Brains in Space
Knowledge gaps, assessment, and potential countermeasures

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Table of Contents

Introduction

Prolonged spaceflight induces both structural and functional changes in the human brain, which may compromise astronaut health, cognition, and performance. MRI studies have consistently reported an upward brain shift, ventricular enlargement, and cerebrospinal fluid (CSF) redistribution following long-duration missions (Koppelmans et al., 2016). These findings suggest an altered pressure environment in the cranial cavity (Roberts & Petersen, 2019; Van Ombergen et al., 2019). In addition to these structural changes, functional MRI has revealed spaceflight-induced changes in brain connectivity, with some modulations persisting for up to eight months after return to Earth (Jillings et al., 2023). Key regions such as the posterior cingulate cortex and thalamus show lasting reductions in global connectivity, while the angular gyrus exhibits sustained increases, possibly reflecting sensorimotor recalibration and altered spatial orientation. Other areas, such as the insular cortex, demonstrate reversible changes, suggesting flexible adaptation in salience and interoceptive processing networks (Wuyts et al., 2025). Functional MRI has revealed decreased connectivity of visual cortical areas when participants perform a working memory task (Salazar et al., 2023), as well as evidence for compensatory recruitment of visual and somatosensory cortices when participants receive vestibular stimulation (Hupfeld et al., 2022).

These cerebral adaptations should be interpreted within the context of substantially elevated radiation, altered gravity, and the associated changes in afferent sensory inputs, prolonged isolation and confinement, limited recreational activity, and the constant awareness of the hostile environment (real and perceived risk). The headward fluid redistribution in weightlessness is suspected to mildly and persistently increase intracranial filling and/or pressure (ICP), reduce the translaminar cribrosa pressure gradient, and impair glymphatic clearance (Lawley et al., 2017; Mathieu et al., 2017; Seidler et al., 2024a; Wostyn & De Deyn, 2018). Additional contributors may include elevated CO_2, dietary composition, radiation exposure, and in-flight resistance exercise (Lee et al., 2020; J. Ong et al., 2023). However, reliable in-flight monitoring of ICP remains elusive, and while non-invasive estimates exist, gold standard measurements such as lumbar puncture or ventriculostomy remain impractical during missions. Thus, most data are acquired post-flight, limiting insights into in-mission dynamics and individual variability (Stern et al., 2023).

Understanding how these environmental and physiological stressors influence cerebral structure and function is critical. While many findings to date stem from ~6-month missions aboard the International Space Station (ISS), future interplanetary travel will expose astronauts to longer mission durations, isolation, and limited communication and medical support. This highlights the importance of advancing brain health monitoring, identifying early indicators of dysfunction, and implementing effective countermeasures.

To address this challenge, the Brains in Space conference convened NASA medical and behavioral operations personnel, international researchers, and industry leaders. The goal was to align operational needs with emerging technologies in brain assessment and stimulation. The following sections summarize current risks and priorities in medical and psychological domains, before highlighting new approaches to brain monitoring and intervention that may support crew health and performance during long-duration exploration missions.

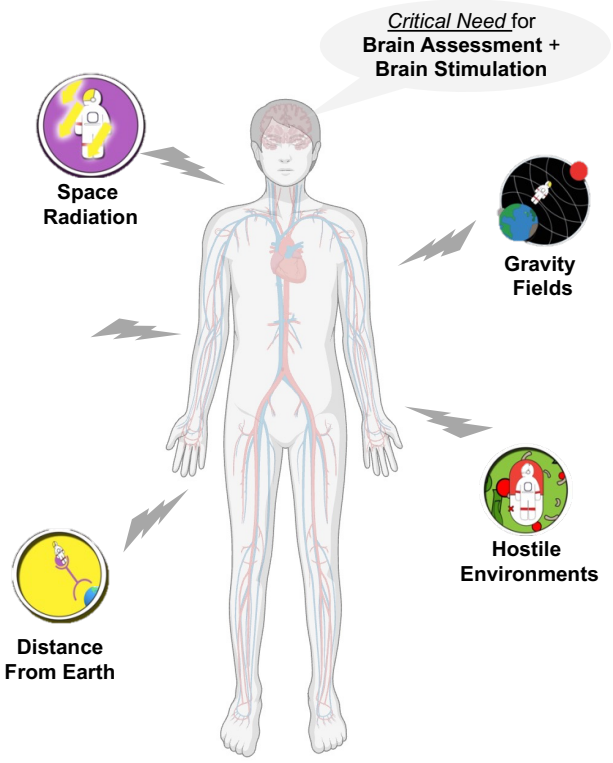

Figure 1: Multiple hazards provide risks for brain health and performance during long-duration spaceflight, demanding advanced techniques for assessment (i.e., monitoring) and stimulation (i.e., treatment).

Medical Operations – Current risks and needs

Besides adaptations in pressure, structural ocular changes have been observed in astronauts, including choroidal folds, optic disc edema, and globe flattening. These changes are grouped under the term Spaceflight-Associated Neuro-ocular Syndrome (SANS) and likely reflect broader alterations in fluid distribution and pressure gradients between the brain and eye (Petersen et al., 2022). While the exact mechanisms remain debated, headward fluid shifts and increases in intracranial pressure have been proposed as contributing factors (Roberts et al., 2017; Roberts & Petersen, 2019).

Mechanical changes, such as an upward shift of the brain and crowding around the sagittal sinus, could potentially cause impaired drainage of cerebrospinal fluid (CSF), which is supported by MRI findings of widening of the 3rd and 4th ventricles. Moreover, these adaptations may contribute to posterior globe flattening and neuro-ocular changes observed in SANS (Roberts & Petersen, 2019; Van Ombergen et al., 2019). These effects appear to increase with mission duration and may relate to impaired venous and glymphatic outflow (Macias et al., 2021; Roberts & Petersen, 2019). Current efforts aim to determine the role of pre-flight screening and predictive factors for SANS, additional biomarkers, and imaging to better monitor early signs and development (Zu Eulenburg et al., 2021a). Lower-body negative pressure (LBNP) is a promising countermeasure, as it can reverse fluid shifts and reduce cranial pressure (Lawley et al., 2020; J. Ong et al., 2023; Petersen et al., 2019).

Understanding the interconnected changes in the brain and ocular compartments remains critical for future medical operations. Non-invasive imaging, fluid biomarkers, and predictive modeling are increasingly viewed as necessary tools to assess and mitigate risks associated with long-duration spaceflight.

Psychological Operations – Current risks and needs

Interplanetary spaceflight implies long-duration isolation and confinement that might lead to increased stress and cortisol levels with negative effects on mood, cognitive processing, decision-making, and anxiety, resulting in an overall increased risk for depression. For missions on the International Space Station (ISS), standardized mood assessment tools, like the Profile of Mood States Questionnaire (POMS), have shown that tension and anxiety were linked to stress by human relations but remained within healthy limits (Sasahara et al., 2020). However, Tays et al. (2021) reported decreased sensorimotor control, balance, mobility, and bimanual coordination after spaceflight missions, which only recovered 30 days post-flight (Tays et al., 2021). Fortunately, assessments in low Earth Orbit (LEO) using the Cognition Test Battery and the Spaceflight Cognitive Assessment Tool for Windows (WINSCAT) have shown no experimental evidence for severe cognitive impairments for mission durations up to 200 days (Strangman et al., 2014). However, data on long-duration spaceflight is still severely limited. Several terrestrial analogs are in use to investigate short (i.e., < 3 months: e.g., HERA, envihab) and long mission durations (i.e., < 3 months: e.g., NEK, Concordia, Antarctica, Hi-Seas). For example, data from the terrestrial 500-day analog mission Mars500 suggested the highest stress levels at the beginning and toward the end of the mission (Rosenberg et al., 2022). These timepoints could coincide with critical mission tasks, like planetary landings.

Current countermeasures for behavioral health and cognition in spaceflight are individually tailored and include a rigorous astronaut selection pre-flight and operational support and monitoring in-flight, with private psychological conferences (PPC) conducted every two weeks. Cognitive performance is assessed using WinSCAT every 30 days in flight, and ROBoT-r offers an operationally-focused research tool (Ivkovic et al., 2019; Wong et al., 2020). So far, no systemic cognitive decrements have been reported in flight, but negative effects for long-duration interplanetary missions are anticipated, and novel monitoring approaches are warranted (Möller et al., 2025). Increased stress, delayed communication, and limited ground support can significantly impact operational performance, particularly during high-tempo operations. Previous recommendations for long-duration missions include the continuous use of WinSCAT and the adoption of the Automated Neuropsychological Assessment Metrics (ANAM) platform (Connaboy et al., 2020) or the Cognition test battery (Basner et al., 2015).

Monitoring psychological and cognitive function during long-duration missions remains challenging, particularly in environments with limited communication and reduced access to expert support. Current tools, such as WinSCAT, offer structured assessments, but they may lack the sensitivity or flexibility required for deep-space missions. To improve early detection and targeted intervention, novel approaches with proven clinical validity are warranted to monitor psychological health and cognition (De La Torre & Gonzalez-Torre, 2023). Techniques under consideration include wearable systems, immersive environments (e.g., virtual reality), and non-invasive brain stimulation, offering potential to maintain or restore function across cognitive, emotional, and sensorimotor domains.

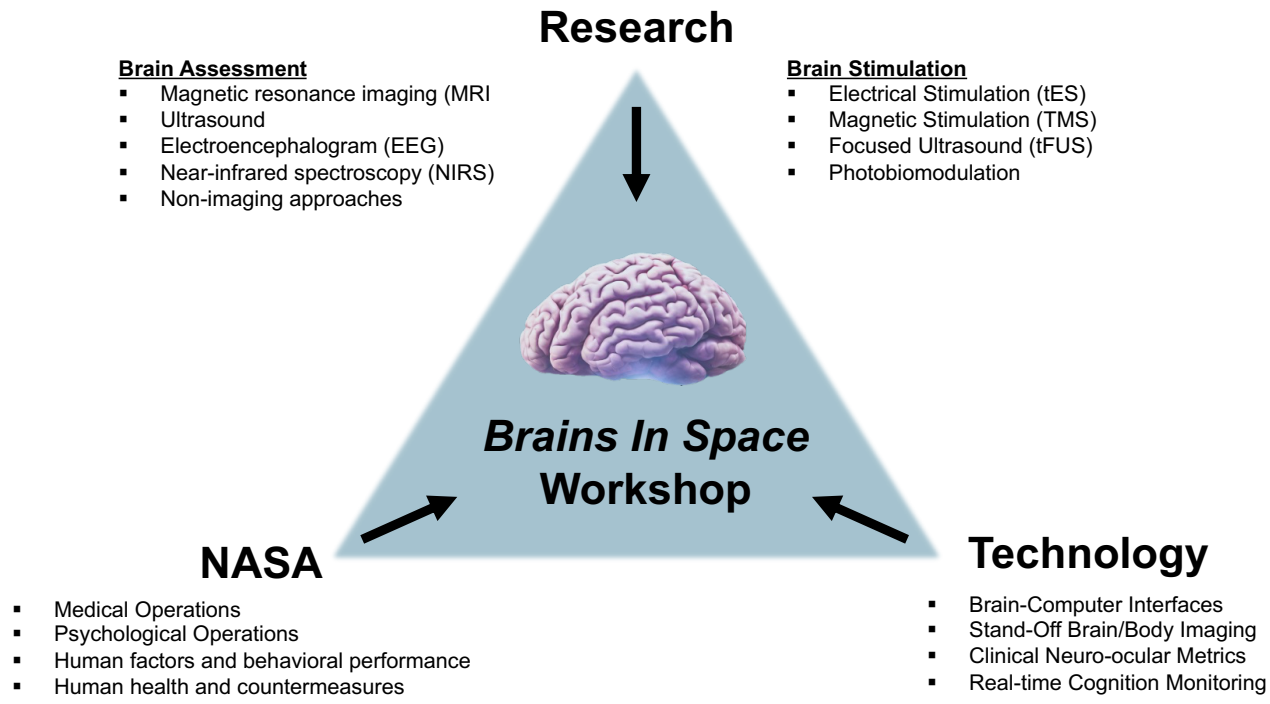

Figure 2: The Brains in Space workshop brought together NASA personnel from psychological and medical operations to communicate operational needs, research experts from the fields of brain assessment and stimulation, and industry leaders presenting state-of-the-art technologies. The Brains in Space workshop enabled open communication to advance the common goal of improving health and performance in spaceflight.

Brain imaging, assessment, and stimulation

Long-duration spaceflight presents ongoing challenges to crew health, safety, and mission performance, but also provides unique opportunities to study brain adaptation in extreme environments. As mission durations and autonomy increase, the ability to monitor brain function in real time will become essential. Cognitive and physiological fatigue, especially during extravehicular activity or surface operations, can compromise decision-making and crew safety. Future tools must provide not only post hoc evaluation but also real-time decision support and early warning of declining function.

In addition to structural and physiological monitoring, techniques must capture changes in brain function that include alterations in attention, cognitive load, sensorimotor coordination, and decision-making. These capabilities are especially relevant in contexts of fatigue, isolation, and high-tempo operations. Tools like EEG, functional ultrasound, or portable neurocognitive tests could offer real-time insights into mission workload and operational readiness. Simultaneously, imaging capabilities like MRI and ocular ultrasound may expand our understanding of cerebrospinal fluid dynamics, intracranial pressure, and glymphatic flow. These factors are implicated in both cerebral and ocular adaptations. Together, these methods could support more individualized brain monitoring and enable adaptive countermeasures that are responsive to changing physiological and cognitive demands.

In parallel, brain stimulation technologies might provide innovative approaches for intervention. Non-invasive methods like transcranial direct current stimulation or magnetic stimulation could support mood, cognition, and sensorimotor adaptation. For these technologies to be adopted in spaceflight, their benefits must clearly enhance mission-critical functions, whether by improving task performance, speeding up training, or reducing cognitive decline. Outcome measures such as attention, vigilance, navigation, and decision-making remain key targets.

The Brains in Space workshop brought together leading experts in neuroscience, clinical medicine, and space operations to explore these frontiers. The following section highlights cutting-edge techniques for both brain assessment and brain stimulation, outlining promising technologies and scientific priorities for brain health monitoring and stimulation during long-duration spaceflight.

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BRAIN ASSESSMENT

High-performance MRI pulse sequences and reconstruction

Emerging MRI techniques to assess brain physiology
My presentation covered three main topics,

- imaging neurofluids using MRI (cerebrospinal fluid (CSF), blood, interstitial fluid (ISF)),
- measuring intracranial pressure, and
- quantitative and mesoscale MRI

In the following, I expand on each of these topics and provide an overview for the acquisition techniques in each domain.

Imaging neurofluids: Neurofluids include blood, cerebrospinal fluid (CSF) and interstitial fluid (ISF) and play a critical role for brain homeostasis. Imaging blood flow and the hemodynamic response have been well established using techniques including phase contrast MRI (PC-MRI) and the blood oxygen level dependent (BOLD) functional MRI. Imaging CSF and ISF dynamics however is an emerging field. While tissues outside of the brain have lymphatic systems for clearance of metabolic waste, it was previously thought that the brain lacked such a system. About a decade ago, it was shown that this is not the case, and the glia-lymphatic (or glymphatic) system was observed and coined (1). According to this, CSF flows into the brain parenchyma via the periarterial space, and enters the interstitial space of the brain tissue via AQP4-controlled water channels. CSF entering the interstitial space removes waste proteins from the tissue, then flows into the perivenous space and is discharged outside the brain (2). Currently, there are three main ways of probing this phenomenon in the living human brain.

(i) Diffusion MRI (dMRI):
is a mature technique for measuring the Brownian motion of water molecules in tissue. A new application of this was in the diffusion tensor image analysis along the perivascular space (DTI-ALPS) technique (3). Here, white matter fibers where the direction of the perivascular space is expected to be perpendicular to the fiber tracts are identified. Projection and association fibers are used as exemplar regions of interest. The projection fibers lie in the head-foot direction and the association fibers lie along the anterior-posterior axis. Subcortical fibers run mainly in the right-left direction in subcortical areas. Consequently, in this area, the perivascular space runs perpendicular to the projection fibers and association fibers. Thus, the diffusivity along the left-right axis at regions with projection/association fibers will at least partly represent the diffusivity along the perivascular space. The ALPS index is defined as the average diffusivity along the perivascular space (i.e. the left-right axis) in the area of projection and association fibers, divided by the average diffusivity in the perpendicular directions. *It is expected that the major difference for water molecule behavior between left-right axis diffusivity in both areas and the diffusivity which is perpendicular to them would be the existence of the perivascular space*. In Alzheimer's patients, mini mental state examinations (MMSE) scores and ALPS indices were compared to reveal significant positive correlation, indicating lower water diffusivity along the perivascular space in relation to AD severity (3).
dMRI generates contrast using magnetic gradient fields which cause signal attenuation along the direction of the applied gradients. If the gradients are relatively strong, signal losses are primarily due to water diffusion in the parenchyma. However, when weaker gradients are used,

microcirculation of blood in the capillary network contributes to signal loss. Such parenchymal and blood perfusion are collectively known as intravoxel incoherent motion (IVIM). The diffusivity due to blood perfusion is an order of magnitude greater than the water diffusion in the parenchyma. In addition to arterial blood flow, IVIM can also probe CSF flow (4). Analysis of the diffusion data acquired at low to high gradient strengths (or "b-values") permit the differentiation of these compartments and visualization of CSF flow.

(ii) Phase-contrast MRI (PC-MRI): uses bipolar gradients (gradients played back to back with opposite polarities but the same amplitude/duration) to encode the velocity of moving spins into the phase of the MR image. By measuring changes in the phase, velocity of spins can be computed. CSF flow patterns across the whole brain can be estimated by using bipolar gradients that are sensitive to slow flow. With rapid acquisition techniques, it becomes possible to perform CSF flow mapping in ventricles and in the subarachnoid space across a cardiac cycle (5).

(iii) Gadolinium (Gd) injection: Serial MRI acquisitions following intrathecal administration of a Gd-based contrast agent in a woman revealed that the Gd contrast agent was distributed throughout the subject's brain over several hours (6), revealing the presence of the glymphatic system in humans after this was first observed in animal models. Such clearance of Gd-based agents is also observed in intravenous injections. However intrathecal and intravenous injections have their own specific routes of distribution and thus clearance of contrast agents. Because of clear differences in relative enhancement patterns, both injection approaches will result in varying sensitivities for assessment of different subparts of the brain clearance system (7). While Gd injection techniques might be considered gold standard in terms of CSF flow patterns, it should be noted that dMRI/PC-MRI methods and Gd injection approaches probe the movement of very different molecules (solvent vs. solute), thus their head to head comparisons/correlation analysis may not be straightforward.

