task is important and challenging. We investigated if 24 hours of total sleep deprivation would affect not only sustained attention in the Psychomotor Vigilance Test (PVT), but also performance in a complex operational task, i.e. simulated manual spacecraft docking (6df).

Methods

Sixty-two participants completed the manual docking simulation 6df and the PVT twice, in counterbalanced order: once after 24 hours of sleep deprivation and once after eight hours of sleep (Fig. 1). The PVT measures reaction time in response to the appearance of a millisecond counter [1]. 6df is a manual docking simulation

developed at DLR for research purposes [2]. Two hand controls are operated to control an abstract spacecraft in six degrees of freedom (Fig. 2, 3). Included docking tasks vary in their complexity and the difficulty level is adapted to the participant's skill. Performance was measured via the accuracy of the docking maneuver flown and the highest difficulty level a participant could complete successfully. We assessed the impact of sleep deprivation on docking performance and PVT response time, as well as the relationship between performance in both tasks.

Results

Docking accuracy decreased significantly after sleep deprivation in comparison with control condition performance (F (1, 754.49) = 6.56, p = .01). However, there was no impact on the highest level participants were able to complete in the adaptive docking task (V = 531.50, p = .18). PVT response speed deteriorated under sleep deprivation as expected (F (1, 61) = 103.90, p < .001, η2 = .63). Impairment in the PVT after sleep deprivation was correlated with changes in docking accuracy (r = .27, p = .03), but not with the highest level reached (ρ= .13, p = .31).

Conclusion

In conclusion, sleep deprivation led to impaired docking accuracy, which was correlated to impairments of sustained attention as measured by the PVT. However, compared to the substantial effect of total sleep deprivation on PVT response speed, sleepiness interfered less with manual docking performance. Elevated motivation levels due to the novelty and attractiveness of the docking task may have helped participants to at least partly compensate for their sleepiness. To understand the effect of sleep loss on astronauts' capabilities and mission performance, future studies should assess the influence of different sleep schedules on performance in a highly trained and proficient population. Operational performance measures like the 6df task could be helpful tools to assess readiness for duty under sleep deprivation during long-duration missions and increase mission safety.

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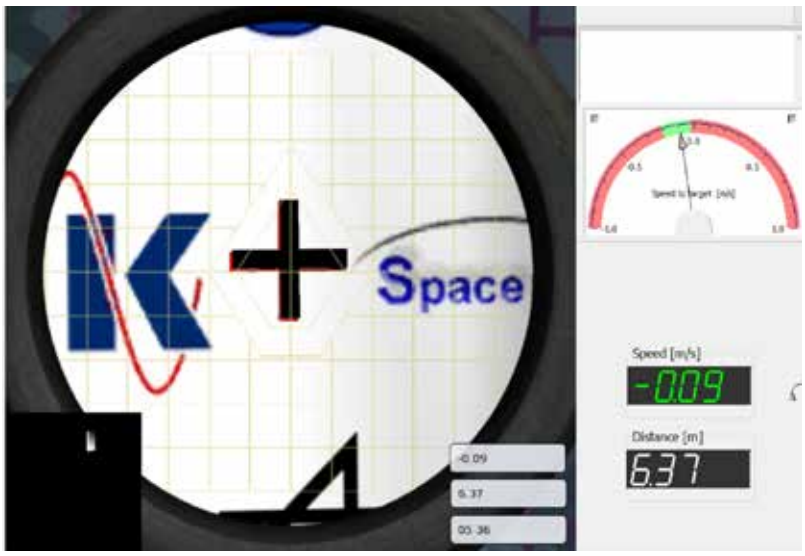

Fig. 2: Screenshot of a 6df manual docking task

Fig. 3: Setup of the desktop-based 6df simulation. The left hand control is used for translational movements and the right one for rotational movements.

Descriptive modelling of fascicle curvature in gastrocnemius muscles

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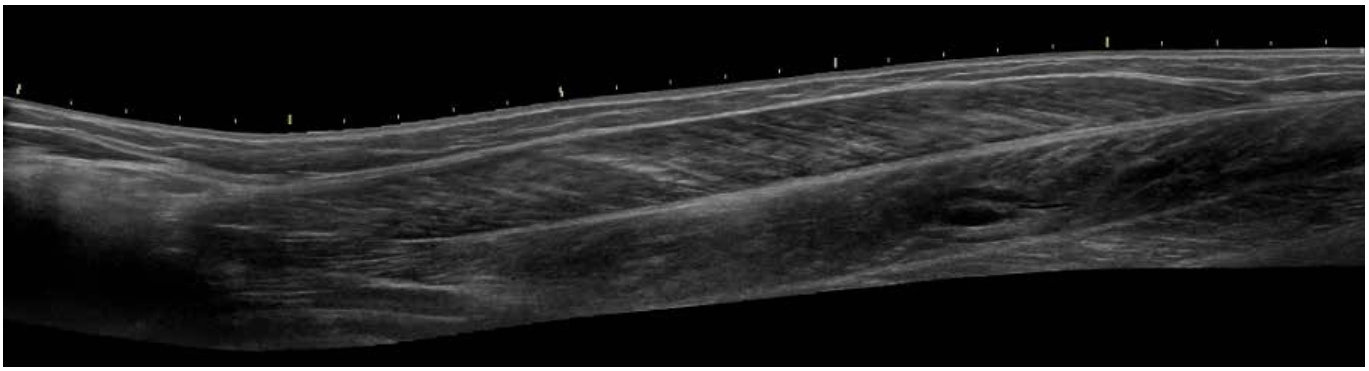

Fig. 1: Panoramic ultrasound image of the medial gastrocnemius from muscle-tendon-junction (right) to the medial knee joint cleft (left) at medio-lateral centre

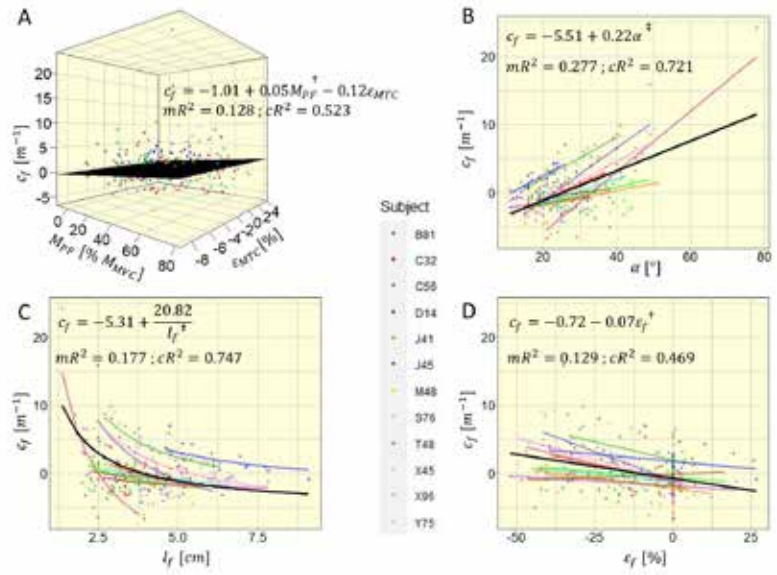

Fig. 2: Four competing models to explain mean fascicle curvature in the medial gastrocnemius with different independent variables:

A with muscle-tendon complex strain ε_{MTC} and contraction level M_{PF}

B with mean deep pennation angle α

C with mean fascicle length l_f

D with mean fascicle strain ε_f

Introduction

Power loss of skeletal muscles remains a major negative side effect of longterm exposure to weightlessness. Besides muscle atrophy also changes in muscle architecture and mechanics have significant force reducing impact. In muscle research it is well established to analyse changes in fascicle's length and pennation angle. Several studies reported that fascicles sometimes curve. This bending could be another mechanical parameter that influences the muscle's force generation. It has been shown that muscle fascicle curvature increases with increasing contraction level (CL) and decreasing muscle-tendon-complex (MTC) length. The analyses in these studies were done with limited examination windows concerning contraction state, MTC length and/or intramuscular position of ultrasound imaging. Additionally, fascicle curving has, to the best of our knowledge, not yet been produced by in-silico muscle models, which suggests that the mechanisms are poorly understood. With this study we aimed to investigate the phenomenon of fascicle arching in gastrocnemius muscles in order to develop hypotheses about its fundamental mechanism and to reproduce the curving with a theoretical mesh-type muscle model.

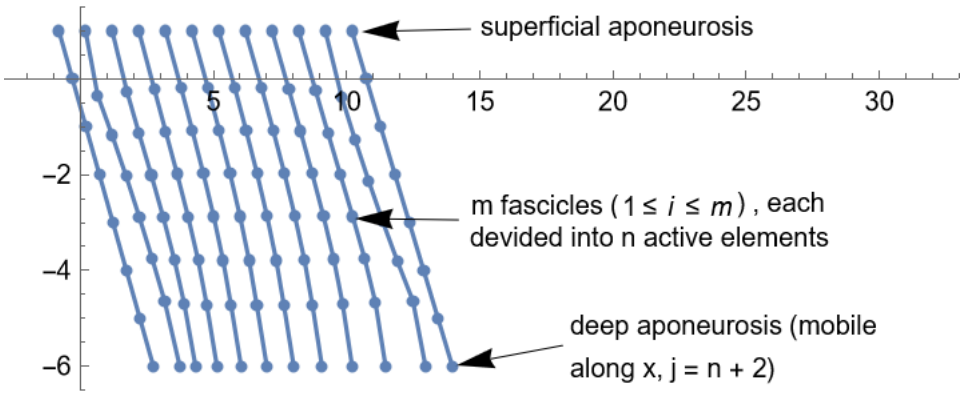

Fig. 3: Final state of the simulation of the muscle fascicle mesh with visible fascicle curvature. Blue lines represent muscle fascicles while superficial and deep aponeuroses are represented by non-visible horizontal connections between upper-most and lowest fascicle nodes, respectively.

Methods

Twelve participants were tested in five different positions (90°/105°*, 90°/90°*, 135°/90°*, 170°/90°* and 170°/75°*; *knee / ankle angle). They performed isometric contractions at four different contraction levels (5%, 25%, 50% and 75% of maximum voluntary contraction (MVC)) in each position. Panoramic ultrasound images of both gastrocnemius muscles were collected at rest and during constant contractions (figure 1). Aponeuroses and fascicles were segmented in all ultrasound images and fascicle parameters curvature, pennation angles, length, strain and intramuscular position have been extracted. Mean curvature of all segmented fascicles within the medial gastrocnemius (c_f) has been analysed by four competing linear mixed models with plantar flexion torque (M_{PF}) and MTC strain (ε_{MTC}), mean pennation angle (α), mean fascicle length (ι_f) or mean fascicle strain (ε_f) as independent variables (models 1A, 1B, 1C and 1D, respectively; figure 2). The best model was expanded for intermuscular (+ muscle type as fixed two-level factor) and for intramuscular (+ intramuscular position as fixed effect) analysis.

Additionally, we aimed to reproduce fascicle curvature with a theoretical simulation that represents the muscle as a two-dimensional mesh of fascicles as a sequence of interconnected active viscoelastic elements and passive viscoelastic elements representing connective tissues and tendon attachments (figure 3).

Results

Mean fascicle curvature of the medial gastrocnemius increased with M_{PF} (+5m^{-1} from 0 % to 100% MVC; p=0.006). ε_{MTC} had no significant impact. α (+0.22m^{-1} per 1°; p<0.001) and ε_f (-0.007m^{-1} per 1%; p=0.004) were correlated linearly with c_f, while lf correlated in a hyperbolic manner (+20 m^{-1} per cm^{-1}; p=0.034; figure 2). c_f as well as the impact of α on c_f differed between muscles (-3.04m-1, p<0.001 and +0.09 m^{-1}, p=0.023 in medial gastrocnemius). Curvature also varied within the muscle (-3.64m^{-1} from muscle centre to muscle-tendon-junctions; p<0.001).

The mesh model was able to simulate fascicle curvature and showed that curving depends on the stiffness at the tendon junctions.

Conclusions

In contrast to previous studies fascicle curvature correlates with contraction level but not with muscle-tendon-complex strain. Curvature can be best explained by the deep pennation angle. Similar correlations with pennation angle can also be seen in studies investigating intramuscular fluid pressure. In future studies it would be of great interest to study correlations between intramuscular fluid pressure and fascicle curvature in regards to a potential causal relationship. In general, analyses of muscle architecture should not treat fascicles as straight lines and fascicle curvature should be included into analysis as architectural parameter.

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Between-subject and within-subject variation of muscle atrophy and bone loss in response to experimental bedrest

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Background

A lack of gravity as during space missions results in physical deconditioning, especially in muscle wasting and bone loss. During long-term missions a bone loss of about 1% per month was observed. Muscle wasting mostly affect the lower extremity, especially the calf musculature. But these adaptations are highly related to individual differences. The best analogue simulating long microgravity exposure on earth are head-down bedrest studies. Therefore, the aim of the present work was to explore variation in musculoskeletal responses to head-down bedrest, and to separate between-subject variation (BSV), within-subject variation (WSV) and measurement related uncertainty.

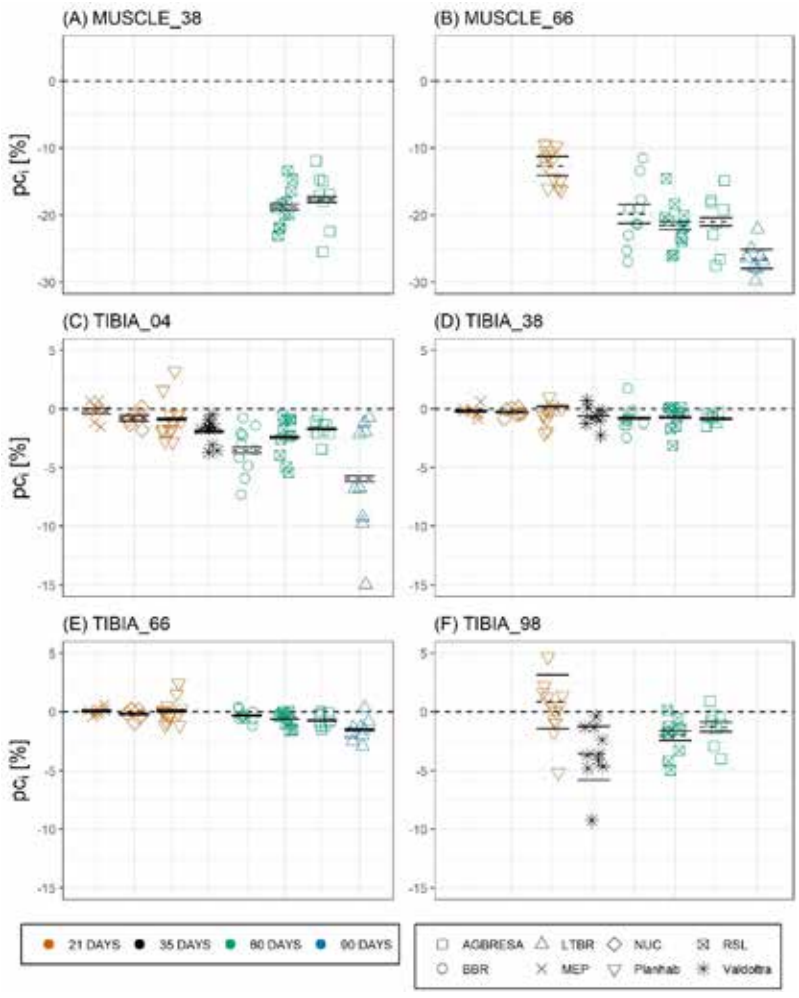

Fig. 1: Chart of the individual percent change (pc) by measurement sites with (A) CSA at MUSCLE_38, (B) CSA at MUSCLE_66, (C) BMC at TIBIA_04, (D) BMC at TIBIA_38, (E) BMC at TIBIA_66, and (F) BMC at TIBIA_98. Mean of the pc as dashed line, upper and lower limit of the 95%-confidence interval based on measurement uncertainty U_{Meas} as solid lines.

Methods

We included datasets of 76 participants which underwent head-down bedrest during eight study campaigns from 2001 till 2019. Three out of eight head-down bedrest campaigns provided two baseline measurements enabling the computation of measurement uncertainty U_{Meas}. The measurements took place at baseline data collection (BDC) and after re-ambulation. All participants were measured with a peripheral quantitative computer tomography (pQCT) at TIBIA_04, TIBIA_38, TIBIA_66, and TIBIA_98, respectively, where the numbers indicate the relative position at the tibia from distal to proximal. At all measurement sites the bone mineral content (BMC) was computed and at the diaphyseal sites (TIBIA_38 and TIBIA_66) the cross-sectional area (CSA) as a value for muscle wasting was analyzed. We defined the observed individual loss of bone or muscle of each subject after BR as the percent change (*pc)*. U_{Meas} was defined as the mean of the individual´s variances between the two baseline measurements for each campaign who provide these two measurements. If the individual percent change exceeded a 95%-confidence interval based on the measurement uncertainty, we defined this as BSV. WSV was defined in this work if there was no correlation between the different measurement sites.

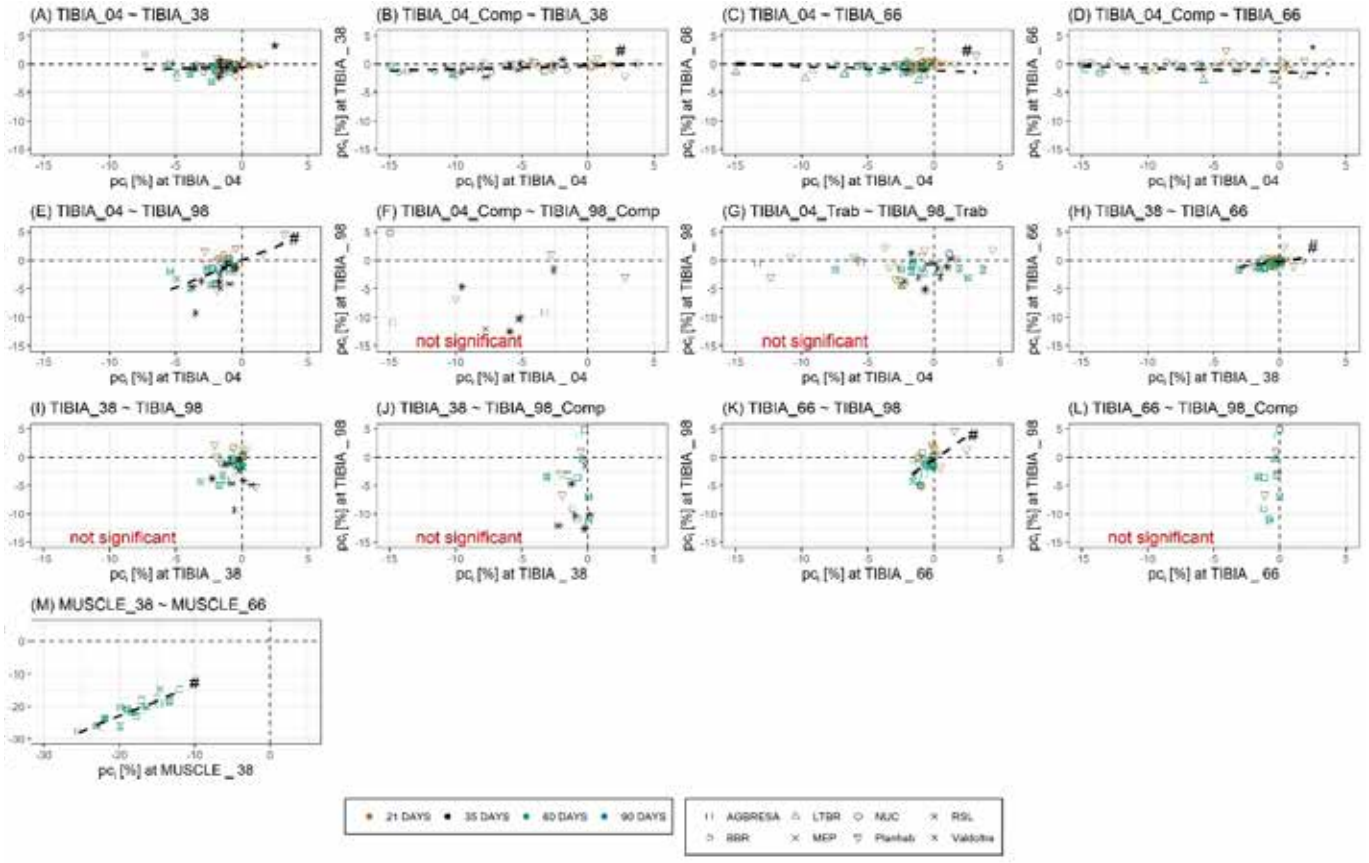

*Fig. 2: Pearson Correlation of the individual percent change of several measurement sites. Comp and Trab indicate compact and trabecular bone loss, respectively. * denotes significant correlation with p < 0.01; # denotes significant correlation with p < 0.001.*

Results

ANOVA indicated a significant difference of U_{Meas} between two studies at TIBIA_66 (p = 0.005), but no further differences existed. As can be seen from Figure 1, the vast majority (82.6%) of the observed individual *pc* exceeds the confidence intervals, indicating significant and substantial BSV. The correlation analysis (Figure 2) shows a very high positive correlation of *pc* between MUSCLE_38 and MUSCLE_66 (r = 0.90, p < 0.001). For BMC, there was no correlation seen between TIBIA_38 and TIBIA_98 (r = 0.29, p = 0.07), whereas the correlation coefficient ranged from 0.34 (TIBIA_04 and TIBIA_38; p = 0.006; low positive correlation) to 0.52 (TIBIA_38 and TIBIA_66; p < 0.001; moderate positive correlation) between the remaining bone site pairs. When differentiating compact and trabecular bone tissue at the epiphyseal bone sites, there were significant correlations between TIBIA_04_Comp and TIBIA_38 (r = 0.51; p < 0.001), and TIBIA_66 (r = 0.39; p = 0.002), respectively, but no correlation to TIBIA_98_Comp (r = 0.29; p = 0.19). Additionally, TIBIA_98_Comp showed no correlation to either TIBIA_38 (r = 0.12, p = 0.54) or TIBIA_66 (r = 0.10, p = 0.62). The loss of trabecular bone within the epiphyseal sites showed no correlation (r = -0.12, p = 0.36).

