This postprint was originally published by Elsevier/Cell Press as:
Stahn, A. C., & Kühn, S. (2022). Extreme environments for understanding brain and cognition. *Trends in Cognitive Sciences, 26*(1), 1–3. https://doi.org/10.1016/j.tics.2021.10.005.

Extreme environments for understanding brain and cognition

Alexander C. Stahn[1,2,*] and Simone Kühn[3,4]

Can life in extreme environments foster our understanding of the limits and adaptability of cognition and brain plasticity? We review characteristics of spaceflight and spaceflight analogues, such as bed rest, dry immersion, parabolic flights, and isolated and controlled confinement, and discuss the potential of utilizing these research settings to advance cognitive neuroscience.

Studying humans in extreme environmental conditions provides opportunities to explore the effects of gravity, social isolation, and environmental deprivation on cognitive and brain plasticity (Figure 1). Specifically, we propose that spaceflight analogs such as long-duration bed rest, isolation studies in controlled settings, and expeditions in extreme environments can provide insights into the role of social and environmental enrichment on cognition and brain health. Spaceflight analogs may offer a unique experimental setting in which to expose healthy humans to potentially adverse environmental conditions and psychological stressors, effects that typically cannot be addressed in classical research settings (Box 1). Over the past few years, work has increasingly demonstrated how spaceflight analogs affect brain and behavior, highlighting that the value of these model environments goes beyond understanding and predicting the neurobehavioral effects of spaceflight and operational stressors. They provide fundamental knowledge to cognitive neuroscience, namely, insights into how behavioral and brain plasticity can be compromised, and how interventions can be advanced to preserve and improve cognition and brain integrity across the lifespan.

Assessing the entire process of health, aging, disease, and recovery

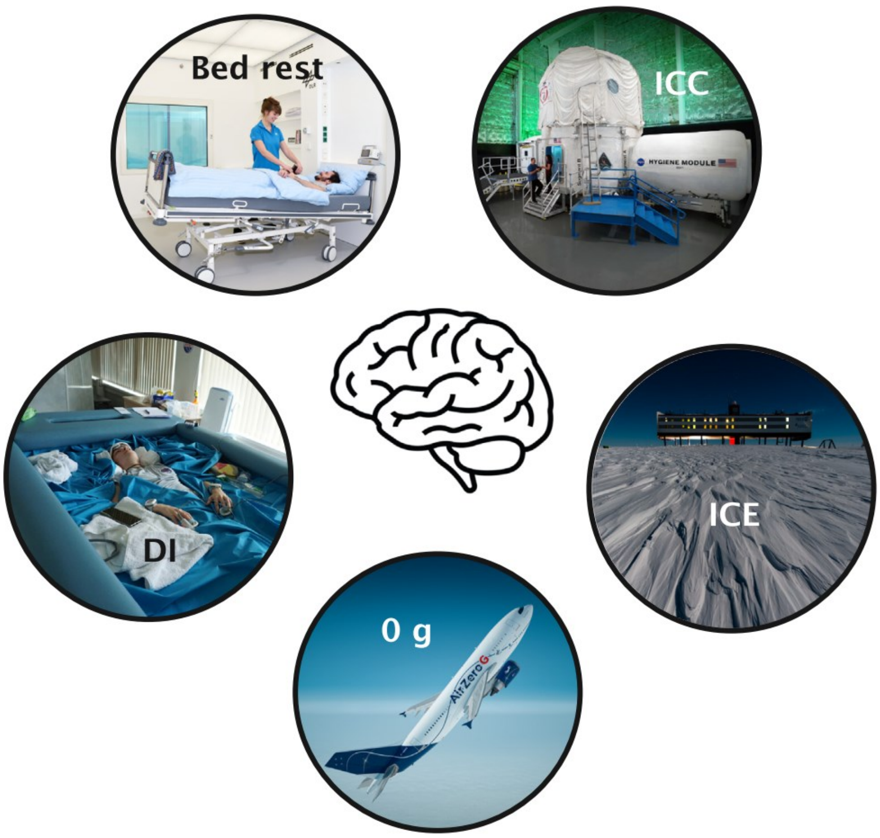
An exceptional characteristic of these models is that they allow healthy subjects to be exposed to potentially hazardous conditions, their responses monitored, and their recovery tracked. Bed rest and dry immersion, for example, can be considered models of aging [1]. They induce similar physiological processes as observed in the aging population, such as reductions in gray and white matter, in a highly accelerated fashion. Changes that typically evolve over years can therefore be studied in timelapse. In addition, such experiments allow the study of healthy individuals without medical conditions, minimizing between subject variation associated with different diseases and disorders.