Measuring intracranial pressure

PC-MRI can also be used to evaluate pressure induced by flowing blood on the vessel wall, i.e. the intravascular pressure. Vessel wall pressure can be estimated by first computing the force of the blood using partial derivatives of the blood velocity, which can be integrated along the vessel wall to yield the intravascular pressure (8). Similarly, the Navier-Stokes equation can be invoked to estimate the blood pressure in 4-dimensions (space+time) using PC-MRI, which has been demonstrated in the estimation of blood velocity and pressure in the aorta (9,10).

While these techniques have been deployed in estimating the blood pressure, a mathematical model has been developed to relate the intracranial pressure (ICP) pulse wave as the result of changes in cerebral blood volume which occur within a rigid space (11). This model illustrates that when ICP is low, the ICP pulse wave is largely different in shape from that of arterial pressure. However, the morphology of arterial and intracranial pressure pulse waves becomes similar when ICP tends to arterial pressure. As such, the estimation of blood pressure using PC-MRI could provide insights into ICP dynamics as well.

Quantitative and mesoscale MRI (qMRI):

Standard clinical MRI acquisitions are *qualitative* in the sense that the obtained voxel intensities are scaled arbitrarily and are dependent on the scanner hardware. Quantitative MRI (qMRI) aims to yield objective tissue-specific parameters which are robust to hardware imperfections. While these

biophysical parameters stem from a wide range of contrast mechanisms (including diffusion, flow and magnetic susceptibility), here I consider MR relaxometry, which characterizes T_1, T_2 and T_2* relaxation rates of the tissue. Relaxometry can help identify physiological changes undetected by qualitative imaging (12), provide specific information to characterize pathologies (13,14), help assess treatment response and repair processes (15), and detect disease before morphological changes appear (16). Importantly, qMRI demonstrates significantly higher inter-site reproducibility compared to standard contrast-weighted imaging (17).

Unfortunately, qMRI is encoding-intensive, and current techniques suffer from lengthy acquisitions (e.g., 3D MR fingerprinting at 1.2 mm isotropic resolution requires 12 min (18)). This challenge can be addressed by accelerating the 3D-QALAS sequence (19), which has shown strong correlation with reference T_1, T_2 and proton density (PD) values in the NIST/ISMRM system phantom and high reproducibility in brain imaging (20). Estimated parameter maps further lend themselves to the generation of contrast-weighted images (e.g., T_1-weighted) via Bloch simulation. Cortical thickness measurements from simulated T_1-weighted volumes had high repeatability and high agreement with standard T_1-weighted acquisitions (21).

Incorporating parallel imaging acceleration enabled a 3 min QALAS acquisition at 1 mm isotropic resolution capable of providing whole-brain T1, T2 and PD maps (22). It is possible to further push the acceleration by incorporating deep learning (DL) based image regularization into the reconstruction to boost the SNR and mitigate potential image artifacts. This way, a 2 min QALAS scan with high-fidelity and whole-brain coverage was developed, which also enabled the synthesis of standard contrast-weighted images that can be used for routine clinical reads (23). The training paradigm of the DL-based regularizer was fully-supervised and required the acquisition of an external training database comprising high quality images at low acceleration levels from several subjects. Such supervised training paradigms may not be feasible or applicable in certain cases, such as dynamic imaging where it is difficult to acquire high-quality data due to constraints on the achievable spatio-temporal resolution. DL models trained in such supervised manner may also fail to generalize to unseen test cases if the training dataset fails to capture the idiosyncrasies of the test data. To combat such issues, a self-supervised training paradigm was utilized to develop *zero-shot deep subspace* QALAS reconstruction (24). This DL regularizer is zero-shot in the sense that it only uses the acquired accelerated data to train the model for each individual subject, without the need for an external database (25,26). The zero-shot QALAS reconstruction retained the high fidelity of its fully-supervised counterpart, enabling a 2-minute acquisition at 1 mm isotropic resolution.

An additional hurdle in the reproducibility of qMRI is the differences due to sequence implementations in each specific scanner vendor. Since each vendor uses its own proprietary sequence development environment, it is challenging to ensure that the resulting sequence is harmonized across vendors. To address this issue, the open-source Pulseq sequence development environment can be used (27). Deploying QALAS using Pulseq allowed for improving the cross-vendor reproducibility in brain T_1 values by 1.1-fold, and T_2 values by 2.1-fold (28). This was possible by ensuring identical timing of sequence events and identical image reconstruction and post-processing steps.

Using the efficiency gain of ultra-high magnetic field systems allows pushing the spatial resolution of such qMRI acquisitions to mesoscale levels (i.e. 100s of microns). Capitalizing on the SNR boost of clinical 7T systems, T_1 mapping at 550 μm isotropic resolution using high parallel imaging acceleration and the efficient MP2RAGE sequence from a 6 min whole-brain acquisition was demonstrated (29). Likewise, using this SNR gain made it possible to push the resolution to 160 um

isotropic in time of flight MR angiography to resolve subtle pial arteries (30). Apart from ultra-high field scanners, emerging systems with ultra-high performance gradients such as the MAGNUS and Connectome 2.0 magnets open up the possibility to probe diffusion MR signals at mesoscale resolutions. Diffusion imaging involves the use of gradient fields to dephase the water molecules moving along the direction of the applied gradients to create contrast. The ability to switch the gradient fields rapidly helps complete this contrast encoding step as quickly as possible, thus maximizing the amount of signal available for image encoding. Using Connectome 2.0's ultra-high gradients (500 mT/m) and slew rate (600 T/m/s), the PRIME sequence was developed to enable high-fidelity, high-SNR diffusion imaging at 550 μm isotropic resolution while eliminating geometric image distortions conventional acquisitions suffer from (31).

Description of NASA-relevant applications and output variables:

- Emerging techniques use diffusion and phase contrast MRI as well as intrathecal/intravenous Gadolinium injection to assess flow of neurofluids.
- Phase contrast MRI is a mature technology for measuring blood pressure on vessel walls.
- qMRI enables the estimation of intrinsic biophysical tissue parameters with high reproducibility and lends itself well to detection of changes in the brain tissue in longitudinal studies with high sensitivity.

Challenges for implementation and possible solutions:

- While dMRI and PC-MRI are non-invasive techniques, intrathecal Gadolinium injection requires a lumbar puncture. Although intravenous Gd injection can also be used to image CSF clearance, this happens through a complicated biologic pathway. Another concern is that both intrathecal and intravenous injections for neurofluid imaging involve off-label use of Gd-based contrast agents.
- Assessing the correlation between dMRI, PC-MRI and Gd-injection techniques for CSF clearance is a topic of ongoing debate and work.
- It is unclear if it is straightforward to reliably estimate ICP from blood pressure estimates from phase contrast imaging through mathematical modeling.
- qMRI at the mesoscale resolution requires long acquisition times to reach adequate SNR levels, which raises concerns about robustness to subject motion. However, existing motion correction techniques can be used to largely mitigate this concern.

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Portable MRI Technology for Brain Imaging in Spaceflight

MRI brain imaging is critical to studying the effects of space flight on brain structure [1], [2], [3], [4], [5], but it has only been possible pre- and post-flight so far. The main drawback of traditional MRI is its lack of accessibility. Conventional MRI scanners are expensive (> $1M), large, and heavy (> 10 tons), and difficult to site. Consequently, an estimated 50-70% of the world's population lacks access to MRI [6], [7], [8], [9]. This has driven recent efforts to develop accessible low-field MRI, which could be extended for in-flight brain imaging in space.

This section focuses on advancements in portable MRI devices and their potential applications in brain imaging for astronauts. These innovations could enable serial MRI brain imaging in-flight to monitor changes and study the effects of spaceflight on astronaut brain structure, with a particular focus on Spaceflight-associated Neuro-ocular Syndrome (SANS).
Background on Low-Field MRI Technology

There is motivation to diversify MRI scanners, trading off some functionality for increased accessibility, to image in unconventional locations such as the patient's bedside in the ICU, rural clinics, LMIC hospitals, ambulances, or even in space. Renewed interest in low-field MRI is driven by the potential for increased accessibility and novel applications like portable brain imaging [9], [10], [11], [12]. However, the major downside of low-field MRI is the decreased signal-to-noise ratio (SNR), which scales proportionally between B_0 and $B_0^{7/4}$, depending on the field strength. As a result of the lower SNR, the resolution of low-field MRI is limited and scan times tend to be longer. Additionally, SNR-dependent sequences, such as diffusion-weighted imaging (DWI), are challenging, and imaging modalities based on magnetic susceptibility, such as SWI and BOLD fMRI, are also limited. Despite these challenges, the key advantages of low-field MRI include reduced weight, the elimination of traditional MRI safety hazards, and decreased power and cooling requirements, making it the only feasible choice for future spaceflight use.

Current and Upcoming Capabilities
Low-field MRI technology is advancing through the development of accessible scanners and purpose-built scanners optimized for specific clinical questions and body parts. There are several permanent magnet scanners are under development, utilizing rare-earth magnets to provide a consistent B_0 field without the need for power or cooling, making them ideal for portable scanners. New image encoding methods, such as RF encoding, are also being explored to reduce the need for traditional high-power gradient systems [13], [14], [15], [16] Specifically, efforts in Canada are focused on using Transmit Array Spatial Encoding (TRASE) in conjunction with low-field MRI to study bone and muscle loss in space [17], [18], [19], [20].

For future MRI brain imaging in space, the most promising recent innovations are head-only permanent magnet-based systems operating in the 0.05-0.2 mT range. These scanners are optimized specifically for brain imaging with a target 20-24 cm diameter field of view. To maintain a compact form-factor, the scanners often extend above the patients' head and stop at the shoulders. For instance, research at the Martinos Center at MGH and at Leiden University has showcased portable MRI brain scanners based on small cylindrical magnet with an approximately 30 cm clear bore. These magnet designs, based on the Halbach cylinder utilizing rotating magnet polarization,

ideally produce a B_0 field transverse to the cylindrical axis [21], [22], [23]. Halbach magnets offer an efficient field-to-weight ratio and a well-contained field pattern, which limits fringe fields and enhances scanner portability. For example, the scanner developed at MGH utilizes an 80 mT magnet measuring 56 x 48 cm and weighing 122 kg [24]. These systems have demonstrated compelling in vivo T1 and T2 imaging capabilities with a resolution on the order of 2 x 2 x 5 mm [24], [25].

Another popular magnet design is yoked dipole magnets, which use two permanent magnet pieces held in place by a high magnetic permeability yoke. The yoke and additional pole pieces guides the magnetic flux lines to create a homogeneous field, but also increase the weight of the magnet. This design is the foundation for several portable MRI brain scanners [26], [27], [28], [29] and a recent portable body imager [30]. The commercially available Hyperfine Swoop scanner also employs this design, with a 64 mT head-only magnet, 635 kg weight, and standard power operation [31] . It is portable and suitable for bedside imaging, demonstrated in various clinical application[32], [33], [34], [35].

Portable MRI scanners rely significantly on Electromagnetic Interference (EMI) mitigation techniques. Traditional MRI scanners are housed in RF shielded rooms to prevent external interference. Portable systems, however, operate outside shielded environments, and must utilize portable passive shielding or active methods to remove interference. To enable this, external detectors can be used to measure the EMI during the scan. The image EMI is estimated and removed use analytical algorithms [36], [37] or deep learning [38], [39] methods.

Current Challenges and Possible Solutions

The primary challenge associated with these compact, portable scanners is the signal-to-noise ratio (SNR) penalty inherent in low-field MRI. This can be partly addressed by exploiting low-field MRI's advantages, such as shorter T1 and longer T2 times for efficient pulse sequences. Lower field strengths also reduce RF heating risks and relax RF power constraints [40]. For instance, long spin-echo trains with frequency-swept RF pulses can be used without significant RF-related heating concerns [24]. Balanced steady-state free precession (b-SSFP) sequences, have a high SNR efficiency ratio at low-fields [40], [41], but face challenges like banding artifacts in very compact systems due to magnetic field variations. Other ongoing strategies to improve SNR include maximizing possible B_0 field strength and enhancing receiver coil sensitivity.

The second challenge is magnetic field inhomogeneity. As the magnet design becomes smaller relative to the imaging field of view, the uniformity of the field pattern decreases, and the electromagnetic gradient coils can become less linear. These inhomogeneities in the main B0 field and non-linearities in the gradient fields can lead to severe image distortion in portable MRI scanners. This issue can be mitigated by using model-based image reconstruction techniques that employ measured magnetic field maps [24], [42]. However, there are limits to distortion correction, and issues like signal pile-up in the images cannot be fully resolved. Therefore, it is crucial to design portable magnets that produce reasonably homogeneous fields and monotonic image encoding fields.

Currently, there are rapid advances in the use of artificial intelligence posed to improve low-field imaging in many ways. This includes methods to accelerate data acquisition [43], improve image

distortions [44], eliminate electromagnetic interference (EMI) [29], [45], and enhance images with "super-resolution" algorithms [30], [46]. Specifically, models have been trained to enhance 50-64 mT MRI images to appear like 3 T MRI images [30], [46], but more validation is needed to test accuracy and robustness in these AI enhanced images.

Despite the progress in portable MRI technology, there are still challenges in achieving the extreme portability and power budget required for spaceflight. While full-brain imaging is a possibility, alternative approaches include focusing on a specific, limited field-of-view target, such as monitoring ventricle volume changes. For instance, there are prototypes of extremely lightweight (<7 kg) single-sided MRI devices capable of imaging small, targeted volumes [47]. Additionally, some small MRI devices are designed to address specific questions without producing traditional image [48], [49]. Ultimately, achieving the desired functionality and image quality will require a tailored MRI scanner design (likely using a head-only permanent magnet scanner) that balances the B0 strength, size, field homogeneity, as well as the gradient fields obtainable with available power.

Conclusion

Low-field portable MRI could enhance NASA's research on the effects of spaceflight on brain structure and function. It could be used terrestrially for convenient and rapid pre/post-spaceflight brain imaging. But more importantly, in-flight scanners could enable serial brain imaging to continually assess changes throughout the flight, including structural changes associated with Spaceflight-Associated Neuro-ocular Syndrome (SANS). This capability would provide insights into the mechanisms of SANS and potential countermeasures.

Overall, low-field portable MRI holds great promise for improving brain imaging access both on Earth and in space. For NASA, this technology could become a crucial tool for studying and monitoring astronaut brain health, aiding in the understanding and mitigation of spaceflight-related health issues such as SANS.

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Electroencephalography in Human Space Exploration

Background

Operational safety and mission success depend on the health and well-being of the spacecraft's crew, including their physical, cognitive, and psychological performance. Risk matrices suggest negative effects on the brain due to prolonged exposure to the hazards of space (Antonsen et al., 2023; Kahn & McCoy, 2014), including microgravity, space radiation, isolation, confinement, and distance from Earth (Kahn & McCoy, 2014; *NASA Hazards*, n.d.; Seidler et al., 2024b). These factors have shown to have a significant effect on brain anatomy, cognitive performance and behavior, and are associated with conditions such as sleep deprivation, transient anxiety or depression and elevated stress(Seidler et al., 2024b).

Electroencephalography (EEG) and magnetoencephalography (MEG) are the only modalities that directly assess neuronal cell activity, in contrast to hemodynamic functional neuroimaging techniques, such as fMRI, fNIRS, PET or SPECT, which infer neuronal activity from cerebral blood flow and metabolic changes. Moreover, neurovascular coupling under microgravity conditions is not well understood or even explored, limiting the interpretability of hemodynamic modalities in spaceflight.

Importantly, EEG remains the only currently spaceflight-ready technology capable of directly and noninvasively recording neuronal activity with high temporal resolution. However, skepticism about in-flight EEG signal quality due to external interference persisted until recently (Fickling et al., 2019). Recent studies demonstrate the high versatility of EEG for brain monitoring in space (Cebolla et al., 2016, 2022; Cheron et al., 2014; Quivira-Lopesino et al., 2025) and the high signal quality with state-of-the-art devices (Fiedler et al., 2023; Radüntz, 2018), underscoring its operational relevance and readiness of this technology for future missions. Nevertheless, EEG utilization in space biology remains limited despite 64 years of human spaceflight activities (Fiedler et al., 2023; Frost et al., 1975; Maulsby, 1966; Parin et al., 1965; Pusil et al., 2023; Shirah et al., 2025; Sommariva et al., 2023), summarized in Figure 1, to a large extent due to limitations and constraints observed in earlier generations of EEG systems: the extensive preparation effort, post-experiment cleaning (scalp and hair hygiene due to conductive gels), stationary systems, and susceptibility to environmental interferences. However, all past operational issues with EEG have been overcome by modern EEG technology, electrode design, and analytical methods (Fiedler et al., 2023; Pusil et al., 2023; Shirah et al., 2025). Current systems are small, lightweight, mobile systems, with substantially reduced sensitivity to environmental noise. Dry electrodes that do not require conductive gel or paste enables easy, comfortable, and self-applicable EEG recording without extensive preparation or subsequent cleaning (Fiedler et al., 2023; Frost et al., 1975; Parin et al., 1965). Moreover, the state-of-the-art mobile EEG devices offer a large number of channels, enabling a high spatial resolution in high-density EEG (HD-EEG) and thus enhancing the understanding of neurophysiological events and the applicability of EEG (Fiedler et al., 2023; Graichen et al., 2015; Puce & Hämäläinen, 2017; Warsito et al., 2023).

The increasing autonomy required during deep space exploration missions necessitates advanced repetitive risk assessment, health monitoring, and clinical support tools (*NASA Human Research Roadmap*, n.d.). EEG provides an objective, portable, and non-invasive measure of cerebral functional integrity and resilience. EEG-based biomarkers, such as alterations in spectral power and

functional connectivity associated with workload, fatigue, and stress, have demonstrated utility in terrestrial operational and analog environments (Kirchner et al., 2010), supporting their potential for spaceflight application. The development of dry HD-EEG systems enables lightweight, rapid-setup monitoring that can be integrated into routine mission tasks.