Conclusions

Variation in muscle and bone responses to head-down bedrest primarily results from between-subject and within-subject variation rather than measurement uncertainty. Nevertheless, measurement uncertainty should be considered in each data analysis, regardless of variation. We observed that BSV and WSV were both lower for muscle than for bone sites. Training status, diet, and genetic predisposition may have contributed to the variation. The substantial variation in bone and muscle responses to deconditioning, be it in bedrest or during space missions, provides an impetus for a more individualized approach to countermeasure prescription.

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Substantial muscle loss in two professional mountaineers during graded normobaric hypoxia

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Hypoxia is associated with profound changes in muscle mass and function in patients with cardiopulmonary disease (1, 2) and in healthy persons exposed to high altitude (3). As more than 500 million people live at altitudes of 1500 m or higher above sea level, a comprehensive understanding of altitude effects on the human body is of great importance (4). Augmented skeletal muscle catabolism has been commonly observed in lowlanders sojourning to high altitude, possibly related to cold exposure, insufficient dietary intake, increased energy expenditure, or decreased physical activity levels. Whether or not muscle remodeling and progressive muscle loss also occur in trained mountaineers accustomed to high altitude exposure, remains unclear. The aim of this case study was therefore to assess the extent of hypoxia-induced muscle wasting in hip, thigh and shank muscles. To that purpose, we assessed muscle volume during progressive normobaric hypoxia exposure in two elite climbers (A and B) with a long history of mountaineering experience.

These professional mountaineers participated in a 35-day intervention of graded normobaric hypoxia with the aim of 14 days exposure to 8% oxygen corresponding to ~7000 m altitude. Volume of the shank, thigh and hip muscles was assessed by magnetic resonance imaging pre and post intervention. Dietary intake and physical activity were monitored throughout the study from food images and accelerometry analysis, together with blood analysis and anthropometric measurements.

Hypoxia was differently well tolerated by the two mountaineers. Arterial oxygen saturation declined throughout the study in both mountaineers with desaturation in B remaining higher than in A throughout the study. Participant A lost 2.3 kg of body weight while participant B lost 1.6 kg of body weight over the 35-day interventional period. Hypoxic exposure lead to a loss of muscle volume (Fig.

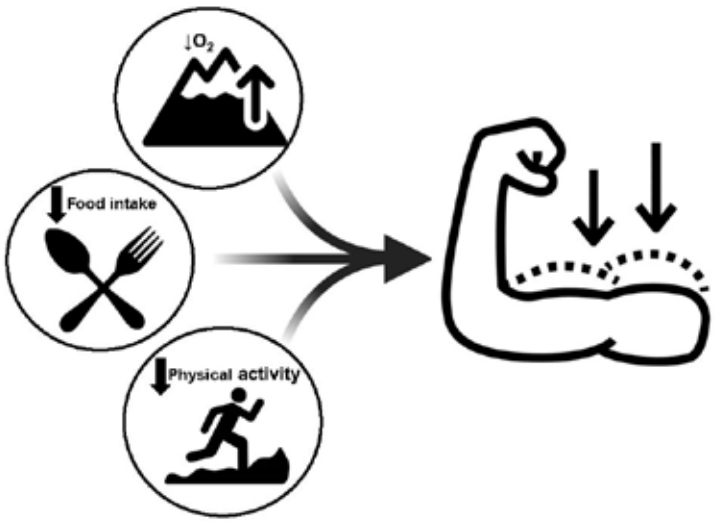

Fig. 1: Hypoxia, together with resultant reductions in caloric intake and physical activity lead to substantial loss of muscle mass in two experienced mountaineers

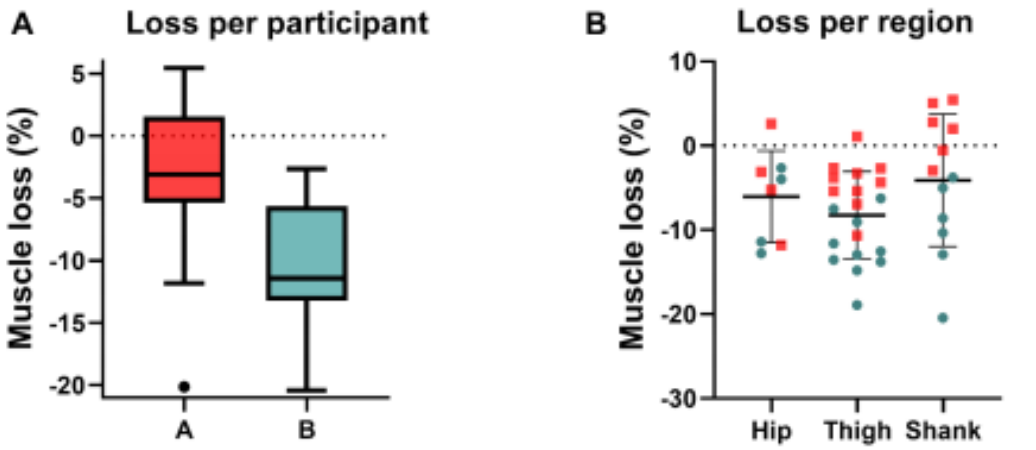

Fig. 2. A: Percent leg muscle loss after 35-days of hypoxic exposure depicted for participant A and B. B: Differential leg muscle loss in the hip, thigh and shank region for A (red squares) and B (green circles)

2AB). When averaged over all leg and hip muscles, participant A and B lost 3.3% and 9.4% of their baseline muscle volume, respectively (Fig. 2A). Over both subjects and all muscles, the change in leg muscle volume over the 35 days of hypoxic exposure amounted to 6.4±7.3%. Assuming a density for muscle of 1.055 g/cm3, A and B depicted total absolute losses of 288±27 g and 642±36 g of leg muscle mass, respectively.

Interestingly, muscle loss was not uniform among different muscle groups. While thigh muscle volume was reduced by 8.3%, the hip and shank losses amounted to 5.4% and 4.1%, respectively (Fig. 2B). Dietary intake only declined during the last week of hypoxic exposure from an average caloric intake of 2983±465 kcal and 2954±392 kcal for the first week to 2290±150 kcal and 2279±176 kcal, in A and B, respectively.

Although being active, participants could not maintain their usual level of climbing and trail running exercise in the chamber but maintained a mild exercise regime throughout the study. Physical activity monitoring revealed that A reduced their walking distance by 52% and B by 94%, respectively, towards the end of the hypoxic exposure.

Our results indicate that hypoxia and resultant reductions in physical activity and caloric intake lead to substantial loss of muscle mass that was accentuated in proximal muscle as opposed to distal muscles. Surprisingly, thigh muscle wasting during this intervention is comparable to that observed during strict 56-day bed rest.

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Myopathological aspects of the master athletic laboratory study of intramuscular connective tissue

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Although endomysium with its relatively high turn-over is thought to be mechanically involved in force transmission, there is little knowledge about its regulatory determinants. Here, we report on the Master Athletic Laboratory Study of Intramuscular Connective Tissue (MALICoT, registration number DRKS00015764), which aims at determining amount and composition of intramuscular connective tissue in human soleus muscle. To analyze effects of physical activity and age, the healthy study participants were categorized into four groups comprising a group of young (20 to 35 years) non-athletic (n=12) subjects, a group of young power-trained athletes (n=10) as well as two groups of aged (60 to 75 years) subjects being either non-athletic (n=11) or power-trained athletes (n=10).

Left soleus muscle biopsies from all participants were taken using a vacuum-assisted biopsy system (Vacora Biopsy System, Bard) with a 10G needle. The physical principle of this automated system with single-use biopsy needles is very similar to the manual Bergström biopsy technique [1,2]. We obtained 43 muscle biopsy specimens of approximately 19 mm length, 3 mm diameter, and 120 mg weight. Part of the tissue cylinders were mounted for transversal cryo-sectioning. Histologically stained soleus muscle sections underwent standard myopathological evaluation as well as an automated deep learning-based artificial intelligence biomedical image analysis of H&E stained sections [3]. Moreover, immunofluorescence images of laminin-γ-1 and collagen IV as well as collagen I and III stained sections were digitally analyzed by standard microscopy software (Zeiss Zen v.3.4, Cell Profiler v.4.2.1) [4].

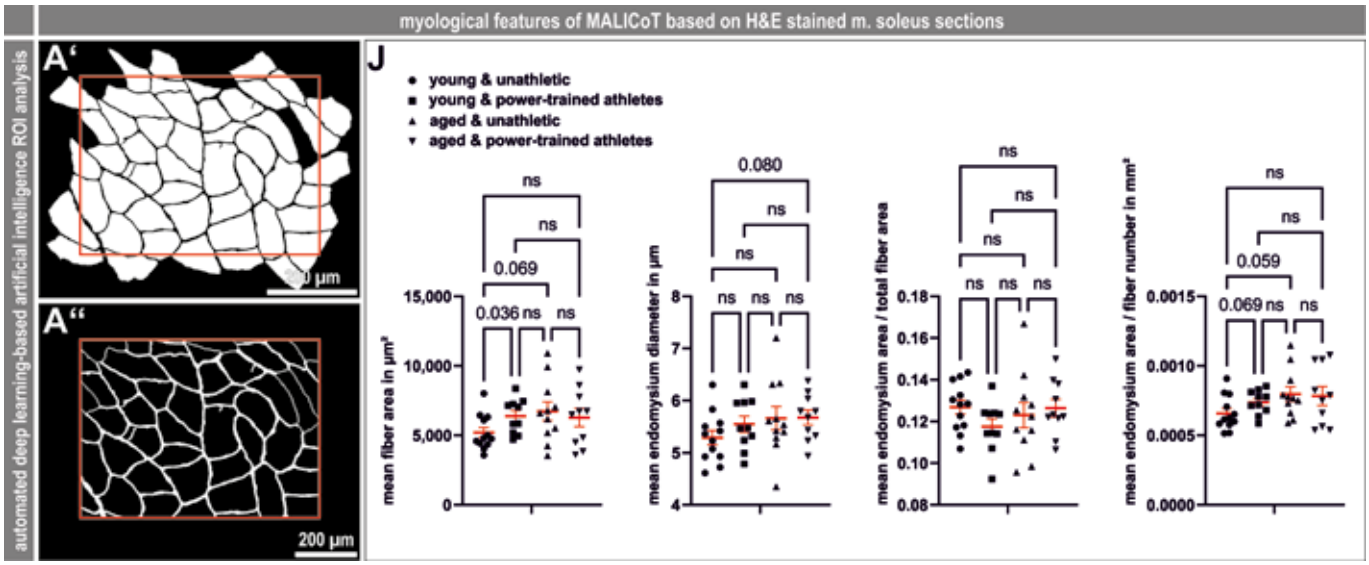

Fig. 1: (A',A'') Exemplary fiber and endomysium masks of a digitalized H&E image derived from automated deep learning-based artificial intelligence image annotation. (I) Using this advanced quantitative image analysis approach, we noted statistically significant effects of physical activity as well as age on the main features 'mean fiber area', 'mean endomysium diameter', and 'mean endomysium area to fiber number ratio'.

Visual evaluation by a trained myopathologist did not reveal significant differences in the amount of connective tissue between the four subject groups. Using the latter fluorescence-based quantitative image analysis approach, no statistical significance could be determined for the main features 'mean fiber area', 'mean endomysium area to total fiber area ratio', and 'mean endomysium area to fiber number ratio'. However, we found a slight but statistically significant increase of 'mean endomysium diameter' in young power-trained athletes as compared to young non-athletic subjects (p=0.04). In contrast, using the previous, advanced quantitative image analysis approach, we determined multiple statistically significant effects of physical activity as well as age on the main features 'mean fiber area', 'mean endomysium diameter', and 'mean endomysium area to fiber number ratio' (Fig. 1).

In contrast to the time-consuming analysis of muscle fiber and connective tissue features by, e.g., fluorescence imaging in conjunction with manual digital image analysis, the fast and automated deep learning-based artificial intelligence image analysis of standard H&E stained muscle sections depicted statistically significant changes. Notably, physical activity led to increased 'mean fiber area' and increased 'mean endomysium area to fiber number ratio'. This new image analysis approach offers a fast, easy to handle, extendable, quantitative, and reliable solution to address connective tissue content and other features in human skeletal muscle biopsy samples.

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Effects of 4-phenylbutyrate on sarcomeric lesion formation and protein-homeostasis in R349P desminopathy mice

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Mutations in the desmin gene cause a spectrum of myopathies and cardiomyopathies [1]. Desminopathies show a progressive course, and no curative or ameliorating therapy is currently available. We previously established a R349P desminopathy mouse model which mirrors essential aspects of the orthologous human R350P desminopathy pathology [2]. Our desminopathy mice display signs of increased myofibrillar instability, i.e., Xin-positive sarcomeric lesions, as previously shown for filaminopathy mice [3]. Exploiting the desminopathy mice, we here focus on the effect of acute, strenuous physical exercise and the administration of the chemical chaperone 4-phenylbutyrate. This drug, approved for the use in humans for the treatment of another orphan disease [4], was reported to reduce the desmin protein aggregation content in skeletal muscle tissue as well as to increase muscle strength in plectin knock-out mice [5].

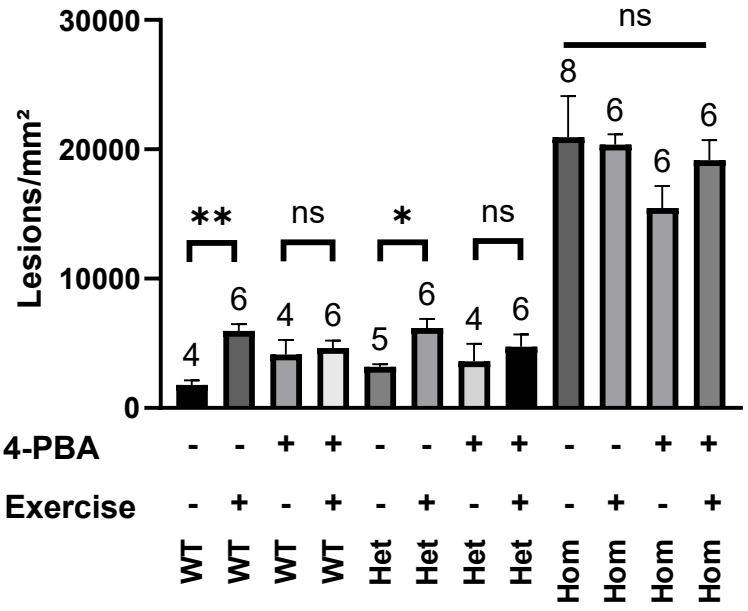

*Fig. 1: While acute strenuous treadmill exercise induced a significant increase in mean sarcomeric lesion density in wild-type and heterozygous that did not receive 4-PBA, this was not observed in corresponding 4-PBA treated subgroups. Homozygous mice already presented a significantly higher number of myofibrillar lesions without clear effects of exercise and drug treatment. No of animals indicated above columns that show mean+sem, *=p<0.05, **=p<0.01.*

To quantitate the extent of myofibrillar damage as reflected by the number of sarcomeric lesions, we established an immunofluorescence protocol to stain soleus muscle cryo-sections employing an antibody directed against Xin in conjunction with confocal image acquisition and digital image analysis based on the open-source software QuPath. Sarcomeric lesion formation was determined in the following groups and combinations of mice: i) hetero- and homozygous R349P desmin knock-in mice and wild-type littermates kept under standard sedentary housing conditions, ii) animals that received either PBS for control or 4-phenylbutyrate (4PBA) via intraperitoneal injection over a time period of two weeks, iii) animals of all genotypes, which received PBS or 4-phenylbutyrate prior to a single strenuous treadmill run. This was further complemented by immunoblot analysis of desmin, p62/Sqstm1, and Hsp70 levels. We report the preliminary results which await completion by inclusion of further animals to reach a number of 15 animals per condition as calculated by statistical power analysis.

The data from our preliminary analysis clearly demonstrated that acute strenuous exercise leads to an increased number of sarcomeric lesions in wild-type and heterozygous R349P desminopathy mice (Fig. 1). Even non-exercised homozygous mice already presented a significantly higher number of such myofibrillar lesions. In wild-type and heterozygous R349P desminopathy mice, 4PBA treatment seems i) to prevent the exercise-induced myofibrillar damage to a certain extent (Fig. 1), ii) not to alter desmin and p62/Sqstm1 levels,

and iii) to increase Hsp70 in heterozygous mice. However, our results need inclusion of data derived from further animals to reach a number of 15 animals per condition as calculated by statistical power analysis.

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Aerospace Psychology

Aerospace Psychology

Dr. Dipl.-Psych. Viktor Oubaid (Acting Head since 06-2022)

Dr. phil. Peter Maschke (Head until 05-2022)

Pilots, air traffic controllers, astronauts, and operators in other skilled professions are, both, an asset and a liability regarding safety in aerospace. Indeed, proper decisions together with functioning human-machine and human-human interactions enhance the reliability of technical system tenfold. Yet, operators are also responsible for the majority of aviation incidents and accidents. By developing, validating, and implementing comprehensive selection systems, the Department of Aviation and Space Psychology makes a significant contribution to safety in aerospace. Research in the field of performance under (simulated) microgravity, flight cockpit design, flight operation of aircrafts and drones, virtual reality and passenger comfort in trains and aircraft expands the research range of the department and promotes cooperation with operators and manufacturers for the benefit of travellers and crews.

Given the importance of human factors, our work will help attaining the goals of Flightpath 2050, an 80% reduction in accidents. Our safety-related research program is of high scientific, economic and societal value, contributes to employment security and job satisfaction of selected candidates, and supports economic development of aerospace industry by reducing training costs and minimizing errors. An additional part of our research addressed acceptance of new technologies, which is a critical barrier for economic success of novel technology.

