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Review article

Progressive increase in the complexity and translatability of rodent testing to assess space-radiation induced cognitive impairment

Richard A. Britten [a,b,c,d,*], Laurie L. Wellman [d,e], Larry D. Sanford [d,e]

[a] Department of Radiation Oncology, Eastern Virginia Medical School, Norfolk, VA, 23507, USA
[b] Department of Microbiology and Molecular Cell Biology, Eastern Virginia Medical School, Norfolk, VA, 23507, USA
[c] Leroy T Canoles Jr. Cancer Center, Eastern Virginia Medical School, Norfolk, VA, 23507, USA
[d] Center for Integrative Neuroscience and Inflammatory Diseases, Eastern Virginia Medical School, Norfolk, VA, 23507, USA
[e] Department of Pathology & Anatomy, Eastern Virginia Medical School, Norfolk, VA, 23507, USA

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ABSTRACT

Ground-based rodent models have established that space radiation doses (approximately those that astronauts will be exposed to on a mission to Mars) significantly impair performance in a wide range of cognitive tasks. Over the last 40 years there has been a progressive increase in both the complexity and the translatability (to humans) of the cognitive tasks investigated. This review outlines technical and conceptual advances in space radiation rodent testing approaches, along with the advances in analytical approaches, that will make data from ground based studies more amenable to probabilistic risk analysis. While great progress has been made in determining the impact of space radiation on many advanced cognitive processes, challenges remain that need to be addressed prior to commencing deep space missions. A summary of on-going attempts to address existing knowledge gaps and the critical role that rodent studies will have in establishing the impact of space radiation on even more complex (human) cognitive tasks are presented and discussed.

1. Space radiation exposure as an unavoidable flight stressor on deep space missions

NASA's decision to undertake inter-planetary explorations has increased the need for information on the health risks associated with prolonged exposure to deep space flight stressors.

Due to inherent limitations of the spacecraft design and uplift capacity, space radiation (SR) exposure will be an unavoidable flight stressor on a mission to Mars. The deep space radiation spectrum (Galactic Cosmic Radiation (GCR)), is composed of highly energetic, high mass ($Z \leq 28$) charged ions. Current estimates suggest that astronauts will be exposed to ~13 cGy of SR during each year of the mission (Cucinotta et al., 2014), the majority of which will be incurred while in transit to Mars. The structure of the spacecraft will offer a degree of shielding to the astronauts, reducing the SR dose and altering the GCR ion spectrum from that seen in free space. The "Local-Field" spectrum (the SR spectrum that the internal organs of astronauts will receive within the spacecraft) calculated using the current spacecraft design specifications predicts that the majority of the physical and dose equivalent SR dose will arise from $Z < 15$ particles (Slaba et al., 2016).

In the mid-1980s NASA launched several ground-based initiatives (primarily using rodent models) to assess the detrimental effects of SR on astronaut health. In addition to establishing carcinogenic risks these initiatives also addressed whether SR exposure will result in cardiovascular and CNS related issues (as suggested by epidemiological data from the Chernobyl accident (Gamache et al., 2005)). This review outlines the evolution of ground-based neurocognitive testing from the early discovery stages to today's highly advanced and translatable approaches, an evolutionary process that has many parallels with the progressive technological evolution of NASA's space flight program.

2. Mercury: the "pioneering" era

The Mercury missions determined astronaut performance issues while in space; for these missions NASA used existing technologies and the simplest and most reliable system designs. The pioneering SR/neurocognitive studies similarly used existing behavioral assays that had been previously help to establish low LET radiation effects.

At the start of the 1980s, the CNS was generally considered to be a radiation resistant organ due to its highly differentiated nature and the

* Corresponding author at: Department of Radiation Oncology, Eastern Virginia Medical School, 700 W. Olney Rd., Lewis Hall, Norfolk, VA, 23507, USA.
E-mail address: brittera@evms.edu (R.A. Britten).

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lack of any detectable histological changes in brain cancer patients (e.g., demyelination) until 60 Gy has been delivered. However by the mid-1980s several clinical (Danoff et al., 1982; Ron et al., 1982; Shore et al., 1976) and laboratory (Garcia et al., 1961; Smith, 1971) studies suggested that the functionality of the brain may be impacted by <1.5 Gy X-rays. The robustness of the clinical findings were questioned due to the adverse socio-economic status of the irradiated children, but the laboratory studies could not be easily overlooked given that these focused on a process that has been evolutionary conserved, the conditioned taste aversion (CTA) response. The CTA is a feeding system defense mechanism, where the animal establishes an association between the taste and the aversive systemic effects of the food, i.e. (aversive) associative cue learning. Pioneering work by Dr. Rabin demonstrated that the CTA response was impacted after exposure to 20 cGy X-rays (Rabin et al., 1985) and by a variety of SR ion species (Rabin et al., 1989, 1991). Concomitant with these studies, the Rabin team determined that low (10 cGy) SR doses altered dopamine mediated neurotransmission in the striatum (Joseph et al., 1992). These early studies suggested that the RBE for SR-induced cognitive impairment was between 0.5–5.0 for the various SR-ions studied (Rabin et al., 1989, 1991), which were generally consistent with the LET-dependent RBE for cell killing (Barendsen, 1968). These seminal papers sparked a major expansion in the number of studies that investigated the impact of SR on many neurocognitive processes (reviewed in Cekanaviciute et al., 2018; Cucinotta and Cacao, 2019; Kiffer et al., 2019: Whoolery et al., 2020).

3. Gemini: the "definition" era

The Gemini program utilized new systems to develop many technologies and skills that would be required for the later manned missions into space. The early "discovery" SR/neurocognitive studies investigated the effect of SR exposure on an expanded range of cognitive tasks.

Many of the SR/neurocognitive studies during this "definition" period were highly hippocampus centric (with the notable exception of Dr. Rabin's studies on the striatum-dependent operant response) for several reasons. The hippocampus has a well-documented role in the formation of new memories about experienced events (episodic or autobiographical memory) (Eichenbaum and Cohen, 1993; Squire and Schacter, 2002). Given that adult hippocampal neurogenesis plays a major role in regulating several cognitive processes (learning, memory, pattern separation, and cognitive flexibility), it was a reasonable assumption that cognitive impairment was the consequence of radiation-induced impairment of neurogenesis. The increased incidence of dysregulated hippocampal neurogenesis in patients experiencing cognitive decline as a result of neurological disorders further reinforced this concept. This led to extensive efforts to establish the impact of SR on hippocampal neurogenesis and performance in tasks regulated by the hippocampus. Spatial learning and memory was investigated using the Morris Water (Manda et al., 2008; Parihar et al., 2018; Shukitt-Hale et al., 2000), Barnes (Britten et al., 2012, 2017) and Radial arm (Denisova et al., 2002; Raber et al., 2004; Villasana et al., 2011) mazes. Learning and memory was also investigated using the Novel Object Recognition (NOR) test (Acharya et al., 2017, 2019; Haley et al., 2013; Parihar et al., 2015, 2016; Rabin et al., 2014).

Other investigators assessed the impact of SR exposure on anxiety (open-field, light-dark box, elevated plus maze), providing information of the amygdala/corticolimbic network (Haerich et al., 2005; Parihar et al., 2018; Acharya et al., 2019). Conditioned fear response studies provided information of the impact of SR on the consolidation of a "powerful" memory, and on the extinction of such responses (Acharya et al., 2019; Parihar et al., 2016, 2018; Raber et al., 2013, 2014, 2015; Villasana et al., 2010). While there is considerable debate on the exact mechanism involved in fear extinction, this is a complex process that requires active "unlearning" of the associative cues, either passively or through consolidation of new (positive) experience based memories. The operant response task provided insight into how SR impacted the motivational status of the rodents to gain a food reward (Poulose et al., 2011, 2017; Rabin et al., 1994, 2003, 2005a,b,c, 2011, 2014, 2015a,b, 2018, 2019a,b), which also provided some indication of reward valuation.

The earlier studies during the "definition" era utilized relatively high SR doses based upon the belief that SR-induced reduction of neurogenesis was the most likely cause for cognitive decline. Performance in many of the cognitive tasks was impaired at doses >10 Gy of X-rays, thus based upon the RBE for cell killing for the most abundant "free-space" GCR particles (2–3 depending upon the LET), it was predicted that ~1−4 Gy of SR would likely result in cognitive impairment. However, as more "discovery" data was published it became evident that performance in many cognitive tasks was impaired at much lower SR doses than originally predicted. While SR exposure did impact both behavioral performance and neurogenesis at the predicted doses, as the SR dose was decreased towards mission-relevant doses (50 cGy), significant changes in neurogenesis were not detected (Rola et al., 2008). However, there were still significant impairments in hippocampus-dependent processes at such doses (Britten et al., 2012, 2017; Shukitt-Hale et al., 2000, 2003). Moreover, other studies suggested that radiation-induced cognitive impairment may also occur by altering processes independent of neuronal cell loss, e.g., Mickley et al. (1982) ameliorated radiation-induced spatial learning decrements in mice by using MK801 (NMDA receptor inhibitor), without impacting neuronal cell loss.

Collectively, these experiences suggested that SR-induced impairment of neurocognition occurs at doses close to those expected on the mission to Mars, but that such impairments arise, at least in part, via mechanisms that are independent of neuronal cell death/loss. There was thus an increased emphasis on establishing SR-induced changes in the neurotransmission properties of neurons within the hippocampus (Bellone et al., 2015; Machida et al., 2010; Marty et al., 2014; Rudobeck et al., 2014; Sokolova et al., 2015; Villasana et al., 2010; Vlkolinský et al., 2008), and later in other parts of the brain (Britten et al., 2014, 2020a; Hadley et al., 2016; Parihar et al., 2018). Recent studies have established that SR (He) exposure also decreases the functional connectivity between the hippocampus and perirhinal cortex (Parihar et al., 2018).