In the spaceflight environment, where microgravity, circadian disruption, and elevated CO_2 levels may impact neurocognitive function, EEG could provide continuous monitoring to detect early detrimental changes and inform countermeasure development. While EEG is currently the most mature neurophysiological modality suitable for in-flight use, it may be further complemented by emerging tools such as functional near-infrared spectroscopy (FNIRS) and ocular metrics. For clinical applications, EEG could facilitate early detection of acute neurological events, though implementation will require artificial intelligence augmented and validated algorithms for automated interpretation. Overall, EEG represents a uniquely viable modality for supporting both operational neurocognitive assessment and clinical readiness during long-duration missions.

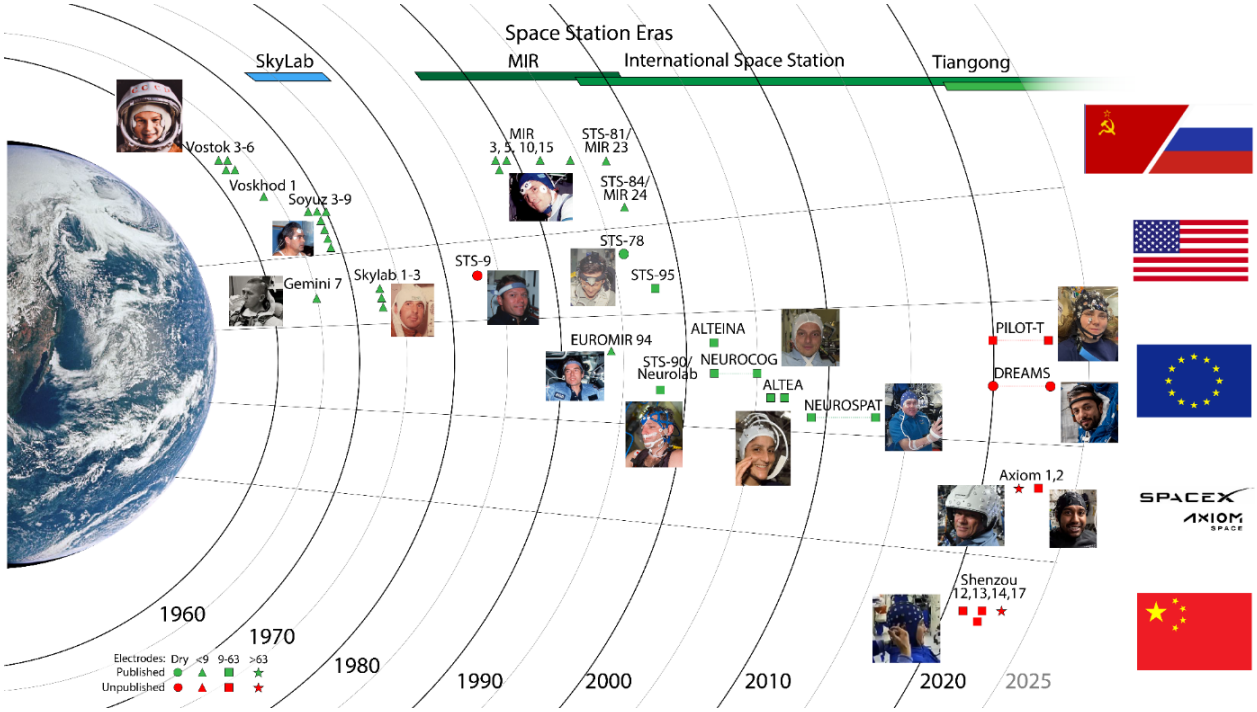

Figure 1: Timeline of EEG research in space. Most EEG studies were related to polysomnography (PSG) and sleep under the condition of micro gravity. Only relatively few studies focused on cognition. There is a renaissance of EEG research in the last few years aiming at operationally relevant problems like fatigue, brain-computer-interfaces (BCI), and other factors. (Courtesy M. Funke)

Current and upcoming capabilities of EEG

Electroencephalography (EEG) is a well-established modality in clinical care and neuroscience research, widely employed for diagnostic and monitoring purposes in conditions such as epilepsy, encephalopathy, and disorders of consciousness (Stoyell et al., 2021). Several EEG applications have direct operational relevance to space exploration, including seizure detection, evaluation of sleep and circadian regulation, assessment of cognitive workload, and monitoring of neural responses to stressors such as microgravity, radiation, and isolation. The engineering of digital EEG amplifiers is a mature field, and recent advances have happened in three domains: (a) sensor development, (b) signal enhancement, and (c) signal analysis. Each of these developments has implications for reducing crew workload, minimizing consumables, and enabling autonomous neurophysiological monitoring during long-duration missions.

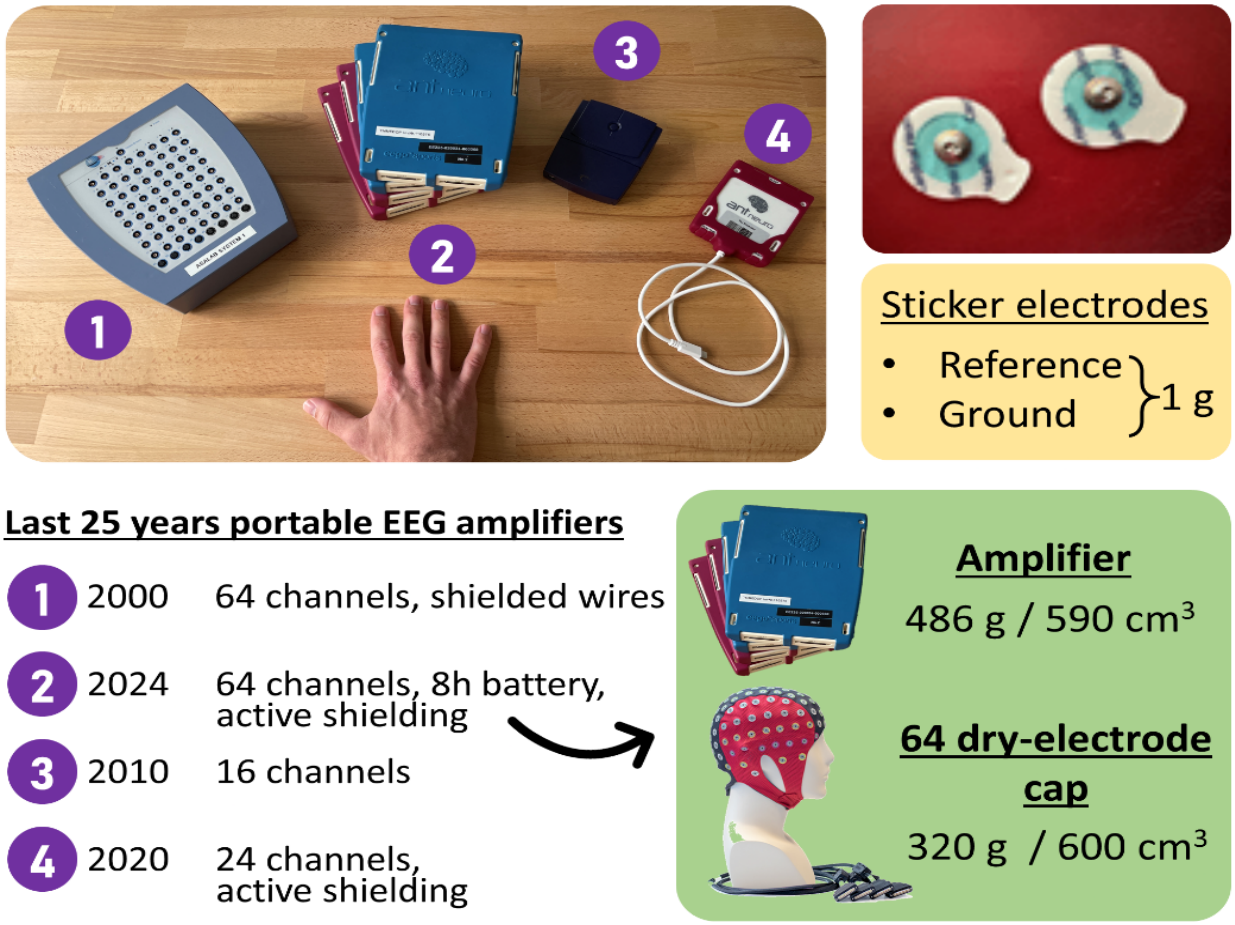

Figure 2: *An exemplary selection of EEG amplifiers from different manufacturers. Only the amplifier of example 2 has a built-in battery for independent operation. The stack of 4 amplifiers allows recording of up to 256 independent EEG channels. Example 4 is USB powered, hence the significant reduction in size. (Courtesy P. Fiedler)*

Sensor development

EEG sensors, or electrodes, detect microvolt-level potentials across a wide frequency range (<1 Hz to several hundred Hz) with high temporal resolution (up to 2 kHz in commercial devices). Modern miniaturized amplifiers achieve input impedances above 1 GΩ, permitting high-fidelity recordings

even when electrode–skin impedance is in the hundreds of kΩ range. This capability has facilitated the development of dry electrodes, which eliminate the need for conductive gels or saline, thereby reducing consumable mass, simplifying setup, and removing the need for technical assistance and post-session cleaning (Lopez-Gordo et al., 2014).

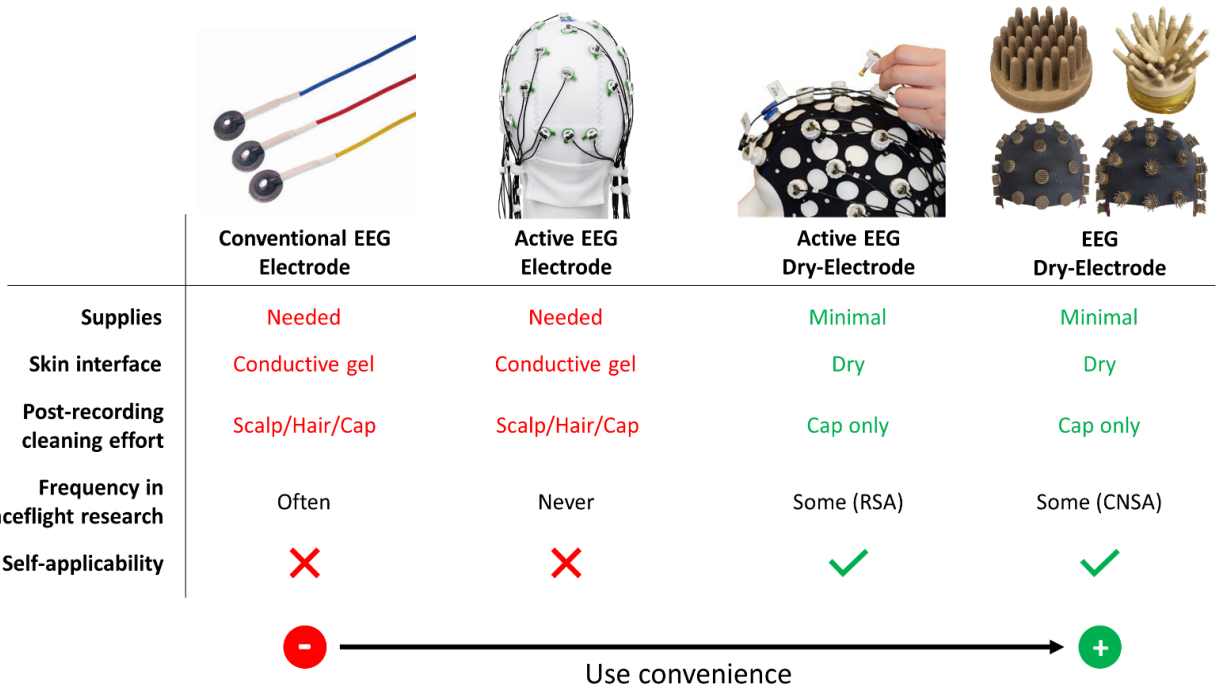

Figure 3: *Development of EEG electrodes technologies and their characteristics relevant to spaceflight applications. (Courtesy M. Funke)*

Signal enhancement

Substantial advances in signal enhancement have occurred over the past two decades (Puce & Hämäläinen, 2017). Methods now extend beyond traditional filtering to include automatic bad-channel detection and artifact classification/reduction. Machine learning algorithms and signal decomposition approaches, such as independent component analysis (Klug et al., 2024; Tamburro et al., 2018) and artifact subspace reconstruction (Yang & Lin, 2023), support reliable separation of neural activity from artifacts arising from muscle activity (EMG), cardiac activity (ECG), eye movements (EOG), and electrode motion.

Recent studies demonstrate that EEG can be acquired during naturalistic full-body movement (Tamburro et al., 2023), enabling assessment of brain-body coordination under operational conditions (Kirchner & Bütefür, 2022). New pipelines enable real-time artifact rejection, a requirement for in-mission monitoring where post-hoc analysis might be insufficient. Integration of EEG with auxiliary sensors (electrodes for EKG, EOG, EMG, accelerometers) further enhances the robustness of artifact correction during dynamic tasks (Markov et al., 2024; Niranjana et al., 2024). Collectively, these advances collectively support the feasibility of autonomous EEG monitoring in spacecraft environments, even under conditions of crew activity or movement.

Signal analysis

Over the past two decades, EEG analysis has shifted from qualitative interpretation of local activity to quantitative assessment of large-scale brain networks, enabled by HD-EEG systems with more than 64 electrodes in equidistant layouts. HD-EEG allows for source reconstruction, thereby localizing cortical generators of scalp signals and providing spatially resolved measures of brain connectivity. This paradigm shift has produced clinically actionable biomarkers in neurology, psychiatry, and cognitive neuroscience (Doesburg et al., 2008; J. M. Palva et al., 2010; S. Palva & Palva, 2007; Sadaghiani & Kleinschmidt, 2016). Modern EEG brain network analysis is mainly based on functional connectivity metrics, which measure the statistical interdependence between two remote EEG signals. Examples of functional connectivity metrics are the phase-locking value (PLV(Lachaux et al., 1999) and amplitude envelope correlation (AEC: (O'Neill et al., 2015)). Based on these, graph-theoretical approaches can subsequently characterize whole-brain networks. These parameters have been linked to cognitive processes including memory (S. Palva & Palva, 2011), attention (Doesburg et al., 2008), and inhibition (Sadaghiani & Kleinschmidt, 2016).

Additionally, recent work increasingly employs machine learning and deep learning to classify EEG signatures of cognitive workload, fatigue, or neurological impairment in real time (Roy et al., 2019). Such quantitative EEG (qEEG) tools have direct operational applications in spaceflight, including the potential for autonomous assessment of crew alertness, detection of early neurological compromise, and monitoring of neurocognitive adaptation to microgravity and radiation exposure.

NASA-relevant applications

Modern EEG systems outperforms earlier EEG systems specifically developed for spaceflight research (Maillet et al., 2007). Currently, EEG devices are compact, lightweight, portable, and require minimal power. They have extremely low need for supplies, generate negligible waste products, and do not require extensive crew time resources for operating (Lopez-Gordo et al., 2014). Moreover, they are highly resilient to the electro-magnetic environment of a typical crewed spacecraft (Fiedler et al., 2023), and on-board and ground-based data analysis can be automated, including with AI-augmented pipelines. Some space agencies have established, based on contemporary technology, permanent EEG research platforms in space within the last 25 years. NASA-funded EEG research has been absent since 1998.

The number of publications and available commercial systems for EEG highlight its versatility for brain monitoring, with a list of applications ranging from clinical routine and medical research, to mobile and home-side non-medical applications. Its operational adaptability, high temporal resolution, and ease of deployment enable multiple important use cases in LEO and long-term spaceflight missions. Key application categories include clinical scenarios, routine (periodic or continuous) monitoring, combination with other training or medical techniques for informed countermeasures and interventions, and research applications. Naturally, these use cases may overlap in part and increase continuously as EEG technology and research evolve on Earth.

Clinical scenarios

LEO operations permit rapid consultation with flight surgeons and, when necessary, medical evacuation within hours. However, the transition to increasingly heterogeneous crews and towards longer and further missions in the Moon and Mars, change this paradigm drastically. In this context, the pharmaceutical supply chain is severed, and the crew has to rely completely on the initial onboard

medical capabilities. Additionally, medical evacuation, if even possible, will likely result in the termination of the mission objectives. Finally, distance also conditions the response delay of Mission Control and flight surgeons (Diamond et al., 2025). All of these factors call for an increased medical autonomy of space crews, and EEG will have a foreseeable role as a diagnostic tool in specific long-distance spaceflight medical/clinical situations under these circumstances. Based on the medical condition list developed by NASA(Blue et al., 2019) and the NASA Human Research Roadmap (*NASA Human Research Roadmap*, n.d.), priority clinical fields include the following..

Seizures could be caused by different etiologies like traumatic brain injury, prolonged hypoxic conditions, or ingestions/inhalation of toxic compounds (Delanty et al., 1998). In this context, EEG is the only modality that can detect non-convulsive seizures, and that can verify seizure cessation (Brenner, 2004; Rossetti et al., 2024). This is especially relevant when seizures do not respond to the first and second dose of rescue medication, turning in a condition known as non-convulsive status epilepticus (Rossetti et al., 2024). EEG can objectify diagnosis by confirming ongoing seizure activity and confirming subsequent treatment success demonstrating abatement of cerebral seizure activity. Complementarily, the recorded EEG data could be sent back to mission control to receive further guidance from the medical team on Earth. This particular clinical scenario necessitates an EEG system with the following specifications: FDA-approved, easily deployable with limited training, wireless, and capable of AI-integrated detection of electrophysiological seizures to ensure crew autonomy. Interestingly, there already exist multiple point-of-care EEG systems that comply with the required features in the market.

Certain types of encephalopathy, a condition that causes overall brain dysfunction, could be caused by similar etiologies as mentioned above. For this specific clinical scenario, EEG can be used for diagnosis and prognostication, based on the detection of burst suppression patterns, post-accident status epilepticus, and non-reactive background activity (Carrasco-Gómez et al., 2021; Willems et al., 2021), providing valuable information to the team to assess the different courses of action to be taken, especially in the absence of any relevant onboard imaging capabilities.