Working Groups

Air Traffic Control (Dr. phil. Hinnerk Eißfeldt until 03-2022; Dr. phil. Yvonne Pecena)

- Job requirements of controllers and UAS operators
- Selection of air traffic controllers
- Inter team cooperation
- Eye tracking methods
- Urban air mobility
- Acceptance of aviation systems

Crew Performance and Transport (Prof. Dr. phil. Dirk Stelling)

- Selection of airline pilots
- Development and validation of diagnostic methods
- Cabin comfort
- Virtual reality
- Selection und support of bed rest candidates

Teams

Space Psychology (Dr. phil. Peter Maschke until 05-2022; Dr. Dipl.-Psych. Viktor Oubaid since 06-2022)

- Selection of astronauts
- Psychological inflight support of astronauts

Effects of conflicting goals and transparency on collaboration in teams

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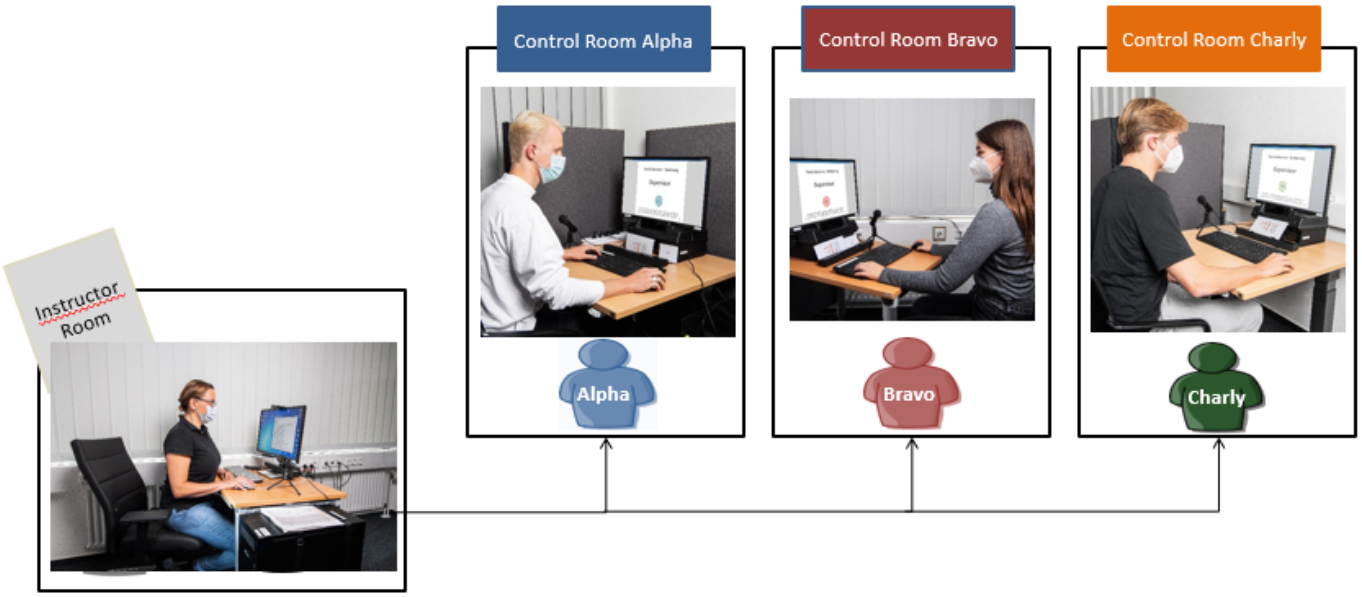

Fig. 1: Experimental study with groups of three in separate rooms

In Air Traffic Management (ATM) multiple teams have to collaborate to achieve efficient and safe operations. Multiple-team operations rely on communication and information sharing between the team members. That is why the interface between the organizations involved (e.g. air traffic control, cockpit crews, airports) is of central importance. Apart from a common goal, different stakeholders may pursue individual goals governed by their own company culture or policies. Therefore, simply sharing all available information may not be appropriate. An experimental study with 47 groups of three (n = 141) with three test scenarios was conducted. This study was part of the interdisciplinary DLR project ITC (Inter-Team Collaboration) with the overall objective to derive guidelines and measurements for collaborative decision-making processes.

To investigate the impact of inducing conflicting goals on performance and collaboration (see figure 1), half the groups were instructed to work in three different organizations and have had to deal with conflicting goals between their own company's goals and the overall goal of the system in which they had to work together. For the other half, no conflicts between the common goal and their individual goal were induced. Additionally, it was examined whether and how transparency in roles, processes, and goals could affect performance, communication, and trust in multi-team systems. For that, a transparency intervention between test scenarios with half of the groups were conducted. Guided by a moderator, group members exchanged information and reflected on their previous decision-making processes.

To investigate team- and multiple-team operations systematically, the synthetic task environment ConCenT (Control Center Task Environment) was used. Teams of three had to collaborate to detect system failures in time, determine their causes, and decide on a solution in order to ensure successful production processes. Measurements of performance, perceived trust, communication, and gaze data were assessed.

Preliminary results of the study show both an effect of conflicting goals on collaborative decision making processes and an effect of transparency on interpersonal trust. In the first scenario, 48% of decisions in groups with conflicting goals were egoistic, meaning that the decision considers only individual goals instead of common goals. In contrast, only 33% of decisions in groups without conflicting goals were egoistic. In the last scenario,

the preliminary findings indicate an interaction effect between conflicting goals and transparency (see figure 2). Only for the groups with conflicting goals, the percentage of egoistic decision differed between groups with (31%) or without (59%) transparency intervention. For groups without goal conflicts, the percentage of egoistic decisions were with 42% and 39% almost identical with or without transparency. These effects had practical implications, which were the amount of egoistic decisions shows systematic correlations to the performance in detecting system failures in time and determining their causes within the groups. Finally, the transparency intervention tends to affect the perceived interpersonal trust within groups. As shown in figure 3, participants rated the interpersonal trust consistent a bit higher, when they experienced transparency between test scenarios.

This study provides answers to the question of how collaborative work processes can best be designed, measured, and evaluated. Conflicting goals and interpersonal trust have the potential to either impair or promote the collaborative work processes. Moreover, the study provides an approach to improving (multiple-)team operations by enhancing transparency and mutual trust through communicative exchange. Further research is needed to enlighten the reported effects by analyzing gaze behavior and communication within groups.

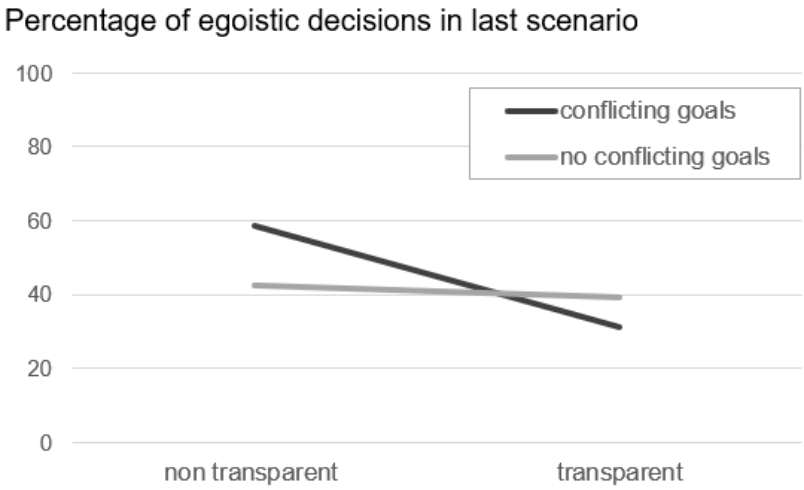

Fig. 2: Percentage of egoistic decisions in last scenario (n=131)

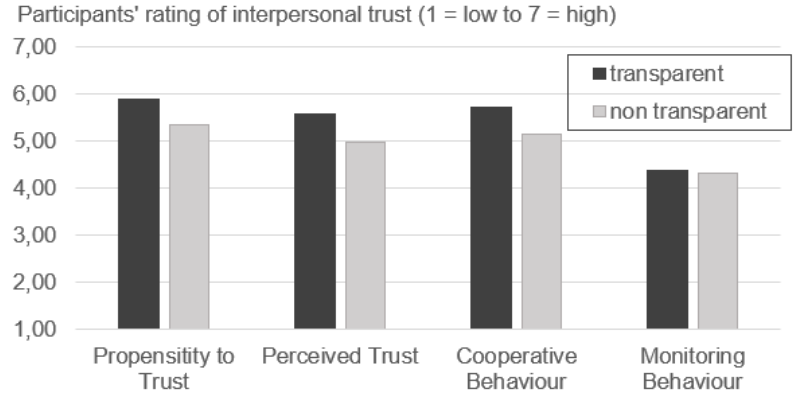

Fig. 3: Ratings (n=137) of Interpersonal Trust Scale (Costa and Anderson, 2011)

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Single pilot operation: Which challenges do pilots envision? Project Next Generation Intelligent Cockpit

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The DLR-Project Next Generation Intelligent Cockpit (NICo) aims to develop an architecture of a future, highly automated cockpit as well as a concept for Single Pilot Operations (SPO). Work package 4.2. is processed by ME-PSY-HH and focuses the human factors of Single Pilot Operations. First study was an online survey amongst pilots on topics like acceptance of Single Pilot Operations, the fit of Evidence Based Training and Single Pilot Operations, practicability of FORDEC in Single Pilot Operations and, feasibility of flight tasks for On-Board Pilots vs Remote Pilots. Study 2 will then be a job requirement analysis for On-Board Pilots and Remote Pilots and study 3 a simulator study attending to trust and behavioral intention towards Single Pilot Operations.
Here we want to present first results from our online survey focusing on the areas pilots identified as to be potentially problematic in implementing Single Pilot Operations. Which challenges do pilots envision?

Introduction

Single Pilot Operation (SPO) does have a mixed reputation (e.g. Stewart & Harris, 2019) - especially amongst pilots. Single Pilot Operations concepts are mostly not through to the end and communication about it is ambiguous. The increase of automation (Tenney, Rogers, & Pew, 1998; Naidoo, Schaap, & Vermeulen, 2014), artificial intelligence (AI) and virtualization changes human-machine-interactions clearly and persistently. In high technology tasks like operating an aircraft, increasing automation already changes the human actions substantially. AI could be the next challenge and the next push.
The first and most important subject to focus on in aviation must be safety. This might be one of the starting points for expected concerns about Single Pilot Operations. For this reason, it is important to systematically investigate the acceptance (e.g. Venkatesh & Bala, 2008) of SPO and the reasons for pilots' attitude towards Single Pilot Operations. One predictor for acceptance and therefore willingness to pilot in Single Pilot Operations is – amongst others - the anticipated threat of flying Single Pilot Operations. The presented study focuses on this aspect. We will present a factor analysis of perceived challenges.

Fig. 1 Example photo of flight simulator at DLR. Picture by A. Scharnweber (DLR)

Setting and Sample

The presented study was embedded in a larger online survey about Single Pilot Operations amongst pilots. Data collection took place from May to September 2021. A total of 136 individuals, all professional airline pilots, could be included in the analysis. The sample includes 64 captains and 72 first officers. Average age was 43.42 years (SD = 10.07). 127 participants identified their gender as male, 6 as female and 3 preferred not to choose a gender. 62% have an Airbus type-rating, 10% Boeing, 14% Embraer, 12% Bombardier and 2% others.

Instruments

For building the questionnaire established literature was consulted and a workshop with pilots was conducted. Twenty challenges for Single Pilot Operations could be identified and were included for further investigation into the online survey. Here answers were demanded on an 8-point Likert-Scale stretching from "1: no problem" to "8: very serious problem".

	1	2	3	4	5
Interaction interfaces	.863				
Taking and returning control of the actors involved	.838				
Distribution of tasks among the actors involved	.747				
Final responsibility	.607			.516	
Communication problems due to loss of non-verbal communication	.559	.388			.341
Interfacedesign in the cockpit	.461				.334
Workload of the SP		.830			
Situational Awareness of the SP		.743		.310	
Lack of redundancy		.605	.352		
Fatigue of the SP		.560	.315	.317	
Crew Ressource Management (CRM)	.436	.560			
Technical implementation of pilot health monitoring			.790		
Survailance through pilot health monitoring			.694		.308
SP incapacitation			.624		
Loss of manual flight skills				.723	
Negligence of the SP through over-reliance on other actors				.692	
Overautomation			.344	.644	
Security of the data link between ground and aircraft					.795
Speed of data connection between ground and aircraft					.793

Fig. 2: Factor analysis; Note: SP = Single Pilot

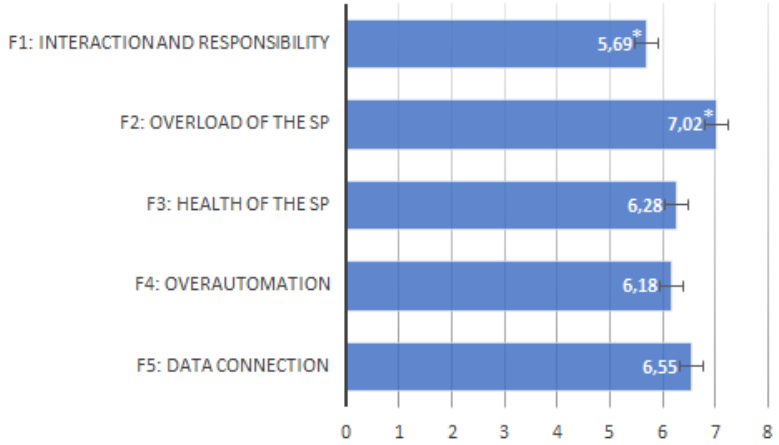

Fig. 3 Identified factors: perceived severity".

Results

A factor analysis on the perceived challenges was conducted. Five factors were extracted (see Fig. 2 + 3), explaining 64% of overall variance. Varimax rotation was applied.

The factors represent five important areas of challenges considering Single Pilot Operations (Fig. 3). The first factor contains challenges concerning interaction, task distribution and communication. The second factor represents the workload – awareness cluster. The third factor incorporates health related variables. The fourth factor represents the concerns about over-automation and therefore the loss of manual flight skills / competencies. The last factor includes data security and data speed.

Then we analyzed if there were significant differences in perceived level of threat between the factors. Cohen´s f = .441 shows strong effects. Factor 1 is perceived significant less severe than all other factors. Factor 2 in contrast is perceived significantly more severe than all other factors. No other factors differ significantly.

Summary

Generally, the skepticism towards Single Pilot Operations is high. The pilots see many unsolved challenges for Single Pilot Operations. We identified five major factors, i.e. areas of challenges. We keep in mind, that safety in aviation is always the major issue for pilots. The biggest challenges are seen in the area overload of the SP, and here especially in workload, fatigue, and CRM. These challenges can be show stoppers for Single Pilot Operation and the pilots' expertise therefore has to be an important part in the research- and development processes towards Single Pilot Operations.

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Passenger VR – Virtual Reality in the aircraft cabin

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Background

Virtual Reality (VR) headsets are becoming more and more widespread in the consumer sector and constantly attract new users. For means of entertainment, VR could be particularly advantageous when users are forced to be in one place and need to pass time, such as during commutes or long airline flights. Lewis (2014) reports that VR applications can distract from physical or auditory stressors on an airplane and thus increase the well-being of its users. Using VR which screens are protected from the view of others, would also have the advantage of increased privacy (Williamson et al. 2019).

While being discussed as an advantage, the greater privacy can on the other hand lead to reduced awareness of what is happening in the surroundings, which presents problems of responsiveness and preparedness in the event of an emergency (McGill and Brewster 2019). Similarly, not being aware of the environment is the main reason why VR was rated less favorably than regular in-flight entertainment (Williamson et al. 2019).

Besides the aforementioned advantages and disadvantages of the technology, the occurrence of cybersickness is always a major concern, especially when introducing VR applications to a large audience from the general population without extensive experience with VR. The airplane, due to its movements in three-dimensional space, is a particularly challenging setting for the use of VR. Unlike with most of VR applications on ground, interaction of displayed (visual) motion information and (possibly conflicting) physical information requires special consideration. For example, when using VR in a car, many passengers develop significant cybersickness (Cho and Kim 2020).

In general, the type of content has a large impact on the provocativeness for cybersickness of a VR application. Content with a high optical flow are more strongly inducing cybersickness than static content (Chang et al.

Fig. 1: Participants experiencing VR in the AVES cabin

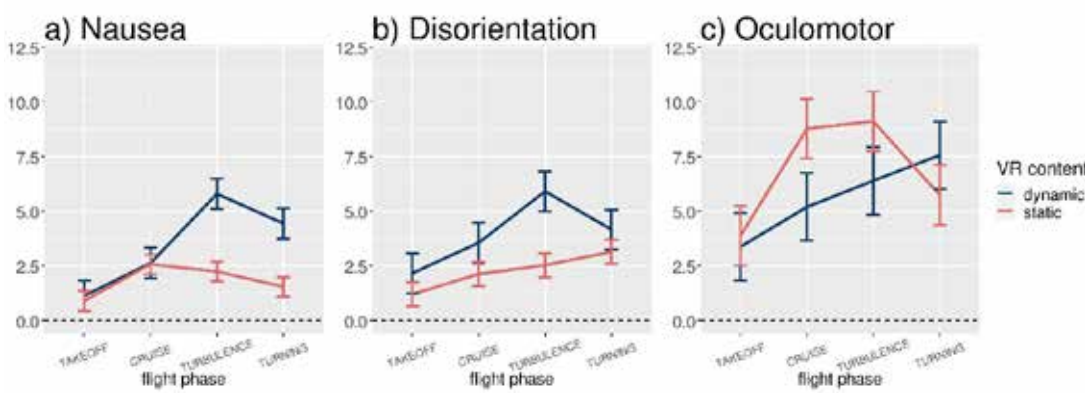

Fig. 2: Levels of cybersickness symptom clusters by VR content and flight phase.

2020). Therefore, it is of special interest to investigate the interaction of different typical aircraft movements and the tolerability of VR content.

Methods

The present study was conducted as part of the DLR project InDiCaD (Innovative Digital Cabin Design) in the Air Vehicle Simulator (AVES) at DLR Braunschweig (Figure 1). We aimed to investigate the applicability of VR in the aircraft cabin and addressed the previously raised aspects of flight phases with different motion profiles (cruise, turning and turbulence) and VR content (static and dynamic). A total of 129 participants were taking part in a simulated flight while experiencing short clips on a VR headset of either dynamic moving or static content.

Results

A linear mixed model for nausea symptoms yielded a significant effect for flight phase in the sense that nausea was significantly higher after Turbulence. Although the interaction of flight phase and VR content did not become significant, increased sickness levels occurred in the dynamic VR content condition under Turbulence and Turning (see Figure 2). Very similar results were observed for symptoms of disorientation. For the third symptom cluster of oculomotor symptoms, none of these effects were observed.

Discussion

Overall, only low to moderate expressions of cybersickness occurred throughout the study. None of the participants had to abort the VR flight or showed severe sickness symptoms. The finding suggests that the use of VR on airplanes is well tolerated with a limited incidence of cybersickness. However, turbulence and flight maneuvers could exacerbate symptoms, particularly after longer immersions. Thus, long-term effects of VR, e.g. in connection with prolonged turbulence, should be investigated in future studies.

In light of our results, the use of VR in the aircraft cabin appears not only feasible, but desired by a broad user community. About two-thirds of the participants in the study said they would use VR in the aircraft cabin.

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European Astronaut Selection 2021/2022: Psychological Evaluation

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Fig. 1: Presentation of the 17 selected candidates of the ESA astronaut class of 2022. Image credit: ESA

Being an astronaut requires a high level of cognitive skills and abilities, teamwork and social competence. At the same time, astronauts in space live in a hostile environment that involves working under stress, long-duration confinement, and physical strain. In addition, space flight is a human endeavor that calls for collaboration in multi-national and intercultural teams (Landon et al., 2017). These extremely specialized and demanding job requirements necessitate a psychological evaluation of astronaut applicants to identify the most suitable candidates (Maschke et al., 2011). For the new astronauts of the European Space Agency (ESA), all of the above qualifications were to be tested in a two-stage process, evaluating the psychological suitability of each candidate.

Similar to the approach in the last European astronaut selection in 2008/2009 (Mittelstädt et al., 2016), the first stage assessed perceptual, cognitive and psychomotor abilities alongside basic skills in English language, physics and mathematics at the DLR Department of Aerospace Psychology in Hamburg. About 1400 candidates from all 25 eligible countries participated in this selection stage. Due to Covid-19 pandemic restrictions, person capacity of the testing facilities was limited to 12-16 participants per day, resulting in 110 separate assessments each lasting the whole day. By inviting candidates with certain physical challenges (e.g. short stature or lower limb impairments), the testing stations had to be adjusted to provide fair conditions for all participants. To ensure fair examination conditions, the German Federal Association of People of Small stature and their Families (BKMF) was consulted in advance and asked for support. Eventually, 410 candidates showed satisfactory performance and were eligible to proceed to the second psychological testing stage.

The second psychological selection stage was

conducted by the DLR Department of Aerospace Psychology in cooperation with ESA and the French Institute de Médecine et de Physiologie Spatiales (MEDES) in Cologne with a special focus on personality, interpersonal behavior and performance under stress. A board comprising DLR, ESA and MEDES representatives and an active or retired ESA astronaut corps member conducted interviews with candidates and observed their behavior during various exercises to provide a final assessment of psychological suitability as an astronaut.