The increasing body of evidence that SR doses approximating those predicted for the Mars mission can impair a variety of cognitive processes (regulated by the hippocampus, striatum and amydala) elevated SR/neurocognitive effects to being "of concern" in NASA's risk assessment models for the Mars mission. This resulted in a change in the mandate for ground-based SR/neurocognitive studies, with a switch from discovery (is there a possible problem?) towards risk assessment (how big of an issue will there be?). While many of the tasks studied prior to 2010 provided information on cognitive processes that humans use extensively, the tasks were relatively simple, had a heavy reliance upon working memory with many not having a direct overlap with human cognitive performance tasks. There was thus a move towards interrogating cognitive processes that would be more pertinent to astronaut performance. Over the last decade there has been a progressive evolution of neurocognitive testing approaches used to establish the detrimental effects of SR exposure, involving changes in the nature of the behavioral tests, the model systems, how data is presented and analyzed, and using more realistic SR exposures (both with respect to ion species and with concomitant flight stressors).

4. Apollo: the first steps towards exploration of the stars

The ground-breaking Apollo missions were a huge technological success and established the feasibility of humans landing on distance objects in space and returning safely. However, the longest Apollo mission lasted just 13 days, leaving many questions unanswered about the ability of humans to survive for extended periods in space. While the earlier SR/neurocognitive studies explored the possibility that SR could impair neurocognitive performance in a general sense, around 2010

there was an increased focus on determining if mission-relevant SR exposures would lead to impairment of more complicated cognitive processes.

Astronauts are routinely screened during space flight for performance in a 10-test battery of cognitive tasks that NASA deemed necessary for mission success (Basner et al., 2015; Moore et al., 2017). Seven of the tasks in the "fit-for-duty" performance battery assess some aspect of executive function. Executive function, in lay terms, can be summarized as the "Triple A": the ability to Assess, Adapt and Achieve. More technically, executive functions are a set of higher order cognitive abilities that animals utilize to keep information 'in mind', attend to appropriate cues (e.g., nonverbal and verbal working memory stimuli), update information as contingencies change and invoke alternative, more appropriate responses to new situations. Astronauts on deep space missions will have to act more autonomously than on previous missions, especially when rapid responses to unexpected problems are required. Creative problem solving skills will thus be of great importance to astronauts on a mission to Mars. Creative problem solving utilizes several executive functions involved in planning, organization, decision making, judgment, task monitoring, attention, hypothesis generation, abstract thinking, and cognitive flexibility (Baron, 2004; Cato et al., 2004; Spinella, 2005; Stuss and Levin, 2002).

During the 2010s there was a rapid expansion of studies that established the impact of SR exposure on more complex cognitive processes. In some cases, more advanced versions of the tests used in the "discovery era" were employed. For example, the NOR test was evolved into the Object-In-Place (Acharya et al., 2019; Parihar et al., 2015, 2016, 2018) and Temporal Order (Acharya et al., 2017, 2019; Parihar et al., 2016, 2018), which provides information on the functionality of hippocampal-cortical circuits (Barker and Warburton, 2015). Recent studies have demonstrated that <30 cGy of SR ions impairs OIP performance (Acharya et al., 2019; Parihar et al., 2015, 2016, 2018). A further refinement of the OIP, the Updating task, incorporates many of the features of the human Mnemonic Similarity Task (MST). The MST is a behavioral task that was designed to tax pattern separation skills in patients with mild cognitive impairments (Stark and Stark, 2017), requiring the participants to respond to "Old", "Similar", or "New" on each trial. Preliminary data from the UCI/NSCOR suggest that <30 cGy SR impairs performance of mice in the updating task (Stark-personal communication). However, it should be noted that SR-exposed mice show enhanced pattern separation performance in the Location Discrimination pattern separation task (Whoolery et al., 2020). It has been suggested that the SR-associated increase in pattern separation skills might result from a SR-induced increase in sparse encoding of entorhinal input. Sparse encoding in the dentate gyrus granule is critical for pattern separation as it minimizing interference between memory representations of similar but not identical experiences (Danielson et al., 2016). Clearly further mechanistic studies are needed, but these apparent discrepancies do highlight the need for studies that assess SR effects on multiple cognitive processes to avoid erroneous risk assessments being generated based upon a single cognitive domain.

Other investigators assessed the impact of SR on rodent versions of tests widely used to assess attention and cognitive flexibility in humans. A notable feature of these predominantly rat-based studies was the use of out-bred strains that better reflected the inherent inter-individual variations seen in humans. Due to logistical constraints, these early studies were almost exclusively conducted in males to minimize the possible confounding impact of fluctuating estradiol mediated radioprotection (Thompson et al., 1969) during the estrus cycle of the rats.

The rodent version of the psychomotor vigilance test (rPVT) is virtually identical to the PVT test that is part of NASA's "fit-for-duty" performance battery on the International Space Station (ISS) (Basner et al., 2015; Moore et al., 2017). PVT performance is sensitive to fatigue, drug use, and age (Blatter et al., 2006; Lim and Dinges, 2008), and has been used in human risk assessment in a range of operational environments (e.g., the military, the aviation and railway industries, first responders) (Basner and Rubinstein, 2011). Drs. Hienz and Davis established that rats exposed to mission-relevant (25 cGy) doses of protons (Davis et al., 2014) had deficits in accuracy (i.e., decreases in percent correct scores), impulsivity (i.e., increases in premature responding), and lapses in attention in the rPVT test, all of which are indicative of deficits in sustained attention. These behavioral changes were associated with SR-induced changes in dopaminergic proteins (Davis et al., 2015) within the prefrontal cortex (PFC). Importantly, this was the first study where the performance deficits in SR irradiated rodents could be definitively linked to SR exposure because this study used rats that had established performance levels prior to being irradiated.

The revelation that SR exposure reduced the ability of rats to sustain attention is worrying in its own right. Human Factors Analysis and Classification System-based investigations of flight accidents in the Navy and Marine Corps revealed that human error (frequently due to lapses of attention) was a primary causal factor in 80 % of cases (Wiegmann and Shappell, 1999). An attentional set is formed when complex stimuli must be discriminated, and classified as relevant or irrelevant to a particular task/situation. A key process that allows humans to rapidly and efficiently adapt to different situations is task- or set-shifting. Set-shifting can be simplistically thought of as the ability to relearn what the most important discriminating stimulus (for a particular endpoint) is in a changing environment. Attentional set shifting (ATSET) thus enables subjects to rapidly adapt and respond to changes in the environment, and to perceive what is important for survival or completion of a task, skills that are required to deal with a sudden emergency. The Wisconsin Card Sorting Test (WCST) has been widely used to assess task switching in humans (Eling et al., 2008). Deficits in task switching are commonly observed in patients with Parkinson's disease (Monchi et al., 2004; Sawada et al., 2012) and autistic patients (Yerys et al., 2009; Brady et al., 2013). The intra-dimensional (IDS) /extra-dimensional (EDS) set shifting task is a modification of WCST that assesses set-shifting abilities in rodents (Birrell and Brown, 2000). The rodent ATSET task is a 7 stage progressive test, where the rat has to form an association between the presence of the food reward and a physical cue (either the digging medium or scent). By altering the combination of scents and digging media, progressively more complex cognitive processes can be tested. The task requires sequential rule learning ability, utilizing information gained in a previous stage to solve the subsequent tasks.

Early studies established that exposure (head-only) to 20 cGy SR (^{56}Fe) significantly reduced ATSET performance in juvenile male rats (Lonart et al., 2012). The experimental design of that study eliminated rats from further testing once they failed a stage twice. This progressive elimination strategy resulted in only 17 % of irradiated rats completing all stages of the ATSET test as opposed to 78 % of the sham rats (Lonart et al., 2012). Subsequent studies determined that whole body exposure to 20 cGy ^{56}Fe impaired ATSET performance in both juvenile and retired breeder male rats, with ~30 % fewer SR-exposed rats completing all stages of the ATSET test than the shams (Britten et al., 2014). The same model system determined that exposure to <20 cGy of ^{48}Ti (Hadley et al., 2016) and ^{28}Si (Britten et al., 2018) ions resulted in similar decrements of performance in the ATSET test. While many ion- and dose-specific changes were observed, the overall consensus from these studies was that SR exposure reduced ATSET performance by primarily increasing the failure rate in the Food Foraging (FF) or Discrimination (Simple (SD) and/or Compound (CD)) stages (Britten et al., 2018, Fig. 1).

The underlying cause of the high failure rate of SR exposed rats in the FF stage remains speculative, but the majority of the rats did start digging for the food reward indicating they understood the nature of the task. Moreover, the non-habituating rats showed no obvious signs of anhedonia (sucrose preference test, or general appearance and activity in the cage), suggesting that SR-irradiated rats may have an inability to maintain attention on the task or reduced motivation/ reward valuation (as suggested by the Operant response data (Poulose et al., 2011, 2017; Rabin et al., 1994, 2003, 2005a,b,c, 2011, 2014, 2015a,b, 2018, 2019a,

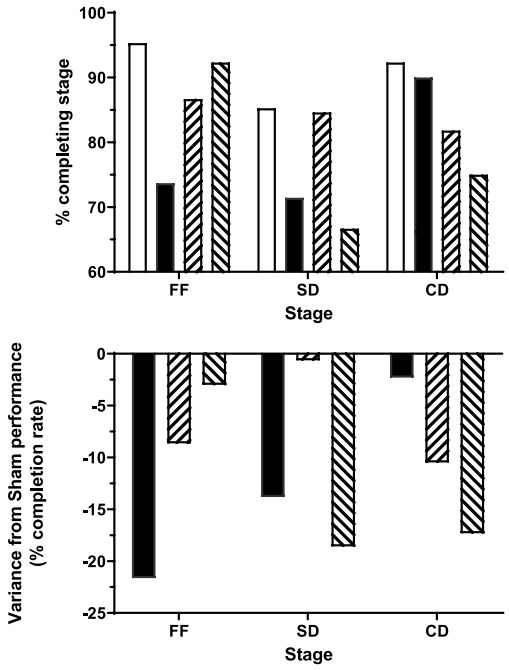


Fig. 1. Impact of "isofluences" of Si, Ti and Fe ions on Food Foraging and Discrimination performance of male Wistar rats within the ATSET task (Data from Britten et al., 2018 **re-analyzed). A.** Stage Completion rate. Percentage of the rats starting the stage that completed that stage after exposure to "iso-fluences" of SR particles: 6.20×10^5 particles cm^{-2} (5 cGy) 600 MeV/n ^{28}Si (□), 5.80×10^5 particles cm^{-2} (10 cGy) 1 GeV/n ^{48}Ti (Ascending hash), 6.22×10^5 particles cm^{-2} (15 cGy) 1 GeV/n ^{56}Fe (Descending hash) or in Sham-irradiated (□) counterparts. FF: Food Foraging; SD: Simple Discrimination; CD: Compound Discrimination. **B.** Variance of the Stage completion rate in SR-exposed rats from that seen in the sham counterparts.

b)).