Highly controlled experimental settings and reduction of confounding factors

Spaceflight analog experiments are performed under highly standardized conditions, controlling various moderators, confounders, and covariates commonly present in human research designs. For instance, in studies investigating the role of exercise on brain and behavior, it is rarely possible to account for differences such as adherence to the exercise schedule, sleep, nutrition, and social complexities. In bed rest experiments, participants are confined to the facility, and the primary variable, that is, physical activity, is fully controlled (all activities including hygiene activities are performed in supine or head-down tilt position for the entire experiment). Given that nutrition, sleep/wake cycles and social activities are standardized across the entire cohort, this experimental design reduces between-subject variability, and can be expected to maximize statistical power and foster the exploration of causal relationships between interventions and cognition as well as brain integrity. We recently showed that prolonged bed rest can affect various cognitive capacities, including selective attention, emotional processing, and episodic memory. We found 30 days of bed rest decreased event-related potentials elicited by pleasant and unpleasant pictures, characterized by reduced electrocortical activity in the posterior cingulate gyrus and insula [2]. We also demonstrated that performance of selective attention and neural indices of selective attention deteriorate during bed rest, and do not fully recovery one week post bed rest [3]. In another 60-day bed rest study, we observed a decrease in neural efficiency during the encoding and retrieval of visual stimuli in functional magnetic resonance imaging [4]. Likewise, we showed that regular physical activity can counteract circadian disruptions associated with long-duration bed rest [5].

Exceptional social and environmental conditions

In addition to spaceflight analogs using dedicated habitats to simulate social isolation and confinement (Box 1), expeditions in extreme environments provide a natural setting to investigate neurobehavioral responses to prolonged isolation and confinement [6]. In crew members overwintering in Antarctica for 14 months, we found a decrease in hippocampal subfield volumes, which were associated with reductions in brain derived neurotrophic factor as well as changes in spatial abilities and selective attention during the expedition [7]. Such conditions cannot be realized in typical laboratory settings. In combination with animal studies mimicking the relative duration of isolation, experiments in extreme environments have the potential to help unravel the neurobehavioral effects of social isolation and environmental



Trends in Cognitive Sciences

Figure 1. Understanding isolation, gravity, and inactivity on Earth. Studying extreme environments associated with spaceflight provides unique experimental settings for understanding cognition and brain plasticity on Earth. Bed rest, prolonged bed rest with 6 degrees head-down tilt (picture credit: DLR/CC BY). Abbreviations: 0 g, zero gravity (picture credit: Novespace); DI, dry immersion (picture credit: IBMP/Oleg Voloshin); ICC, isolated controlled confinement (picture credit: NASA); ICE, isolated and extreme environments (picture credit: Stefan Christmann, Alfred-Wegener-Institut/CC BY).

deprivation in humans, which has recently received increased interest due to COVID-19-related restrictions. It will be of particular interest to disentangle effects related to reduced social complexities as compared to loneliness or limitations in experiential diversity. Glucocorticoid hormones and hypothalamic–pituitary–adrenal axis feedback mechanisms are anticipated to play a key role in explaining adverse effects of stressors such as immobilization or isolation and confinement on brain structure and function. Yet, we expect that other factors such as the limited variation in physical locations; that is, the lack of exposure to novel experiences and environments, will contribute to the adverse effects of sustained stress levels [8]. By systematically varying the degree of confinement and group size it will be possible to disentangle the role of social complexities compared to environmental diversity in response to isolation and confinement.