Adequate sleep is essential for maintaining normal physiological and cognitive function, with sleep deprivation linked to impairments in decision-making, memory, attention, and alertness, factors especially critical for astronauts. The unique stressors of spaceflight, including microgravity, isolation, and radiation exposure, have been shown to negatively impact sleep quality, as evidenced by historical reports of sleep disturbances and the use of hypnotics by a high proportion of astronauts to induce sleep on demand (Barger et al., 2014). While polysomnography remains the gold standard for sleep assessment, its complexity makes it impractical for space. Alternatively, resting-state EEG offers a simpler, more feasible method for assessing brain activity and has demonstrated correlations with sleep quality, particularly through spectral and functional connectivity changes in various frequency bands (Corsi-Cabrera et al., 2016; Worley, 2018). Complementarily, wearable devices such as the Waveband diadem, based on dry electrode EEG, can provide sleep staging and analysis comparable to polysomnography (J. L. Ong et al., 2024), providing actionable insights on the astronaut’s sleep quality that cannot be obtained by actigraphy alone.

Routine monitoring scenarios

EEG is sensitive to operationally relevant changes in mental state and cognition. Routine EEG monitoring can therefore provide operational value by enabling early detection of detrimental changes. Such changes may manifest as fatigue, disorientation (as observed in Apollo 12), reduced cognitive capacity, performance decrements, or other neurocognitive symptoms. Continuous or periodic EEG surveillance can inform individuals, flight controllers, and team members about mental workload and capacity, thereby supporting operational decision-making.

Spectral and functional connectivity measures have been used to identify neuronal hypersynchrony, a phenomenon commonly observed in neurological and psychiatric conditions. Hypersynchrony is associated with amyloid-related toxicity to inhibitory neurons and can be detected in very early stages of clinically relevant changes in cognition, including in individuals with subjective memory complaints (García-Colomo et al., 2024; López-Sanz et al., 2017). Spaceflight has been shown to increase circulating amyloid and tau biomarkers (Zu Eulenburg et al., 2021b). Serial EEG assessments could therefore serve as an early noninvasive indicator of inhibitory neuron or microglial dysfunction during long-duration missions.

Quantitative EEG (qEEG) provides biomarkers for detecting and monitoring physical fatigue, mental fatigue, and cognitive load. Repeated EEG acquisition during activities known to induce stress, fatigue, or high workload allows tracking of these states over time, by measuring parameters such as the theta/alpha power ratio (Keskin et al., 2020) of EEG signals, or the amplitude of the P300 event related potential (Ismail & Karwowski, 2020) . Such monitoring could inform mission planning, for example by rescheduling tasks with high cognitive or physical demands, or adjusting the timing of EVA sessions to mitigate risk.

Research application scenarios

The NASA Human Research Program (HRP) has outlined five principal hazards to astronaut brain health (*NASA Hazards*, n.d.): microgravity, space radiation, isolation, confinement, and distance from Earth. Although some evidence has accumulated for the effects of these individual space-flight stressors, little information is currently available on the effects of their combined exposure on the brain, and the dynamics of recovery after return to Earth. As space missions extend to 1 year or longer, the cumulative effect of these stressors becomes even more critical. Characterizing this effect is necessary not only to ensure astronaut performance and completion of mission objectives but also to maintain crew health during and after the mission.

EEG has historically been used to study brain function under spaceflight conditions, from the earliest missions to recent work conducted by ESA, ROSCOSMOS, and CSA. Topics include the interplay between microgravity, noise, confinement, social interaction, and galactic cosmic radiation on neural activity. However, around 90% of this research has revolved around sleep. Consequently, future data collection should exclusively follow experimental settings comparable over multiple missions and astronauts. The development of standard research recording protocols, as previously proposed for MRI (Roberts et al., 2020), is needed for the advancement of spaceflight neuroscience, including EEG that could easily be implemented at specific timepoints of most missions.

EEG is frequently integrated with other physiological recordings to capture the complex interplay between central and peripheral nervous system activity as well as autonomic regulation. Multimodal studies often include ECG, EMG, respiration measures (effort, flow, volume), or metabolic indices (including fNIRS), all synchronized with EEG. This approach would enable a more comprehensive assessment of brain-body interactions under spaceflight conditions. Polysomnography represents the most extensively applied multimodal paradigm in space research. By combining EEG with ECG, EMG, and respiratory data, these studies have provided valuable insights into sleep architecture and disturbances in microgravity. Findings have highlighted alterations in both normal and abnormal sleep patterns, underscoring the importance of sleep monitoring for maintaining cognitive performance and crew health (Seidler et al., 2024b).

Another use of EEG is the development of EEG-based brain–computer or brain–machine interfaces, which can decode neural signals to control devices, adjust system settings, or support robotic operations. These applications are actively studied on Earth for workload reduction and performance support, and mainly use signal features such as P300 evoked potentials, sensorimotor rhythms, or visual steady-state evoked potentials (McFarland & Wolpaw, 2017). In spaceflight circumstances, BCIs could, for example, help astronauts control external devices during EVAs, though further in-situ research is needed to adapt terrestrial findings to space conditions.

Implementation Challenges

Translating EEG insights into operational practice requires overcoming several methodological, technological, and interoperability challenges. Addressing these gaps will be critical for establishing EEG as a standard tool in exploration-class missions.

Methodological challenges

Most available data derive from low-density EEG, often within the context of polysomnography, and provide limited spatial resolution. Critically, no longitudinal EEG studies of astronauts exist to date, leaving major gaps in knowledge about neurocognitive adaptation across mission phases. Systematic, high-density, and repeated measurements are needed to establish reliable biomarkers of brain function in space.

Technological challenges

EEG is inherently noninvasive, portable, and well-suited for spaceflight, yet several key developments are needed to optimize its utility. A permanent EEG research platform in space would enable standardized, continuous data collection across missions. EEG Data transmission protocols, also paramount for medical capabilities, must support both on-site storage and remote monitoring/analysis. To minimize crew workload, individualized, self-applicable headsets should be developed, ideally with high-density electrode arrays. High-density EEG should be prioritized to maximize versatility across clinical, routine, and research applications.

Interoperability challenges

EEG has the potential to inform and guide countermeasure development, such as neuromodulation approaches targeting oscillatory activity (e.g., tACS). To realize this potential, EEG should be fully integrated into NASA's broader human spaceflight research framework. This includes ensuring compatibility with third-party devices, standardizing interfaces for multimodal research, and establishing a permanent EEG research platform in orbit. Such integration would help close current knowledge gaps and enable EEG-derived biomarkers to guide both operational decisions and countermeasure strategies.

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Diagnostic and therapeutic ultrasound in the brain

The major anatomical challenge for ultrasound diagnostic imaging and image-guided therapy in the brain is two-way propagation through the skull.[1] Ammi *et al*.[2] performed intracranial measurements of the acoustic pressure field in five human skull specimens for 0.12, 1.03, and 2.00-MHz pulsed ultrasound to quantify phase aberration and attenuation. Transducer alignment relative to the skull was a significant determinant of the focal characteristics and acoustic field inside the skull. For optimal ultrasound penetration, insonation normal to the temporal bone was needed. The lowest ultrasound pressure reduction was observed at 0.12 MHz (22.5 – 25.5%). At 1.03 and 2.00 MHz, the ultrasound pressure reduction was 37.4 – 91.6% and 77.1 – 96,6%, respectively. The highest attenuation at 1.03 and 2.00 MHz was measured in two skulls which had an insufficient temporal bone. Thus, strategies to model, and compensate for both phase aberration and attenuation are needed to enable trans-skull ultrasound imaging of the brain, particularly at center frequencies above 1 MHz.

Bouchoux *et al*.[3] developed an accurate finite difference model of acoustic propagation through the skull based on computed tomography (CT) images. The computational approach, which neglected shear waves, was compared with intracranial measurements in four human skulls *in vitro*. High correlation between the predicted and measured transmitted wave amplitude ($R^2 = 0.93$) demonstrated that this model was suitable for a quantitative estimation of intracranial acoustic fields generated for sub-MHz ultrasound center frequencies. Acoustic simulations were also performed based on CT scans of 20 stroke patients to enable a protocol for transtemporal transducer alignment for consistent insonation of thrombi in the middle cerebral artery.[4]

Phase aberration correction using acoustic lenses provides an inexpensive and effective strategy for correcting distortion caused by ultrasound passage through the skull. Daniel *et al*.[5] employed a novel phase unwrapping technique to design multifrequency (0.25 – 1.0 MHz) acoustic lenses coupled with geometrically focused transducers. Though an uncorrected intensity map was highly distorted by the presence of a human skull at 1 MHz, the unwrapped lens exhibited tight focusing and achieved broadband aberration correction (see Fig 4a and 4b in Daniel *et al*.[5]). Favre *et al*.[6] tested the focusing capability of a sparse 2D, 1-MHz matrix array, constructed of 4 x 4 elements with compound diverging lenses made of Stycast 1090SI Epoxy (Henkel Loctite) and a supplementary layer made of elastic silicone (Elite Double 8, ZHERMACK) through a human skull. The -6 dB focal beamwidth was 2.3 mm with a sufficient point spread function to enable ultrasound localization microscopy *in vitro*.

Ultrasound localization microscopy is an emerging technique for super-resolution imaging of the microvasculature using FDA approved contrast agents consisting of micron-sized gas-filled cbles.[7] A post processing strategy is employed to track the centroid of scattering from individual microbubbles with sub-pixel precision.[8] By tracking individual microbubbles over successive image frames, not only can the morphology of the vascular trees be visualized, but also flow velocities can be obtained.[9] Functional ultrasound imaging detects transient changes in blood volume in the whole brain at superior spatiotemporal resolution than other brain imaging modalities such as functional magnetic resonance imaging.[10] Functional ultrasound imaging uses high frame rate plane-wave insonification and can measure changes in blood volume due to neurovascular coupling.[11] By combining these two techniques, exquisite functional ultrasound images of the rat brain have been

rendered after visual and optical stimulation.[12] Functional ultrasound images can also be rendered with ultrafast 3D power Doppler imaging without intravenous injection of an echo contrast agent.[12]

NASA has identified spaceflight-associated neuro-ocular syndrome (SANS) as a high priority health risk to astronauts in space.[13] Ocular and transcranial ultrasound imaging systems have been transported to the International Space Station and have contributed to the diagnosis and monitoring of SANS.[14] Ocular trauma or other ocular conditions, which can be significantly debilitating in space, can be detected and managed in spaceflight using ultrasound imaging.[15] With the advent of phase aberration techniques using acoustic lenses, future ultrasound imaging studies of blood flow in the neurovasculature, and cerebrospinal fluid and glymphatic transport might help explain the pathophysiology of SANS.

In recent years, a remarkable expansion of clinical applications of therapeutic ultrasound technology has been enjoyed.[16] Indications now span the clinical spectrum of neurological and psychiatric diseases, including FDA-approved incisionless magnetic resonance (MR)-guided focused ultrasound thalamotomy to treat essential tremor and tremor-dominant Parkinson's disease using thermoablation from the ExAblate Neuro 4000 system (InSightec, Haifa, Israel). This system utilizes a 1024-element phased array cap operating at 650 kHz in a 3T MR scanner (MR750, GE Healthcare, Milwaukee, WI, USA). Other neurotherapeutic applications depend on ultrasound-mediated blood brain barrier disruption to enhance drug delivery to treat neurodegenerative conditions such as Alzeimer's disease and Parkinson's disease.[17] A 256-element 400-kHz phased array, the NaviFUS® (NaviFUS Corp., Taipei City, Taiwan) device employs pre-treatment MR and CT imaging coupled with intra-operational neurosurgical navigation techniques.[18] Two SonoCloud® devices (CarThera®, Paris, France) avoid attenuation by neurosurgical implantation of either a single transducer or a 9-element matrix array to replace a section of the skull, which opens the blood brain barrier using low intensity 1-MHz ultrasound to enhance drug delivery to treat Alzheimer's disease and tumors in the central nervous system.[19-21]

Blood brain barrier disruption can also be utilized to release cancer biomarkers into the blood stream to enable diagnosis via simple venipuncture, termed "sonobiopsy".[22] This concept obviates the need for neurosurgical tissue biopsy, which carries significant risk. The technique utilizes a cylindrical array of 650-kHz transducers to insonify microbubbles after an intravenous injection of an echo contrast agent. Thus ultrasound-induced blood brain barrier disruption enables two-way trafficking between the brain and blood, allowing brain tumor-specific biomarkers to be released from the brain into the blood. Cordance Medical (Mountain View, CA) has licensed this intellectual property from Washington University in St. Louis[23] and has been granted breakthrough device designation by the U.S. Food and Drug Administration for clinical testing.

Microbubbles filled with a perfluorocarbon such as octafluoropropane and a bioactive gas stabilized with a phospholipid shell have also been designed to deliver xenon (Xe),[24,25] nitric oxide,[26] and oxygen,[27] into the bloodstream. The bioactive gas is released upon ultrasound exposure above the rupture acoustic pressure threshold.[28,29] Targeted delivery of Xe, a noble gas with antiproteolytic properties, using ultrasound sensitive microbubbles is under development for treatment of stroke and traumatic brain injury.[24,30-37] Color Doppler ultrasound-triggered release of Xe from microbubbles loaded with octafluoropropane and Xe (Xe-MB) was tested in a juvenile porcine intracerebral

hemorrhage (ICH) model[38,39] and compared to treatment with air-filled microbubbles (Air-MB).[40] Successful delivery of Xe to the brain was achieved via destruction of Xe-MB under color Doppler ultrasound guidance in the common carotid artery with a commercially available system. Ultrasound-triggered Xe delivery at a total dose of 48 µmol/kg over a 1-hour infusion produced over an order of magnitude decrease in apoptotic cell burden 1 mm from the hematoma (Figure 1). This pre-clinical ICH model demonstrated initial proof-of-concept and efficacy of Xe-MB for cerebroprotection.

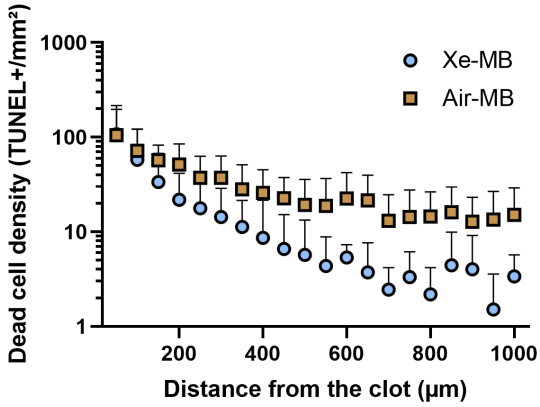

Figure 1. Apoptotic cell death density as a function of distance from the thrombus in the penumbra N=5 for Air-MB (sham) and N=5 for Xe-OFP-MB treatment protocols.

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Unobtrusive Cognitive & Emotional Assessments

Background

The past decade has seen an evolution in the technology and application of digital assessments of cognitive and emotional function. In particular, the field has evolved beyond mere digital versions of pen-and-paper assessments to passive technologies that utilize digitally captured biomarkers of function, such as eye tracking, retinal changes, and changes in voice or micro-movements.

The ubiquity of smart devices, including wearable technologies such as the Apple watch, aura ring, and a few specific headsets, has led to a revolution in our capability to identify early markers of all six areas of cognitive function as defined by DSM-V, complex attention, executive function, learning and memory, language, perceptual-motor function, and social cognition. Furthermore, advanced machine learning models have allowed us to extract novel features in data sets that correlate with known biological changes in the brain, such as hippocampal atrophy, synuclein changes, the presence of P-tau 218, the presence of amyloid beta and other indicators of brain-related changes associated with diseases such as Parkinson's Disease, Alzheimer's and other dementias.

Since the beginning of space flight with the Gemini and Apollo Missions, NASA has been using sensors to monitor the physical health of astronauts in space flight. Technology has evolved to allow us to go beyond elements of the four vital signs, such as blood pressure and heart rate, to measure the effects of space flight on brain function and associated volumetric changes in structure that occur in space flight. There is increasing evidence that spaceflight is associated with various adaptations of the brain, including intracranial fluid shifts, gray matter changes, white matter declines, and sensory reweighting and neural compensation (Klaus, 2019; Maruco et al., 2020; McGregor et al., 2023). Evolutions in microsensors and remote monitoring technologies represent the evolving capability to take real-time measurements during space flight, including using passive modalities, which are discussed herein.

How Technology is Changing Measurement Paradigms for Cognition

Table 1. Fourteen neurocognitive assessments covering five cognitive domains and dexterity were performed by a neuropsychologist. Shown are the group mean and standard deviation, range of score, and the correlation between each test and the cross-validated prediction constructed from the digital biomarkers for that test

Cognitive predictions			
	Mean (SD)	Range	*R* (predicted), *p*-value
Working memory			
Digits forward	10.9 (2.7)	7–15	$0.71 \pm 0.10, 10^{-4}$
Digits backward	8.3 (2.7)	4–14	$0.75 \pm 0.08, 10^{-5}$
Executive function			
Trail A	23.0 (7.6)	12–39	$0.70 \pm 0.10, 10^{-4}$
Trail B	53.3 (13.1)	37–88	$0.82 \pm 0.06, 10^{-6}$
Symbol digit modality	55.8 (7.7)	43–67	$0.70 \pm 0.10, 10^{-4}$
Language			
Animal fluency	22.5 (3.8)	15–30	$0.67 \pm 0.11, 10^{-4}$
FAS phonemic fluency	42 (7.1)	27–52	$0.63 \pm 0.12, 10^{-3}$
Dexterity			
Grooved pegboard test (dominant hand)	62.7 (6.7)	51–75	$0.73 \pm 0.09, 10^{-4}$
Memory			
California verbal learning test (delayed free recall)	14.1 (1.9)	9–16	$0.62 \pm 0.12, 10^{-3}$
WMS-III logical memory (delayed free recall)	29.4 (6.2)	18–42	$0.81 \pm 0.07, 10^{-6}$
Brief visuospatial memory test (delayed free recall)	10.2 (1.8)	5–12	$0.77 \pm 0.08, 10^{-5}$
Intelligence scale			
WAIS-IV block design	46.1(12.8)	12–61	$0.83 \pm 0.06, 10^{-6}$
WAIS-IV matrix reasoning	22.1(3.3)	12–26	$0.80 \pm 0.07, 10^{-6}$
WAIS-IV vocabulary	40.6(4.0)	31–50	$0.67 \pm 0.11, 10^{-4}$

To identify digital biomarkers associated with cognitive function, the team at MindStrong Health analyzed human-computer interaction from 7 days of smartphone use in 27 subjects (ages 18–34) who received a thorough neuropsychological assessment at baseline.