The SD stage interrogates the rats' decision making abilities. The CD stage interrogates the rat's ability to maintain focus on the previously learnt relevant aspects of the task by introducing changes in the irrelevant perceptual modality, i.e., a measure of distractibility. Should similar effects occur in astronauts, these data suggest that they would have a reduced ability to identify key events in a new situation, and would be more easily distracted by extraneous variables.

Some of the tasks that astronauts will have to perform during a mission will be event sensitive, i.e. they have to be done correctly on the first occasions, others will be time sensitive, i.e., they have to be done quickly (and typically accurately). It is thus important to determine whether SR exposure impacts the efficiency with which an individual completes a task. In-depth analysis of the ATSET performance data revealed that in addition to the significantly lower SD and CD completion rates, SR-exposed rats that did complete the CD stage took significantly more attempts (ATRC) than shams rats to do so (Hadley et al., 2016). Moreover, when SR-exposed rats did make a correct choice, they took significantly longer to do so (Mean Correct Latency- MCL) (Britten et al., 2014).

Performance within the SD stage is regulated by the mPFC (Bissonette et al., 2008), but based upon data from the "Dig task", a simplified version of the SD task, the frontal cortex may also be involved (Martens et al., 2013). Performance in CD stage is regulated by perirhinal cortical region, (Eacott et al., 2001; Feinberg et al., 2012; Lindquist et al., 2004; Norman and Eacott, 2004) and also requires optimal dopamine D2 receptor activation in the PFC (Glickstein et al., 2005). Collectively these studies indicate that mission-relevant SR doses impact cortex dependent performance, in addition to the previously documented deficiencies in hippocampus-dependent tasks. From a risk analysis perspective it was important to determine whether there was a subset of rats that were sensitive to SR-induced performance deficits in both PFC- and hippocampal-dependent tasks. Rats were thus screened for performance in the Barnes Maze (hippocampus-dependent spatial memory) and then in the ATSET task (Britten et al., 2016). When cohort performance data was compared, SR exposed rats had significantly worse performance in both tests; however when the relative performance of individual rats in each task was compared there was no correlation between SR-induced loss of performance in each task (Britten et al., 2016; Fig. 2). These data again suggest that risk assessments for SR-induced neurocognitive impairment derived from a single cognitive domain may greatly underestimate the severity of the problem.

5. The Sky-lab "feasibility" era

An important objective of the Skylab mission was to prove humans could live and work in space for extended periods. While the Skylab missions were not glamorously portrayed many fundamental issues were resolved during this era. Similarly, the SR/neurocognitive studies that employed more appropriate ("astronaut-like") rodent models, and/or developed analytical approaches that were more amenable to risk analysis estimates, have not made headline news.

The discovery that SR exposure impairs cortex-dependent executive functions necessitated that future studies be conducted in model systems that resembled astronauts as much as possible within the constraints of a rodent model system. There has been an increase in the use of more astronaut "age-appropriate" rodents, but in many cases the "aged" rodents did not resemble astronauts with regards to physical or mental fitness, often being unfit and obese (with associated health and mobility issues) and with a high level of lethargy/cage weariness. Some investigators started using aged rats that were maintained on a low fat diet coupled with a moderate exercise regimen (Véras-Silva et al., 1997). In addition to the overall health benefits arising from the exercise, the exercise-induced increase in BDNF (Quirie et al., 2012) or reelin (Seo et al., 2013) has been shown to increase spatial memory performance (Seo et al., 2013; Vaynman et al., 2004). Moreover, the repeated exercise (2–3 times a week for the duration of the study (Britten et al., 2020a; Jewell et al., 2018)) helped acclimatize the rats to the handlers, while being repeatedly taken out of cages and placed in new environments served to reduce anxiety. Astronauts are selected to have a high stress resilience, partly as a result of their training, that allows them to stay calm when confronted with a new situation. Exercised rats are thus

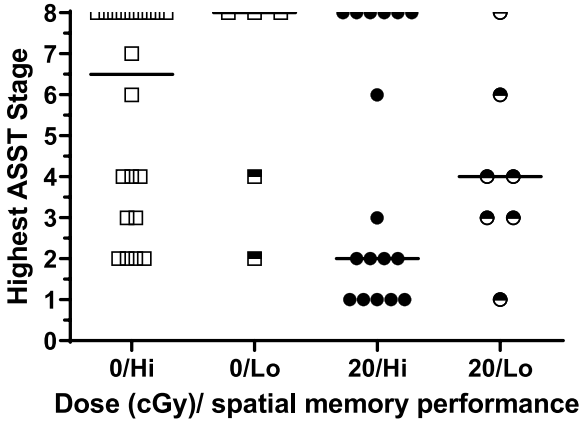


Fig. 2. ATSET performance of sham and irradiated (20 cGy 1 GeV/n ^{56}Fe) Wistar rats that have high or low spatial memory performance (Data from Britten et al., 2016 **re-analyzed).** Individualized assessment of ATSET performance (highest stage completed) in sham rats with high spatial memory performance (0/Hi), sham rats with low spatial memory performance (0/Lo), irradiated rats that retained a high spatial memory performance (20/Hi), or had low spatial memory performance (20/Lo). Horizontal bar represents the median performance of each cohort.

much more astronaut-like in their stress/anxiety handling ability when put into a testing chamber than a rat that has not been exercised.

Astronauts are highly trained individuals who have a high level of cognitive reserve, and highly developed executive function skills. Clearly, the use of rodents directly shipped to BNL from the supplier, without any kind of selection for cognitive performance are not representative of the high cognitive reserve of astronauts. The poor performance of sham rats in the complicated executive function tests (e.g., ~25 % fail to complete all stages of the ATSET tests (Britten et al., 2014)) serve to dampen the magnitude of the SR effects and raised questions on how many of the "impaired" rats following SR exposure had marked SR-induced deficiencies as opposed to a slight worsening of a pre-existing mediocre performance. The rPVT study by Davis et al. (2014) was the first to attempt to increase the translatability of the rodent studies to astronauts by using rodents that had a documented high level of cognitive performance prior to SR exposure.

In addition to increasingly the likelihood that any performance decrements observed in SR-exposed rats were a result of the SR exposure, the use of previously screened rats also provided an opportunity to determine if SR exposure impacted long-term working memory. Using physically fit male retired breeders that had been prescreened for a high level of ATSET performance, the Britten lab demonstrated that both the sham and SR-exposed (15 cGy ^{56}Fe) rats had almost perfect performance when presented with an identical ATSET task to that used in the prescreening process (Jewell et al., 2018). When naïve-rats are presented with the prescreen version of the ATSET test (where the rewarded perceptual domain in the SD-IDR and EDS/EDR stages are odor and digging media respectively), the ATRC performance profile exhibited the "classic" higher CDR/CD IDR/IDS and EDS/IDS ATRC ratios (Fig. 3A). When sham and SR exposed rats (Fig. 3B) rats were represented with the identical ATSET test (90 days after irradiation, ~ 110–130 days after completion of prescreening), both cohorts of rats completed all (with the exception of IDR) stages of the test in close (ATRC < 7.2) to the minimum number possible (ATRC = 6) (Fig. 3B). Importantly the EDS/IDS differential was not evident (as it was when first presented with the task), suggesting that the rats knew the structure of the task and anticipated the change in perceptual domain. Rats have a well-developed ability to "predict" food rewards using transitive inference (Dusek and Eichenbaum, 1997; Jennings and Keefer, 1969; Sultan et al., 2011). Transitive inference can be defined as the ability to use known relationships to infer unknown relationships, often referred to as deductive reasoning in humans. Irrespective of radiation dose, all rats performed better in the post-exposure screening, in some cases reaching criterion in half the number of attempts than in the prescreening protocol (Fig. 4). These data are consistent with the rats retaining a working memory of the rules for the food reward for 100–120 days (since they passed the pre-screening), even after being irradiated with 15 cGy ^{56}Fe. Should similar effects occur in humans after SR exposure, astronauts would most likely be able to perform the tasks that they had been previously trained to do.

Using a second version of the ATSET test that was structurally the same as the prescreening test, but where the relevant (rewarded) perceptual domains have been transposed it was possible to determine whether SR exposure impacted long-term working memory of cue identity, test structure, ability to switch attention/identify new rules (relevant perceptual modality), and also further interrogate the transitive ability of the rats.

The performance of the prescreened sham rats in the new "transposed" version of the ATSET test (where the rewarded perceptual domain in the SD-IDR and EDS/EDR stages are digging media and odor respectively) was qualitatively similar (Fig. 5A) to that observed when being represented with the prescreen version of the ATSET test (Fig. 3B). However, the sham rats took ~ 40–50 % more attempts (10 vs 7 ATRC) to complete the SD in the new version of the test than they did when presented with a previously experienced version of the test. With the exception of the CDR stage, the sham rats completed the transposed variant of the test in under 10 ATRC (Fig. 5A). Importantly there was no EDS/IDS differential, once again suggesting that the rats knew the structure of the task and anticipated the change in perceptual domain.