Box 1. Spaceflight analogs on Earth

Bed rest lasting from a few days to 2 months and longer provides a unique setup to investigate the efficacy of treatments and interventions to mitigate adverse effects of prolonged immobility. Dry immersion is another model to simulate hypokinesia and immobilization. Subjects are immersed in a waterproof fabric in a supine position into a deep bath. Although similar to bed rest, the support load is completely eliminated relative to bed rest, creating a flotation condition as experienced during weightlessness. Parabolic flight provides repeated exposure to short periods of weightlessness (up to 30 s per flight trajectory, typically repeated 30–60 times). Human centrifuges use acceleration to induce varying inertial forces along different body axes. They are used to understand the acute effects of hypergravity and transitions between gravity levels. Isolation experiments utilize dedicated laboratory facilities to simulate the effects of confinement, social isolation, and environmental deprivation. In contrast to most laboratory studies, Antarctic expeditions allow researchers to assess the effects of prolonged social isolation in a real-life setting. These missions are characterized by low privacy, variations in meaningful work, lack of opportunities to quit the expedition, sensory monotony, and limited rescue operations.

Spaceflight analogs may also unravel new mechanisms of cognitive and brain plasticity that cannot be studied in standard laboratories. For instance, projections of the vestibular pathways to the limbic system and neocortex play a critical role in brain plasticity including spatial learning and memory formation [9]. Peripheral lesions of the vestibular pathways have been linked to atrophy in the hippocampus and spatial memory impairments that are long-lasting and possibly even permanent [10]. Using human centrifuges and parabolic flight experiments, it is possible to study the interaction between the vestibular system and cognition in response to different gravity levels in a systematic manner. Along these lines, we recently demonstrated that altered gravity can impair spatial updating; that is, the ability to continuously form and update transient sensorimotor representations about self-to-object relations during locomotion [11].

Countermeasures: mitigating cognitive impairments

Spaceflight analogs can also provide a unique testbed for investigating the effectiveness of lifestyle interventions such as exercise and nutritional programs. Using a pattern separation task, we showed that a high-intensity exercise program can mitigate the neural inefficiency caused by 60 days of bed rest [4]. Furthermore, there is evidence that it may not be physical activity *per se*, but the stimulation of the vestibular system that explains the positive effects of exercise programs on brain and behavior [9]. Combining physical activity interventions with artificial gravity could help elucidate the role of vestibular stimulation for cognitive and brain plasticity. Beyond this, more specific interventions such as using virtual environments for sensory augmentation and fostering spatial exploration can be applied to mitigate adverse neurobehavioral effects under highly controlled conditions.

Potential positive effects of extreme environments: the dose makes the poison

Importantly, extreme environments should not be understood as negative only. Stress responses are a well-orchestrated natural reaction to a potentially dangerous situation. Likewise, restrictive environmental stimulation can have restorative functions [12]. Prolonged isolation may even result in decreased epigenetic aging [13]. Some crew members staying in Antarctica for 14 months reported experiencing the expedition as exceptionally pleasant. Dry immersion has revealed positive effects on choice reaction time in Parkinson's patients, hemodynamics and brain edema in premature babies, and rehabilitation of children with central nervous system disorders [1]. Likewise, bed rest is a medical treatment in the first place – the dose makes the poison.

Concluding remarks

Environmental and social diversity is a central driver of cognitive and brain plasticity. Housing conditions, opportunities for environmental exploration, and voluntary exercise affect the volume, number of neurons, dendritic branching, and function of the brain in animal models [14]. These data are valuable because they reveal the molecular and cellular mechanisms underlying different environmental and social conditions. However, it is unclear to what extent these data translate to humans [15]. It remains to be determined whether a causal relationship between adverse social and physical environments and brain plasticity is also evident in humans exposed to prolonged deprivation, such as in the aging population, bedridden patients, those social distancing in the face of a pandemic, or those on a space mission from Earth to Mars. The examples from spaceflight analogs summarized here have the potential to further understanding of the neurobehavioral effects of exceptional social and environmental conditions and potential mitigation strategies in highly controlled experimental settings.