All candidates who were considered highly suitable after both psychological evaluation stages subsequently took part in the medical examinations and further interviews (e.g. with the ESA Director General). In November 2022, 17 selected candidates were finally presented (Figure 1). Of these, five enter the astronaut corps directly as "career astronauts". Eleven will remain in their current positions as "astronaut reserves" and may begin astronaut training in the future. In addition, one person with a physical impairment was selected and included in a feasibility study.

The past ESA astronaut selection was the largest astronaut selection campaign Europe has ever seen and was performed under the challenging conditions of a global pandemic. In addition, for the first time ever, an astronaut with physical impairments was selected.

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Radiation Biology

Radiation Biology

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The Radiation Biology department conducts biophysical and cell biological research to elucidate mechanisms of cell damage and repair following radiation exposure. The goal is to improve individual risk prediction for space missions, in aeronautics, and on Earth. Radiation exposure can initiate and promote carcinogenesis and cause cell death, cellular senescence, and genetic defects, or even acute radiation sickness. Therefore, cosmic radiation remains a major limiting factor for long-term space missions and an important occupational health issue at aviation altitudes.

Our findings are applied to improve radiation protection in aviation and spaceflight. Moreover, we closely collaborate with leading medical partners to translate our findings from space radiobiological research to advance the knowledge of aging-associated diseases and oncologic radiotherapy. Another focus of our department is microbiology which in addition to providing cell models for radiation biology research is applied to elucidate biotic and abiotic factors limiting microbiological life and adaptation to extreme conditions. We apply this knowledge to develop novel approaches to limit the spread of infectious agents, to investigate the human microbiome, and to support the search for extraterrestrial life and habitable environments on other celestial bodies.

Working Groups

Aerospace Microbiology (Prof. Dr. rer. nat. Ralf Möller)

- Radiation response of microorganisms
- Human microbiome research, biofilm formation, antimicrobial materials and decontamination approaches

Astrobiology (Dr. rer. nat. Petra Rettberg)

- Life in extreme environments and microbiome of confined habitats

Biodiagnostics (PD Dr. med. vet. Christine E. Hellweg)

- Molecular mechanisms of space radiation effects in CNS and other target organs, modifiers of radiation response and radiosensitivity

Biophysics (Dr. rer. nat. Thomas Berger)

- Space radiation dosimetry and modeling from ISS to Moon and Mars

Genome Maintenance Mechanisms in Health and Disease (Prof. Dr. rer. nat. Boris Pfander)

- DNA break repair and genome maintenance of eukaryotes
- Methodology development for quantification of DNA breaks and radiation damage

Team

Radiation Protection in Aviation (N. N.)

- Radiation effects in the atmosphere
- Development of products and services for the aviation industry and the society

Germ-Free Flying: Addressing microbial challenges in airplane cabins

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Aircrafts are an important vector in worldwide public health, as civil air travel easily bridges long distances and connects regions that were geographically confined in the past. In this context, the airplane cabin represents a location where infectious diseases can spread, resulting in the need to effectively control potential microorganism transmission inside an aircraft. Especially during flights with a high number of passengers and restricted seating space, frequent passenger contacts with certain touch-surfaces (like e.g. door handles) leads to an accumulation of microorganisms on these so-called „hot-spot" areas, making certain aircraft cabin surfaces main trajectories for microbial transmission between passengers during flights.

Since several studies have reported that microorganisms are capable of not only surviving but being infectious on touch - surfaces for extended periods of time, innovative strategies concerning the development of antimicrobial surfaces or decontamination approaches are needed, to reduce the microbial load and limit surface-related transmission of diseases within the aircraft cabin environment.

Fig. 1: Logo of the Germ-Free Flying project

Germ-Free Flying (GFF; *Keimfreies Fliegen*) is an interdisciplinary project, funded by the DLR aviation program "Wettbewerb der Visionen", connecting microbiologists, material scientists and engineers from three DLR institutes (Figure 1), to develop multi-layered solutions towards a safe microbial presence in airplane cabins (Figure 2).

In GFF, aircraft surfaces are targeted for the integration of novel multi-functional materials with antimicrobial properties (composite materials with antimicrobial agents, as well as self-heating surfaces). These materials will enable simple and self-sustained disinfection of cabin equipment which would significantly reduce the all over infection risk.

The co-developed materials (by FA & WF) act passively and actively against the spread of microbial contamination. Established aircraft surface materials for interior cabins are enhanced with nanoparticles that are known to be effective in preventing microbial growth on surfaces like ZnO (zinc oxide), CuO (copper oxide) and Ag (silver) or chitosan. These nanoparticles are incorporated into or sputtered onto biopolymers (Furolite-C, transfuran chemicals) which were proven to be useful for the preparation of pre-impregnated fiber materials used for interior cabin surfaces (Figure 3).

For validating test surfaces, safe-to-use microorganisms, which are typically associated with airplane cabins, are included in laboratory testing to identify the antimicrobial potential of the novel surface materials. These tests are performed in both in miniaturized laboratory set-ups as well as real-size cabin mock-up scenarios. The antimicrobial potential is determined by measuring changes in the microbial physiology and survival.

The microbial and surface test-data will be integrated and transferred into virtual reality (SL). This will allow us to visualize contamination hot-spots and to track the efficiency of the novel integrated antimicrobial approaches (surfaces and decontamination methods) in

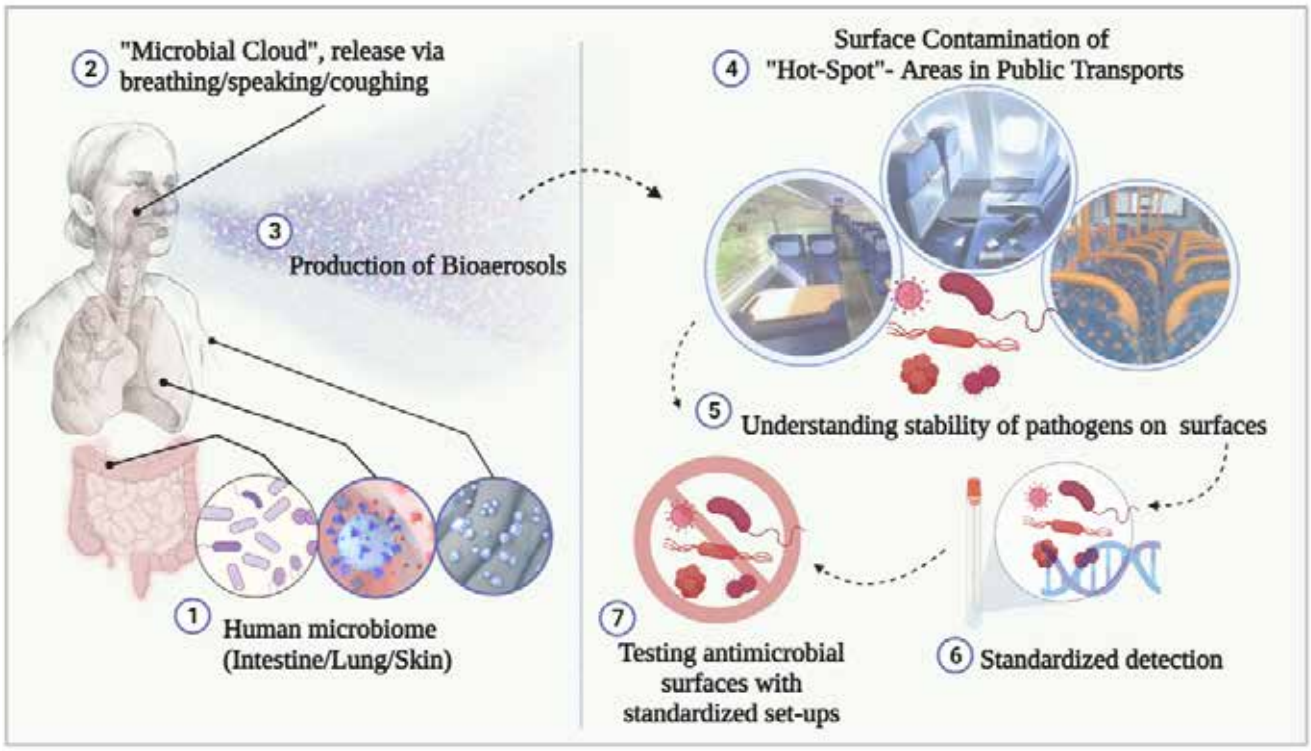

Fig. 2: Scheme of microbial distribution within a built environment illustrating the GFF Use-Cases. (1) Design of synthetic bioaerosol composed of safe human-associated microorganisms. (2) and (3) Mimicking the release of a "microbial cloud" which can be released via different "emitting events". After the release of human-associated microorganisms into the direct environment via droplets, these droplets (4) will reach surfaces in built environments (like trains, buses, or the airplane cabin). After understanding how stable and desiccation-resistant the released microorganisms are on certain touch - surfaces (5), we detect them via DNA-based methods (6) and test potential antimicrobial surfaces in standardized lab-conditions (7). Figure created and partly adapted from Biorender.

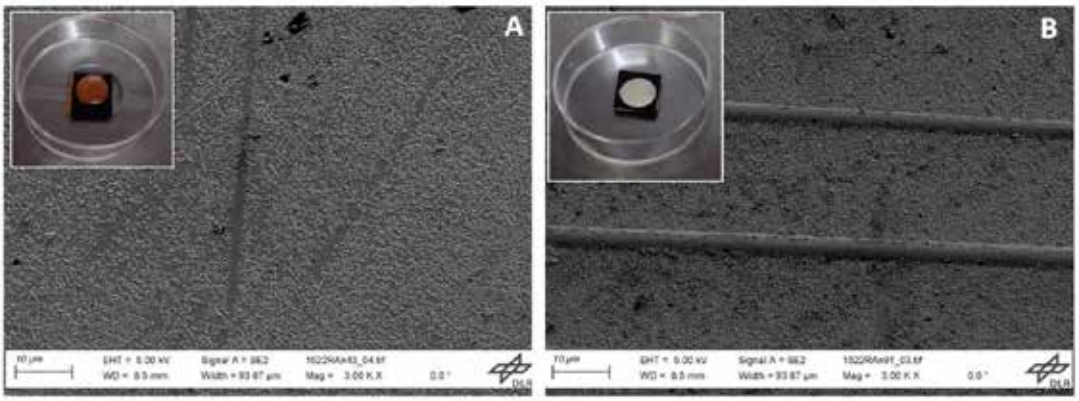

Fig. 3: Macroscopic and surface Scanning Electron Microscope (SEM) pictures of sputtered/coated GFF surfaced with different nanoparticles. A) Copper coated Hexply913 Hexcel Duromer and B) Silver coated Hexply913 Hexcel Duromer. Macroscopic picture shows a microbial testing set-up for "Wet – Contact – Killing" (determination of the efficiency of antimicrobial properties).

reducing microbial load on the airplane cabin. Additionally, different cabin seating concepts, that include the combined application of novel antimicrobial surfaces in key-contamination areas, will be explored as part of the multi-layered solution. Results will provide valuable information on the best combined strategies to reduce microbial load in airplane cabins.

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Elucidating mechanisms underlying the "Space-Brain": Radiation response of murine astrocytes

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Exposure to ionizing radiation as part of space radiation is a major limiting factor for crewed space exploration. Astronauts will encounter different types of space radiation, which may cause cognitive damage including detrimental effects on learning and attention, elevated anxiety and depression. In addition, astronauts are exposed to weightlessness, causing fluid shifts and bone and muscle loss, and affecting cellular processes. Due to its limited regenerative potential, the central nervous system (CNS) is vulnerable towards radiation-induced damage. Astrocytes, the most abundant glial cells of the CNS, have different crucial functions in the CNS, e.g. maintaining normal brain function. Currently, it is not known whether astrocytes can repair space radiation-induced DNA damage and whether DNA repair is altered in microgravity. Heavy ions represent space-relevant high linear energy transfer (LET) radiation and are biologically highly damaging.

Therefore, induction and repair of DNA damage by high-LET iron ions was determined in astrocytes and compared to the effects of low LET X-rays. To unravel possible combined effects of microgravity and radiation, the influence of clinostat-simulated weightlessness on repair of DNA damage by X-irradiation was measured.

Primary murine astrocytes were irradiated with different doses of X-rays and iron (^{56}Fe) ions at the heavy ion accelerator GSI, Darmstadt, Germany. As DNA double strand breaks (DSBs) are the most harmful DNA lesions induced by ionizing radiation, the histone variant H2AX which is phosphorylated at sites of DSBs (γH2AX) resulting in foci formation was used as marker for DNA damage and repair. Immunofluorescence staining of γH2AX was followed by fluorescence microscopy and semi-automated counting of γH2AX foci. Furthermore, DNA DSBs induction and repair were investigated after exposure to X-rays in combination with incubation on a 2D clinostat.

Our results revealed distinct responses of primary murine astrocytes towards the two different radiation qualities, X-rays and ^{56}Fe ions. Induction of radiation-induced DNA DSBs and the respective repair were dose-, LET- and time-dependent (Fig. 1). The number of γH2AX foci reached a maximum at 1 h after X-rays exposure (Fig. 1A) and 4 h after irradiation with ^{56}Fe ions (Fig. 1B). The repair of X-rays-induced DNA double strand breaks (Fig. 1A) was faster compared to those induced by iron ions as indicated by the decreasing number of γH2AX foci over time after the maximum was reached (Fig. 1B). DNA damage induction and repair were not significantly influenced by simulated microgravity (Fig. 2B). Also, the number of spontaneous γH2AX foci in astrocytes was not significantly changed by incubation in a 2D clinostat (Fig. 2A).

Primary murine astrocytes were shown to be fully repair-proficient for DNA DSBs induced by low- and high-LET radiation. The number γH2AX foci built up for a longer time after iron ion exposure compared to X-irradiation, and their repair was delayed. Both are usually seen as an indication of complex, difficult to repair DNA damage by heavy ions. These results suggest that astrocytes could be able to continue their supportive function for neurons in case of a heavy ion hit, as damages can be repaired within a short time period. The DNA damage response does not only encompass sensing and repair of DNA damage, but also cell cycle arrests, gene expression changes or even cell death. Therefore, further studies to understand the radiation response of astrocytes and its effects on neighboring microglia, neurons and oligodendrocytes are required.

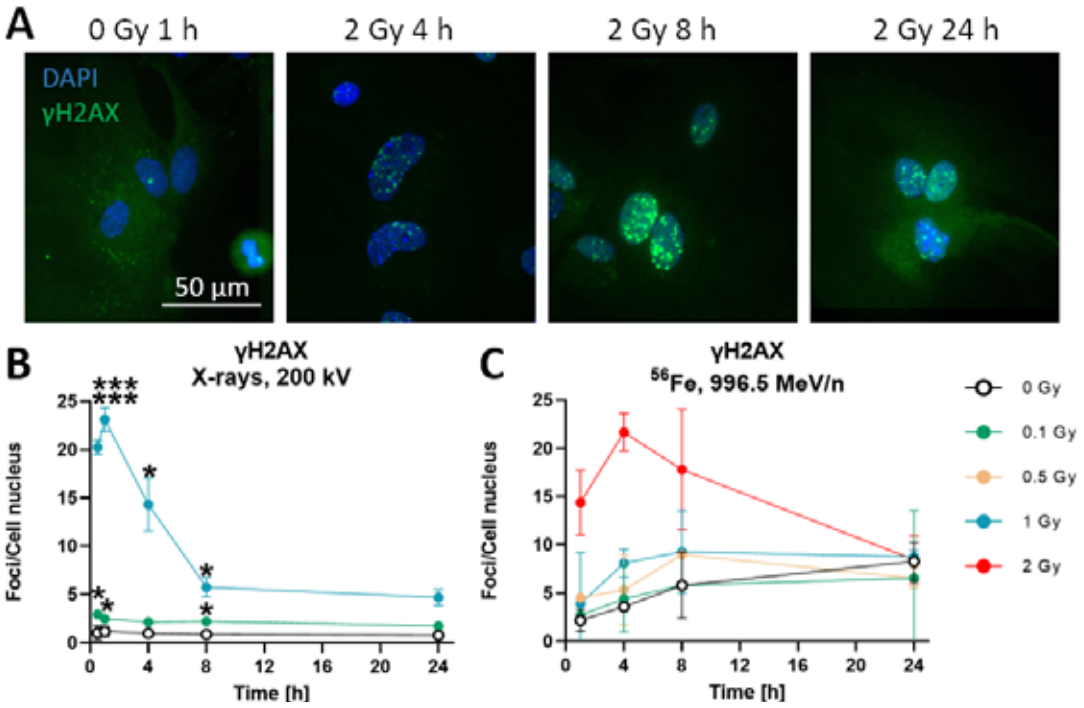

*Fig. 1: Astrocytes encounter DNA damage and are fully repair-proficient (A) γH2AX (green) immunostaining of unirradiated and irradiated (2 Gy of ^{56}Fe ions) astrocytes at different time points (exemplary images). The nucleus was stained with DAPI (blue), bar: 50 µm. (B) The DNA damage induction and response, quantified by the number of γH2AX foci per cell nucleus after exposure to 0.1 Gy and 1 Gy of X-rays (200 kV, 15 mA) for up to 72 h. The samples were compared via 2way ANOVA (Tukey's multiple comparisons test), based on a sample size n=3 ($p<0.05$); *, $p < 0.05$, ***; $p < 0.001$, Astrocytes showed a dose- and time-dependent DNA damage induction and repair. (C) The number of γH2AX foci per cell after irradiation with different doses of ^{56}Fe ions (LET 151 keV/µm, 996.5 MeV/n) revealing a dose-dependent DNA DSB induction (n=2).*

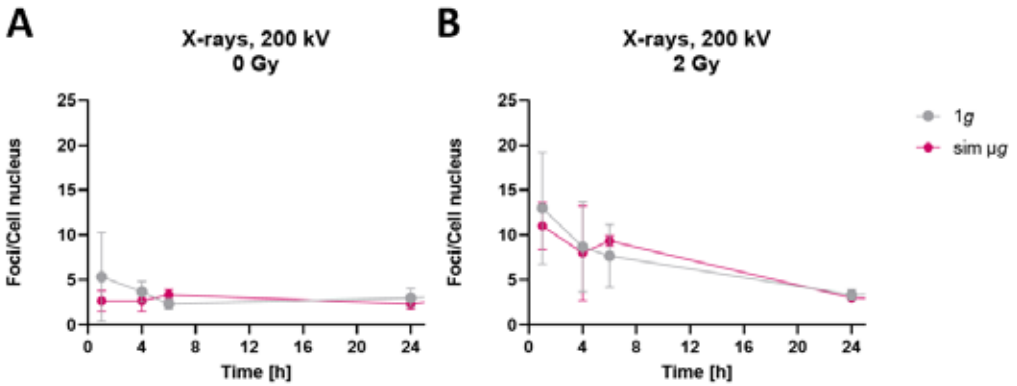

Fig. 2: Simulated microgravity did not influence DNA damage induction by X-irradiation and repair of the DNA double strand breaks (A) The number of γH2AX foci per cell of unirradiated astrocytes exposed to either simulated microgravity (µg) by clinorotation or an untreated 1g control. No significant differences between the 1g control cells and cells exposed to µg were observed. Samples were compared via 2way-ANOVA (n=3). (B) Number of γH2AX foci per cell for astrocytes irradiated with 2 Gy of X-rays and exposed to simulated microgravity by clinorotation or 1g as a control. No significant differences between cells exposed to µg or 1g were found.

Acknowledgments

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DLR GANDALF graduation school: Tackling pandemic threats in public transportation

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Public transportation connects cities and countries. As such, public transportation also acts as a medium for the spread of diseases, as seen vividly during the COVID-19 pandemic. Humans can act as carriers of pathogenic microorganisms such as viruses or bacteria, posing high infection risk in a closed environment. Interdisciplinary research is required to develop innovative solutions to prevent or slow down the next pandemic. GANDALF is a collaborative effort between six DLR institutes to implement practices and technologies in public transportation, making it epidemiologically safer (Figure 1).

Through the collaboration of researchers with engineering, modeling, transportation, and medical expertise, GANDALF will inform about the role of the public transportation in the current pandemics and introduce technologies that aim to reduce the spread of future pandemics. Various experiments and models are performed in the public transportation context (Figure 2).

Within the GANDALF project, a standardized microbial community, representing the most abundant microorganisms of sub- and airway transportation, will be used as a reference and standard for testing microbial stability in the environment. This microbial community, along with multidrug-resistant (clinical) bacteria and variety of different viruses, will be exposed to decontamination approaches such as innovative antimicrobial surfaces or use a surrogate in bio-aerosol research (Figure 3). All microbial species will be applied to different (rapid versus sensitive) detection approaches based on molecular biology and bioinformatics methods such as cultivation, quantitative real-time polymerase chain reaction (qPCR), and metagenomics. Testing and improving of the detection of the microorganisms will contribute to improve microbial monitoring, which depicts an important part in the goal of GANDALF, to counteract future pandemic threats.