When the rats exposed to 15 cGy ^{56}Fe were presented with the new version of the ATSET task, they took almost double the attempts that the

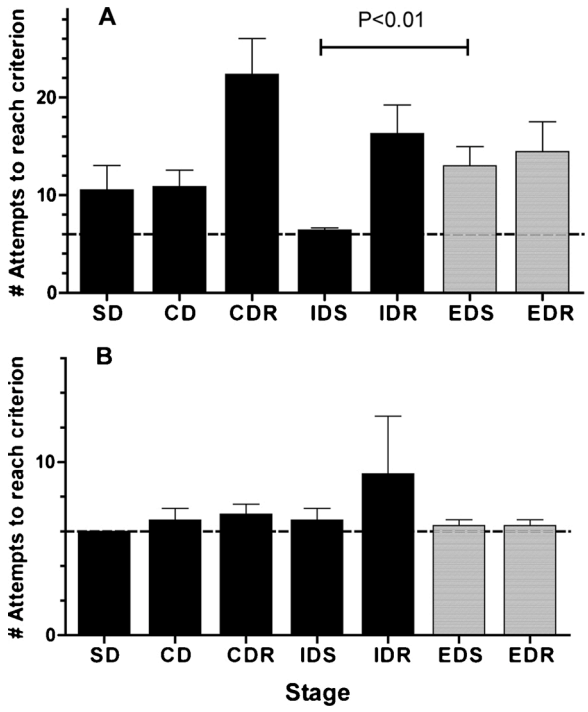


Fig. 3. (Data from Jewell et al., 2018 re-analyzed). **A.** The performance (ATRC) of naïve (previously untested) male Wistar rats in the various stages of the ATSET test Stage abbreviations are FF: Food Foraging; SD: Simple Discrimination; CD: Compound Discrimination; CDR: Compound Discrimination Reversal; IDS: Intra-Dimensional Shifting; IDR: Intra-Dimensional Shifting Reversal; EDR: Extra-Dimensional Shifting and EDR: Extra-Dimensional Shifting Reversal. Graphs show means ± SEM. Associative cues: odors (solid bar), digging medium (hashed bar). **B.** ATSET performance vetted male Wistar rats when challenged with the same set of associative cues 3 months later.

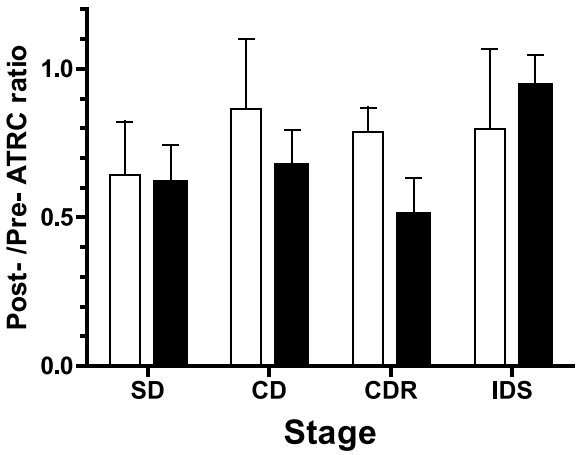


Fig. 4. (Data from Jewell et al., 2018 **re-analyzed).** Relative ATSET performance (Post/Pre ATRC ratio) in the pre- and pre-exposure screenings of rats exposed to 15 cGy 600 MeV/n ^{56}Fe ions (solid bars) or sham irradiated rats (open bars). Graphs show means ± SEM. Stage abbreviations are FF: Food Foraging; SD: Simple Discrimination; CD: Compound Discrimination; CDR: Compound Discrimination Reversal; IDS: Intra-Dimensional Shifting; IDR. Graphs show means ± SEM.

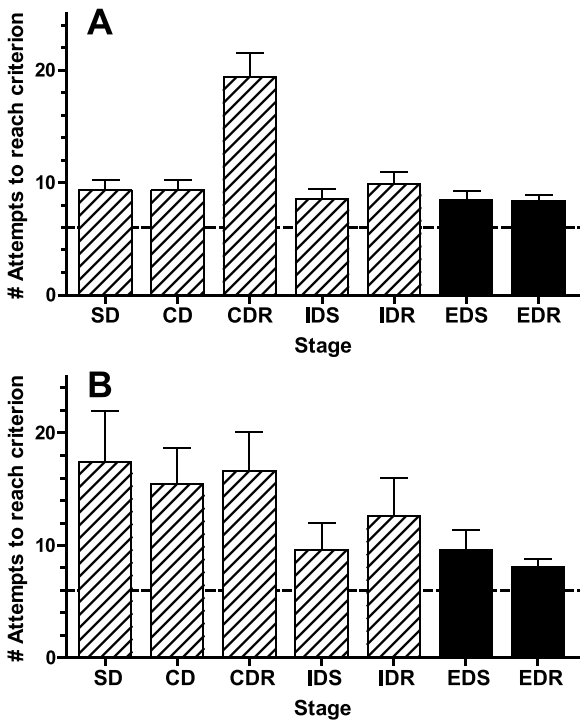


Fig. 5. (Data from Jewell et al., 2018 re-analyzed). ATSET performance of vetted male Wistar rats when challenged with a new sequence of associative cues 3 months later. **A.** Cohort average ATRC values for sham-irradiated rats; **B.** Cohort average ATRC values for rats exposed to 15 cGy ^{56}Fe. Stage abbreviations and associative cue symbols are as listed in Fig. 1.

shams rats required to reach criterion in the discrimination (SD and CD) stages, but their performance within the shifting stages (Fig. 5B) was comparable to that observed in the shams (Fig. 5A). SR exposed mice also take longer to reach criterion in Pairwise Discrimination and touchscreen training (Whoolery et al., 2020). Thus exposure to 15 cGy of ^{56}Fe reduced the rats' ability to establish the identity of the associative cue for the food reward (rule learning) in the discrimination stages, but did not appear to impact their ability to set shift or use transitive inference. Should similar effects occur in humans, astronauts would a decreased ability to identify and maintain focus on relevant aspects of the task being conducted, but from an operational perspective, these performance deficits may only be manifested in scenarios where the astronauts have to transitively apply their knowledge to solve problems that they have not previously encountered.

Subsequent studies using the same vetted rat model system revealed significant impairments in CD performance after exposure to Ti (Parihar et al., 2016), Si (Britten et al., 2020a) and protracted low dose low dose rate neutrons (Britten et al., 2019). In some instances, the SR exposed rats also took significantly longer to correctly choose the food reward (Britten et al., 2020a; Jewell et al., 2018). The SR-induced impairment of performance in the CD stage of the ATSET test, further added to the growing body of evidence from multiple rodent based studies (Britten et al., 2014,2018,2020a; Parihar et al., 2015,2016) that SR exposure has pronounced effects on perirhinal dependent behaviors.

The ATSET performance studies using prescreened rats provided definitive evidence that there were marked inter-individual variations in the severity of ATSET impairments induced by SR (Britten et al., 2019; Jewell et al., 2018), as well as in the rPVT (Davis et al., 2014). Traditional cohort analysis of the CD performance revealed that ^{56}Fe exposed rats had a significantly worse performance than did the sham cohort, but many of the SR-exposed rats had comparable performance to that seen in sham rats; however 30–50 % of SR-exposed rats had ATRC metrics more than double that seen in the shams (Jewell et al., 2018) (Fig. 6). Thus not

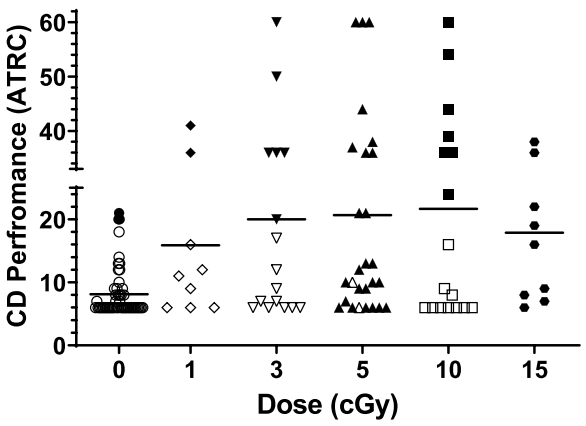


Fig. 6. Inter-individual variation in CD performance (ATRC) of sham (Circles) and 600 MeV/n ^{56}Fe irradiated (1: (Diamonds), 3: (Descending Triangle), 5: (Ascending Triangle), 10: (Squares) and 15 cGy (Hexagons)) vetted male Wistar rats. (Data from Jewell et al., 2018 re-analyzed). Horizontal bars represents cohort mean value. Symbols represents individual rat data, with solid symbols representing individual rats that had ATRC $\geq$ 19 (KDE-derived 5th percentile).

all individuals will experience SR-induced ATSET deficits.

While the ATSET test provides considerable insight into the executive function capacity of rats, it is limited in that it only measures the ability of rats to shift attention between a constrained set of options. Problem solving in humans involves complex situations in which there is a broader, unconstrained set of possible solutions (unconstrained cognitive flexibility), that require the generation of a hypothesis (requiring abstraction and transitive inference). There has been a recent evolution of the ATSET test that utilizes a novel problem-solving task in rats (Hecht et al., 2014), analogous to the tasks recently employed to examine creative problem solving in other species (Bird and Emery, 2009; Foerder et al., 2011). The Unconstrained Cognitive Flexibility (UCFlex) assay (Hecht et al., 2014) requires that after the rats have completed all of the tasks in the ATSET, they then have to complete a new task where the food reward is no longer present in either reward pot (as it was for all seven stages of the ATSET assay); instead the reward is located in a third location that the rat had limited experience with, requiring the rat to develop a novel solution to obtain the food reward. Thus, the UCFlex version of the ATSET provides the ability to measure both constrained and unconstrained cognitive flexibility within individual rats. In two recent studies, UCFlex performance is inhibited after protracted low dose and low dose rate neutron exposure (Britten et al., 2019) and after exposure to 10 cGy Si (Britten et al., 2020a,b) ions (Fig. 7). Rats exposed to neutrons took longer to solve the problem but eventually did complete the task at a comparable rate to the shams (Britten et al., 2019). In comparison, exposure to 1–10 cGy Si resulted in a 30 percentage point drop in the UCFlex completion rate than was seen in the sham cohort (Britten et al., 2020a).