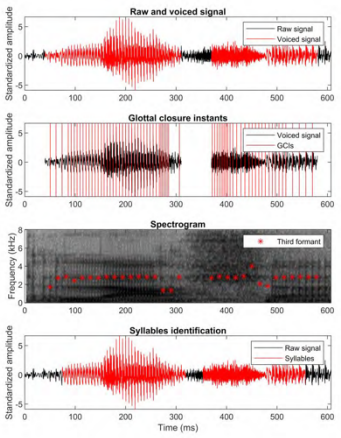
For several neuropsychological constructs (working memory, memory, executive function, language, and intelligence), the study found a family of digital biomarkers that predicted test scores with high correlations ($p < 10-4$). These preliminary results indicate that passive measures from day-to-day smartphone use could be a continuous ecological surrogate for laboratory-based neuropsychological assessment. The table at left shows the predictive p value correlates of passive smartphone digital biomarkers with gold standard measures of cognitive function in multiple domains (Dagum, 2018).

One of the primary ways users interact with their smartphone is through keypresses and related keyboard dynamics that are passively collected via a modern smartphone's virtual keyboard.

A recently published paper titled; Typing speed as a digital biomarker for processing speed: replication across studies reproduced prior work demonstrating that data derived from interactions with a smartphone keyboard can be used as a measure of processing speed. Also consistent with prior research, the keystroke data exhibits a consistent and reproducible diurnal pattern throughout the day (Alfalahi et.al., 2022).

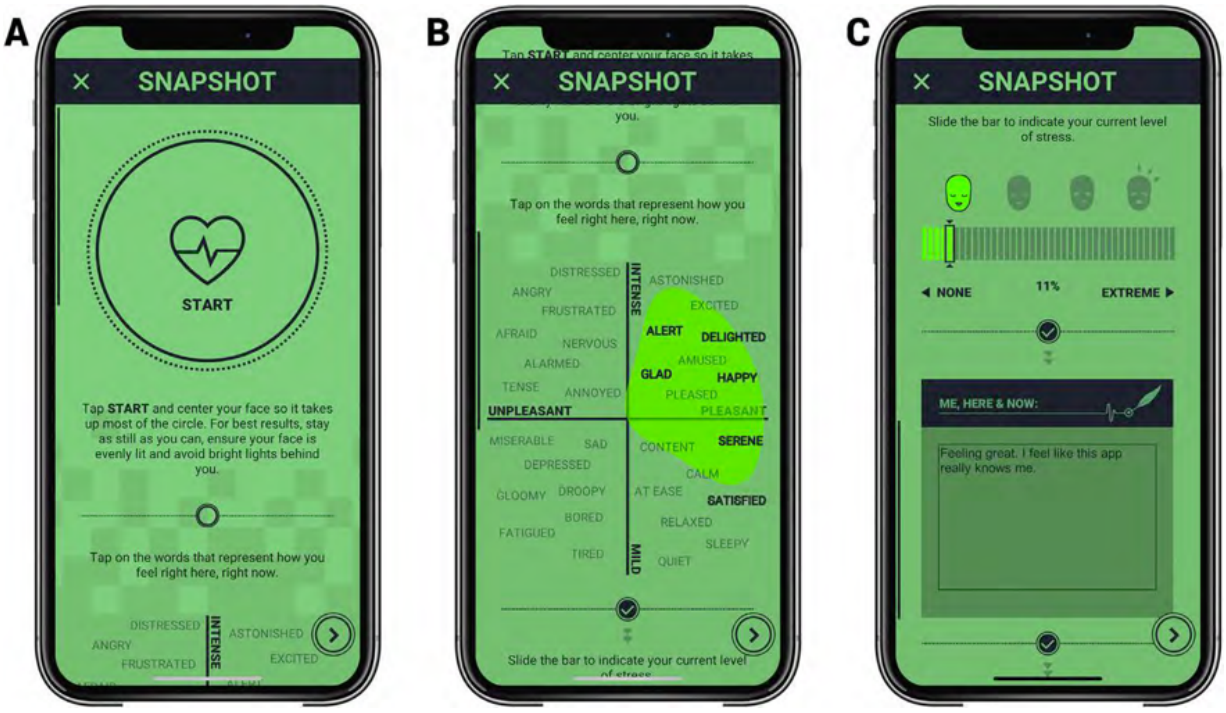
Another company, Keywise, has demonstrated keystroke dynamics refer to keypress-related metadata, for example, the general category of the keypress, the corresponding timing information of key down press and release time, incidences of autocorrect and other data collected on the smartphone keyboard but not the actual words written. From these data, we can confirm that typing on a smartphone keyboard utilizes multiple cognitive domains (Alarcon et al., 2024).

Another set of promising passive measures of cognitive function are alterations in speech associated with early changes in brain activity. The team at Ellipsis Health conducted a study to determine whether individuals with early mild cognitive impairment can be identified from those with normal cognitive function based on a set of acoustic features derived from spontaneous speech. The results are encouraging for further clinical evaluation. The study demonstrated that features derived from normal day-to-day ecologically collected free speech patterns can moderately discriminate between healthy controls and subjects with mild cognitive impairment (Ambrosini et al., 2019; see figure at right).



As camera and headset capabilities have evolved and become less expensive, eye tracking to detect early cognitive changes has emerged as a digital biomarker for deficits in cognitive function. Companies such as HarmonEyes and ViewMind are leveraging VR headset capabilities to track eye movements as measures of affective state, cognitive load, and cognitive function and even to differentiate subtle changes in eye movements that indicate early markers for differential diagnosis of diseases such as Parkinson's from PSP or essential tremor or Alzheimer's Disease from other types of cognitive impairments (Pina et al., 2024). Unlike passive monitoring utilizing smartphones, immersive environments represent unique opportunities to replicate advanced testing conditions and potentially replace traditional in-clinic neuropsychological batteries with shorter, more accurate guided experiences in VR and AR environments.

Finally, wearable sensors, including those embedded seamlessly into fabric, represent unique approaches to remote health monitoring, particularly for cognition and stress, including affective state. A study utilizing in-home sensors was recently published. It took on the challenge of assessment through the analysis of the indoor movements of the participants as a marker for cognitive status (Bowman et al., 2021). The methods included extracting visual cues from trajectories, considering sensor activations, their position and direction, object interactions, CRF and SURF, which are well-known features in computer vision tasks, the application of SMOTE, and incorporating classical ML algorithms. The results, based on a real-world dataset of cognitively healthy older adults and persons with known dementia, show promising short-term and long-term cognitive assessment accuracy. This model classifies trajectories into four distinct movement patterns: Direct, random, lapping, or pacing. Cognitively healthy (CH) individuals typically follow a direct path, whereas random, pacing, and lapping patterns are characteristic indicators of dementia. While still in the early stages of development, such technologies represent opportunities to accurately monitor health using remote sensors and identify changes early (Zupanc et al., 2024; Stein et al., 2024).



Mobi Health uses facial photoplethysmography (PPG) and deep neural networks to quantify how well therapy works for each patient objectively, and personalizes safe and effective treatments accordingly. The resulting “measure-treat-measure” system has been clinically demonstrated to reduce anxiety, depression, and stress across the full severity spectrum of mental illness in a multitude of randomized controlled trials. The visuals in Mobio presented in the figure to the left, give feedback on progress to both the patient and the provider to guide treatment efficacy.

Accurate measurement of human stress at scale is a major mHealth challenge. Mobio has harnessed the potential for deep neural networks (DNNs) to improve remote and objective stress quantification from voluntary selfie videos captured through mobile device front-facing cameras. Two DNNs were trained with heart rate (HR) and heart rate variability (HRV) data obtained through photoplethysmographic imaging (PPGI) of 11,823 mobile device selfie videos captured in tandem with self-assessments of stress (Chwyl et al., 2024). These were then compared to contemporary algorithms used to estimate stress from HR and HRV data. The results demonstrated a classification DNN and predictive DNN determined self-reported stress with 86 % accuracy and a mean absolute error of 0.001, respectively. While this study needs to be reproduced to confirm utility in a clinical environment, it demonstrated that well-trained DNNs can objectively and remotely quantify stress at scale (Krzyzaniak et al., 2024, Makki et al., 2024).

Finally, EEG, initially a leading technology to assess and monitor brain activity and function, has seen relatively less utilization. In contrast, eye tracking and other technologies emerged as interesting novel approaches. However, remote EEG represents a well-understood and valid approach to monitoring brain activity and function. Interaxon’s Muse headset has demonstrated the ability to record high-quality EEG, prompting researchers to investigate remote brain health monitoring capabilities. Investigations with the Muse EEG and the use

of ML techniques have demonstrated successful capability to detect stroke severity (Wilkinson et al., 2020), measuring pain (Pu et al., 202), stress classification Nishtha et al., 2022), trait anxiety detection, and measuring cognitive domains such as concentration, affective state, cognitive fatigue, and overall cognitive performance (Arsalan et al., 2022; Maddox et al., 2015).

Ethical considerations are raised by the collection, capture, storage and use of such sensitive personal data in ML algorithms. One consideration is that algorithms are as biased as the training sets that underlie their construction. This represents an ongoing challenge for developers and researchers to ensure that training sets are representative of variables such as sex, gender, ethnicity, and race, education, and income, as well as other factors that can influence algorithm generalizability. The issue of data privacy also arises as many users accept Terms of Service (TOS) and privacy policies without reading how their data will be used, and there is the ongoing debate about who owns a person's health record: the person, their insurance carrier, the technology company used to gather the data, or their healthcare provider. These are all ethical challenges that must be addressed, and regulators already lag in keeping pace with evolving data capture and analytics.

Conclusion

The clinical research in the technologies outlined here demonstrates the promise in large language models, affective computing, and the implementation of ML models to interpret signals from human interaction to revolutionize our ability to respond to passive sensor data with active inquiries as to state of mind or being at the time of measurement – this has the power to fundamentally change the way that we both assess cognitive and behavioral health as well as how we intervene early to prevent the evolution of disease; whether that is dementia or a mood disorder such as depression or anxiety. Passive sensor technologies to evaluate cognitive and emotional status have direct applications for spaceflight. The sensor technology that is already in use in spacecraft can be used to provide continuous monitoring of all individuals on board. The ability to passively monitor, apply models to predict likelihood of progression to disease state and to use technology to intervene early can impact human lifespan and human health span in space and here at home.

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BRAIN STIMULATION & COUNTERMEASURES

Transcranial electrical stimulation (tES)

Background - Non-Invasive Brain Stimulation Techniques

Understanding the short- and long-term impacts of extended space missions on brain function is crucial, and while physiological measurements can provide insights, exploring new strategies to enhance brain health and mitigate these effects is necessary. A recent review highlighted non-invasive brain stimulation (NIBS) as a novel approach to address potential negative impacts of spaceflight on astronauts' health (Romanella et al., 2020). NIBS techniques utilize electromagnetic principles to influence neural activity without invasive procedures, by generating electrical fields in the cortex (Rossi et al., 2009a). As a standalone solution, NIBS offers a portable, safe, and remotely controlled method for neuroenhancement, which can be used to monitor changes in brain health and counteract disruptions in brain activity and cognitive performance. Furthermore, NIBS protocols can be applied while participants engage in tasks, allowing for integration with other interventions. Research has demonstrated that NIBS can enhance cognitive and motor performance, with benefits extending to real-world scenarios such as improving the performance of professional athletes, soldiers, surgeons, and Air Force pilots (Ciechanski et al., 2017, 2018; McKinley et al., 2013a; Okano et al., 2015). Given these promising outcomes in ground-based populations, NIBS may be a valuable tool for boosting astronauts' visuomotor and cognitive skills during space missions, potentially improving training efficiency and mitigating space-related stressors.

Among NIBS techniques, transcranial electrical stimulation (tES) stands out as a promising tool for space exploration. tES modulates neuronal activity using a weak electric current (typically 1 to 4 mA) delivered through scalp electrodes, altering membrane excitability without causing neuron action potentials. Different tES protocols can adjust cortical excitability and synchronize brain oscillations (Paulus, 2011a). The main approaches within tES are transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). These techniques have been applied in various cognitive tasks, demonstrating improvements in mental functions such as alertness, multitasking, language, visuomotor coordination, visual acuity, and working memory (Brunoni and Vanderhasselt, 2014; McKinley et al., 2013b; Santarnecchi et al., 2017). They have also enhanced higher cognitive functions like abstract reasoning, fluid intelligence, and insight (Dockery et al., 2009; Santarnecchi et al., 2013, 2019). The safety and portability of tES make it especially appealing for clinical and research applications (Antal et al., 2017).

tDCS: This technique involves applying a low-amplitude (0.5-2 mA) direct current to modulate brain excitability by altering neuronal membrane potentials depending on the direction of the electric field. Anodal tDCS increases excitability under the anode, while cathodal tDCS decreases it under the cathode (Nitsche et al., 2005). Anodal tDCS over the motor cortex (M1) has been shown to enhance motor-evoked potentials (MEPs), whereas cathodal tDCS reduces them (Paulus, 2011). tDCS affects neuronal firing thresholds, potentially increasing levels of glutamine and glutamate (Hunter et al., 2009) and/or decreasing γ-aminobutyric acid (GABA) concentrations (Bachtiar et al., 2015; Stagg et al., 2011). NMDA receptor-dependent mechanisms and brain-derived neurotrophic factor (BDNF) also contribute to its effects (Fritsch et al., 2010; Liebetanz et al., 2002; Nitsche et al., 2003).

tACS: This technique involves delivering an alternating current that shifts between positive and negative electric fields, thereby inducing periodic changes in the transmembrane potential. tACS aims to synchronize brain oscillations with the stimulation frequency, potentially enhancing control over brain activity and behavior. By modulating cortical oscillations at specific frequencies, tACS has shown effects on various cognitive domains including sensorimotor, visual, and higher-order cognitive functions (Feurra et al., 2011, 2013; Kanai et al., 2008; Polania et al., 2012; Santarnecchi et al., 2013, 2017, 2019).

tRNS: Unlike other tES techniques, tRNS uses random noise with a broad frequency spectrum (0.1–640 Hz) to increase cortical excitability. This approach is believed to enhance cortical plasticity through mechanisms like repeated sodium channel activation or stochastic resonance, where noise amplifies weak signals (Terney et al., 2008; Miniussi et al., 2013). While research on tRNS is still developing, preliminary studies suggest it can improve performance in motor, sensory, and visual tasks (Fertonani et al., 2011; Terney et al., 2008). For example, tRNS applied over visual areas has been shown to accelerate learning in motion integration tasks, with benefits persisting long after training (Herpich et al., 2019).

Current and upcoming capabilities of the technology

Non-invasive brain stimulation (NIBS) holds potential as a valuable tool for (1) enhancing motor learning during Earth-based pre-flight training. Additionally, various NIBS techniques might (2) lessen the impact of spaceflight-related factors such as interplanetary cosmic exposure (ICE), microgravity, and cosmic radiation on brain health during space missions or extended planetary surface stays. This could be achieved by promoting psychological well-being and preserving cognitive performance` when used in conjunction with different training or therapeutic methods, as well as by directly addressing disruptions in brain activity.

While the potential of NIBS protocols to influence cognitive and motor functions is well-established and frequently replicated, it is crucial to consider factors that might affect stimulation outcomes (see Krause and Cohen Kadosh, 2014 for a comprehensive review). Space-related stressors induce changes in brain anatomy, including variations in cerebrospinal fluid (CSF) volume and distribution, alterations in gray matter, shifts in the skull-to-brain distance due to upward brain displacement, and modifications in brain oscillations and regional cortical activity (Roy-O'Reilly et al., 2021). These changes may affect how electrical signals propagate in the brain, leading to different neural network activations compared to normal gravity conditions. Consequently, biophysical modeling studies are recommended to validate NIBS applications in space. By utilizing individual neuroimaging data, such as structural Magnetic Resonance Imaging (MRI), it is possible to predict the electric field distribution resulting from transcranial electrical stimulation (tES). Software models employing biophysical algorithms have been developed to create realistic 3D head models for simulation purposes (Saturnino et al., 2019; Thielscher et al., 2015). Personalized models offer better control of the electric field, enhancing the efficacy of NIBS for space exploration. A recent study demonstrated this by simulating the electric field induced by transcranial magnetic stimulation (TMS) over various brain regions using MRI T1-weighted scans from 15 Roscosmos cosmonauts before and after an average of six months on the International Space Station (ISS), and seven months post-re-entry (Romanella et al., 2023). This computational analysis revealed differences in the TMS-induced electric field in the primary motor cortex (M1) and angular gyrus of cosmonauts compared to controls, attributed to

functional and structural changes associated with spaceflight. The study optimized stimulation protocols based on observed brain changes, offering solutions to compensate for potential differences in the electric field due to spaceflight. This personalized NIBS approach can enhance potential benefits and serve as a foundation for its application in space missions.

Going further, transcranial electrical stimulation (tES) can be combined with electroencephalography (EEG) recording (tES-EEG). In this setup, tES protocols are integrated with neurophysiological tools like EEG to improve experimental insights (Boyle et al., 2013; Roh et al., 2014). EEG measures the state of cortical areas affected by tES, whether at the stimulation site or connected regions, and assesses changes in connectivity and excitability within a functional network (Miniussi et al., 2012). EEG recording enables the analysis of Event-Related Potentials (ERPs), which are EEG responses time-locked to specific external or internal stimuli (Buzsáki, 2009). The amplitude and latency of ERPs in response to sensory, visual, or auditory stimuli can reveal how tES modulates activity in specific cortical regions (Miniussi et al., 2012). Additionally, rhythmic approaches such as tACS-EEG can be employed to evaluate changes in brain oscillation frequencies within specific areas or across the entire brain (Miniussi and Thut, 2010; Thut and Miniussi, 2009).

Ootential applications of transcranial electrical stimulation (tes) in space exploration

Motor Learning. Effective motor learning and consolidation are crucial for operating the Space Station Remote Manipulator System (SSRMS) on the International Space Station (ISS). Proper handling of this robotic arm is vital for advanced repairs on the ISS, necessitating extensive training on pre-planned motor patterns and sequences using various simulators. Astronauts must maintain high levels of visuomotor coordination, multitasking, and sustained attention. In this regard, tDCS has been used to enhance motor learning and procedural skills (Buch et al., 2017). tDCS has been demonstrated to improve both overall motor performance and specific aspects of motor learning and consolidation (Kang and Paik, 2011; Krause et al., 2016; Orban de Xivry and Shadmehr, 2014). Its effects can last for months due to its influence on brain plasticity. For instance, Reis et al. (2009) found that tDCS applied over five consecutive days, combined with a motor learning task, improved performance not only during the task but also for at least three months afterward. Similarly, tRNS applied to the motor cortex (M1) for 10 minutes has been shown to enhance implicit motor sequence learning and produce excitatory aftereffects lasting up to 1.5 hours (Terney et al., 2008).

