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Commentary

A rationale for the use of rehabilitative approaches to ameliorate possible space radiation induced loss of cognitive and sensorimotor function during a mission to Mars

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Background

NASA is on the verge of its second and most challenging phase of space exploration, returning to the Moon and then onto Mars. The proposed missions will be markedly different in nature from previous Apollo and ISS missions, which may result in many additional health concerns for astronauts. Astronauts will endure prolonged exposure to multiple fight stressors that may seriously impact their health. Prolonged exposure to microgravity is a greater health concern than for shorter duration flights, but NASA has spent decades developing approaches to minimize microgravity effects on astronauts that should be effective for deep space missions. However, other space flights stressors, including the increased sense of isolation and inability to return to Earth in the event of an emergency, raises the likelihood of stress-related health decrements that will require new operational approaches from those used previously during ISS missions. Due to inherent limitations of the spacecraft design and uplift capacity, space radiation (SR) exposure on long duration deep space flights will also be an unavoidable flight stressor that may have significant health effects for astronauts and may have disastrous consequences for the mission.

NASA has devoted considerable efforts to establish the incidence and severity of the impact that SR exposure has on the functionality of the central nervous system (CNS). There is an ever-growing body of evidence from ground-based rodent studies that SR exposure impairs performance in many cognitive processes, ranging from relatively fundamental processes to complex analogs/homologs of human cognitive tasks (reviewed in [1-5]). The deleterious effects of SR on the CNS are not limited to cognition with an increasing number of studies reporting SR-induced changes in rodent psycho-social behavior [6-11] and alterations in sensorimotor function, including gross [12-15] and fine motor skills [16]. Translating the results from ground-based rodent studies into tangible risk estimates for astronauts is an enormous challenge, even when direct homologs or analogs of human cognitive tests are employed. However, working on the premise that data generated from rodent models represents the worst-case scenario in astronauts exposed to SR, it is essential to develop countermeasures to minimize or ameliorate these CNS issues.

The Problem

Astronauts on deep space missions will have to act more autonomously than ever before due to a radio delay of 8-42 minutes roundtrip depending on planet positions [17]. In the event of an emergency, astronauts will have to manage the crisis themselves, so any potential stressors that reduce their cognitive or sensorimotor function have the potential to be life threatening. Astronauts are routinely screened during space flight for performance in a 10-test battery of cognitive tasks that NASA deemed necessary for mission success [18,19]. Seven of the tasks in the "fit-for-duty" performance battery assess some aspect of executive function. Creative problem solving integrates several executive functions involved in planning, organization, decision making, judgment, task monitoring, attention, hypothesis generation, abstract thinking, and cognitive flexibility [20-23]. Exposure to ≤ 15 cGy SR leads to impaired performance in several of these cognitive processes [11,15,24-34].

Recognizing the nature of a problem is an essential part of problem solving, but an equally important component is the ability to physically implement a solution. Transition of astronauts to microgravity initially results in severely compromised sensorimotor functionality, with a reduced ability to perform object manipulation tasks (i.e., peg board; [35]). However, within a few days, astronauts adapt to microgravity by "reprogramming" the neural circuitry to operate under the new perceptive stimuli (for review see [36]). Exposure to any flight stressors that would interfere with the ability of the CNS to recalibrate itself may have significant operational consequences, e.g., inability to manipulate tools, land the Human Landing System, perform seat egress, or conduct the exploration missions on the surface of the Moon or Mars. SR exposure alone has recently been shown to lead to alterations in sensorimotor function, including tasks that involve fine motor control [16].

Practical Arguments for not Using Pharmacological Countermeasures

There are a wide range of FDA-approved pharmaceutical drugs that could be repurposed to ameliorate some of the SR-induced CNS impairments. However, while many studies have reported SR-induced loss of cognitive performance, there is a paucity of information on the underlying cause for the cognitive impairment. Exposure to SR invokes multiple changes in synaptic function [29,37-41] which likely leads to a reduced ability to regulate synaptic plasticity and also the functional connectivity between different brain regions [25]. Three studies suggest that SR-induced changes in dopamine signaling in the striatum and prefrontal cortex are associated with the loss of attention in exposed rats [12,15,42]. Performance in some of the cognitive flexibility tasks that have been shown to be impaired by SR exposure (e.g., ATSET and UCFlex) are known to be influenced by the functionality of α-adrenergic (ATSET) [43] or β-adrenergic receptor (UCFlex) [44] signaling; however, there is currently no information on whether alterations in such pathways underlie the observed SR-induced loss of performance. There is even less information on the impact of SR on signaling pathways that regulate sensorimotor performance. Thus, at present, the use of FDA-approved pharmaceuticals as countermeasures for SR-induced CNS deficits has no specific justification, other than they act upon the brain.