In both studies (Britten et al., 2019, 2020a) there was no consistent concomitant impairment of UCFlex and ATSET performance. Approximately 26 % of rats exposed to 10 cGy Si had impaired UCFlex performance (Fig. 7), however half of the rats that had a functional UCFlex performance (37 % of total population), had impaired performance in at least one ATSET stage. Thus 63 % of the irradiated rats had a measurable decrement in at least one aspect of cognitive flexibility: 1.7–2.4 fold higher than would be predicted from a single paradigm assessment. These data once again suggests that risk assessment values based upon a single behavioral end-point may not fully represent the cognitive deficits induced following SR exposure, even within the cognitive flexibility domain.

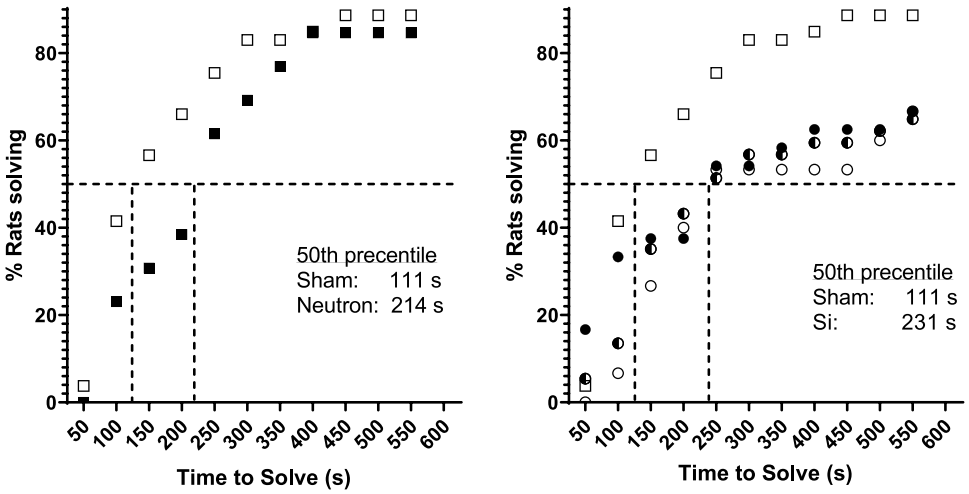


Fig. 7. The impact of SR on Creative problem-solving performance. Cumulative frequency plot of the time individual male Wistar rats to solve the problem for sham rats (□) or rats exposed to 18 cGy neutrons (Britten et al., 2019) or 1 (□), 5 (half-filled circle) or 10 (●) cGy 600 MeV/n ^{28}Si ions (Britten et al, 2020). Dashed lines represent the 50th percentile for problem solving performance.

6. Refining approaches for data analysis to facilitate risk assessment

Traditionally ground-based studies have typically determined if the cohort average value of the metric being investigated differed significantly between the sham and SR exposed subjects. Typically some form of Gaussian-based statistical analysis is conducted on the generated data. Such analyses are problematical in many regards. Firstly, there are few instances when a "perturbing" agent leads to a constant level of performance decrements across the entire population, resulting in treatment-related skewness (gamma distributed) in the performance metric, which has to be analyzed using non-parametric statistical methods. Secondly, cohort analyses does not provide any indication of what proportion of SR-exposed subjects have significantly poorer performance than the shams, nor how much the performance of individual subjects varied from that seen in non-exposed individuals. A 20 % decrease in the cohort's performance metrics could reflect 100 % of individuals performing at 80 % of the sham's performance level, or could reflect 50 % of individuals performing at 60 % performance level with the rest having comparable performance to the shams.

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. NASA flight planning includes Probabilistic Risk Assessments (PRA) as part of its standard risk assessment activities (NPR, 8705.5, 2004), where risk is characterized by three quantities: 1) the importance to mission success (I) of the process impacted by the adverse event; 2) the probability of an adverse event occurring (P), and 3) the severity of the adverse event (S):

PRA = I*P*S.

In order for ground-based studies to be of any value in establishing SR-related risk estimates, individualized performance data has to be presented, which then has to be analyzed in a manner that will quantify how many individuals have "severe" impairments. Clearly, it is only possible to calculate the probability of an adverse event occurring if there is some definition of what loss of performance constitutes an adverse event, which will be highly context specific. One frequently used metric to define significantly different from "normal" is the standard score of +2 score reflecting the 95th percentile of the population's metrics. However, standard scores are only valid when there is a normal Gaussian distribution of data.

The studies that have established that SR exposure impacts various aspects of attention clearly demonstrated that there is a dichotomous response to SR (Fig. 6; Britten et al., 2019, 2020a, 2020b; Davis et al., 2014; Jewell et al., 2018). Some irradiated rats have performance metrics comparable to that of the shams, while others struggle to complete the task, even when given a second opportunity. These data suggest that some individuals are able to ameliorate the deleterious effects of the SR, while others are unable to do so. In statistics, kernel density estimation (KDE) is a non-parametric way to estimate the probability density function of a random variable, and is frequently used to make inferences about a population based on a finite data sample. KDE is thus a useful tool to assign a (potentially variable) level of performance that can be considered to be sub-optimal for the task under consideration. That metric can then be used to quantify the numbers of individuals within the test population that display a severe impairment. In the Britten lab studies (Acharya et al., 2019; Jewell et al., 2018; Britten et al., 2019), the level of performance that was considered to represent severe impairment was set at the 5th percentile of the sham cohort performance profile (conceptually analogous to a standard score of -2). In the event that a task requires a higher or lower level of performance to safely/effectively perform that task, the same data set could be reanalyzed using other (e.g. the 1st or 60th) percentiles as the cut-off value. KDE analyses revealed that relative to the 5% impairment threshold in control rats, 41 % of neutron- (Britten et al., 2019), and ~44 % of ^{56}Fe- (Jewell et al., 2018) exposed rats had severely compromised performance in the SD stage of the ATSET test. Interestingly, this is almost identical to the conclusions in a parallel study on OIP performance in mice exposed to protracted neutrons (Acharya et al., 2019).

The Numbers Needed to Harm (NNH) algorithm is a measure that is increasingly used to express the potential harmful effects of an intervention in clinical trials. A similar approach can be used to generate the probability of SR-induced cognitive impairment, where SR would serve as the intervention. Substituting the derived values for severely impaired individuals (from the KDE analysis of the data from the neutron studies) into the NNH algorithm provides estimates of absolute risk and the frequency that severely impaired cognitive performance will occur following SR exposure. Should similar effects be induced in humans, the NNH value of 2.8–3.4 from the rodent studies (Acharya et al., 2019; Britten et al., 2019) would mean that in a crew of five astronauts traveling to Mars, two would display severe deficits in one executive function (ATSET) by the time they return to Earth.

7. The ISS era

ISS missions have helped resolve many of the issues that could prevent astronauts to successfully living and operating in the deep space environment. A notable feature of the ISS era was the increasing proportion of female astronauts with the 2013 astronaut class having parity between the sexes. SR/neurocognitive studies have started to employ more appropriate ("realistic") SR exposures, and most ground based studies are increasingly assessing the SR effects in both male and female rodents.

Recent technological advances have now made it possible to assess the impact of more realistic SR exposures. The calculation of the Local-Field spectrum (average radiation flux within human tissues behind vehicle shielding during solar minimum (Slaba 2015)) led to the development of several multi-ion, multi- energy composite beams at NSRL. While it is possible to do long duration SR exposures at NSRL, it is only feasible to do these in a fractionated manner, where the instantaneous dose rate per fraction will be far higher than would be experienced in space. One approach to model the impact of protracted SR exposure has been the development of a facility at Colorado State University (CSU) that can provide insight into the health risks associated with exposure to high LET radiation at dose rates and durations relevant for the mission to Mars (Borak et al., 2019). The CSU facility has a ^{252}Cf source, that provides a continuous source of neutrons at a dose rate of 1 mGy per day (with photons contributing 20 % of the total dose) and that serves as a proxy for some aspects of GCR exposure (Borak et al., 2019). We have recently shown that exposure to protracted low-dose (18 cGy) neutrons resulted in significant impairment of constrained cognitive flexibility in mice (Object-In-Place (OIP) task (Acharya et al., 2019)), and rats (ATSET (Britten et al., 2019), as well as unconstrained cognitive flexibility in rats (Britten et al., 2019)).

8. Additional spaceflight stressors, the role of sleep deprivation

Concomitant with the move to multi-ion beams there has been a move towards multi-flight stressor exposures. For multiple reasons, astronauts sleep less while in space than they normally do on Earth (Barger et al., 2014; Frost et al., 1976; Santy et al., 1988; Whitmire et al., 2013), and also the quality and structure of sleep in space is altered. During spaceflight there are quantitative changes in various sleep metrics including altered latency to rapid eye movement sleep (REM), shorter REM episode duration, and a redistribution of slow-wave sleep (SWS) between the first and the second sleep cycles (Gundel et al., 1997). There is also 27–50 % reduction in REM and SWS sleep time in space compared to that on Earth (Evans-Flynn et al., 2015; Moldofsky et al., 2000; Stickgold and Hobson, 1999), and astronauts on the ISS exhibit increased sleep pressure (greater theta activity in the EEG and more local sleep events during waking) (Petit et al., 2019). Astronauts extensively use sleep-promoting drugs during spaceflight to mitigate some of these effects (Barger et al., 2014), but such agents tend to not promote restorative sleep. It should also be noted that there can be variations across studies in reported changes in sleep during spaceflight.