To tackle aerosol spread, mathematical modeling is used for infection risk assessment in closed environments. Calculation is based on the aerosol particle distribution. Exhalation, fluid dynamics, and inhalation of virions are combined to calculate the deterministic infection risk of airborne diseases. To adequately evaluate the risk of exposure to infectious aerosols, an ultra-sensitive, spectroscopy-based sensory system is developed, capable of detecting virus-carrying aerosols from

Fig. 1: GANDALF logo (left) and the team of PhD researchers with their supervisors (right). The researchers from six DLR institutes work together to fight the spread of pathogenic organisms in public transport.

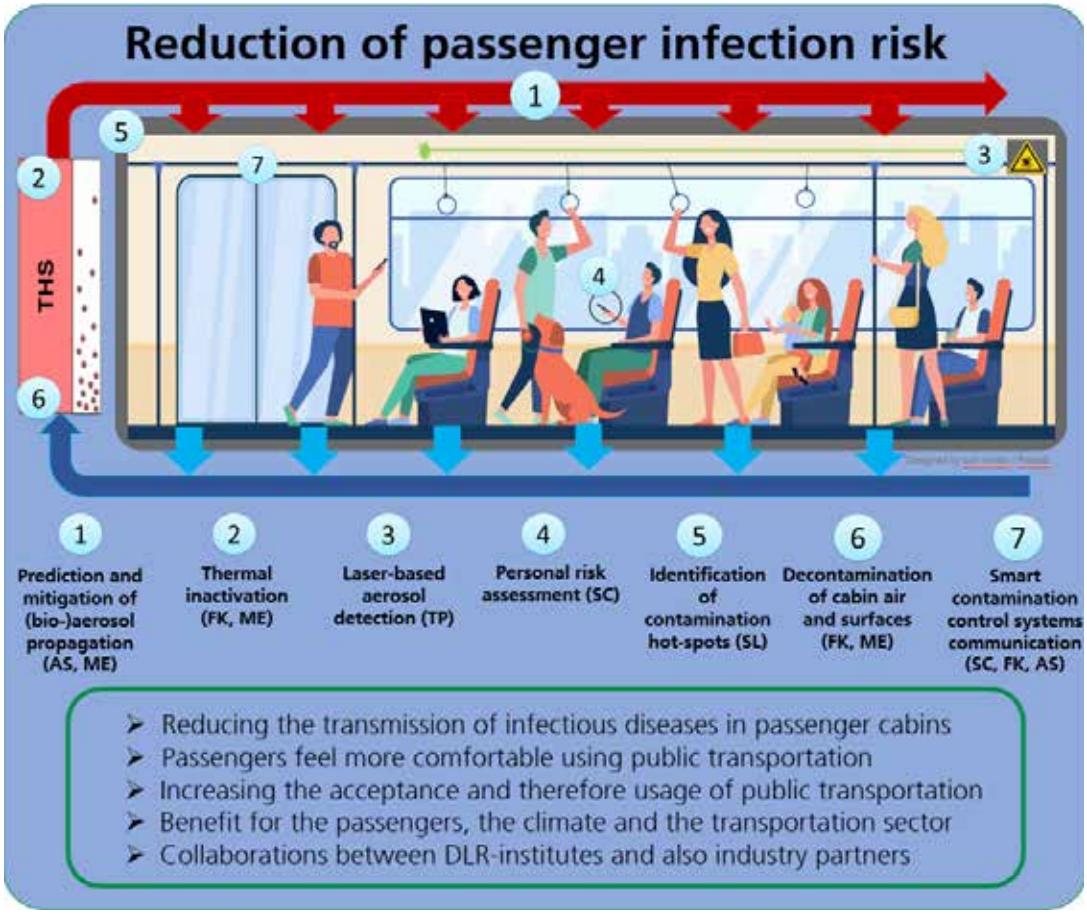

Fig. 2: Overview of joint research interest and experiments topics within GANDALF.

the air. In accordance with modeling, new ventilation concepts are tested in closed environments for microbial removal. One of these concepts, that is already commonly used, is the "air curtain". The behavior of aerosol particles will be studied inside the air curtain separating confined spaces. In order to do so, sensor-based airborne particle measurements are combined with optical volumetric velocity measurements in the air curtain.

For reducing airborne infectious pathogens in passenger cabins, heat inactivation is evaluated. A heating system for passenger cabin is developed, tested and compared to other solutions for improving indoor air hygiene. A thermal storage is the system's heat source, whereby the range of electric vehicles in winter can be increased.

To assess the personal infection risk in the public transport, data sources such as contact tracking data, social media, local incidents, and underlying medical conditions are combined. Using machine learning, network analysis, natural language processing and privacy protection, an informative personal infection risk will be estimated without violating privacy.

The GANDALF project is a joint interdisciplinary effort of PhD students of DLR institutes to fight the pandemic spread in public transportation. The students from the project meet twice to three-times a year in person at different DLR premises and regularly online to foster collaborations and teamwork. In GANDALF, knowledge exchange between students and supervisors of different fields enables interdisciplinary research to address and counteract current and future pandemic threats and results in education of a new generation of researchers in this field.

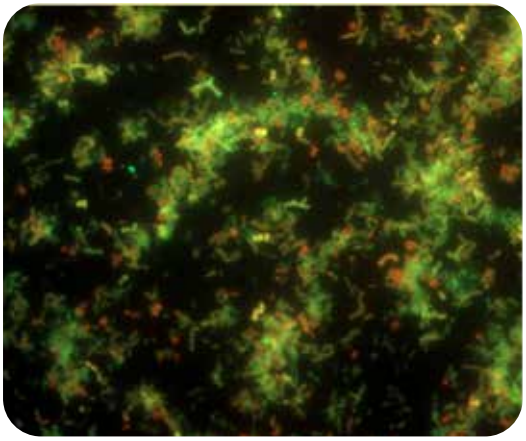

Fig. 3: Fluorescently labeled bacteria after exposure on a brass surface (a technical usable antimicrobial surface material for public transportation; red: damaged bacteria; green: intact bacteria).

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MARE – Matroshka AstroRad Radiation Experiment: Astronauts' radiation exposure during Moon missions

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The winter of 2022 saw the launch of the NASA Artemis 1 mission with the Orion spacecraft flying to the Moon and back as the first stepping stone for the NASA Artemis program (https://www.nasa.gov/specials/artemis/). Artemis 1 will be followed in the upcoming years with the first crewed missions aiming to send humans back to the lunar surface over 50 years after the Apollo mission. One of the main obstacles to overcome for long duration deep space human exploration missions is the increased radiation load humans will encounter and thereby the relevant possible increase of cancer risk.

To tackle the question of how much radiation humans will encounter in free space – as for their journey to the Moon and back – DLR together with NASA, Lockheed Martin (LM), Isreal Space Agency (ISA), and StemRad is flying the MARE (https://www.dlr.de/mare_en/) hardware as one of the secondary payloads inside Orion. MARE consist of two female phantoms named Helga (the German phantom) and Zohar (the Israeli phantom) which were mounted on their respective crew seats as passengers in Orion. Both phantoms are manufactured out of epoxy resins with various densities to simulate relevant organs of the female body. Zohar is in addition equipped with a radiation protection vest (the AstroRad vest) developed by StemRad and funded by ISA.

With this configuration both phantoms were exposed to the space radiation environment, but Zohar was in addition protected by the AstroRad vest. For MARE the project team at DLR was responsible to develop, built and test the phantoms with their DLR built crew seats. The crew seats enabled Helga and Zohar a safe travel inside Orion and kept them fixed to the relevant mounting platforms as provided by NASA. Figure 1 shows as example Zohar mounted on a vibration table at DLR, Bremen to test the setup for the relevant vibration loads as Zohar and her seat encountered during the launch of the NASA Space Launch System (SLS).

Fig. 1: Zohar during the final vibration tests at DLR, Bremen

In addition to the structural elements needed for a safe flight of Helga and Zohar, DLR was also integrating thousands of small radiation detectors (so called thermoluminescence detectors (TLDs)) in relevant cut-outs as provided by the layers of the phantoms. With these detectors positioned at over 1440 positions in each phantom was it possible to measure the radiation load throughout the phantoms, thereby providing data to generate a three-dimensional dose distribution for the radiation received during the flight. This data gives the baseline to calculate the organ doses for each of the phantoms. In addition to the passive radiation detectors Helga and Zohar were also equipped with active (battery powered) systems. DLR and NASA together provided 34 active radiation detectors, the DLR M-42 and the NASA CAD systems. Figure 2 shows exemplarily the integration of one of the NASA CAD detectors in the so called "poncho" of Helga as performed during final hardware integration at NASA, KSC in August 2022. The data from the active radiation detectors, positioned inside the phantoms at radiation sensitive organs, but also beneath and above the AstroRad vest show the relevant radiation dose received in a time resolution manner, since data from the active detectors (as for example the DLR M-42) were stored every 300 seconds, thereby showing in detail the dose profile over the mission.

The NASA Artemis I mission launched on November 16th 2022 and Orion and with Orion Helga and Zohar returned safely back to Earth on December 11th 2022 – after the flight to the Moon and back. The DLR crew travelled to NASA, KSC in January 2023 to retrieve the hardware and as a first step already successfully read out the dose values as measured with the sixteen DLR M-42 radiation detectors. The full readout and evaluation of the passive radiation detectors will follow upon the return of Helga and Zohar to DLR.

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Fig. 2: Integration of the NASA CAD radiation detector in Helga

Fig. 3: Mounting of Zohar and Helga in the Orion spacecraft

Microbes from extreme anoxic sites on Earth for the assessment of Mars' habitability

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In preparation of the upcoming return of original samples from Mars, studies of analog environments on Earth are of high importance. These analog environments should resemble Mars in as many conditions as possible. One main criterion is the absence of oxygen since the Martian atmosphere contains only 0.15 vol% O_2. Within the EU-funded project MASE (Mars analogues for Space Exploration; grand agreement n° 607297), six Mars analog environments in Europe were investigated with respect to their microbial diversity. Samples were taken from these sites and new isolates were obtained via cultivation experiments and characterized with respect to their tolerance to Mars-relevant stress factors (low water activity, monochromatic / polychromatic / ionizing radiation, perchlorates, low nutrient availability, elevated salinity). These stress tests were done as single stress tests as well as in combination to get an overview of the ability of organisms to survive Martian relevant stress conditions [1].

After successful sampling campaigns at Lake Graenavatn (Iceland) (Fig. 1), at Sippenauer Moor (Germany), at Boulby Mine (United Kingdom), at a glacier (Austria) and processing the samples provided from Rio Tinto (Spain), and from permafrost samples (Iceland) over 300 enrichments and 31 pure cultures could be obtained (Fig. 2 from [1]). In particular, a number of highly valuable model organisms has been retrieved, which directly feeds into the other goals of the MASE project, namely studying the limits of growth of selected isolates, deciphering the molecular principles of resistances [2, 3, 4], analyzing the genomic and metabolomic inventory of representative microbes [5, 6], studying the fossilization processes and detectability of biomarkers during artificial fossilization [7] and the optimization of automated life detection [1, 8].

The microbiome data from the Mars analog environments were collected and analyzed by our colleagues from the Medical University of Graz [9]. This study has contributed novel insights into the microbiology of analogue sites. The information retrieved from microbiome analyses on the intact microbial communities thriving in the MASE sites, together with the 31 isolated microorganisms and the successful binning of 15 high-quality genomes allowed us to observe principle pathways, which pinpoint specific microbial functions in the MASE sites compared to moderate environments.

The microorganisms were characterized by an impressive machinery to withstand physical and chemical pressures. All levels of our analyses revealed the strong and omnipresent dependency of the microbial communities on complex organic matter. Moreover, we identified an extremotolerant cosmopolitan group of 34 poly-extremophiles thriving in all sites (Fig. 3).

However, numerous tasks remain to be accomplished in future. These include (i) a comprehensive re-evaluation of the potential impact of the terrestrial organic load on the biology of analogue environments for space research, (ii) the extension of the dataset with additional microbiome data from other extreme environments, (iii) testing of the hy-

Fig. 1: Lake Graenavatn in Iceland where several new model organisms have been isolated from (e.g. Yersinia intermedia MASE-LG-1*). Image Credit: University of Leiden*

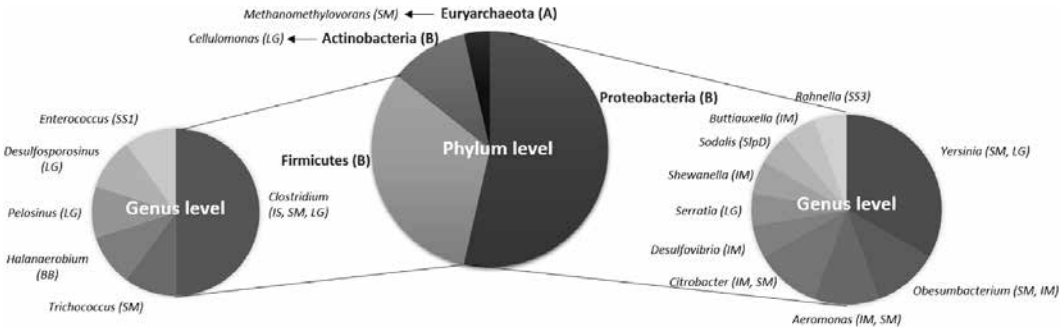

Fig. 2: Summary of isolates obtained from enrichment cultures (from [1])

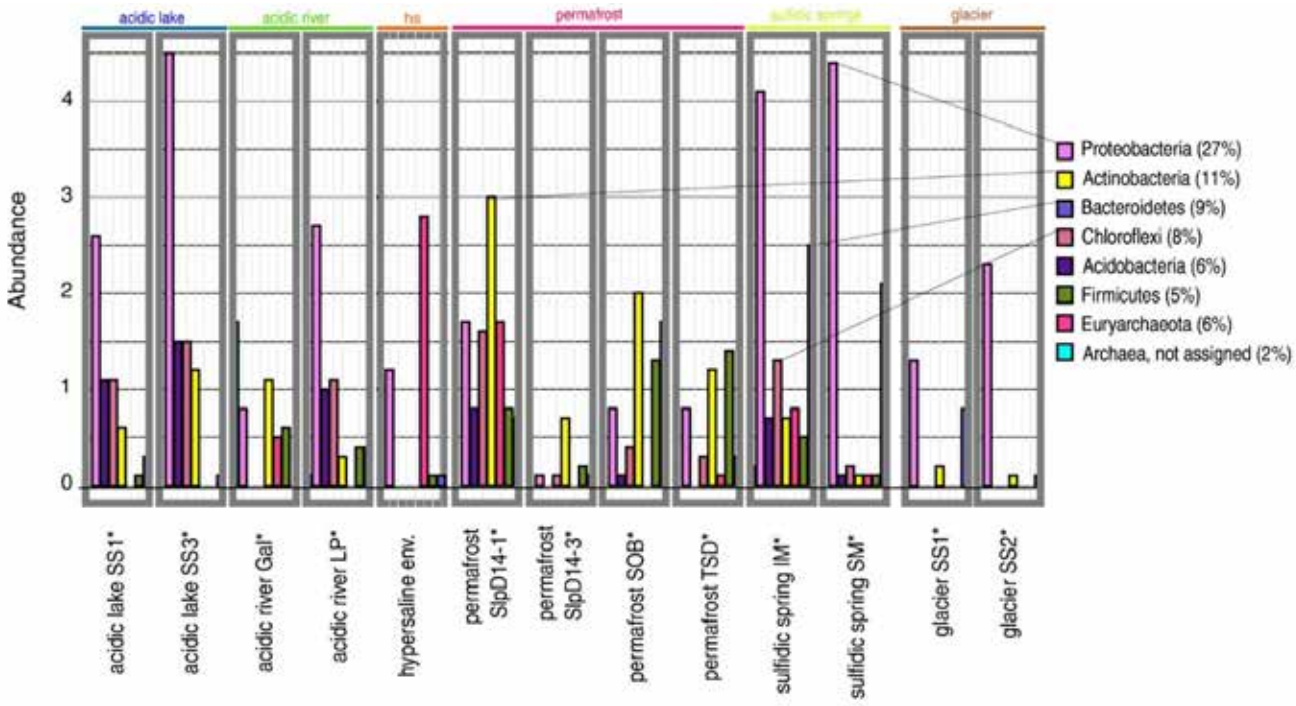

Fig. 3: Archaeal and bacterial profiles of intact microbial communities from MASE environments. Panel displays the most abundant phyla of the microbial community. The relative abundance of each taxon is shown on the y-axis. The total relative abundance, summed up for all samples, is given in brackets behind the taxa names in the legends. For unclassified ribosomal sequence variants (RSV) the highest assigned taxonomic level is given. For instance, "Archaea, not assigned" reflects all RSVs which were classified on Archaea level, but could not be assigned to other taxonomic levels (from [9]).

pothesis that a core microbiome in extreme anoxic environment exists, (iv) further identification of so-far unknown microbial taxa found in our molecular survey (v) and the improvement of (targeted) cultivation strategies to increase the available culture collection of microorganisms thriving in extreme, astrobiology-relevant terrestrial sites. It is obvious that an investigation based on high throughput ~omics-technologies in combination with cultivation-based studies is essential. Only together can an all-encompassing picture of the environment be obtained.

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Gravitational Biology

Gravitational Biology

PD Dr. rer. nat. Ruth Hemmersbach (Head)

Dr. rer. nat. Christian Liemersdorf (Deputy)

Life evolved in terrestrial gravity, which is the only environmental factor that has remained constant for billions of years. The lack of gravity during space travel poses health challenges to astronauts while providing unique insight in the fundamental mechanisms of gravity- and mechano-sensing. Indeed, biological systems perceive gravity directly and indirectly through mechanosensitive structures and pathways. The main scope of the Gravitational Biology Department is to better understand the impact of gravity on biological systems. Moreover, we assess implications of altered gravity on technology development.

Our goal is to elucidate molecular mechanisms of gravity perception and resulting biological responses ranging from single cells to human beings. We apply the acquired mechanistic knowledge to develop and refine countermeasures for space travel. Moreover, we translate findings on cellular mechano-sensing to terrestrial medicine in collaboration with medical departments in the Institute and elsewhere.

Another main focus is to improve closed biological life-support systems, which are a prerequisite for long-term human space missions. With our innovative DLR C.R.O.P.® (Combined Regenerative Organic food Production) technology we aim at optimizing waste recycling for food production. The technology is applicable for stations on Moon and Mars, but also for sustainable agricultural systems on Earth. Our Gravitational Biology research builds the basis for long-term human space exploration, guides human health research, and contributes to sustainable economic development on Earth.