It may be possible to identify drugs that can ameliorate some of the SR-induced deficits in cognition and sensorimotor performance in ground-based studies, but their efficacy to do so on a deep space mission may be different due to altered pharmacokinetics under microgravity. Given that the long-term use of such agents is often associated with multiple side effects, some of which (anxiety, paranoia) could have adverse impacts upon team cohesion, their use may not be advisable. Furthermore, while FDA approved drugs have an acceptable neurological toxicity profile on Earth, such data has been derived using control subjects (i.e., have normal blood brain barriers, pharmacological activation/deactivation, and glymphatic clearance from the brain). Exposure to flight stressors, such as SR, stress, and sleep loss, have marked impacts upon the aforementioned parameters. Importantly, SR exposure leads to blood brain barrier dysfunction (for review see [45]), that is likely to alter pharmacokinetics [18], which may alter the efficacy and/or alter the neurological sequelae of pharmaceutical treatments.

In contrast, clinical experience in treating several neurological disorders suggest that rehabilitative training approaches, especially those that lead to increased functional connectivity (and/or rewiring of neural circuits), may be beneficial to ameliorate SR-induced CNS deficits. With the Artemis missions starting within the next decade, it is important to consider non-pharmacological approaches as possible countermeasures for SR-induced CNS deficits.

Practical Arguments for the use of Rehabilitative Medical Approaches to Ameliorate SR-Induced CNS Effects

Rehabilitative approaches are extensively used to ameliorate both the loss of cognitive and sensorimotor performance in patients who have been subjected to various forms of insults to the brain. Similar approaches may help to reduce the emergence of SR-induced loss of performance. Two different rehabilitation strategies have been employed in the clinic to treat patients with stroke and other neurological disorders: 1) compensational strategies, where the training aims to compensate for the lost function by using remaining intact functions [46]; 2) restitution strategies that aim to restore brain functions.

It is important to note that astronauts traveling in space are highly trained individuals with a large amount of cognitive reserve and frequently superior sensorimotor function. Thus, in contrast to many neurological disorders where cognitive/sensorimotor deficits are already present when clinical interventions are required, SR-induced effects on the CNS are not present at the start of the mission and incur across time in deep space. Astronauts will continue to train and learn during the mission under changing environmental demands. In contrast, most of the ground-based rodent studies assessed cognitive performance at 1-3 months post SR exposure, during which the time the rodents have not performed in any cognitive tasks. Thus, the data generated from these rodent studies may represent the worst-case scenario in astronauts exposed to SR. Small daily performance decrements arising from relatively minor CNS perturbation following SR exposure may be easily compensated for during routine activities by astronauts in various cognitive and sensorimotor tasks. However, training exercises and games that specifically target vulnerable processes should be developed that allow astronauts to continuously hone their skills in operationally relevant domains throughout the mission. Astronauts, like many people, grow bored with predictable games or training tasks. "Discovery" style computer games have many features that make them ideal candidates for cognitive rehabilitation. The number of possible scenarios in such games is extremely high and appear virtually unique every time the game is played. Several studies have documented the positive effects that large, immersive 3D video game playing has on hippocampal-based memory ability [47-50] with the level of exploration in the game correlating with the amount of improvement [47]. Further, computer-based and motor imagery training that promote physical fitness [51] may be implemented to encourage astronauts on board a space craft to reach specific sensorimotor training goals.

While such daily training is likely to reduce the emergence of SR-induced CNS performance loss, similar approaches also have proven efficacy in situations where there is overt loss of cognitive performance. When older adults (60-80 years) played