Attention, Vigilance, Working Memory, and Multitasking. Strangman (2014) reviewed cognitive functions in spaceflight, noting anecdotal reports of difficulties with attention, cognitive slowing, and memory issues despite no significant empirical evidence of cognitive decline. Studies have suggested that cosmic radiation can induce cognitive deficits through synaptic pruning (Britten et al., 2016, 2012; Chakraborti et al., 2012; Denisova et al., 2002; Lonart et al., 2012; Parihar et al., 2018). Given these concerns, tES applications for improving vigilance, attention, multitasking, and working memory are particularly relevant for long-duration space missions. For example, a study by the U.S. Air Force showed that tDCS enhanced vigilance and target detection in pilots. In this study, 27 Air Force pilots underwent 90 minutes of preparatory training during a tDCS session (2 mA for 30 minutes, anode positioned at F10 on the forehead). Anodal tDCS improved visual search accuracy by about 25% compared to a sham group (McKinley et al., 2013). This method could be beneficial also for mission control operations on Earth.

In a related study, the same research group applied anodal tDCS over the dorsolateral prefrontal cortex (DLPFC) to 20 participants, enhancing multitasking abilities and improving information processing compared to a placebo (Nelson et al., 2016).

Sleep. Space missions often report sleep issues, including sleep loss, fatigue, and poor quality, attributed to disrupted light-dark cycles, noise, and altered circadian rhythms (Barger et al., 2014; Dijk et al., 2001; Stampi, 1994). Increased noise levels on the ISS have sometimes required anti-noise earplugs. Although some studies suggest minimal differences in sleep patterns compared to Earth, a reduction in total sleep time and alterations in circadian rhythms have been noted (Dijk et al., 2001; Frost et al., 1976). Sleep disruptions can impact performance, leading to errors, anxiety, and higher cortisol levels (Buckey, 2006). Reduced melatonin levels in microgravity have also been reported (Holley et al., 1991). While medication is generally avoided due to side effects, some sleep aids have been used with medical approval.
tACS has been investigated as a means to enhance sleep quality by targeting slow-wave sleep (SWS). Ketz et al. (2018) used closed-loop tACS to match SWS during NREM sleep, improving sleep efficiency and increasing SWS. Saebipour et al. (2015) found that 0.75 Hz tACS during SWS in insomnia patients deepened sleep, decreased time spent in lighter sleep stages, and reduced wake time after sleep onset. Atri et al. (2016) applied tACS at 5 Hz on the frontal area to induce sleepiness, demonstrating changes in subjective sleepiness and EEG activity.

Depression. Depression and anxiety can significantly impact mission performance, as evidenced by historical space missions and Antarctic expeditions (Kanas and Manzey, 2008; Linenger et al., 2000). Even though depressive and anxious states are often subjective, they are recognized issues among astronauts (Barger et al., 2014). Cosmic radiation has been linked to anorexia in animal models (Fajardo et al., 2001; Hunt et al., 1989; Rabin et al., 2000, 1994, 1991, 1989).
tES has been used to alleviate symptoms of various neuropsychiatric disorders, including depression. Traditional tDCS protocols typically involve stimulating the left DLPFC. Although initial studies showed mixed results (Boggio et al., 2012; Fregni et al., 2005; Loo et al., 2010), recent extensive trials have demonstrated positive effects. The largest randomized study (n=120) compared tDCS with sertraline and found that tDCS was superior to sham and sertraline monotherapy in reducing depressive scores (Brunoni et al., 2013).

Positive mood effects have also been observed in healthy subjects, often as a secondary benefit in experimental paradigms. Marshall et al. (2004) reported mood improvements with anodal tDCS on bilateral DLPFC, while McIntire et al. (2017) found reductions in depressive scores and increased task engagement following tDCS in sleep-deprived participants. These findings suggest that tDCS may help mitigate stress-related effects, such as fatigue, potentially improving mood in both clinical and healthy populations.

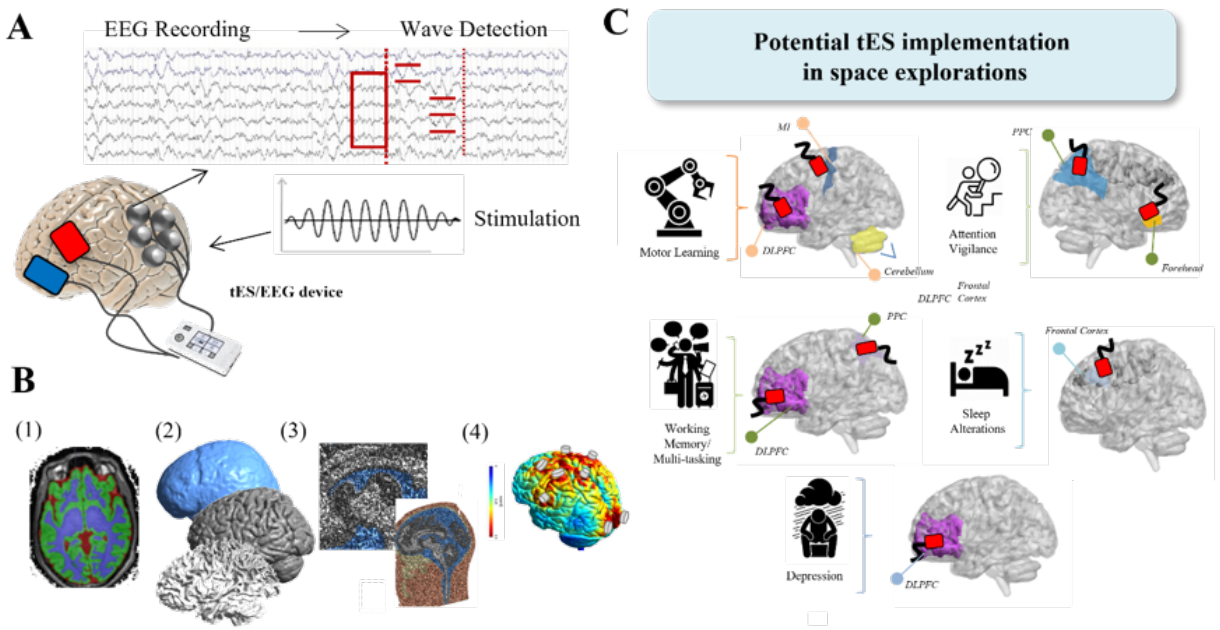


Figure 1: Panel A: Transcranial Electrical Stimulation (tES). tES consists, at minimum, of two electrodes (red anode, blue cathode) applied directly on the scalp. More channels can be added to extensively record EEG or modulate brain activity via so-called multifocal/multielectrode protocols (Ruffini et al., 2013). **Panel B. Biophysical modeling and personalized NIBS simulations.** To increase NIBS efficacy and precision, we can personalize the stimulation setting and parameters, thanks to individual neuroimaging data. We segment the T1-weighted anatomical image for each subject into class types (skin, bone, CSF, eyes, gray matter, and white matter). For better visualization, we show segmentation of CSF (red), gray matter (green), and white matter (blue; B1). We can then calculate the head volume of 3D meshes composed of tetrahedral elements (CSF: blue; gray matter: gray; white matter: white; B2 and B3). Personalized tES simulations are run to compute the current reached by the chosen cortical region of interest (ROI) for everyone. Furthermore, we can run optimization algorithms to find the best position/orientation of the coil/electrodes to increase NIBS's beneficial effect and specificity and compute the resulting electric field (B4). **Panel C: Potential Applications in Modulating Brain Health and Improving Performance.** We offer an example of potential applications of tES methods (with a focus on anodal tDCS) in domains relevant for spaceflight and Moon or Mars installations.

Considerations for non-invasive brain stimulation (NIBS) in space

While NIBS techniques have demonstrated high safety and effectiveness in both healthy and clinical populations (Antal et al., 2017; Rossi et al., 2009), their application in space missions requires careful consideration. Space environments, such as the ISS, spacecraft, the Moon, and Mars, differ significantly from Earth in factors like temperature and pressure (NASA IG-18-021), which could potentially affect stimulation devices. Therefore, in-flight NIBS applications need thorough testing. Below, we explore the feasibility of NIBS techniques and address the unique environmental characteristics that must be evaluated to ensure the technology meets the requirements for TMS/tES devices. We also consider how cerebrospinal fluid shifts in microgravity might present new challenges for brain stimulation.

Environmental Challenges

On Planetary Surfaces: On Earth, NIBS technology is used in clinical settings with the support of trained specialists and technical assistance. In contrast, environments on other planets like Mars or the Moon are less controlled. If the equipment survives the spaceflight, it will encounter extreme temperature fluctuations and potential radiation. Additionally, the equipment must be operated by crew members with limited training, and communication with ground control may be delayed, especially on Mars with a minimum 20-minute delay. Thus, testing both hardware and software in these conditions is crucial (Seyedmadani, 2019).

During Launch or Recovery: Given the constraints of volume and cost, lightweight, compact devices are preferred. Payloads launched on cargo systems experience variable gravity, temperature changes, and intense vibrations. Consequently, any technology chosen for space missions must withstand these conditions (Duncan, 2007).

On Board Spacecraft: Within spacecraft, environmental conditions such as temperature, humidity, and oxygen levels are regulated. For tES to be effective, the conditions must match those onboard. For example, the ISS maintains atmospheric pressure at 101.3 kPa (NASA/TP-2015–218570), which is just above the device's operational range (700-1,000 hPa). Weightlessness affects hardware performance, including heat dissipation, and radiation effects need further investigation.

Technological Requirements

Beyond environmental factors and launch limitations, available technology resources on the spacecraft must be carefully selected. NASA guidelines, such as SSP 30423 and MIL-STD 810-G, are followed for hardware used on the ISS. Considerations include material compatibility, thermal management, limited resupply options, the prohibition of lithium batteries due to fire risks, control of electromagnetic interference (EMI), radiation impact, toxicity, and crew training requirements.

While tES devices are generally simple to use, issues such as the supply of gel electrodes and EMI limitations during sessions need addressing. Another concern is the potential impact of solar particle events on current levels during stimulation protocols. Additionally, tES software must be compatible with onboard technology, and EEG data management requires space and time for downloading. Crew training is essential for managing and adjusting protocols. The interaction between software and hardware via WiFi or Bluetooth depends on spacecraft capabilities. Radiation and particle events could affect the system's electrical board, potentially causing false readings. Therefore, comprehensive radiation testing is necessary for the device.

TRANSCRANIAL MAGNETIC STIMULATION AND HUMAN SPACEFLIGHT

A. Background introduction to TMS

Transcranial magnetic stimulation (TMS) is a medical device that can be used to safely and non-invasively stimulate the brains of awake individuals to induce neuroplasticity as a treatment for various brain disorders.[1] TMS first received approval from the U.S. FDA in 2008 for the treatment of depression[2,3] and is now used in psychiatric clinics throughout the US[4]. TMS has also received FDA approval for the treatment of obsessive compulsive disorder and for the treatment of migraine headaches and pain. Demonstrating its versatility as clinical tool, it is currently under investigation for numerous additional applications in behavioral health and performance, including sensorimotor neuroplasticity/stroke rehabilitation, sleep disorders, vestibular disorders, treatment of anxiety, and to promote resilience and enhance cognitive function.[5]

TMS is able to focally stimulate the superficial cortex by creating a dynamic magnetic field generated by a brief but powerful electrical current passed through an electromagnetic coil [6]. By Maxwell's equations and Faraday's law, this creates a powerful but very focal magnetic field, on the order of 2 Tesla. This localized pulsed magnetic field over the surface of the head depolarizes underlying superficial neurons.[7,8] The magnetic field induced by TMS diminishes rapidly as distance increases away from the coil. This allows TMS to be used in environments with complex equipment (like a space capsule) without interfering with other devices. For example, we have successfully used TMS to treat pain conditions inside the crowded intensive care unit.[9,10] Studies combining TMS with functional imaging have shown that TMS applied to cortex can activate cortical-limbic loops deep within the brain which are functionally connected to the superficial cortical site of TMS activation.[11-14] There is also mounting evidence that TMS causes changes in effective connectivity and plasticity within these circuits which is critical for the antidepressant and other therapeutic properties of TMS.

B. TMS state-of-the-art

Protocols for applying TMS vary widely and are specified by the type of TMS coil used, intensity of the electromagnetic pulse, single pulse versus repetitive TMS (rTMS), patterned versus non-patterned TMS, time interval between sessions, use or not of neuronavigation systems, and whether or not open or closed-loop brain state-dependent TMS is employed.

- Active and placebo coils:

In the early days of TMS, the placebo condition used in studies simply consisted of angling the TMS coil away from the cortical area of interest while applying an active TMS pulse. In recent years, in order to enable rigorous clinical trials, sophisticated placebo coils have been developed which simulate the audible click and slight sensation on the scalp that occurs with each TMS pulse.[15,16] These coils use various techniques to keep both the patient and the TMS operator blinded to active versus sham conditions. Another consideration is the choice of TMS coil used for a particular application. TMS coil geometry is important in determining the distribution and strength of the induced electric field at the desired site of TMS stimulation along the brain.[17,18] Advanced TMS coils that enable stimulation of deep brain structures[19] are commercially available and FDA approved. Also recently commercially available platforms exists that allow multi-site application of TMS pulses simultaneously.[20]

- Personalized TMS dosing

For improved reproducibility across TMS clinical trials, the use of standardized TMS dosing is important.[21] Dosing parameters include the intensity at which TMS is applied, the total number of pulses, pulse repetition frequency, duration of and interval between bursts or trains of TMS pulses, and for repeated session, the interval between session and the total number of sessions.[21] To choose the appropriate TMS intensity for individual patients, a standard procedure is to apply TMS over motor cortex in order to determine the minimum amount of electromagnetic power required to move the thumb. This value is the patient's resting motor threshold (rMT). TMS is then applied at a set percentage of the patient's rMT, for example at 120% rMT.[22] However, the rMT is sensitive to various factors including intrinsic variability in corticospinal excitability, the presence of exogenous substances such as caffeine or pharmacological agents,[23] location of the coil in relationship to the optimal site of cortical stimulation, and the scalp to cortex distance.[24] A very slight shift in coil position along the scalp can result in TMS stimulation being off-target and ineffective. Recent advances towards personalized TMS have been made addressing these factors which contribute to variability in the TMS dose that a patient ultimately receives. These include improvements in neuronavigation systems incorporating depth adjusted TMS intensity, directed TMS targeting and brain-state dependent TMS.

- Accelerated protocols

TMS can be applied as single pulses at intervals greater than 4 second (single pulse TMS) or as a series of repeated pulses of TMS at frequencies ranging from 1 to 50 hertz (repetitive TMS, rTMS). In general, TMS applied at 1 Hz or less is considered inhibitory while rTMS applied at 5 Hz and higher is excitatory.[25] Guidelines have been developed setting operational limits to ensure the safe use of TMS.[26] rTMS is thought to induce neuroplasticity through long-term potentiation and long-term depression which out last the TMS session.[27]

Conventional TMS protocols for the treatment of depression typically require daily 30 minute sessions over a period of up to six weeks.[28] However, in cases of psychiatric emergencies, time can be crucial. The need to decrease the time to achieve an antidepressant response while improving antidepressant efficacy resulted in the more recent development of accelerated TMS protocols.[28] Accelerated TMS protocols are characterized by a larger number of TMS pulses applied per session, increases in the TMS intensity relative to the patient's rMT, and the use of multiple stimulation sessions per day. [28,29] Various accelerated rTMS protocols have obtained FDA-clearance and are being used clinically.[30] A commonly used accelerated protocol is intermittent theta burst TMS (iTBS). iTBS is modeled after theta burst stimulation used in studies of animal brain slices which efficiently induces plasticity in that model.[31] An example of an iTBS protocol would be TMS triplets at 50 Hz for 2 seconds repeated every 10 seconds for a total of 190 seconds (approximately 3 minutes). Studies have shown that the use of accelerated rTMS protocols are safe and well tolerated with antidepressant efficacy comparable to conventional, once daily rTMS protocols.[28]

- Guided targeting (beyond the 6 cm rule)

TMS protocols for the treatment of depression target the left dorsal lateral prefrontal cortex (DLPFC). Initial clinical trials of TMS for the treatment of depression, prior to advances in neuronavigation, where based on choosing the site of TMS stimulation as 6 cm anterior to motor cortex. Despite its ease of use, this simple method of TMS targeting can lead to substantial variation in the actual brain networks engaged by TMS due to individual variability in neuroanatomy and brain network

connectivity.[32] Inadvertently engaging different functional brain networks across individuals could contribute to reduced efficacy and response rates in clinical trials.
More recently efforts to personalized TMS stimulation, both spatially (based on individual functional and anatomical localization and connectivity) and temporally (based on EEG activity), to maximize activation of targeted networks have been incorporated into TMS protocols.

Spatial optimization of TMS targeting

- Depth adjusted intensity
- fMRI- functional connectivity (fMRI and rsfMRI)
- MRI – structural connectivity (DTI)
- rMT varies widely between individuals, with nearly 60% of the between individual variance due to differences in the scalp to cortex distance[33]. If variability in this distance is not accounted for, TMS doses may be inaccurate. As the scalp to cortex distance increases a greater amount of electromagnetism is required to induce cortical activation. Kozel et al. have suggested that within a narrow range, every 1 mm increase of scalp to cortex distance would result in a 2.9 point increase in TMS motor threshold.[33] To account for these differences, protocols have incorporated depth adjusted intensity. As a global shift in the brain occurs in astronauts during long-term spaceflight,[34] TMS dosing may need to be adjusted to account for brain shift.[35]
- TMS pulses induce a transient electric field in underlying excitable neuronal tissue in an approximately 2 to 3 cm area below the TMS coil in superficial cortex[36,37] Studies have shown that a shift as little as <0.5 cm in the coil position is functionally significant.[38] A shift in coil position is more readily detectable if applying TMS at an intensity above rMT over motor cortex, for example, by loss of a visible contraction in the targeted muscle, however, areas of cortex important for treating psychological conditions typically target the prefrontal cortex. When targeting prefrontal cortex, for example, a slight shift in coil position could go undetected and inadvertently lead to unplanned activation of non-targeted neural circuits. To avoid this, neuronavigation systems incorporating functionally defined targets can be used.
- Functional organization and connectivity of the brain varies widely among individuals.[39] This is particularly true of the prefrontal cortex which is the target area for many of the clinical applications of TMS.[39] Recent research has aimed to improve the efficacy of TMS treatment protocols by tailoring TMS targeting to individual brain anatomy as defined by functional mapping.