Working Groups

Bioregeneration (Dr. rer. nat. Jens Hauslage)

- Analysis of biogenic waste degradation by microbial trickle filters, optimization of the filters to generate maximal efficiency in producing plant nutrients
- Conversion of the laboratory set-up to applications in space and on Earth with the goal to reclaim water while generating fertilizers for space travel and terrestrial agriculture (urine, slurry)

Cellular and Molecular Neuromuscular Research (Prof. Dr. med. Christoph Clemen)

- Biochemistry, genetically modified cells and organisms, cellular and animal studies
- Identification of gravity-sensitive responses of individual cell types that model various behavioral and physiological deconditioning phenotypes in humans with the focus on neurons, astroglia and skeletal muscle cells
- Verification of ground-based studies under hypergravity/simulated microgravity conditions in real microgravity using various platforms including DLR Mapheus sounding rockets, drop-tower, parabolic aircraft flights, and the Biolab-device on the ISS

On-line electrophysiological recording of neuronal network activity under microgravity within the drop tower

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During spaceflight, humans are subjected to various environmental factors that differ markedly from terrestrial conditions. In particular, microgravity poses a major challenge to the human body eliciting complex neural adjustments that may affect human psychology and physiology in astronauts returning from space missions. However, most studies exposing neural and non-neuronal components of the nervous system to altered gravity conditions focused on structure and function of individual cells. For example, electrophysiological experiments in single cells using patch-clamp techniques (Meissner & Hanke, 2005) demonstrated the gravity- dependence of the action potentials (APs) propagation velocity. This observation has led to the hypothesis that altered gravity exposure may directly impact spontaneous neuronal activity patterns and trigger more intricate responses in neuronal networks. However, the complex interplay

Fig. 1: MEA system workflow. TiN = titanium nitride, iNGN = inducible neurogenin cell line (Busskamp et al., 2014)

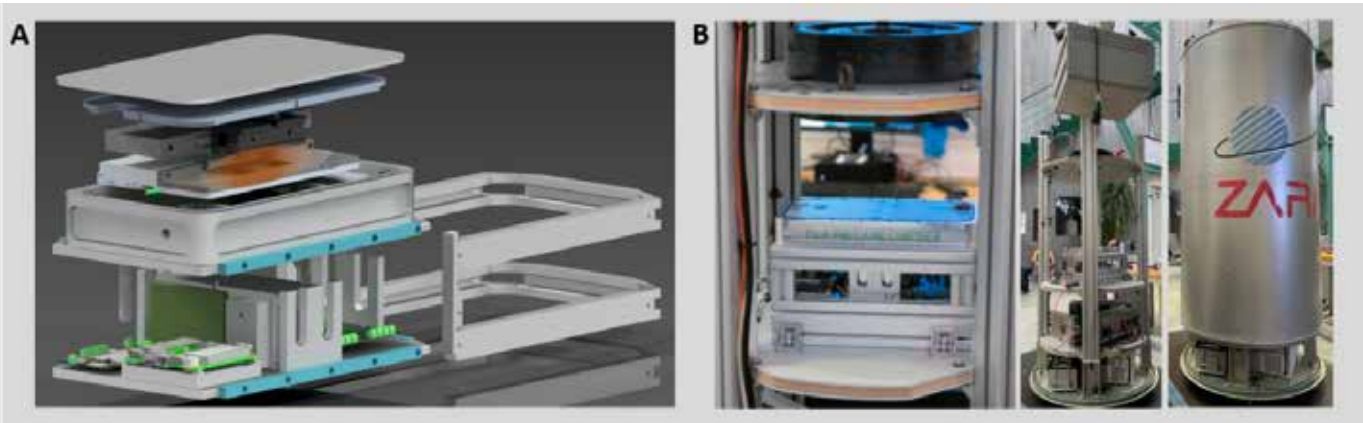

Fig. 2: MEA system integration into the Drop Tower capsule platform. (A) MEA module: MEA system enclosed in pressure chamber (upper part) and environmental control and data storage unit (lower part). (B) MEA module mounted on the Drop Tower capsule platform (Bachelor Thesis: M. Sturm).

within neuronal networks or between neurons and other cell types has not been captured explicitly so far.

By employing the Microelectrode array (MEA) technology, we advance the electrophysiological approach from a single-cell to a complex network level. To do so, neuronal cells are grown on a grid of 8 x 8 or 6 x 10 microelectrodes, which are inserted into a heated MEA headstage. When excited, neurons create an electric potential between the inner and the outer side of the cell membrane, which is translated into an electric current by the detecting electrodes. The signal is then transferred to the MEA headstage, where data is recorded and can be further processed for data analysis.

In contrast to patch-clamp assays, MEA technology allows for non-invasive measurement and can be used for assessment of functional connectivity of multiple neuronal cells. The system was adapted for the implementation on different gravity research platforms, allowing for on-line activity data recording throughout the entire experiment. The hardware containing iNGN neuronal cultures was integrated into the ZARM Drop Tower platform (Bremen, Germany), exposing the entire system to 4.7 sec. of high-quality microgravity (≤10-5 g). With this setup we were able to evaluate the functional activity patterns of iPSC-derived neuronal networks subjected to microgravity, while keeping them under controlled and stable temperature and pressure conditions.

Neuronal activity data was registered constantly and the action potential frequency in each experiment phase was calculated for the single electrodes. Data revealed that during the microgravity phase the mean action potential frequency across the neuronal networks was significantly elevated and further increased during the impact phase, during which cells temporarily experience 30g. The electrical activity re-adapted back to baseline level within 10 minutes of post-drop recordings.

Our data shows that real-time, electro-physiological recording of neuronal network activity based on MEA technology is possible under altered gravity conditions as applied in the Drop Tower. Gravity-induced differences in activity can be detected already within 4.4 sec. of microgravity.

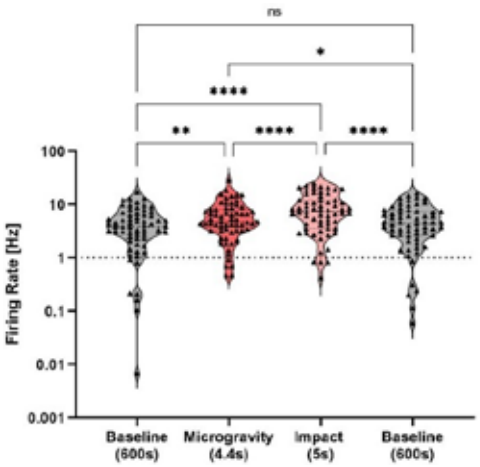

Fig. 3: Comparison of log-distributed firing rate data of neuronal cells during pre-drop baseline, microgravity phase, impact phase (0.2s + 4.8s adaptation allowance) and post-drop baseline. Average of 63 units of five MEAs (5 drops) from three independent preparations.

Fig. 4: The project MIND Gravity (MEA Investigation of Neuroactivity Dynamics under Altered Gravity) was supported by the ESA education program "Drop Your Thesis", From left to right: Laura Kalinski (DLR), Maximilian Sturm (DLR), Johannes Striebel (University of Bonn), Nils Drouvé (University of Applied Sciences Cologne), Yannick Lichterfeld (DLR).

The MEA set-up will now be used under increased microgravity time in the range of 5-6 min. during the DLR rocket mission MAPHEUS 12, to study activity and adaptation of neuronal networks.

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Desmin knock-out cardiomyopathy: a heart on the verge of metabolic crisis

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Changes in skeletal muscle structure and function are an important challenge to performance and health in astronauts on longterm missions and in patients with muscle disorders. Studies in genetically defined diseases provide mechanistic inside and may guide countermeasure development for aerospace medicine. Desmin gene mutations cause a broad spectrum of familial and sporadic cardiomyopathies [1]. In addition to perturbing the contractile apparatus, both the lack of desmin and the presence of mutated desmin negatively impact mitochondria number, structure, and function [2,3]. In addition, impaired myocardial metabolism secondary to mitochondrial dysfunction can conceivably exacerbate cardiac dysfunction [4]. In order to address the metabolic status of left ventricular cardiac tissue, we performed high-fidelity metabolic myocardial phenotyping in desmin knock-out mice, which are a well-established disease model for rare human autosomal-recessively inherited desminopathies with a complete lack of desmin protein in striated muscle tissue [5].

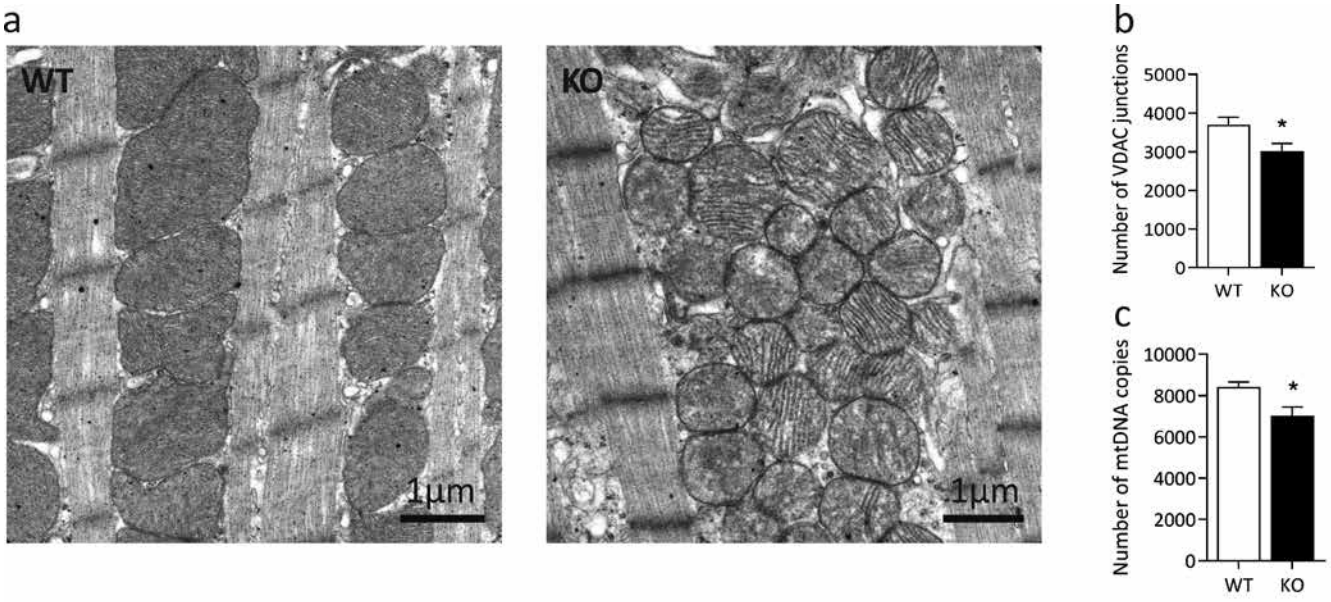

Fig. 1: (a) Electron microscopy revealed focal clustering of mitochondria in conjunction with marked coarsening of the mitochondrial cristae in desmin knock-out cardiac tissue (KO). (b) Quantitation of VDAC1-positive mitochondrial contact sites revealed a significant rarefication of the mitochondrial network in the desmin knock-out genotype. (c) mtDNA copy number quantitation confirmed a significant decrease of the mitochondrial content in cardiac tissue of desmin knock-out mice.

We analyzed left ventricular cardiac muscle tissue in six-month-old homozygous desmin knock-out mice and wild-type siblings. Employing morphological, clinical chemistry, biochemical, genetic, and proteomic techniques, we addressed features of energy-providing substrate metabolism. In detail, we performed standard histological, immunofluorescence (Desmin, Vdac1, Glut1, Glut4, Hk1, Hk2, Ckm, Ckb), and ultrastructural analyses, various enzyme activity measurements (Mdh, Cs, Hk, Pfk), high-resolution respirometry, immunoblotting (CD36, Glut1, Glut4, Hk1, Hk2, Mtck, Ckm, Ckb), mtDNA copy number and deletion quantitation, and proteomics in left ventricular cardiac tissue as well as mass spectrometric analysis of acylcarnitine and amino acid levels in blood.

Desmin deficient left ventricular cardiac tissue showed significantly decreased mitochondrial number in conjunction with ultrastructural mitochondrial defects (Fig. 1A). Mitochondria-related metabolic pathways including fatty acid transport, activation, catabolism, and respiration rate were significantly impaired accompanied by increased levels of circulating short, medium, and long-chain acylcarnitines and branched-chain amino acid concentrations. In contrast, insulin-independent glucose transporter 1 and hexokinase-1 expression as well as hexokinase enzyme activity were significantly increased. While mitochondrial creatine kinase expression was markedly reduced, fetal creatine kinase B expression was increased. Quantitative proteomic analysis of left ventricular cardiac tissue revealed significantly reduced expression of proteins involved in mitochondrial electron transport mainly of complexes I and II, oxidative phosphorylation, citrate cycle, beta-oxidation including auxiliary pathways, amino acid catabolism, and redox reactions and oxidative stress.

Our findings highlight the importance of desmin in linking cardiac contractile function and metabolism. Desmin deficiency is associated with a secondary cardiac mitochondriopathy with severely impaired oxidative phosphorylation and fatty and amino acid metabolism. Increased glucose utilization and fetal creatine kinase upregulation likely portray compensatory attempts to maintain myocardial energy supply. It may be prudent to avoid medications that worsen mitochondrial function, and metabolic stressors like intensive physical exercise as this may worsen cardiac function. Therapeutic interventions for primary mitochondriopathies might also improve the secondary mitochondrial disfunction and general metabolic condition in desmin deficient hearts.

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On the skeletal muscle pathology of R405W desmin knock-in mice

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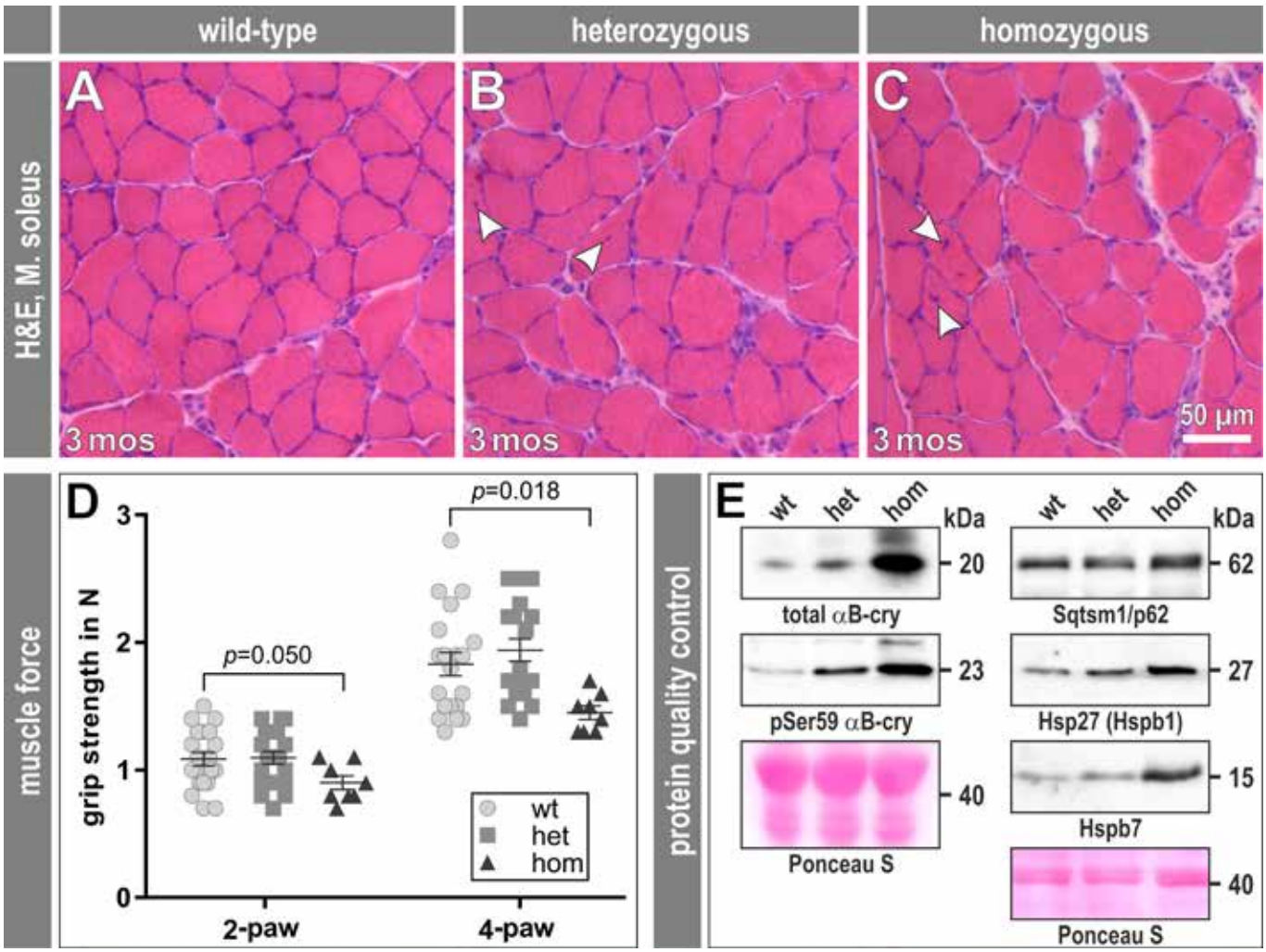
Mutations in the desmin gene cause a broad spectrum of familial and sporadic myopathies and cardiomyopathies [1]. To unravel the pathophysiology of the human heterozygous R406W desmin gene missense mutation, which causes a severe cardiac disease manifestation [2], we generated orthologous R405W desmin knock-in mice. Unexpectedly, homozygous mice die at three months of age due to a smooth muscle-related gastrointestinal pseudo-obstruction [3]. In our previous work, we demonstrated that R405W desmin exerts its cardiotoxic potential by an uncoupling of desmin filaments from intercalated discs and induction of their structural disorganization [3].

We analysed cohorts of three-month-old heterozygous and homozygous R405W desmin knock-in mice and wild-type siblings. In addition to in vivo muscle force measurements, we characterized soleus muscles employing morphological, biochemical, and proteomic techniques. In detail, we performed grip strength measurements, H&E stains, desmin immuno-fluorescence, immunoblotting (αB-crystallin, p62, Hsp27, Hspb7), ultrastructural analysis, and proteomics. Here, we report on the first results of our multi-level analysis of the skeletal muscle pathology in this R405W desminopathy knock-in mouse model.

While examination of H&E-stained cryosections of soleus and gastrocnemius muscles only showed minor myopathological alterations in the hetero- and homozygous genotypes (Fig. 1A-C), 2- and 4-paw grip strength was reduced in homozygous mice (Fig. 1D). Desmin immunofluorescence analysis showed the presence of small, dot-like desmin-positive protein aggregates in heterozygous and more pronounced in homozygous tissue. Ultrastructural analysis revealed signs of myofibrillar degeneration, sarcomeric micro- and macrolesions as well as several mitochondrial abnormalities regarding focal accumulation, morphology, and cristae structure in both hetero- and homozygous muscles. Immunoblotting showed markedly increased levels of total and phospho-serine αB-crystallin, Hsp27, and HspB7, and a moderate increase of Sqtsm1/p62 (Fig. 1E). Moreover, our study was complemented by a proteotypic peptide-based quantitative proteomic analysis of soleus muscle tissue from hetero- and homozygous R405W desmin knock-in mice and wild-type littermates; this data is currently being analyzed.

Though the clinical presentation of the human R406W desminopathy is often dominated by the severe cardiac disease manifestations, our work highlights the noxious effects of the R405W mutated desmin on skeletal muscle tissue, where it invokes desmin protein aggregation in conjunction with degenerative changes of the myofibrillar apparatus and mitochondria. In analogy to other desmin mutations, R405W desmin induces a broad disbalance in protein homeostasis. Thus, in addition to our previously established R349P desminopathy mouse model [4], the R405W desmin knock-in mouse line [3] is also a valuable model truly mimicking human desminopathies.



(A-C) Haematoxylin & Eosin-stained cryo-sections of soleus muscle revealed minor myopathological alterations comprising internalized nuclei, muscle fiber rounding, and increased endomysial tissue. **(D)** 2- and 4-paw grip strength was reduced in homozygous mice. **(E)** Immunoblotting showed increased levels of total and phospho-serine59 αB-crystallin, Hsp27, and Hspb7, and slightly increased Sqtsm1/p62.

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On the nuclear pathology of recessive desminopathies

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Mutations of the desmin gene cause a spectrum of autosomal-dominant and recessive myopathies and cardiomyopathies [1]. The very rare autosomal-recessive forms consist of three subgroups, one with complete lack of desmin, a second with sole expression of mutant desmin and protein aggregate formation, and a third with presence of mutant desmin but no aggregate formation [2]. In general, the recessive desminopathies have an earlier disease onset and a different and more severe disease phenotype than the more prevalent dominant forms [1]. A recent study reported that knock-down of desmin in isolated cardiomyocytes led to shrinkage and infolding of myonuclei [3]. However, neither the impact of mutated desmin nor the complete absence of desmin on myonuclei in human and murine skeletal muscle tissue have been studied.

Areas of myonuclei were determined in H&E stained sections of skeletal muscle tissue from normal controls and autosomal-recessive desminopathy patients by means of digital image analysis using a deep learning approach. The same method was used for myonuclear area determination in skeletal muscle from desmin knock-out and R349P desmin knock-in mice and wild-type siblings. Morphology of myonuclei in skeletal muscle tissue of the mouse models and derived cultured myoblasts was studied by immunofluorescence imaging, 3D stimulated emission depletion (STED) imaging, and electron microscopy. This was complemented by RNAseq analysis of murine desmin knock-out soleus muscle. Here, we report on the first results of our analyses of myonuclei in human and murine desminopathy skeletal muscle tissue.