Both sleep deprivation and sleep fragmentation (SF) have been linked to reduced neurocognitive functioning in humans and animals (Martin et al., 1996; McCoy et al., 2007; Nair et al., 2011). Sleep deprivation has a major impact upon performance in multiple cognitive domains (Alhola and Polo-Kantola, 2007), including the PVT (Christie et al., 2008), ATSET (McCoy et al., 2007) and spatial learning (Ramesh et al., 2012) tasks. Even a single night of very mild sleep restriction (2 h reduction) can negatively impact vigilance and impact cortical indices of motor preparation and execution (Stojanoski et al., 2018). It is thus likely that neurocognitive functioning will be reduced in astronauts who have disturbed sleep. Two recent studies have established how inadequate/disturbed sleep alters the severity of SR-induced impairment of executive function. A single session of fragmented sleep uncovered latent ATSET performance deficits in rats exposed to both protracted neutron (Britten et al., 2019) and Si (Britten et al., 2020b) irradiation that had no obvious defects in performance under rested wakefulness conditions. SF selectively impaired performance in the more complex IDR, EDS and EDR stages of the ATSET test in the both neutron and Si irradiated rats. Set shifting performance has rarely been impacted by SR exposure in studies conducted with rats tested under rested wakefulness conditions. Thus, SR-induced cognitive impairment may not be fully evident in normally rested rats, substantially underestimating the level of impairment that may occur when astronauts are on mission. Cognitive testing may thus have to be conducted under both rested wakefulness and SF conditions to get a more accurate assessment of SR-induced neurocognitive impairment.

It should be noted that the SF protocol used in these studies was relatively mild (disruptions every two minutes over the course of ~ 14.5 h). Similar protocols have been reported to fragment, but not reduce, overall sleep (Kaushal et al., 2012b; Nair et al., 2011; Ramesh et al., 2012). This makes the SF-induced unmasking of latent set shifting deficits even more concerning given that during missions astronauts will likely experience prolonged periods of restricted and disrupted sleep in conjunction with SR exposure and experiencing other inflight stressors. Another notable aspect of the SF/SR interaction studies was the marked inter-individual variation in the post-SF ATRC values given that only rats with almost perfect ATSET performance under normal wakefulness were used in the study (Britten et al., 2019, 2020b). These data highlight the need to understand system level variability in sleep and arousal, and in the ability to perform in environments that promote chronically disturbed sleep, even in cohorts of the highly screened individuals that are selected to be astronauts. It will also be critical to understand how SR impacts overall sleep and the sleep-related processes that exacerbate SR-induced performance decrements.

There have been minimal attempts to understand whether and how SR directly impacts sleep and its regulatory system. It is generally accepted that sleep is important for cognitive performance, and both non-rapid eye movement sleep (NREM) and REM have been implicated in learning and memory (Born and Wilhelm, 2012; Havekes et al., 2015; Stickgold, 2005; Stickgold and Walker, 2007; Walker, 2009, 2010). Additionally, REM may have a specific role in the adaptive processing of emotional memories (Cowdin et al., 2014; Hutchison and Rathore, 2015), with post-stress REM activity reflecting differences in resiliency and vulnerability (Sweeten et al., 2020; Wellman et al., 2016, 2018b). PTSD patients have lower levels of REM theta wave activity than do resilient patients (those who experienced a trauma, but did not develop long-term symptoms) (Cowdin et al., 2014). Thus, determining the specific effects of SR on sleep has importance for understanding a broad range of performance and psychological issues that may arise on interplanetary spaceflights. On-going studies in our laboratories are assessing the effects of SR on basic sleep regulation, and whether those alterations have consequences for the ability of astronauts to appropriately process fearful events they may encounter while on mission.

In addition to SR and sleep issues, astronauts on deep space missions will have to contend with microgravity and social isolation issues. Microgravity has well-documented effects on the skeletal, microbiome, gut mucosa, sensorimotor and ocular systems (e.g., (Doty et al., 2005; Li et al., 2014; Mader et al., 2011; Morey-Holton and Globus, 1998, 2002; Musacchia and Fagette, 1997; Zhou et al., 2012)). It also produces significant effects on the brain, particularly in cerebellar, sensorimotor, and vestibular brain regions (Reviewed in Van Ombergen et al., 2017). Brain activity may also change in response to the need for increased processing required for postural stabilization, and integration of conflicting vestibular information in the microgravity environment (Cebolla et al., 2016). At the cellular level, simulated microgravity result in persistent changes in the mitochondrial function and lipid metabolism of human oligodendrocytes (Espinosa-Jeffrey et al., 2016). Oligodendrocytes are essential for providing metabolic support to neurons, rapidly transferring (through cytoplasmic "myelinic" channels and monocarboxylate transporters) short-carbon-chain energy metabolites like

pyruvate and lactate to neurons (Philips and Rothstein, 2017). Such microgravity induced metabolic perturbations are likely to be deleterious to neuronal function in their own right, but will likely exacerbate SR-induced changes in neuronal functionality.

Social isolation is a significant concern for astronauts on interplanetary missions who will spend prolonged periods confined within a spacecraft with limited social interactions and separation from their families and social support networks. In general, work in both humans and animals demonstrate deleterious effects of social isolation on multiple systems (Friedler et al., 2015). Social isolation is associated with increased risk of depression and reduced cognitive functioning (Adam et al., 2011; Bhatti and Haq, 2017; Hawkley et al., 2003), and alterations in brain neurotransmitter systems and morphology (Djordjevic et al., 2012; Ferdman et al., 2007; Krupina et al., 2020; Shams et al., 2012; Zubkov et al., 2019). Humans with poor social support have exaggerated blood pressure and heart rate responses to stressful situations with slower recovery times (Grant et al., 2009). Social isolation can also increase the risk for obesity and type 2 diabetes mellitus (Nonogaki et al., 2007) and cardiovascular disease (Menendez-Villalva et al., 2015), and it can impact inflammatory responses and the ability to respond appropriately to other stressors (Menendez-Villalva et al., 2015).

Determining how astronauts respond to the single, compound and potentially synergistic effects of mission related stressors will be crucial for understanding and mitigating factors that can impair performance and damage health. On-going ground based studies are now establishing the impact that multi-flight stressor exposure have on neurocognitive performance. However, such studies will need to appropriately model the order, duration of the various stressors. While microgravity will be a constant stressor, SR exposure will be a continuous series of intermittent (and variable with respect to ion species and temporal separation) exposures, while perceived social isolation can be episodic or prolonged. The order, duration, and ability to resolve a given stressor, are important as prolonged stress and the failure to appropriately cope with stress can increase vulnerability to subsequent stress (Menard et al., 2017) thus, there is reasonable expectation that exposure to multiple inflight stressors will increase the occurrence and severity of altered cognitive performance and physical health issues. Added to the general difficulties of sleeping in space, the prolonged Mars mission may lead to additional sleep issues (Basner et al., 2014). Moreover, essentially all stressors have the potential to impact sleep (Sanford and Tang, 2009; Sanford et al., 2015) and prior and ongoing sleep disturbances impact responses to new stressors (e.g., (Bryant et al., 2010; Gehrman et al., 2013; Koren et al., 2002; Lavie, 2001)) and the ability to recover from them (McEwen and Karatsoreos, 2015), likely through negative effects on cognition and emotion (Bryant et al., 2010). Sleep deprivation in healthy adults can result in elevated resting cortisol release and greater cortisol release in response to a stressor, indicative of elevated hypothalamo-pituitary-adrenal axis activity (Minkel et al., 2014). Social isolation also can exacerbate inflammation resulting from sleep disturbances (Cho et al., 2015). Across age groups, social isolation is associated with disturbed sleep (Adam et al., 2011; Hawkley et al., 2003; Vanhalst et al., 2013) and work in animals have demonstrated that social isolation in mice can blunt the homeostatic sleep response to acute sleep deprivation (Kaushal et al., 2012a). In recent studies we (Wellman et al., 2017b) have found that SF can concurrently promote inflammation in the brain and suppress immune function in the mesenteric lymph nodes (MLNs) (Wellman et al., 2017b). The MLNs are important for maintaining the gut mucosal barrier (Balzan et al., 2007; Deitch, 2002), which, as noted above, also is altered in microgravity.

Given the widespread health issues arises from space-flight related stress and subsequent sleep issues, there is a real need to understand individual differences in the ability to cope with stress and also the effects of heterogeneous stressors (Gordon, 2018). Individual resilience and ability to adapt should also be considered when selecting and training astronauts for missions in the extreme and variable conditions that space exploratory missions will entail (Bartone et al., 2018). Much of the focus in understanding factors that mediate adaptive and maladaptive stress responses is related to their relevance for mental and physical disorders. However, understanding these factors is of particular importance for astronauts who will be subjected to chronic and potential intermittent stressors in a unique environment that can impact their mental and physical health and ability to perform mission related tasks (Bartone et al., 2018). Just as individual differences are found in the cognitive performance of SR exposed rats (Britten et al., 2014; Davis et al., 2014), there likely will be differences in how SR and additional stressors impact and interact with sleep and other systems. We have found that outbred Wistar strain rats show significant variations in the effects of inescapable footshock stress on sleep, even though standard indices of fear learning (freezing) and the stress response (stress-induced hyperthermia) are virtually identical. Sleep vulnerable (Vul) rats show significant reductions in REM after shock training (ST) whereas resilient (Res) rats do not. Sleep and stress responses to fearful contexts are virtually identical (Wellman et al., 2016, 2017a; 2018b). The rapidly normalized and enhanced REM in Res rats suggests a rapid recovery of sleep homeostasis (Wellman et al., 2018b) which is consistent with stress resilience.