Several neuroimaging techniques are available to map individual functional brain anatomy and these data can readily be incorporated into TMS neuronavigation systems. For example, diffusion-based techniques such as diffusion tensor imaging evaluate white matter connectivity.[40] Task-based functional MRI (fMRI) utilizes the blood oxygen level dependent (BOLD) signal to map out areas of the brain in individuals which become active during specified tasks. Resting state fMRI also maps the BOLD signal but with the patient at rest. Spontaneous low level fluctuations in the BOLD signal can be detected which relate to ongoing spontaneous neural activity. The degree of synchrony of the BOLD time-series between different brain regions reflects functional connectivity.[41]

Temporal optimization of TMS targeting

A limitation of neuroimaging guidance, using techniques such as fMRI, is poor temporal resolution. To further personalize TMS protocols, electroencephalography (EEG) data, recorded at millisecond resolution, can be used to guide TMS application in the temporal domain. There are various methods for incorporating EEG data into TMS protocols:

Spatial targeting

Functional neural networks may be identified by detecting temporal correlations of spontaneous neurophysiological activity on EEG of remote brain regions, which can then be used for targeting TMS to specific functional networks.

Clinical response prediction

EEG patterns may serve as biomarkers predictive of recovery in response to TMS.

Choosing rTMS frequency of stimulation

The stimulation frequency of rTMS can be chosen to phase match that of endogenous oscillations on EEG.

Brain-state dependent, brain oscillation–synchronized rTMS

In addition to inter-individual variability, functional organization can also vary within individual patients in real-time with changes in brain state.[39] Neural oscillations reflect rapidly changing brain excitability states. The efficacy of TMS depends on the current state of the brain at the time of TMS application. If the timing of TMS pulses is adjusted to occur during a state of high-excitability, as opposed to a low-excitability, TMS can more effectively induce lasting modification of the stimulated circuits.[42]

EEG can be used to dynamically trigger TMS within individuals such that a TMS pulse is delivered at the optimal time to induce neuroplasticity. There are two main types of brain state-dependent stimulation protocols: (1.) open-loop brain state-dependent stimulation in which pulses are delivered when an a priori defined target brain state is detected, and (2.) closed-loop brain state-dependent stimulation in which TMS stimulation parameters are dynamically adjusted, based on the outcome of each TMS pulse, in an attempt to achieve a desired outcome.[43]

- Combining Techniques
  - Interleaved fMRI/TMS
  - EEG/TMS
  - fMRI/EEG/TMS

C. NASA-relevant applications

1. Mental and Behavioral Health

Future exploration-class missions, such as a mission to Mars, are characterized by long mission durations and extreme isolation in hostile environments with performance pressures on crew members who must work optimally together as a team at all times. Under these conditions, the possibility of adverse behavioral issues is quite significant and could lead to mission failure or loss of life. To detect and mitigate behavioral issues, NASA has traditionally depended on psychological

support with private consultations between psychiatrists and crew members. However, on future Mars missions, Earth-based communications will occur via a time delay of approximately 20 minutes making remote diagnosis and treatment of any potential behavior condition challenging. Medical kits are available on-board US spacecraft which include medications to treat anxiety, insomnia, depression and psychosis[44]. In extreme circumstances, a physical restraint system and sedatives are available to ensure the safety of all crew members until evacuation back to Earth can occur[44]. From low Earth orbit (LEO) or the Moon, evacuation could take hours to days. However, if a life threatening behavioral disorder, such as suicidality, were to occur during an exploration class mission at a time when evacuation is not feasible or could require months to return to Earth, more advanced, humane protocols must be in place for crews to manage the situation acutely and autonomously. Medications could be considered, however antidepressant medications usually require several weeks to achieve significant therapeutic benefit,[45] display altered pharmacokinetics in the microgravity environment,[46] have expiration dates, and add to payload mass and volume. In the event of an acute major depressive crisis at a critical point in a Mars mission, treatment alternatives beyond long-term physical restraint and sedation are needed.

A highly effective FDA-approved treatment for severe major depressive disorder unresponsive to medication or psychotherapy or for which there is associated catatonic or psychotic features, is the use of electroconvulsive therapy (ECT).[47,48] However, ECT requires general anesthesia and results in a generalized seizure making it undesirable for use by astronauts in emergency situations.[48]

Beyond ECT, TMS is the only FDA-approved medical therapy shown to be effective in multiple clinical trials to treat pharmacological-resistant depression and suicidality. (Slide 31) For example, a meta-analysis was performed which included 23 studies of treatment-resistant depression in which patients were enrolled only after failing traditional treatments including medication. The efficacy of rTMS for major depressive episodes in these patients consistently showed response rates ranging from 39.5 to 70% and remission rates ranging from 16.6 to 76.9%.[49] Furthermore, the antidepressant response resulting from TMS has been shown to be long-lasting, with 53% and 46% of those who respond to acute rTMS having sustained responses lasting 6 and 12 months after treatment, respectively.[49]

While traditional TMS protocols can require weeks to complete, more recently accelerated protocols have been developed which optimize treatment based on neuroscience-informed stimulation protocols. These TMS treatments protocols have been shown to achieve higher antidepressant efficacy, without serious adverse events, in a matter of days and are therefore well suited for the treatment of patients in an emergency setting.[50]

An example of an accelerated TMS for treatment resistant depression is the Stanford neuromodulation therapy (SNT) protocol.[50] The anti-depressant efficacy of the SNT protocol compared with placebo was evaluated in a double-blinded, sham controlled randomized trial for the rapid treatment of severe depression. The study included 29 patients with treatment resistant depression. TMS was applied using an intermittent theta burst protocol (iTBS) for ten 10-minute sessions per day for 5 days. Personalized targets were determined for each participant guided by functional connectivity at MRI and TMS dosing was adjusted, based on individualized cortical depth, to receive 90% resting motor threshold. The mean percent reduction from baseline scores on a

depression scale 4 weeks after treatment was 52.5% in the active treatment group and 11.1% in the sham treatment group. At the 4-week follow-up, 78.6% of patients in the active treatment group, compared with 13.3% in the sham treatment group, met criteria for remission.[50]
(Slide 33)

Further clinical trials are needed to assess the applicability of TMS as a behavioral health countermeasure for long-duration missions. Particularly needed are clinical trials of accelerated TMS protocols in astronaut-like cohorts undergoing realistic analog missions incorporating mental health challenges analogous to those crews are likely to encounter on missions remote to Earth, such as a trip to Mars.

As the effect of antidepressant medications requires several weeks to develop, it is clear that medications alone will be unlikely to provide the capability to quickly and effectively treat a depressive crisis. Therefore, NASA should consider the incorporation of non-invasive brain stimulation technologies, such as accelerated rTMS, as an approach to emergency situations where rapid-acting treatments are needed, such as a crew member on an exploration class mission without access and long-term physical restraint and sedation of a crewmember is untenable.
(Slides 36-40)

2. Sensorimotor Neuroplasticity

Another application to highlight in regards to long-term, exploration-class missions that NASA might consider is the use of TMS for evaluating and promoting sensorimotor neuroplasticity.
Exercise has long been a countermeasure used by NASA to physiological deconditioning during spaceflight. In addition to maintaining muscle and cardiovascular fitness, exercise is believed to promote neuroplasticity and re-learning of motor skills after long periods of disuse. While NASA has conducted considerable research into optimizing exercise protocols on the basis of functional motor and cardiovascular outcomes,[51,52] little attention has been paid to optimizing neuroplasticity. In this regard, TMS may serve as a useful indicator of the effectiveness of various exercise regimes for promoting neuroplasticity. TMS measures such as rMT, MEP (motor evoked potentials = electromyographic recordings from peripheral muscles in response to motor cortex stimulation) amplitude and latency, and intra-cortical inhibition reflect the balance between excitation and inhibition within motor cortical circuits and these measures have been shown to be associated with individual levels of physical fitness. For example, in 45 healthy adolescents, sex-dependent associations were noted with specific TMS indices of corticospinal excitation and physical fitness.[53] In 15 untrained adult males, in addition to the typical cardiorespiratory benefits, aerobic activity performed for 8 to 12 weeks induced changes in cortical excitability with a reduction in rMT, decreased MEP latency, and an increase in MEP amplitude.[54]

Furthermore, TMS may itself serve as a countermeasure to promote long-term neuroplasticity and sensorimotor recovery following extended stays in micro- or low gravity environments. Since its introduction in the 1980's, TMS has been applied over motor cortex to investigate the response of stimulation in healthy individuals. In patient populations, extensive research has been conducted demonstrating the utility of TMS in the promotion of neuroplasticity following stroke.[55,56] Fewer studies have specifically utilized TMS to enhance performance during athletic training.[54,57-59]

In one such study, twenty female volley ball players underwent a single course of either active or sham 10 Hz rTMS to the DLPFC.[58] Performance on the Posner test and cortical excitability was measured before and after rTMS. The Posner test is a measure of one's ability to redirect one's attention in response to various environmental situations and is a crucial aspect of selective attention for athletes, or crews in extreme environments. We have previously demonstrated microgravity during parabolic flight alters visuospatial attention as measured by the Posner test.[60] Following active but not sham rTMS, the volleyball players showed improved performance on the Posner test with significant decreases in the percentage of errors and decreased reaction times. They also showed significantly decreased rMT of the ipsilateral motor cortex.[58]

During competitive sports, fatigue with a decline in muscle strength has a large impact on performance. In addition to peripheral changes at the level of the muscle, fatigue also is the result of a substantial central component due to changes in the excitability of the central motor pathways. During the execution of maximal voluntary contractions, fatigue partially results from a sub-optimal output from the primary motor cortex leading to sub-optimal firing rates of motor neurons.[61] This might be another potential target for performance enhancement with TMS. In such a study, Giboin et al.[62] used intermittent theta burst (iTBS) treatment and showed improved with rTMS in a cycling task.

As another example, TMS can be used to enhance post-training consolidation of motor learning. rTMS applied to the M1hand area of the nondominant hand facilitated posttraining consolidation assessed 6 hours after training in an explicit motor learning task.

Future studies aimed at enhancing motor performance and neuroplasticity could incorporate individualized application of TMS stimulation in the spatial and temporal domains. The result of TMS depends upon the excitability of the brain at the time of TMS application. In motor cortex, the level of corticospinal depolarization, as reflected by phase of the sensorimotor μ-oscillation, determines the degree of corticospinal plasticity induced by low-frequency rTMS.[63] Larger motor evoked potentials (MEPs) can be induced if TMS is applied over primary motor cortex during the trough rather than the peak of the sensorimotor mu rhythm.[64] The negative peak of the sensorimotor mu rhythm reflects a corticospinal high-excitability state and 1-Hz rTMS applied during the negative peak condition induces long-term potentiation (LTP)-like plasticity vs long-term depression (LTD)-like plasticity if applied during the positive peak condition.[64]

3. TMS for Enhancing Cognitive Performance

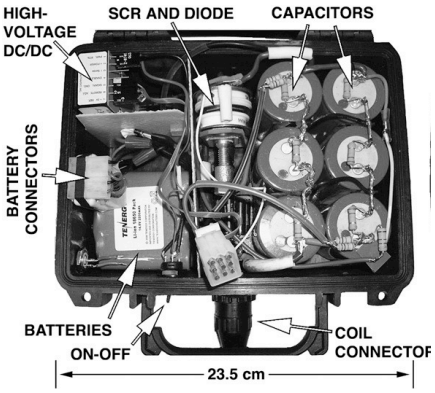
Cognitive improvements have been reported as ancillary benefits to conventional[28-30] as well as accelerated[31] therapeutic rTMS for cognitively intact depressed patients. Accordingly, rTMS has also been shown to improve cognition as the primary outcome in studies of mild cognitive impairment[32]. Few studies have attempted to directly enhance cognitive performance in healthy individuals. We recently completed a randomized, double-blinded dose finding study of rTMS for enhancing performance and promoting resilience in healthy adults. We randomized 40 adults of astronaut age and education to receive one of 10 doses of intermittent theta burst rTMS. Multiple standard measures of cognitive performance, including the NIH Toolbox, WinSCAT, and Penn Cognitive battery, were obtained before, immediately after, and one month after rTMS treatment. Measures of treatment acceptance and participant resilience were also obtained. We found that rTMS statistically

improved measures of fluid, but not crystallized cognition ($p < 0.001$). Concerning pre- to post-treatment change scores on the WinSCAT, we found a linear dose response. Separating low vs high dose responses, we found at low dose levels, there was a trend towards improvement post treatment which became significant at the 3 month followup. But at high dose levels, the immediate post treatment scores were significantly higher than pre-treatment scores ($p = 0.006$).
While TMS is a promising tool for enhancing cognitive function and promoting resilience on future spaceflight missions, further work is necessary to refine treatment protocols.

D. Considerations for the implementation of TMS into spaceflight missions

TMS Equipment
Weight, volume, and power considerations are important for spaceflight mission planning. We have previously created a proof-of-concept, man-portable TMS system capable of performing the treatment protocols described above. The unit fits into a small brief case and runs off of a 12 volt battery or 120AC current. This device weighs about 20 lbs, can deliver antidepressant doses of rTMS (3000 stimuli/day).[65] With further optimization, we suspect the weight can be reduced to below 5 pounds.

Portable TMS Unit picture copyrighted



Consideration of these variables for TMS should be done in the context of alternative behavioral health treatment regimes (medications, cognitive behavioral therapies) and risk to mission if behavioral health conditions were to go untreated. As discussed above, medications add to payload mass and volume and have expiration dates. Furthermore, medications are typically targeted to specific mental conditions (e.g. anti-depressants, anxiolytic, analgesics, performance enhancers) with the necessity to include several drug classes within the mission pharmacy. Cognitive behavioral and talk therapies will be difficult to implement due to communication time delays and distance from healthcare providers.

On the other hand, TMS therapy has several unique advantages for a potential exploration class mission:

1.TMS is virtually side effect-free. The dropout rates in clinical trials is <10%, compared to dropout rates in medications studies of 40% or more. This is likely due to the very low side effect profile. The actual stimulation is mildly unpleasant, but patients accommodate quickly to the discomfort, likely

due to the fact that prefrontal TMS releases endogenous opiates, akin to a runner's high.[11,66] Moreover, because TMS is focal, it has no drug-drug interactions or systemic side effects.
2.TMS can be used indefinitely, and expanded as needed. When one considers which antidepressant medications to include on a Mars mission, there are concerns about drug pharmacokinetics in microgravity, efficacy, side effects, and dose. Only 30% of patients respond to the first antidepressant they are prescribed, even if they can tolerate the side effects. [67] Thus when planning an extended duration mission, one would have to choose several medications, determine the doses needed, the duration, and how many crew members might need treatment. With TMS, the remission rate in non-treatment resistant patients is likely near 100%, and the only limit on dose is the electricity available.

3.TMS is FDA approved for various behavior health conditions and is under investigation for many others. TMS protocols can be easily customized and prescribed by behavioral health providers remotely. There are likely other therapeutic indications to emerge for TMS between now and a Mars mission, including stroke recovery or tinnitus.

4. Importantly, TMS is not addicting like the opiates, has no side effects or abuse potential, and is not sedating.

5. TMS does not expire and if equipment should malfunction, replacement parts can be easily constructed using 3D printing techniques.

TMS and Microgravity
Living in a microgravity environment has significant physiological effects on the human body[68-70]. For example, the pharmacokinetics of drug administration is altered in microgravity[46] and psychotropic medications are known to have reduced efficacy during spaceflight [71]. Likewise, there is the potential that TMS may operate differently in a microgravity environment. For example, studying the MRI brain scans of astronaut before and following spaceflight, we have recently shown there is a shift of brain tissue within the skull post-flight[34]. This observed upwards shift of brain tissue could potentially alter the dosing of TMS as the effectiveness of TMS depends on the distance from the TMS coil (which is placed on the scalp) to the underlying cortex[24]. In addition, cephalad fluid shifts which occur in astronauts[72] and during parabolic flight[73-75] may alter the neurophysiological response to TMS. Therefore, it is important to understand the physiological response to TMS in a microgravity environment.

Several TMS measures of cortical excitability have been described; however the most basic is determination of the TMS resting motor threshold (rMT). Accurate estimation of rMT is of utmost importance in both research and clinical studies as it is the unit most commonly used for rTMS dosing[76]. Inaccurate estimation of rMT can lead to subject/patient over- or under-dosing.
In order to investigagte the physiological response to TMS in a microgravity environment, we developed and refined head-worn TMS systems capable of reliably and quickly determining the rMT. We then collected rMTs in 10 healthy adult participants in the laboratory at baseline, and subsequently at three time points onboard an airplane: (T1) pre-flight at Earth gravity, (T2) during zero gravity periods induced by parabolic flight and (T3) post-flight at Earth gravity. Overall, the subjects required 12.6% less electromagnetism applied to the brain to cause thumb muscle

activation during weightlessness compared to Earth gravity, suggesting neurophysiological changes occur during brief periods of zero gravity. Potential explanations for this finding, including upward shift of the brain within the skull, acute increases in cortical excitability, changes in intracranial pressure, and diffuse spinal or neuromuscular system effects. All of these possible explanations warrant further study prior to the development of TMS protocols for use during spaceflight missions.

TMS Safety

TMS is considered a safe and well-tolerated treatment for depression and other behavioural health disorders and has been FDA-approved since 2008. There are published expert guidelines describing the safe use of TMS which are updated on a regular basis.[77] The most frequently adverse reaction is a temporary headache or pain at the TMS stimulation site relieved by over-the-counter medications. Other safety concerns include hearing degradation, malfunction of implanted intracranial devices, and theoretically undesired cognitive effects. The most serious risk of TMS is the potential for TMS-induced seizures.