Our morphological analysis of skeletal muscle tissue derived from two cases of very rare human autosomal-recessive desminopathy with lack of desmin displayed abnormally shaped myonuclei. Moreover, Plectin and DAPI stains of isolated extensor digitorum longus muscle fibers from homozygous R349P desminopathy mice depicted a rounding of myonuclei (Fig. 1A,B). Furthermore, our ultrastructural analysis of myonuclei from desmin knock-out mice showed irregularly shaped nuclear envelopes and widening of the intermembrane space (Fig. 1C-H). This prompted us to set up an artificial intelligence-based detection of nuclei in H&E-stained skeletal muscle sections derived from several cases of autosomal-recessive desminopathy with either remaining or lack of desmin protein and measurement of the nuclear cross-sectional area. We are currently awaiting the quantitative data derived from a total number of eight cases of recessive desminopathies. Results of a RNAseq analysis of soleus muscle tissue derived from groups of homozygous desmin knock-out mice and wild-type littermates revealed multiple significantly upregulated mRNAs (Cnnm4, Fhl1, Lmna, Lmo7, Macf1, Nes, Tmem43, Vma21, Wfs1) and few downregulated mRNAs (Creld1, Nup133, Ryr1) suggesting a disbalance in nuclear envelope composition and function. Quantitative analysis of the nuclear size in cultured, immortalized desmin knock-out myoblasts derived from the desmin knock-out mouse line revealed significantly smaller myonuclei in knock-out than in wild-type cells. Currently, we are analyzing the myonuclear envelope of desminopathy myoblasts and murine desminopathy skeletal muscle tissue by lamin A/C and nuclear pore immunostains by mean of high-resolution STED microscopy.

Overall, our preliminary data from human and murine autosomal-recessive desminopathies with complete absence of desmin or presence of mutated desmin point into the direction of alterations of the nuclear shape as well as size

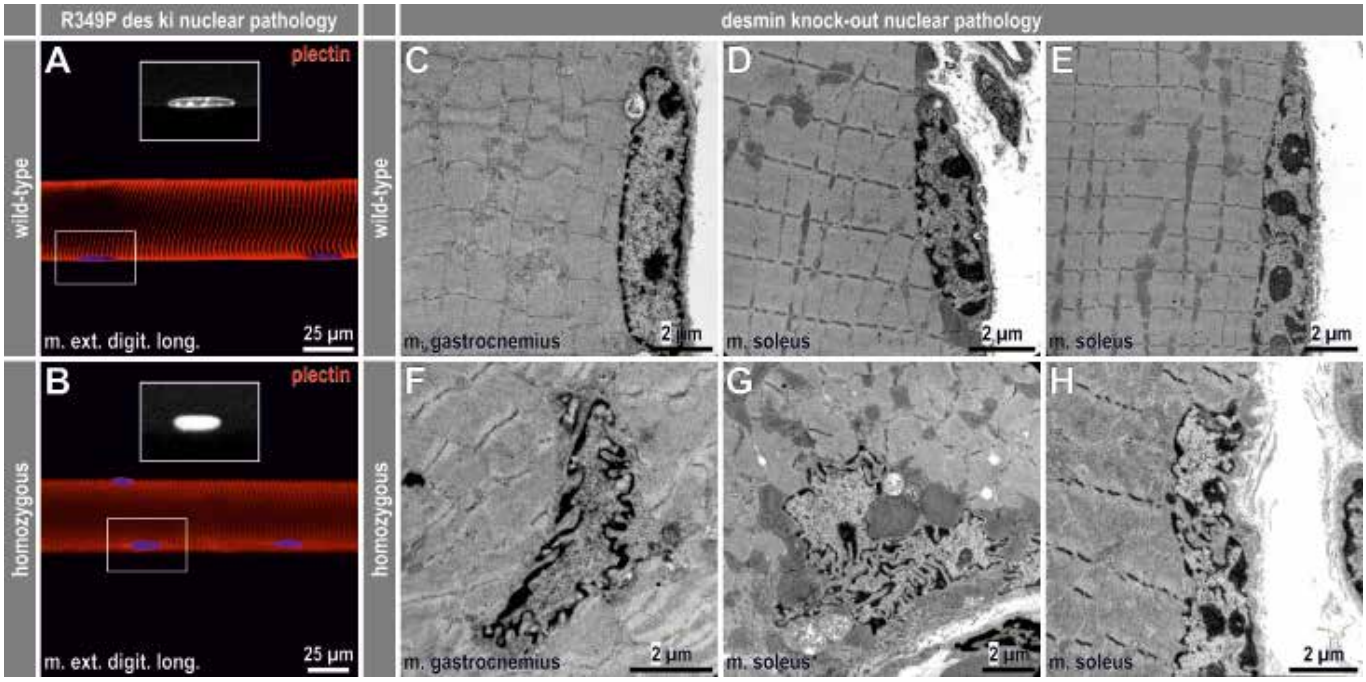

Fig. 1. (A,B) Plectin and DAPI stains of isolated extensor digitorum longus muscle fibers from homozygous R349P desminopathy mice depict a rounding of myonuclei. (C-H) Electron microscopy of gastrocnemius and soleus muscle tissue from desmin knock-out mice demonstrates irregularly shaped nuclear envelopes and widening of the intermembrane space.

and structure of the nuclear envelope in conjunction with disbalanced expression of nuclear envelope related genes. The current work demonstrates that at least the lack of desmin impacts on the morphology of nuclei and thus likely on their function. Our findings provide a first explanation that the LINC-complex myopathy like phenotype in the rare recessive desminopathies with lack of desmin may be caused in part by nuclear disfunction.

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Study Team

Study Team

The DLR study team comprises scientific and non-scientific employees having specialized knowledge in neurology, human nutrition, biology, study assistance, and management. The study team supports internal and external human physiologic studies at the DLR and implements own scientific projects.

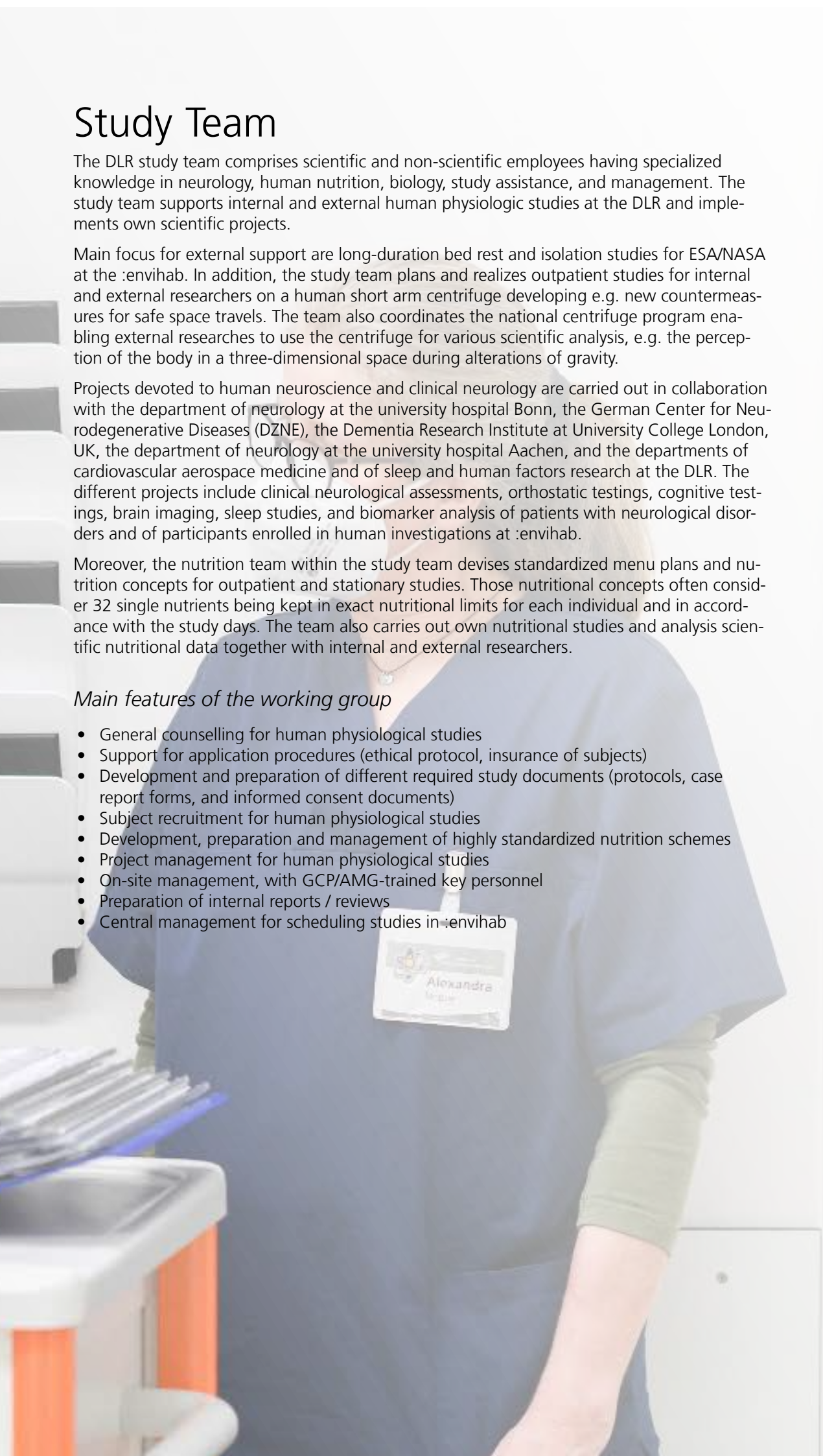
Main focus for external support are long-duration bed rest and isolation studies for ESA/NASA at the :envihab. In addition, the study team plans and realizes outpatient studies for internal and external researchers on a human short arm centrifuge developing e.g. new countermeasures for safe space travels. The team also coordinates the national centrifuge program enabling external researches to use the centrifuge for various scientific analysis, e.g. the perception of the body in a three-dimensional space during alterations of gravity.

Projects devoted to human neuroscience and clinical neurology are carried out in collaboration with the department of neurology at the university hospital Bonn, the German Center for Neurodegenerative Diseases (DZNE), the Dementia Research Institute at University College London, UK, the department of neurology at the university hospital Aachen, and the departments of cardiovascular aerospace medicine and of sleep and human factors research at the DLR. The different projects include clinical neurological assessments, orthostatic testings, cognitive testings, brain imaging, sleep studies, and biomarker analysis of patients with neurological disorders and of participants enrolled in human investigations at :envihab.

Moreover, the nutrition team within the study team devises standardized menu plans and nutrition concepts for outpatient and stationary studies. Those nutritional concepts often consider 32 single nutrients being kept in exact nutritional limits for each individual and in accordance with the study days. The team also carries out own nutritional studies and analysis scientific nutritional data together with internal and external researchers.

Main features of the working group

- General counselling for human physiological studies
- Support for application procedures (ethical protocol, insurance of subjects)
- Development and preparation of different required study documents (protocols, case report forms, and informed consent documents)
- Subject recruitment for human physiological studies
- Development, preparation and management of highly standardized nutrition schemes
- Project management for human physiological studies
- On-site management, with GCP/AMG-trained key personnel
- Preparation of internal reports / reviews
- Central management for scheduling studies in :envihab



α-Synuclein conformations as novel blood biomarkers in patients with Parkinson's disease

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The protein α-synuclein (αS) is the major constituent of pathological neuronal inclusions in PD and other synucleinopathies. Importantly, the protein can aggregate in brain neurons and glial cells, but also in peripheral tissues such as skin or the gut. To date, it is still unclear whether some diseases associated with the accumulation of αS start in the periphery according to the "gut first theory" or begin in the brain itself ("brain first theory"). Thus, a profound understanding of the development of neurodegenerative diseases will lead to health benefits not only for patients but also (yet) healthy people in every day life. This is quite critical for aeronautic personal on a long term. We are consequently investigating physiological, benefical forms of the αS protein. In this regard, the αS protein has been initially characterized as natively unfolded, and data collected in the last decade suggest that αS can exhibit different conformations under physiological conditions, which in turn help in governing aggregation propensity. The unfolded $αS^U$ form, initially described in the literature as the only physiological species, exhibits spontaneous aggregation dependent on increased protein concentrations or long incubations into the pathological amyloid fibrillar form ($αS^F$), a pathological hallmark of synucleinopathies. Conversely, the cytosolic helically folded, multimeric form ($αS^H$) resists disease-associated changes. We already showed that destabilization of αS multimers is associated with familial Parkinson's disease due to *SNCA* mutations. In addition, we could demonstrate a

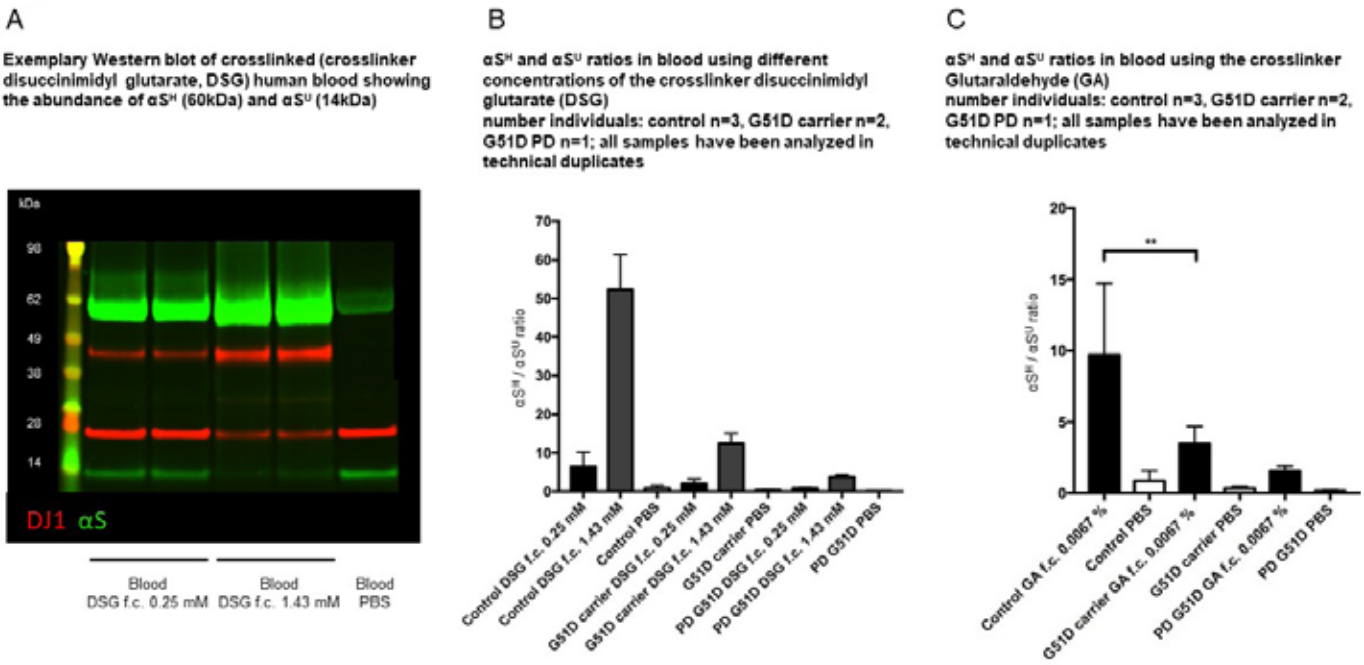

Fig. 1: Reduction of αSH / αSU ratios in blood from fPD patients with G51D mutations. αS = alpha-Synuclein, PD = Parkinson's disease, f.c. = final concentration, PBS = phosphate-buffered saline.

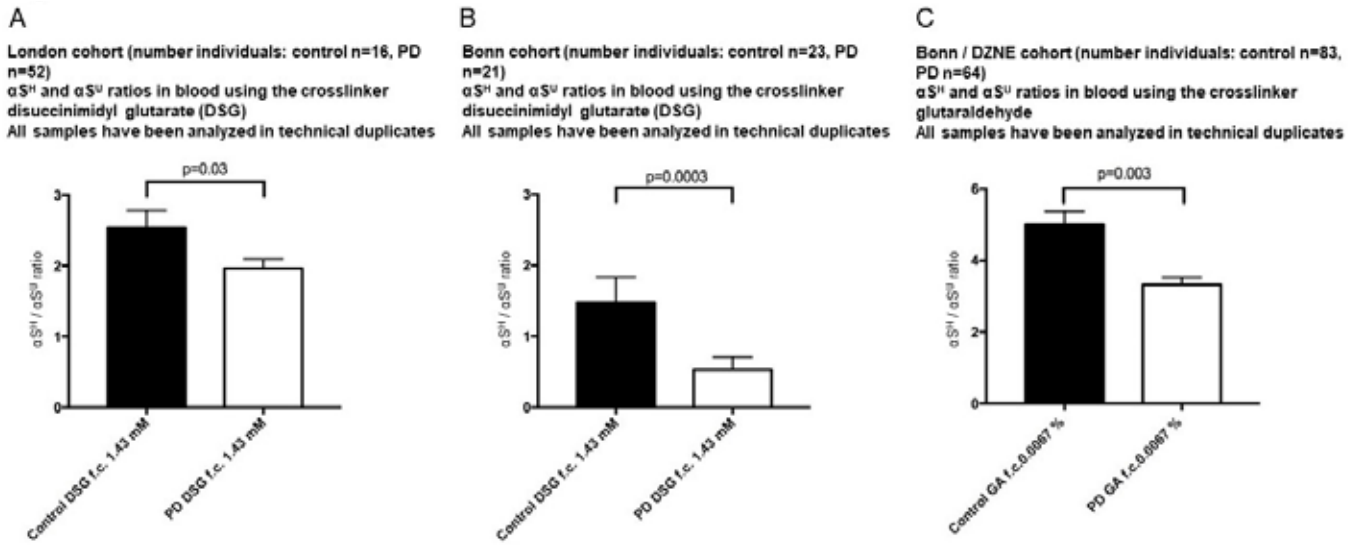

Fig. 2: Reduction of αS^H / αS^U ratios in blood from iPD patients. αS = alpha-Synuclein, PD = Parkinson's disease, f.c. = final concentration.

brain-region specific alteration of αS multimers in idiopathic PD (iPD) patients according to the classical Braak spreading theory. Thus, the proposed project addresses the question whether physiological, aggregation-resistant αS multimers are also decreased in blood from iPD patients.

The detection of αS^H is based on an *in vitro* crosslinking protocol of frozen EDTA blood samples. Samples were depleted of Hemoglobin and crosslinked using the aminolinker disuccinimidyl glutarate (DSG). αS^H and αS^U are visualized via SDS-Page and Western blotting. Thanks to Henry Houlden and Thomas Bourinaris, we were able to analyse blood from patients with familial PD, two G51D carriers and one individual with a G51D mutation who had already developed Parkinson's disease. Samples from iPD patients were provided by the DZNE in Bonn, Ullrich Wüllner and Rimona Weil.

Thus, we assessed the αS^H/αS^U ratios in asymptomatic and symptomatic G51D carriers, iPD patients and healthy controls. An exemplary Western blot of analyzed blood is shown in Fig. 1 A. Interestingly, the αS^H/αS^U ratio is already decreased in the asymptomatic G51D carriers being at risk to develop PD (Fig. 1 B,C). This supports the hypothesis that αS^H destabilization precedes the development of clinical PD. We were also able to detect a significant decrease in αS^H/αS^U ratios in iPD patients compared to controls (Fig. 2). We did see a significant negative correlation of the relative levels of helical and unfolded αS and disease duration in the London and DZNE iPD cohort (data not shown). Interestingly, a lot of patients seem to drop during 5 and 10 years after the diagnosis, whereas patients with longer disease durations as seen maintain relative αS^H /αS^U ratios above 2.5 (data not shown). As we did not see any correlation with the UPDRS or cognitive scores, the impact of the different levels for each patient on these clinical markers remains unclear. We are currently analysing longitudinal data investigating whether some patients drop during disease duration or whether each individual has low or high αS^H /αS^U ratios levels which makes them more or less susceptible towards PD.

Overall, our current findings provide a novel mechanism, in which the equilibrium of physiological aggregation-resistant helical αS and physiological, aggregation-prone unfolded αS is disturbed in blood from iPD and fPD patients. There seems to be an association with disease duration and we propose that a further investigation of this blood-based biomarker using specific antibodies against the helical alpha synuclein might solve the different questions raised with the current analysis. We propose that a stabilization of physiological aggregation-resistant αS^H in PD patients may be beneficial in slowing down the process of neurodegeneration, analogous to efforts currently underway toward stabilizing transthyretin in familial amyloid polyneuropathy.