Res and Vul rats differ in pre-stress plasma levels of BDNF which is thought to be involved in mediating stress resilience and vulnerability (Chou et al., 2014). Low plasma BDNF are linked to impaired neuropsychological performance in patients with subjective complaints of insomnia and actual short sleep duration (< 6 h) (Fan et al., 2018). In contrast, exercise induced elevation of BDNF levels are associated with increased spatial memory performance (Vaynman et al., 2004). Thus, BDNF may also be useful for predicting performance under conditions of reduced or disturbed sleep.

Preliminary work in our labs show that after SR (^{28}Si, 10 cGy), Res and Vul rats exhibit differential sleep recovery in response to SF (interruption of sleep every 2 min for 6 h). After SR, Vul rats showed increased sleep disruption during SF whereas Res rats showed similar responses to SF both before and after SR (Fig. 8; percentage change compared to baseline (Base)). Additionally, after SF, Res rats showed a modest, and rapidly recovered, disruption in NREM and essentially no alteration in REM. By comparison, Vul rats showed delayed recovery for both NREM (Fig. 9A) and REM (Fig. 9B). These data suggest that after SR in Vul rats, sleep may be more easily disrupted. Interestingly delta wave activity (DWA), an index of sleep homeostasis, did not differ in Res and Vul rats in response to SF (Post-SF DWA calculated as a percentage baseline for SR treated rats (Vul: 100.75 ± 11.04; Res: 107.28 ± 5.68)). This is not unexpected as SF can disrupt sleep and impair functionality without reducing DWA in the EEG (Ramesh et al., 2012; Zhang et al., 2014). Vul and Res rats may also differ in the effects of SR on TWA: SR treated Res rats had greater TWA both before and after SF than did Vul rats. Given the putative role of theta frequency oscillations in supporting

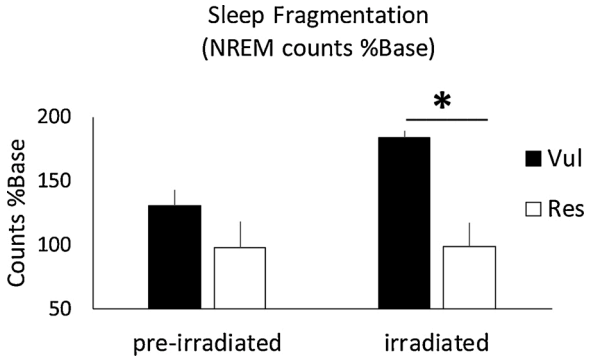


Fig. 8. Effects of sleep fragmentation on the number of non-rapid eye movement sleep (NREM) episodes before and after SR (10 cGy Si) treatment in vulnerable (Vul) and resilient (Res) rats. Vul and Res categories based on sleep response to uncontrollable footshock stress. N = 3 to 4 per group; * $p < .02$.

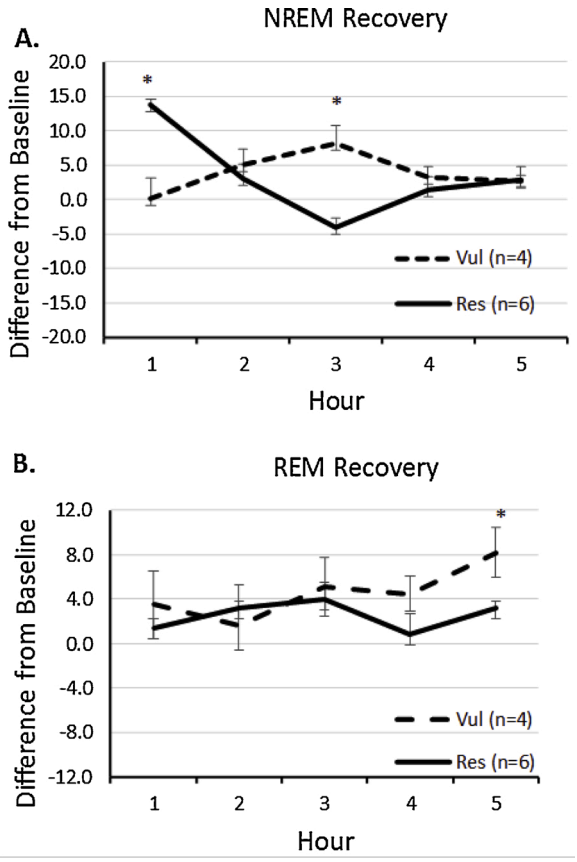


Fig. 9. Recovery of A. non-rapid eye movement sleep (NREM) and B. rapid eye movement sleep (REM) sleep over 5 h after sleep fragmentation for 6 h in SR (10 cGy Si) treated vulnerable (Vul) and resilient (Res) rats. Vul and Res categories based on sleep response to uncontrollable footshock stress. *, $p < .05$.

large-scale coordination of neural subsystems (Buzsaki, 2005; Sarnthein et al., 1998), these differences may reflect differences in functional decrements between Vul and Res rats.

9. Sex differences in the response to SR and spaceflight stressors

In general, males and females show different vulnerabilities to stress (Wellman et al., 2018a) that may have relevance for astronaut performance and their ability to cope with stress. For instance, females have greater vulnerability to stress- and fear-based disorders, such as anxiety and PTSD, and these differences are attributed in part to gonadal hormones (Maeng and Milad, 2015). On the other hand, in animal models, females show cognitive resilience, and even improved performance, in response to chronic stressors which impair male cognitive function in spatial tasks including the radial arm maze, radial arm water maze, Morris water maze, Y-maze and object placement (Luine et al., 2017; Krukowski et al., 2018a, b). Also, memory in females is not affected by stress in non-spatial memory tasks like recognition memory and temporal order recognition memory while males show impaired memory following stress (Luine et al., 2017). There also may be sex differences in extinction memory and recall (Maeng and Milad, 2015).

Females have also been reported to be more resilient to the long-term effects of a single exposure to SR (Rabin et al., 2019a; Parihar et al., 2020) and simulated GCR (Krukowski et al., 2018a, b). In male mice, reduced social interaction with a novel mouse and reduced open field activity were observed at 50 cGy and impaired recognition memory in the novel object recognition test was observed at both 15 and 50 cGy. The behavioral deficits in males were associated with microglia activation and synaptic alterations in the hippocampus (Krukowski et al., 2018a, b). By comparison, no significant behavioral deficits or changes in the hippocampus were observed in females at either dosage.

Lastly, while sex-based differences are generally regarded as global differences between males and females (Bartone et al., 2018), individual characteristics in both males females may impact their ability to cope with stress and their ability to adapt to the spaceflight environment. This suggests that identifying resilient and vulnerable males and females may enable advantaging relative strengths and mitigating weaknesses. NASA funded studies are now thoroughly investigating the impact of flight stressors in both male and female subjects.

More realistic modeling of the physical environment and challenges of extended spaceflight also needs to consider how responses among astronauts will vary. Astronaut crews are comprised of males and females and are highly selected and capable individuals. However, even in this select group, spaceflight and ground based studies have found large individual differences in physiological and neural adaptation (Van Ombergen et al., 2017). Correspondingly, Basner (Basner et al., 2014) reported that most “adequate and inadequate psychological and behavioral reactions” observed in Mars 520 crewmembers varied amongst individuals and were observed early and consistently through the mission. Individual differences in vulnerability to sleep disturbances have been suggested to be important in interplanetary missions (Goel and Dinges, 2012). These differences appear to be stable within individuals (Van Dongen et al., 2004), but their effects may vary across tasks (Tkachenko and Dinges, 2018). Our work in animals suggests differences in the ability to withstand the effects of stress (Sweeten et al., 2020; Wellman et al., 2016, 2018b) and potentially SR on sleep. Individual differences have been found for cognitive performance (Britten et al., 2014; Davis et al., 2014). Sex differences have also been found for multiple variables related to stress responses and SR. This suggests that work in rodents may be able to ascertain core attributes underlying innate stressor resilience and vulnerability in males and females that mediate the physiological and psychological consequences of the stressful challenges that astronauts will face during interplanetary spaceflight. Such information could guide mitigation efforts that can safeguard astronaut health and ensure mission success.

Existing work amply demonstrates that disturbed sleep, SR and other inflight stressors can significantly impact astronaut performance. However, it does not fully address their potential effects and interactions during long spaceflights, nor how they may continue to affect astronauts after their mission is over. Basic research on SF and sleep deprivation demonstrate a negative impact on cognitive performance, though these effects are generally reversible given sufficient recovery sleep. Similarly, removal from microgravity and SI may also allow recovery from many of their effects though all three stressors may be continuous or relatively persistent while in space. By comparison, SR-induced effects on the brain appear to be permanent and how its effects may be influenced by other stressors is not known. SR will occur while astronauts are in microgravity, potentially while experiencing social isolation, and either during wakefulness or during natural or drug aided sleep, any of which may alter its effects. Subsequently, SR–induced changes in the brain may impact the ability of astronauts to recover from, or cope with, other stressors they experience while on mission. Post-mission, persisting effects of SR could also influence how they may cope with experiences that reduce sleep or social interactions.

10. Orion/artemis preparation: SR effects on “primate specific” cognitive task performance

The collective experience gained from NASA’s manned-space exploration program is now being utilized to develop and refine the missions that will lead to humans landing on Mars. Similarly, the NASA-funded ground based animal research program is in the final stages of establishing the risk of SR-induced impairment of performance in neurocognitive processes of importance to the astronauts on the Mars mission. Ground-based rodent studies suggest that SR exposure impairs

performance in many cognitive processes, ranging from relatively fundamental processes to complex analogs/homologs of human cognitive tasks. At the time of writing, a wide variety of cognitive domains have now been shown to be impacted by SR exposure (Table 1). The ongoing multi-flight stressor studies described above will provide further insight into what processes will be most impacted by SR either alone or in conjunction with other spaceflight hazards (e.g., the prolonged stress of isolation, altered gravity).