To systematically investigate the effects of extreme environments, future studies should leverage these models and foster a transdisciplinary approach that includes, but is not limited to, the following methodologies and outcomes: multimodal brain imaging combined with innovative cognitive tasks; neurovestibular and ocular examinations, cardiovascular and exercise testing; and biochemical measures including neurohumoral, immunological responses, oxidative stress markers, and advances in multiomics. Furthermore, to fulfill their potential, studies should (i) include comparable control groups not exposed to any extreme conditions; (ii) account for practice effects associated with repeated cognitive test administrations; (iii) control and/or correct for critical moderators such as sleep, nutrition, and phenotypic differences that are known to affect cognition and brain; and (iv) be complemented by animal studies paralleling identical interventions. Such endeavors will foster an understanding of the impact of immobilization, confinement, and social isolation on brain and behavior. In addition to supporting human space exploration, these efforts may help people on Earth, where sedentary lifestyles and social individualism and have reached extreme levels.

Acknowledgments

This material is based upon work supported by the National Aeronautics and Space (NASA), European Space Agency (ESA), and German Aerospace Center (DLR), including grants 50WB1225 and 50WB1519.

Declaration of interests

No interests are declared.

[1] Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

[2] Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Physiology, 10117 Berlin, Germany

[3] Lise Meitner Group for Environmental Neuroscience, Max Planck Institute for Human Development, 14195 Berlin, Germany

[4] Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany

[*] Correspondence: astahn@pennmedicine.upenn.edu (A.C. Stahn).

References

1. Tomilovskaya, E. *et al.* (2019) Dry Immersion as a groundbased model of microgravity physiological effects. *Front. Physiol.* 10, 284
2. Brauns, K. et al. (2019) Electrocortical evidence for impaired affective picture processing after long-term immobilization. *Sci. Rep.* 9, 16610
3. Brauns, K. *et al.* (2021) Effects of two months of bed rest and antioxidant supplementation on attentional processing. *Cortex* 141, 81–93
4. Friedl-Werner, A. *et al.* (2020) Exercise-induced changes in brain activity during memory encoding and retrieval after long-term bed rest. *Neuroimage* 223, 117359
5. Mendt, S. *et al.* (2021) Regular exercise counteracts circadian shifts in core body temperature during long-duration bed rest. *npj Microgravity* 7, 1
6. Choukér, A. and Stahn, A.C. (2020) COVID-19 – The largest isolation study in history: the value of shared learnings from spaceflight analogs. *npj Microgravity* 6, 32
7. Stahn, A.C. *et al.* (2019) Brain changes in response to long Antarctic expeditions. *N. Engl. J. Med.* 381, 2273–2275
8. Heller, A.S. *et al.* (2020) Association between realworld experiential diversity and positive affect relates to hippocampal–striatal functional connectivity. *Nat. Neurosci.* 23, 800–804
9. Smith, P.F. (2017) Is hippocampal neurogenesis modulated by the sensation of self-motion encoded by the vestibular system? *Neurosci. Biobehav. Rev.* 83, 489–495
10. Smith, P.F. *et al.* (2010) Move it or lose it – is stimulation of the vestibular system necessary for normal spatial memory. *Hippocampus* 20, 36–43
11. Stahn, A.C. *et al.* (2020) Spatial updating depends on gravity. *Front. Neural Circuits* 14, 20
12. Suedfeld, P. and Bow, R.A. (1999) Health and thxrapeutic applications of chamber and flotation restricted environmental stimulation thxrapy (REST). *Psychol. Health* 14, 545–566
13. Nwanaji-Enwerem, J.C. *et al.* (2020) A longitudinal epigenetic aging and leukocyte analysis of simulated space travel: the Mars-500 Mission. *Cell Rep.* 33, 108406
14. Kempermann, G. (2019) Environmental enrichment, new neurons and the neurobiology of individuality. *Nat. Rev. Neurosci.* 20, 235–245
15. Voss, M.W. *et al.* (2013) Bridging animal and human models of exercise-induced brain plasticity. *Trends Cogn. Sci.* 17, 525–544