Several reviews have been published concerning the safety of TMS in various patient groups. For example, the safety of TMS for treating behavioral disorders has been recently reviewed. A systematic review & meta-analysis of 53 randomized sham-controlled trials with 3,273 participants confirmed the safety of TMS for the treatment of unipolar depression.[78] The authors reported no increased risk of serious adverse events (active TMS intervention group=0.9%, sham TMS intervention group=1.5%, odds ratio = 0.67, 95% CI= 0.29-1.55, P = 0.35). There was an increase in the risk of non-serious adverse events including headaches, discomfort and pain at the stimulation site, but these non-serious events were mostly mild and transient after TMS treatment.

Concerning the induction of seizures by TMS, Chou et al.[79] reported 41 cases of TMS-associated seizures were published in the literature up to February 2020. This number is very small given the extensive use of TMS in research and treatment centers worldwide.[77] In a survey including respondents from 174 laboratories and clinics worldwide actively administering TMS, 24 seizures were reported across a total of 318,560 TMS sessions (0.08/1000 sessions).[80] If TMS was delivered within published guidelines to participants without recognized risk factors, only 4 TMS-induced seizure events occurred across 242,067 sessions (< 0.02/1000 sessions).

While the potential to induce a seizure remains the most serious risk of TMS, according to the latest published expert guidelines, “The risk of rTMS in inducing a seizure is definitely low, even in patient populations taking drugs acting on the central nervous system, at least with the use of traditional stimulation parameters and focal coils for which large data sets are available. While this is reassuring and helpful information for subjects, it remains necessary to be prepared to deal with a seizure that might arise in any experimental protocol.”[77]

E. Conclusion

Noninvasive brain stimulation is a novel method for enhancing performance across multiple cognitive domains. We have already developed a battery-powered TMS unit weighting only 6 pounds for use on deep space missions following flight certification. Further work is necessary to optimize TMS protocols for specific mission profiles and for astronaut populations.

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Near-infrared light therapy

In the context of space exploration, astronauts face significant challenges including isolation, separation from loved ones and friends, and the psychological impacts of prolonged space travel also resulting from altered environment and saccadian rythms (1, 2). Current measures at the International Space Station (ISS), such as viewing windows, regular psychological evaluations, and support from loved ones, mitigate some of these challenges (3). However, future deep space missions, like those to Mars lasting over a year, present heightened isolation where real-time communications and psychological support will be limited or absent.

To address potential mental health concerns during extended missions, there is a growing interest in therapies that do not rely on internet connectivity, operational expertise and are operationally straightforward. Recently, near-infrared light therapy, though not new, has garnered attention for its emerging efficacy and portability, with growing experimentation in treating conditions like depression and anxiety(4). This therapy involves a compact device that emits near-infrared light, offering a promising and secure option for maintaining mental health in deep space when needed.

Such technologies could prove invaluable by providing astronauts with a self-administered therapeutic option that enhances psychological resilience without the need for continuous external support. This approach aligns with the critical need for robust mental health strategies tailored to the unique challenges of deep space exploration missions, where crew members endure prolonged periods of isolation and separation from traditional support systems.

This technology is not new to NASA, the “WARP 10” device was developed by NASA in the late 80´s and in 1995 it made its official debut in the second space shuttle mission(5), this technology showed improvement in pain management and reduction of inflammation through increasing energy inside human cells(5). This therapy known as photobiomodulation (PBM), also known as low-level light therapy or cold laser therapy, utilizes specific wavelengths of light to stimulate biological processes in tissues. This therapeutic approach has garnered attention due to its ability to induce beneficial effects without causing adverse reactions when applied at optimal fluences and wavelengths. PBM's primary mechanism of action is attributed to the photo stimulation of the mitochondrial electron transfer chain, particularly targeting cytochrome c oxidase (CCO), a key enzyme involved in cellular energy production(6).

Biologically, tissues contain various chromophores such as water, hemoglobin, and cytochromes, which absorb light differently across the electromagnetic spectrum The therapeutic window for PBM falls within the red to near-infrared (NIR) spectrum (600-1000 nm), where wavelengths are minimally absorbed by water and maximize penetration into tissues. Within this range, CCO exhibits absorption peaks, notably around 630 nm and 830 nm, allowing light to influence cellular processes through excitation of CCO's metal centers(7, 8)

Regarding this therapy´s impact on brain tissue, research has shown that PBM at these wavelengths enhances cerebral blood flow (CBF), augments brain energy metabolism, and boosts antioxidant defenses(9-11) . Moreover, PBM modulates cellular responses by influencing anti-apoptotic and pro-

apoptotic mediators, inflammatory signaling molecules, and neurotrophic factors, thereby promoting neuronal protection and survival (12-15). As research continues to explore PBM's applications, particularly in neurological and psychiatric domains, it holds promise as a non-invasive and potentially effective therapeutic modality. Further clinical trials and studies are necessary to establish its efficacy across various conditions and to refine treatment protocols for optimal outcomes. Regarding spaceflight and long term mission, this therapy could come in handy as not only it improves neurological conditions that may occur during space flight such as traumatic brain injury(16) but also enhances cognition(17), and decision making, crucial during difficult situations in spaceflight, finally it has shown in multiple studies its impact on anxiety and depression reducing substantially the symptomatology of these pathologies(18-23).

Finally, this therapy may have several applications in space exploration, particularly in enhancing muscle performance. Numerous animal and human studies have demonstrated its effectiveness in improving muscle strength and recovery. This could significantly impact astronaut muscle viability, as microgravity conditions tend to cause muscle atrophy due to disuse(24).

PBM in space missions faces several challenges and trade-offs specifically in this area, such as still ongoing research on its efficacy, standardization and safety for treating mental health conditions, equipment and power constraints, individual variability in response, and unknown long-term effects in microgravity and radiation environments. Potential solutions include robust pre-clinical and clinical trials, developing compact and energy-efficient PBM devices, creating personalized treatment protocols using the help of new tools such as artificial intelligence to use an individualized medicine approach, and investigating PBM's effects under space-specific conditions through ISS experiments. While these avenues of development are promising, technical feasibility, scalability, and regulatory concerns should be considered. Collaborative efforts, international partnerships, and rigorous testing are essential to achieve the integration of PBM into space health programs.

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Transcranial Focused Ultrasound in Space Health-Brain Stimulation and Beyond

Low-intensity transcranial focused ultrasound (tFUS) offers a noninvasive means to deliver **acoustic energy to region-specific brain area** through an intact skull with high spatial selectivity and depth penetration[1-3]. The acoustic pressure waves can either excite or suppress region-specific neuronal activity as a noninvasive brain stimulation (NIBS) technique or enhance glymphatic solute clearance from the brain via acoustic streaming effects[19,24,25]. Thus, tFUS techniques are anticipated to provide unprecedented opportunities for promoting brain health in space.

tFUS is generated using single-element piezoelectric FUS transducers mounted on lightweight, custom-made wearable headgear that fits individual head anatomy ergonomically and reproducibly. A phased-array FUS transducer configuration, which uses multiple ultrasound elements surrounding the entire head, generally achieves a tighter acoustic focus for reaching deep brain areas compared to a single-element transducer. However, the size of the array transducer, which is crucial for achieving a tight acoustic focus[4], along with the weight and volume of the driving circuit, makes it impractical for use in space. This impracticality of phased-array configuration also extends to conjunctional use with other neurophysiological measurement modalities, such as electroencephalography (EEG). The wearable FUS transducer configuration has a much smaller form factor, offering many practical advantages. This is particularly beneficial when participants in spaceflight actively engage in behavioral tasks across multi-day experimental sessions. Additionally, this configuration allows for simultaneous EEG acquisition, enabling the capture of FUS-evoked neuronal responses to various sonication parameters, including the assessment of somatosensory evoked potentials.

The skull inevitably introduces acoustic beam attenuation and distortion, presenting significant challenges in accurately navigating the FUS focus to a desired brain target and consistently delivering controlled in-situ acoustic intensity across subjects. To address these challenges, we implemented an image-guided navigation technique augmented with a numerical approach that simulates intracranial ultrasound propagation in near real-time. The performance of this technique, in terms of focal location and in-situ intensity, has been validated[5].

Research on both small and large animal models has collectively provided the following information regarding the effects of FUS parameters on modifying neuronal activity: (1) fundamental frequency (FF) in the 200~700 kHz range yields excellent neuromodulatory efficiency than the use of higher FF[6], (2) pulsing sonication at 50-70% duty cycles (DCs) generates greater excitatory responses compared to continuous sonication (100% DC) or to lower DCs[14], (3) sonication given in low DCs (<~20%) for a longer duration (on the order of minutes) suppresses neural tissue responses, while the use of higher DC (>~50%) given in short duration (~ 500 ms) induces excitation[7-910-14].

To examine the efficacy of tFUS in stimulating the brain, we developed a portable tFUS device operating at 250 kHz and applied pulsed sonication to stimulate somatosensory circuits in human volunteers, targeting the primary sensory area (S1) of the hand and the ventral posterolateral nucleus (VPL) in the thalamus unilaterally[15]. Four experimental conditions were used, including three different pulse durations and a sham condition, and the effects were evaluated using EEG data. Additionally,

we assessed the offline stimulation effects and their duration with resting-state functional MRI conducted before and at various times after the stimulation. We also investigated the safety of tFUS through comprehensive neurological and neuroradiological evaluations. Our findings identified a specific parameter set—0.5 ms pulse duration given at 70% duty cycle for 200 ms—that yielded superior stimulation efficacy. tFUS-mediated neuromodulation, with an excellent safety record, provides a non-invasive, non-pharmacological means to modulate region-specific brain function. The effects of tFUS last for more than an hour, demonstrating its therapeutic potential.

In addition to its utility in neuromodulation, we found that low-intensity FUS can promote brain lymphatic clearance in a completely non-invasive manner. Recent evidence has begun to recognize aberrant brain lymphatic clearance associated with prolonged spaceflight, such as enlarged basal ganglia and white matter perivascular spaces, and their link to spaceflight-associated neuro-ocular syndrome (SANS)[16-18]. Ultrasound pressure waves can create localized fluidic flow in the media, known as acoustic streaming. We were motivated to use these acoustic streaming effects to promote solute transport by inducing convective bulk flow of cerebrospinal fluid (CSF) along the perivascular space (PVS)[19]. To test this idea in a rodent model, we first intracortically injected fluorescent Texas-red ovalbumin (OA) and fluorescent dextran into rats. Then, we applied 200 kHz FUS to the injection site in a pulsed manner for 30 minutes. We found that the application of FUS propelled both OA and dextran from the original injection site. We also examined the presence of fluorescent OA in the cervical lymph nodes and found that enhanced solute transport was accompanied by a marked increase in lymphatic drainage without disrupting the blood-brain barrier (BBB)[20]. In a separate study, we also found that a specific sonication parameter achieves maximal transport efficiency[21].

Put together, tFUS may offer a unique opportunity to modulate specific brain functions, such as non-pharmacological performance enhancement or the provision of countermeasures for psychiatric episodes. Additionally, we note that the same tFUS device, with modification of sonication parameters, can be used to enhance the clearance of waste products from the brain, which have been shown to be compromised in the microgravity environment in humans and in animal models.

To make this technology applicable to space health, several challenges must be addressed. Firstly, improvements are necessary in terms of the ergonomic aspects and form factor of the headgear. Additionally, further parameter optimization, including suppressive effects, and a more detailed assessment of temporal effects from a single-session tFUS (i.e., up to 1 week) are needed among human participants. Separately from the utility as a NIBS modality, enhancing brain lymphatic clearance must be validated in human volunteers for example, by conducting diffusion-weighted magnetic resonance imaging (MRI) that examines the interstitial solute movement imposed by the tFUS.

Technically, more sophisticated target engagement is necessary to accommodate complex shapes and multiple acoustic foci. To achieve this while maintaining a smaller form factor of the transducer, we plan to adopt an acoustic hologram approach[22 23], where custom-made acoustic lens creates user-defined shape and location of focus, without requiring a multi-array transducer. Acoustic stimulation is also a crucial aspect of this process, and we are currently developing a machine-learning-based simulation algorithm to achieve sub-second processing times[26,27]. Additionally, while

low-intensity tFUS has demonstrated an excellent safety record, it is essential to carefully evaluate both the short- and long-term effects of FUS.

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Cutting-edge technology talks

New approaches to measure glymphatic function via MRI

Recent advances in MRI-based imaging of glymphatic function offer promising insights into brain health and ocular changes during spaceflight. The glymphatic system, responsible for the clearance of interstitial and cerebrospinal fluids, plays a vital role in maintaining neural homeostasis and may contribute to the development of Spaceflight-Associated Neuro-ocular Syndrome (SANS) (Iliff et al., 2012). By employing contrast-enhanced MRI techniques, researchers can visualize fluid movement within perivascular and intraspinal spaces, revealing significant structural and functional changes under spaceflight analogs such as head-down tilt bed rest (Jillings et al., 2023). Notably, elevated CO_2 levels (1.5%) appear to inhibit signal enhancement in the vitreous chamber, suggesting a mechanistic link between environmental CO_2 and altered ocular fluid dynamics (Seidler et al., under review). Increases in perivascular space volume observed in novice astronauts, but not in experienced ones, highlight potential adaptation effects (Hupfeld et al. 2022), while greater ALPS index changes in non-SANS bed rest participants point to individual variability in glymphatic responsiveness (Richmond et al., 2024). These findings underscore the utility of glymphatic imaging for monitoring brain health and guiding countermeasures to preserve neuro-ocular function during long-duration missions.

End-to-end brain-computer interfaces

Non-invasive, wearable brain-computer interface (BCI) technology offers a promising solution for real-time cognitive monitoring and hands-free control during spaceflight. By integrating electroencephalography (EEG), eye-tracking, and functional near-infrared spectroscopy (fNIRS) into compact wearables such as smart glasses, this approach enables continuous assessment of cognitive states including attention, fatigue, and workload. For example, combined EEG/EOG systems embedded in glasses have been used to decode visual imagery and detect target speakers, showing promise for adaptive human-computer interaction in dynamic environments (Kosmyna et al., 2023b, 2023a). These systems can also assess internal and external attention in augmented reality, demonstrating applicability for cognitive monitoring in operationally relevant tasks (Kosmyna & Hauptmann, 2024). The integration of EEG-fNIRS modalities has been shown to enhance classification accuracy of cognitive workload, supporting their potential for real-time monitoring in space (Kosmyna et al., 2024). Wearable BCI systems have also been tested during parabolic flight, validating their functionality in microgravity and demonstrating feasibility for future in-flight brain monitoring applications (Kosmyna et al., 2023). Combined with machine learning, such BCIs can enhance operational performance, reduce training demands, and support psychological resilience during long-duration space missions.

Non-contact laser-ultrasound for biomedical and brain imaging

Non-contact laser-ultrasound (LUS) systems represent a novel and promising approach for non-invasive biomedical and brain imaging, especially in extreme environments such as spaceflight. These systems use a laser to rapidly heat and thermally dilate surface tissue, generating acoustic waves without requiring physical contact, transforming any exposed skin or tissue into an ultrasound source or receiver. This remote excitation and detection enable safe, sterile, and portable imaging,

especially valuable in space where conventional contact-based systems may be limited. The frequency differencing technique improves signal clarity by isolating useful acoustic information from background noise, thereby enhancing image resolution and tissue differentiation. Importantly, this technology shows potential for penetrating through the skull by combining laser-based ultrasound generation with RF antenna arrays or microwave-based receivers, facilitating the transition from soft tissue to bone-brain imaging. Such capability is particularly relevant for continuous or real-time monitoring of neurophysiological changes during long-duration spaceflight by offering insights into intracranial dynamics, cerebrovascular health, or brain injury risks without the constraints of physical probes or gel-based contact transducers.

Oculometrics to identify clinical conditions affecting the brain and behavior

Oculometric technologies offer advanced, non-invasive capabilities for monitoring brain and behavioral function during spaceflight. By measuring parameters such as rapid eye movements, saccades, pupillary responses, and both vertical and horizontal pursuit, these systems can detect subtle changes associated with intracranial pressure shifts and neurological status. Compact eye-tracking tools with standardized imaging and assessment protocols enable repeated, objective evaluations throughout a mission. In microgravity, where headward fluid shifts and altered sensory inputs affect ocular dynamics, oculometric monitoring can contribute to the early identification of conditions such as spaceflight-associated neuro-ocular syndrome (SANS) and support ongoing assessments of cognitive and sensorimotor performance. These technologies represent a valuable component of autonomous health monitoring frameworks for long-duration missions.

Continuous, real-time monitoring of cognitive load and fatigue

HarmonEyes is an offline-compatible eye-tracking software pipeline that quantifies cognitive workload, fatigue, and stress in real time using second-by-second inferences from oculometric data. The system is hardware-agnostic, supports multiple eye-tracking platforms, and includes robust signal preprocessing, adaptive calibration, and validated machine learning models trained on over 11 million annotated records. It achieves ≥94% classification accuracy with RMSE <0.2 against standardized ground-truth scales. Outputs include continuous estimates of cognitive and affective state without requiring user interaction or data storage, making it suitable for constrained environments. In spaceflight, this enables unobtrusive, high-resolution tracking of neurocognitive health during EVA preparation, docking, robotic tasks, and long-duration operations under isolation, altered gravity, or circadian disruption.

Conclusion

The TRISH Brains in Space workshop brought together NASA personnel, researchers, and technology experts to address one of the most complex challenges of human spaceflight: protecting and optimizing brain health and performance during long-duration missions. The presentations and discussion shared the priority to move beyond isolated assessments toward integrated, individualized, and operationally relevant approaches for monitoring and supporting brain function in space. The workshop emphasized that brain adaptations to spaceflight are both structural and functional, as well as behavioral. These changes include shifts in cerebrospinal fluid dynamics, connectivity changes in neural networks related to sensory integration, and cognitive and emotional adjustments to isolation and operational stress. The risk landscape will only intensify with missions beyond low Earth orbit, requiring new methods that are compact, non-invasive, and responsive in real time.

A recurring theme was the need for continuous assessment tools that are capable of capturing fluctuations in cognitive readiness, physiological strain, and emotional state. Equally important are effective and feasible interventions for brain stimulation, behavioral strategies, immersive environments, and countermeasures such as lower-body negative pressure. Importantly, these technologies must still be matched to specific mission needs and validated in spaceflight-relevant conditions.

The Brains in Space initiative established the groundwork for a new interdisciplinary research agenda centered on brain performance in extreme environments. Ongoing collaboration among NASA, academia, and industry will be crucial to translating these insights into solutions that protect astronaut health, improve mission performance, and push the boundaries of human exploration.