Super Mario 3D World for 4 weeks they improved their ability to a level observed in subjects 15-20 years younger [49]. Cognitive rehabilitation strategies also have demonstrated efficacy in situations where there are pronounced losses in cognitive performance. Stroke commonly results in cognitive and sensorimotor impairments, such as aphasia, neglect, reduced processing speed, impaired attention, and executive dysfunction [52,53]. More than 60% of patients that survive from stroke reported mild to severe cognitive impairment up to 10 years later [54,55], and approximately 80% of patients experience long-term upper limb dysfunction [53]. Rehabilitative approaches have been shown to be essential in ameliorating these cognitive and sensorimotor impairments. Multiple computer-based training programs have been developed to facilitate both approaches [56,57]. Many forms of cognitive deficits have been reduced by these approaches in stroke patients with training generally most effective in the domain that the training program primarily addressed [58-62]; however, training programs that combine memory and attention tasks resulted in transfer to other working memory and attention tasks that were not part of the training program. For example, the RehaCom training consists of several graphical games that adapt to the performance of the participant and use a variety of stimuli, such as playing cards. RehaCom training improved performance in seven working memory tasks (both auditory and visual) and an attention task [63,64]. Patients who underwent the RehaCom training showed increased performance in the Trail Making Task-B (TMT-B) and increased functional connectivity as assessed by functional magnetic resonance imaging of the hippocampus with several regions of the frontal and parietal lobes (right inferior, right middle, left middle, left inferior and left superior frontal gyrus, left parietal lobe) [64] that regulate TMT-B performance. While SR exposure has not been reported (outside of conference proceedings) to impact performance in switch tasks that are similar to the TMT-B task, poor performance in the TMT-B has been reported after X-ray [65] and proton [66] treatments.

Multiple sensory systems may be targeted during rehabilitation, especially to promote sensorimotor function (motor: strength and endurance, sensory: proprioception, visual: mirror neurons). For example, the Rood technique uses sensory stimulation, including a fast brush or light touch on skin or tapping on muscles, to encourage neuromuscular responses [67], of which light touch has been shown to increase postural stability [68] that may be attributed to the reinforcement of active movements. Further, proprioception may be improved within the sensorimotor system via proprioceptive neuromuscular facilitation which modulates muscular contractions by the proprioceptive sensory system and facilitates motor rehabilitation [69]. Stimulation of the sensory system during rehabilitation may even enhance sensorimotor function through anti-inflammation or neuroprotection [70]. Since the sensorimotor system is highly integrated and responsive, rewiring neural circuitry through rehabilitation should aid in the performance of astronauts following SR-exposure.

Many patients with breast cancer who are treated with chemotherapy (CTX) subsequently experience difficulties with concentration, memory, multi-tasking, and planning ability, commonly referred to as “chemobrain”. The incidence of chemobrain is uncertain, but 28-75% of CTX-treated patients with breast cancer have reported cognitive impairments [71] that frequently involves impairment of executive function [72-74]. Cognitive training led to significant improvements in cognitive flexibility, verbal fluency, and processing speed [75,76]. Furthermore, a meta-analysis conducted on over 900 patients with cancer which involved the CNS revealed that undergoing rehabilitation led to functional gains in performance, including sensorimotor function [77].

The Defense Health Agency is using rehabilitation protocols (ideally tailored to the individual patient’s symptomatic condition) to improve many cognitive and sensorimotor processes in active or former military personnel who have suffered traumatic brain injuries (https://dvbic.dcoe.mil/cogrehab/index.html). Similar cognitive rehabilitation approaches improve cognitive performance (especially processing speed and working memory) in patients with multiple sclerosis [78]. A 4-week motor rehabilitative training session has also been shown to improve motor function in patients with multiple sclerosis which correlated with functional neural reorganization in the sensorimotor network [79]. Neurodegenerative disorders, such as Parkinson’s disease, eventually lead to severe sensorimotor disruptions that require pharmaceutical treatment. Yet an eight-week sensorimotor rehabilitation program for patients with Parkinson’s disease improved balance and promoted better overall motor performance [80]. Improvements from this training protocol were correlated with increased levels of glutamate and glutamine within the basal ganglia [80] that may promote neuroplasticity processes and set the foundation for the functional restoration of interactions among motor areas. NASA has funded the development of wearables and other devices to use to detect changes in both cognitive and sensorimotor function during space missions. This equipment should be used to track performance, identify decrements, and monitor changes in function accrued by rehabilitative strategies in an online fashion that allows for real time adjustments in training.

Summary

Extensive clinical experience has shown that multiple cognitive or sensorimotor performance decrements, arising from different neuropathological conditions, have been ameliorated by rehabilitation approaches. Not only do rehabilitative approaches enhance the functionality of intact neural processes after injury, they are also effective in increasing the functional connectivity between brain regions [64]. Rehabilitative training may thus be sufficient to ameliorate SR-induced disruptions of the functional connectivity between brain regions resulting from deep space flights [81]. Thus, while NASA should explore the utility of pharmacological countermeasures, there are compelling arguments for NASA to implement rehabilitation approaches to combat SR-induced CNS changes.

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