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Resting energy expenditure (REE) is decreased due to inactivity in healthy individuals

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Resting energy expenditure (REE) depicts the amount of energy required to sustain all vital functions in individuals at rest. REE depends on fat free mass, which refers to all body components except fat and can therefore be altered by physical (in-)activity be it in weightlessness or on Earth. Indirect calorimetry is considered as gold standard to determine REE by measuring pulmonary gas exchange (O_2 consumption and CO_2 production). Though various predictive equations exist to calculate the REE in a fast and easy way, they do not account for all (patho-)physiological conditions and individuals. An insufficient determined REE can lead to malnutrition or overfeeding.

It is still unknown how and to what extend the REE changes during long periods of inactivity in healthy individuals. Moreover, the accuracy of commonly used predictive equations compared to measured REE in inactive humans was investigated.

To answer these questions, we measured REE via indirect calorimetry in healthy individuals expo-sed to strict head-down tilt bedrest for 60 days, which is, while extreme, a good tool to investigate inactivity. Overall, 24 subjects participated in the AGBRESA (Artificial Gravity Bed Rest study with ESA) conducted in 2019 at the :envihab facility in Cologne, Germany. The sudy was a joint venture by NASA, ESA and DLR. REE was measured over 30 minutes under highly controlled conditions on four time points throughout the study: on the first study day (BDC-14), on day 32 (HDT32) and 55 (HDT55) of bed rest and 12 days after bed rest (R+12). The measured REE was then compared to frequently used and well evaluated predictive equations (Harris-Benedict, WHO/FAO/UNU, Müller, Owen, Cunningham and Mifflin) and a new one, created for mostly inactive, sitting humans (Uchi-zawa). In addition to that, fat free mass was determined using dual-energy x-ray absorptiometry, a device capable of measuring bone mineral density and body composition. These measurements were performed twice during baseline data collection, bi-weekly throughout the 60 days of bed-rest, and once during the stationary recovery phase correlating REE and fat

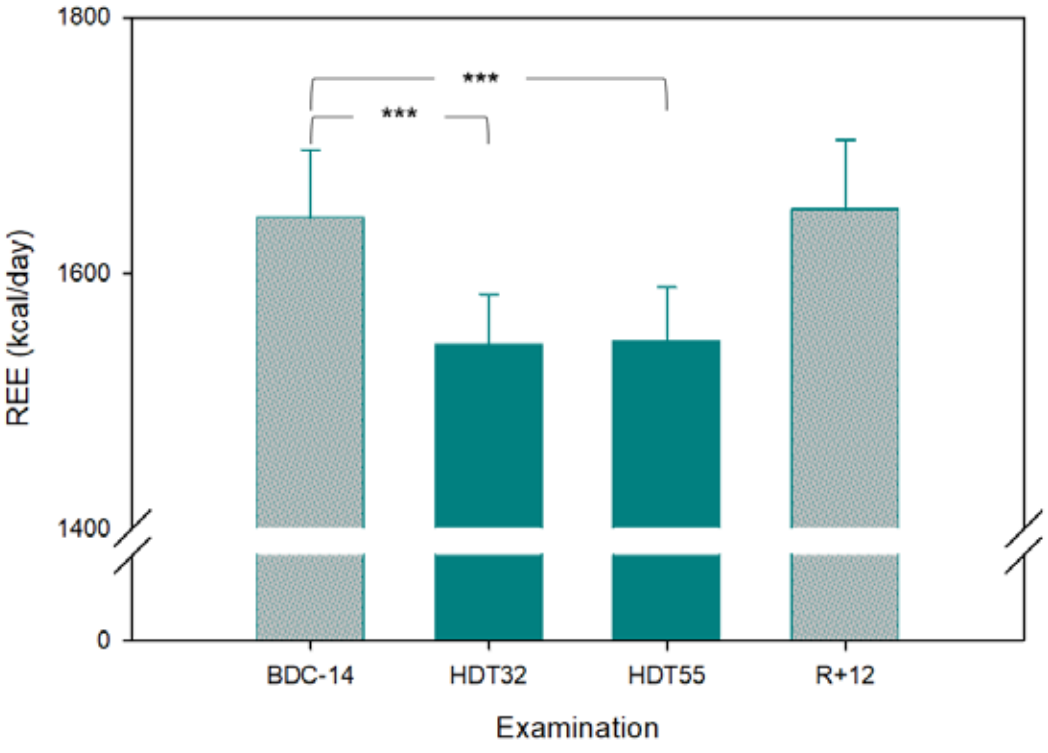

Fig. 1: Resting energy expenditure (REE) was measured on four times points throughout the study: on the first study day (BDC-14), on day 32 (HDT32) and 55 (HDT55) of bed rest and 12 days after bed rest (R+12). Results show a significant decrease of the REE due to bed rest induced inactivity. After a short phase of normal activity, the REE increases back to baseline level.

Fig. 2: Resting energy expenditure (REE) measurement via indirect calorimetry

free mass changes.
The results show, that measured REE significantly decreases by about 120 kcal/day ($p<0.001$) after 32 days of bedrest. After 55 days of bedrest no further significant decrease could be detected. The-se findings align with a reduction of fat free mass by 2.6 kg ($p<0.001$) during bedrest. However, 12 days after termination of bed rest REE and fat free mass had increased back to baseline levels. Most of the predictive equations were quite accurate in calculating REE during the ambulatory pha-se, but overestimated REE in bedrest compared to measured REE. One predictive equation (Owen) matched measured REE in bedrest in nearly 96 % of datapoints but underestimated REE at baseline. While being created for mostly inactive, sitting individuals Uchizawa's predictive equation overes-timated REE in bedrest.
We conclude that approximately 80% of the decrease in REE during inactivity due to strict head-down bedrest can be explained by reduced fat free mass. Most predictive equations yield inaccura-te REE estimates for bed rest. However, Owen's equation seems to perform better in estimating REE under these conditions. In addition to improving conduct of future head-down bedrest studies, our findings highlights the importance of physical activity in societies struggling with increasing pre-valence of obesity and associated cardio-metabolic diseases.

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No serological evidence for neuronal damage or reactive gliosis in Neuro-COVID-19 patients with long-term persistent headache

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Circulating biomarkers for acute neurological damage are highly relevant for aerospace and for terrestrial medicine. However, we are still lacking information which neurological deficits e.g. after viral infections, indeed lead to brain damage. Therefore, we are using neurological model diseases for a better understanding and investigation of blood circulating biomarkers indicating neuronal or glial damage. For example, we are using neurological post-acute sequelae of SARS-CoV-2 infection (PASC) as a model disease. PASC are common, although direct viral infection of the central nervous system (CNS) is rare. Instead, inflammatory mechanisms, parenchymal hypoxia or microvascular injuries may contribute to the development of CNS injury, raising the possibility that these long-term symptoms may be accompanied by systemic biomarkers of neuronal damage or neuroinflammation.

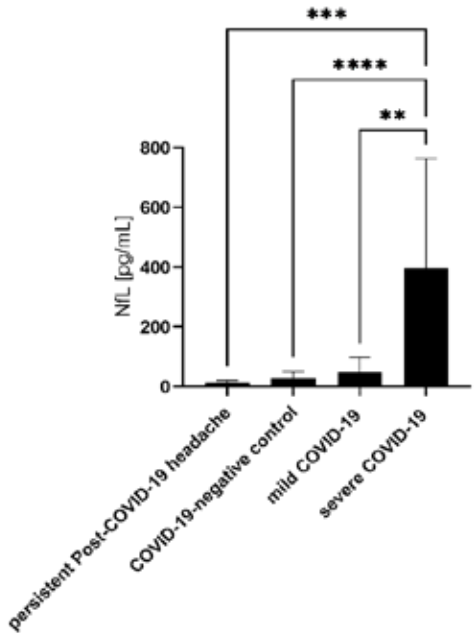

Fig. 1: Levels of NfL in blood comparing persistent post-COVID-19 headache patients to controls with no acute or history of COVID-19 infection, other mild COVID-19 patients and severe COVID-19 patients.

Accordingly, recent studies evaluated neurofilament light chain (NfL) as a marker of neuronal injury and glial fibrillary acidic protein (GFAP) as a marker of reactive astrogliosis and neuroinflammation in the blood of patients with acute COVID-19 and PASC. Headache was a leading symptom associated with increased NfL and GFAP levels and increased mortality in acute COVID-19 patients. Moreover, new persistent headache may also be an initial sign of chronic CNS inflammation such as cerebral vasculitis or autoimmune encephalitis.

Therefore, in this pilot study we investigated NfL and GFAP levels in blood from Post-COVID-19 patients with new daily persistent headache (n = 6), defined as being different from previous primary headaches (if any), having started after the initial serological diagnosis of SARS-CoV-2 infection and persisting longer than 12 weeks. These patients had been classified as mild during acute infections according to the WHO definition, meaning they did not require high flow oxygen therapy or ventilation. In comparison, we also analyzed blood NfL levels at different time points in patients having been diagnosed with mild COVID-19 (n = 17), severe COVID-19 (n = 11), and COVID-19-seronegative control subjects (n = 14). Specimen were obtained 14 ± 24 weeks after the initial diagnosis in mild and 8 ± 19 weeks in severe COVID-19 patients, and 33 ± 17 weeks in Post-COVID-19 headache

patients. GFAP levels were analyzed in all patients with Post-COVID-19 headache, but were only available in n = 8 patients with mild COVID-19, n = 4 severe COVID-19, and n = 8 COVID-19-negative controls. All measurements were performed on a SIMOA analyzer (Quanterix) using the corresponding SIMOA assay kits.

We found that NfL levels were similar in patients with persistent Post-COVID-19 headache, mild COVID-19 and COVID-19-seronegative controls, but significantly elevated in severe COVID-19 compared to patients with persistent Post-COVID-19 headache (Fig. 1). Similarly, GFAP levels were comparable in patients with persistent Post-COVID-19 headache, mild COVID-19 and COVID-19-seronegative controls, but significantly elevated in severe COVID-19 compared to persistent Post-COVID-19 headache patients (Fig. 2).

Thus, in contrast to severe COVID-19, we did not detect serological signs of CNS damage or reactive astrogliosis in patients presenting with persistent headache after mild COVID-19. Therefore, our data argue against persistent headache as an indicator of ongoing or progressive parenchymal damage or neuroinflammation. Moreover, our study indicates that persistent post-COVID-19 headache may be pathophysiologically and prognostically different from headache during acute COVID-19, which is often associated with elevated Nfl and GFAP levels and may indicate increased mortality. However, patients with severe COVID-19, even without any primary neurological manifestations, should probably be closely monitored for ongoing CNS damage as this subgroup exhibited increased NfL and GFAP levels even after the acute phase of COVID-19. Observations in patients with defined medical conditions provide insight in the utility of such biomarkers in detecting acute neurological damage in extreme environments such as in space.

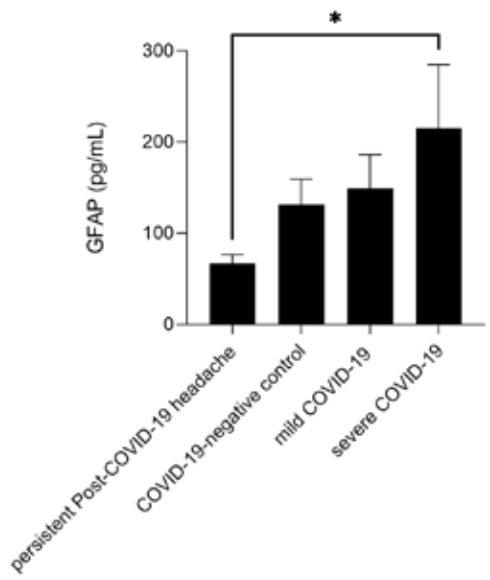

Fig. 2: Levels of GFAP in blood comparing persistent post-COVID-19 headache patients to controls with no acute or history of COVID-19 infection, other mild COVID-19 patients and severe COVID-19 patients.

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Annex

Scientific activities

Teaching activities

Name	University	Subject
Aeschbach, Daniel	Harvard Medical School, Boston	Sleep Medicine
Anken, Ralf	University of Hohenheim	Space Biology
Berger, Thomas	International Space University, Straßburg	Master of Space Studies
Berger, Thomas & Hellweg, Christine	University of Bonn	Radiation Protection
Clemen, Christoph	University of Cologne	Biochemistry and Molecular Biology
Elmenhorst, Eva-Maria	RWTH Aachen University	Aviation and Travel Medicine
Elmenhorst, Eva-Maria	RWTH Aachen University	Space Medicine
Gerlach, Darius	University of Cologne	Physiology
Goerke, Panja / Marggraf-Micheel, Claudia	University of Applied Sciences Wedel	Communication skills
Hauslage, Jens	University of Veterinary Medicine Hanover	Gravitational Biology
Hauslage, Jens	La Trobe University	Gravitational Biology
Hellweg, Christine	Freie Universität Berlin	Immunology
Hellweg, Christine	Freie Universität Berlin	Pathology
Hellweg, Christine	University of Bonn	Radiopharmacy
Hemmersbach, Ruth	University of Bonn	Zoology
Heußer, Karsten	University of Cologne	Physiology
Liemersdorf, Christian	University of Bonn	Molecular Genetics
Lindlar, Markus	University of Applied Sciences Bonn-Rhein-Sieg	Advanced Methods in Health Telemeticx
Lindlar, Markus	University of Applied Sciences Bonn-Rhein-Sieg	Business Systems in Health Care
Mittelstädt, Justin	University of Hamburg	Psychological Diagnostics
Möller, Ralf	University of Applied Sciences Bonn-Rhein-Sieg	Microbiology
Möller, Ralf	University of Applied Sciences Bonn-Rhein-Sieg	Bachelor program: Space Microbiology
Möller, Ralf	University of Applied Sciences Bonn-Rhein-Sieg	Master program: Space Biotechnology / Medicine
Pecena, Yvonne	International Space University	Space Psychology
Pesta, Dominik	University of Cologne	Medicine
Pfander, Boris	University of Cologne	Medicine

Pfander, Boris	University of Cologne	Seminar at the Institute of Genome Stability in Aging and Disease
Pfander, Boris	University of Cologne	Journal Club at the Institute of Genome Stability in Aging and Disease
Pfander, Boris	University of Cologne	Molecular Mechanisms of Human Disease
Pfander, Boris	University of Cologne	Cologne Graduate School of Aging Research
Pfander, Boris	University of Cologne	Research Track Lecture
Pustowalow, Willi	University of Applied Sciences Bonn-Rhein-Sieg	Computer Science
Stelling, Dirk	Hochschule Fresenius	Differential Psychology
Stern, Claudia	International Space University	Human Vision System
Stern, Claudia	University of Braunschweig - Institute of Technology	Aerospace Medicine
Stern, Claudia	University of the Bundeswehr	Space Medicine
Stern, Claudia	European School of Aviation Medicine	Basic Course
Stern, Claudia	European School of Aviation Medicine	Advanced Course
Tank, Jens	Hanover Medical University	Propaedeutics
Zange, Jochen	University of Cologne	Medicine
Zinn, Frank	University of Hamburg	Psychological Diagnostics

Graduations

Supervised Doctoral Students

University	Space	Aviation	Traffic
German Sport University Cologne	1		
Justus Liebig University Giessen	1	1	
Ludwig Maximilians University Munich	2		
Manchester Metropolitan University	1		
Hanover Medical University	3		
Radboud University	1		
Ruhr University Bochum	2		
RWTH Aachen University	5	2	1
University of Braunschweig - Institute of Technology	1		
Dresden University of Technology		1	1
University of Bonn	7		
University of Duisburg-Essen	2		
University of Düsseldorf		1	
University of Jena		1	
University of Cologne	14	1	
University of Oldenburg	1		
Leiden University		1	
University of Hamburg		1	

Doctorates

University	Space	Aviation	Traffic
Hanover Medical University	2		
Ludwig Maximilians University Munich	1		
University of Cologne	1		

Bachelor Degrees

University	Space	Aviation	Traffic
Albstadt-Sigmaringen University	1	1	
German Sport University Cologne	1		
University of Applied Sciences Aachen, Campus Jülich	1		
University of Applied Sciences Aachen	1		
University of Applied Sciences Bonn-Rhein-Sieg	4	2	1
University of Applied Sciences Niederrhein, Krefeld	1		
University of Bonn	4		
University of Düsseldorf		1	
University of Cologne	1		
University of Regensburg	1		
Goethe Unversity Frankfurt	1		

Diploma Theses/Master Degrees

University	Space	Aviation	Traffic
Ruhr University Bochum	1		
Eberhard Karls University Tübingen	1		
Bremerhaven University of Applied Sciences	1		
University of Applied Sciences Koblenz	1		
South Westphalia University of Applied Sciences, Iserlohn	1		
Dresden University of Technology		1	
University of Bonn			
University of Cologne	2		
University of Applied Sciences Aachen	1		
Leiden University	1		
University of Münster		1	1
University of Porto, Portugal	1		

Scientific Exchange

Annibale, Paolo	MDZ Berlin & St. Andrews University, UK
Celso, Dutra de SouzaHugo	Ribeirãro Preto Medical School, University of São Paulo
Drouve, Nils	Cologne University of Technology
Hoffmann, Fabian	University Hospital Cologne
Hönemann, Jan-Niklas	University Hospital Cologne
Kramer, Tilmann	University Hospital Cologne
Limper, Ulrich	University Hospital Merheim
Rashid, Anas	University of Turin
Sohail, Iqra	MDZ Berlin
Striebel, Johannes	University of Bonn
Weis, Henning	University Hospital Cologne

Awards

Beblo-Vranesevic, Kristina
Best Presentation Award, EANA 2022

Cortesao, Marta
Add-on Fellowship for Interdisciplinary Life Science 2021 der Joachim Herz-Stiftung

Department ME PSY
EAAP Award

ESA astronaut selection team
ESA Teamwork Excellence Award

Gerlach, Darius A.; Manuel, Jorge; Hoff, Alex; Heusser, Karsten; Jordan, Jens; Tank, Jens
High Impact Paper for Summer 2021 in the category of basic science of the journal "Hypertension": "Medullary And Hypothalamic Functional Magnetic Imaging during Acute Hypoxia in Tracing Human Peripheral Chemoreflex Responses"

Hinnerk Eißfeldt
EAAP Honorary member

Magliulo, Maria
Three Minute Thesis competition, University of Essex

Palomeque Dominguez, Hector Hugo
4th place of the Space Factor Contest, EANA 2022

Rettberg, Petra
International Astronautical Federation Distinguished Service Award

Weber, Laura; Paulke, Tim; Stock, Johannes
3rd place business plan competition KUER.NRW

Events, lectures, workshops at the Institute

22 February 2022
Institute Seminar: Laura Weber and Tim Niklas Paulke, Technology transfer from space to agriculture: Manure treatment for more efficient crop production

4 March 2022
Kompetenznetzwerk Immobilisationsbedingte Muskelstörungen KNIMS (online)

8 March 2022
Institute Seminar: Dr. rer. nat. habil. Markus Braun, Research and Exploration/Life Sciences

22 March 2022
Institute Seminar: Dr. Petra Mittler and Dr. Jürgen Schlutz, LUNA Habitat

5 April 2022
Institute Seminar: Dr. Philipp Rathert, Epigenetics: coordinated gene regulation beyond the DNA sequence

23 August 2022
Institute Seminar: Dr. Carmen Bruder, DLR-Projekt LOKI – Kollaboration von Luftfahrt-Operateuren und KI-Systemen

22 November 2022
Institute Seminar: Prof. Prof. (Hon) Nikolaus Netzer MD PhD, Human HIF triggered metabolism – possible impact on longer space and commercial flights under moderate hypoxia

3 December 2022
7th Human Physiology Workshop

8-9 December 2022
Microbiome Symposium 2022: Space Research meets Medical Microbiology

Publications

Publications with an impact factor above 10

Baqué, M., Backhaus, T., Meeßen, J., Hanke, F., Böttger, U., Ramkissoon, N., Olssen-Francis, K., Baumgärtner, M., Billi, D., Cassaro, A., de la Torre Noetzel, R., Demets, R., Edwards, H.G.M., Ehrenfreund, P., Elsaesser, A., Foing, B., Foucher, F., Huwe, B., Joshi, J., Kozyrovska, N., Lasch, P., Lee, N., **Leuko, S**., Onofri, S., Ott, S., Pacelli, C., **Rabbow, E.,** Rothschild, L.J., Schulze-Makuch, D., Selbmann, L., Serrano, P., Szewzyk, U., Verseux, C., Wagner, D., Westall, F., Zucconi, L., de Vera, J.P.P. (2022) *Biosignature stability in space enables their use for life detection on Mars.* Science Advances. 2022;8(36):eabn7412. American Association for the Advancement of Science (AAAS). doi: 10.1126/sciadv.abn7412. ISSN 2375-2548.

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