Paradoxically, despite an enormous body of data on the impact of SR on neurocognitive processes, the mechanistic basis for these changes is largely unknown. While many neurological processes, (e.g., neurotransmission, dendritic structure and neuroinflammation) have been shown to be impacted by SR exposure, there is no definite evidence on what the critical target cell type for these changes is. Historically, neurons have been the principal cell type investigated since they execute and control almost all the brain functions such as recognition, memory, depress, anxiety, etc. However, the brain is comprised on both neuronal and non-neuronal cells, with the non-neuronal "helper" cells (pericytes, endothelia, and glial cells) outnumbering of neurons by ~ 10-fold (the exact number varies in different brain regions). Glia cells are broadly classified into three different types: microglia, astrocytes, and oligodendrocytes, with each cell type playing a critical role in regulating and maintaining neuronal function. Moreover, there is increasing evidence to show that the gut microbiome impacts CNS function. Further research is clearly needed to establish the relative importance of these cell types/targets in regulating the severity of SR exposure on neurocognition so that effective targeted countermeasures can be developed.

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. One approach being pursued by NASA's Cross-Cutting Computational modeling initiative is to incorporate ground-based derived SR decrement data into the Medical Extensible Dynamic Probabilistic Risk Assessment Tool (MEDPRAT). At present it is unclear if pertinent data on SR-neurocognitive effects are available to feed into the MEDPART algorithm. Historically, the final step in the evolution of rodent models to address human conditions is validation of the findings from rodent studies in non-human primates (NHPs). Whether the rodent SR studies have established sufficient concerns to necessitate NHP-based cognitive testing remains a matter of intense debate. Whether NHP studies will actually advance the accuracy of SR-neurocognitive risk analysis over that provided by the rodent studies is a subject that has not been addressed/debated as thoroughly.

Traditionally NHPs have been considered to have higher order thought processes much closer to humans than do rodents and thus represent a good validation model for translating rodent based research findings to humans. NHPs do share many advanced social, psychological and cognitive processing with humans. However, some aspects of human nature like drive and motivation are probably impossible to model even in NHP models. Astronauts will continue to train/learn/compensate during the mission, which will probably allow astronauts to compensate for any loss of neurocognitive function arising from SR, something that even NHP studies are not able to fully model given the current limitations to Earth-based SR delivery. Thus the argument for the need for NHP testing thus lies solely in the fact that NHP have cognitive processes that require advanced neural architecture available only in primate brains.

The ability to conceptualize, categorize with numerosity, to generate hypotheses, and to perform abstraction were not considered to be inherent cognitive processes for rodents. Thus there has been little progress in establishing whether such advanced and critical cognitive tasks will be impacted by SR exposure, with such studies being deferred until NHP testing was initiated. However, this is an outdated and spurious approach given that several "primate-specific" cognitive tasks can be directly interrogated using rats, viz: metacognition (Kepecs et al., 2008), counting- or timing-like processes for encoding serial position, rule abstraction and hypothesis generation (Muller and Fountain, 2010) and prospective timing (Whishaw and Gorny, 1994).

Confidence regarding a choice/decision has often been thought of as an instance of "metacognition", thinking about thinking, which was thought to require advanced neural architecture available only in primate brains (Flavell, 1979; Metcalfe, 2003; Smith et al., 2003). However, in a seminal study, Kepecs et al. (2008) demonstrated that rats are capable of making confidence estimates on decisions they have made. In that study, rats had to first make an estimate of the probability of getting a reward based upon their perception of the relative balance of rewarded and non-rewarded odors within a test mixture, the composition of which was randomly varied. As time progressed without the food reward being

Table 1

Constructs interrogated within various cognitive tasks, and the extent that space radiation effects have been established in those tasks. Solid block represents construct involvement or studies conducted (space radiation particles).

	Cognitive Task														
Construct	Conditioned Operant response	ATSET	Barnes/Morris water maze	Fear Extintion memory	Food protection	Meta-cognition	Novel Object Recogntion	Odor span sequence	Object in Place Temporal Order	Pairwise Discrimination	PVT	Rodent Gambling Task	Switch Task	UCFlex	Updating Task
Abstraction						■		■						■	
Associative Recogntion Memory	■	■		■		■		■		■				■	■
Attention		■		■				■		■	■	■			
Causal Reasoning	■	■		■				■			■	■	■		
Dual Tasking								■					■	■	
Hypothesis generation	■					■		■		■		■			
Interference Avoidance	■	■		■				■		■		■			■
Metacognition						■									
Motivation	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Numerosity								■						■	
Patten Separation								■		■		■	■		■
Propsective Timing					■	■									
Risk decision/probability				■	■	■						■	■		
Sequence recognition		■						■		■				■	■
Set shifting		■						■		■					
Spatial L&M			■				■		■						■
Working Memory		■	■	■		■	■	■	■	■		■	■	■	■
SR Effects Established *															
GCRSim	IP	IP		IP			■		IP					IP	IP
Fe	■	■	■	■			■			■					
H+	■	IP					■				■				
He	■	IP	■	■			■		■					IP	IP
Neutrons		■		■			■							■	
O	■			■			■		■						IP
Si	■	■		■						■				■	
Ti	■	■	■	■			■		■						

* - Refer to Kiffer et al (2019) or papers cited in this review for energy and dose details.
IP- denotes studies known to be In Progress.

delivered the rat had the chance to assess its confidence in getting the food reward and had the option to reset the task. The conclusion from these experiments was that rats were capable of generating confidence estimates based upon incomplete data, a process that is believed to involve metacognition and conscious awareness.

Utilizing a series of complicated, partially overlapping odor recognition tasks, it was possible to determine that rats use at least three cognitive processes concurrently in serial pattern learning tasks, namely, item memory involving external discriminative cues, counting- or timing-like processes for encoding serial position, and rule abstraction for encoding an internal representation of pattern structure (Muller and Fountain, 2010).

Time perception is a complex function that is essential for temporal organization of complex tasks (e.g., decision making, action planning, memory storage and recall, etc.) and for integrating cognition with perceptual and motor activities (Buonomano, 2007; Coull et al., 2011; Merchant et al., 2008b). It operates over varying duration ranges (e.g., micro- to milli-seconds, seconds to minutes, hours and days, and longer) and works to assimilate different types of information (e.g., discrete events, explicit vs. implicit information, stimuli from different sensory modalities).

Based on neuroimaging studies, subcortical structures are thought to be more involved in the estimation of sub-second time intervals whereas cortical areas are thought to be more involved in the estimation of time intervals above the 1-sec range (Nani et al., 2019). Additionally, discrete regions of the brain regulate critical aspects of neural time-keeping, e.g., precision task related timing in the cerebellum (Ivry and Spencer, 2004; Spencer et al., 2005), timing of auditory and visual stimuli in right posterior parietal cortex (Bueti et al., 2008), and hippocampal time-cells focused that respond to time and distance (Kraus et al., 2013).

Some astronauts have reported a "time compression syndrome" in orbit, whereby time is subjectively sensed as compressed relative to the perceptions gained during training and simulation (Albery and Repperger, 1992). Another perception experienced by the astronauts is that longer time than normal is required to execute standard mental activity (Manzey and Lorenz, 1998). These reports suggest that astronauts may have altered temporal perception across multiple scales that could have far reaching impact on mission performance across tasks that range from the ability to consciously attend to the passage of time to the ability to perform simple mission related responses (e.g., pressing a button at the required time).

The ability to perceive time and plan accordingly has traditionally been thought to be only present in primates. However, rodents alter their food protection behaviors (attending to an approaching "intruder" rat) based upon their estimation of the time remaining to consume the food item. First, a rat will exhibit a lateral movement when a conspecific approaches during the consumption of a food item. The type of lateral movement elicited depends on the rat's perceived time to consume the food item (Whishaw and Gorny, 1994). Early in the consumption of a food item, rats will exhibit a dodge or a large lateral movement that involves transferring the food item to the mouth and using the forelimbs to evade the approaching conspecific. As the estimated time to consume the food item decreases, dodging behavior will become less frequent and bracing behaviors will increase in frequency. On-going studies in our laboratories are currently assessing temporal perception in rats exposed to a variety of flight stressors, using time-dependent touchscreen bases assays and food entrained, anticipatory activity (Luby et al., 2012).

A critical issue for any mission's success is team cohesion, but even more so on the prolonged deep space mission. NASA has devoted considerable effort to ensure team cohesiveness is effective as possible, using a variety of confinement homologs (Mars 500, NEMO, HISEAS and the Antarctic winter studies). The data from such studies indicates that this may be a major issue. Anecdotal reports from the investigators who have studied cognitive performance in rodents suggest that SR results in several diverse aberrant behaviors. While the loss of executive function has mainly been considered a problem from a cognitive performance perspective, executive functions are also critical in controlling impulsivity. There is an increasingly body of evidence that SR impacts social recognition (either in real time or via odor recognition), manifested as indifference to litter-mates (Krukowski et al., 2018a,b; Mange et al., 2018). Whether such changes persist after repeated social encounters remains to be determined. Once again, it was thought that the impact of SR on cooperativity /cohesiveness would have to be conducted in NHPs. However, there are a number of studies that show that rats will develop rescue strategies to free "trapped" litter mates as a consequence of altruistic/empathetic behaviors (Ben-Ami et al., 2011). Such pro-social (empathetic) behavior was previously only thought to occur in primates.

11. Summary

It may never be possible to fully model how SR will impact the cognitive performance of astronauts using ground-based models. The unique psychological aspects of these highly motivated individuals, coupled with the high cognitive reserve and ability to reinforce the functionality of neural circuitry necessary for advanced cognitive processes/thought could very well compensate for SR-induced decrements in neuronal function/integration that could otherwise lead to loss of cognitive performance. The information gained from rodent studies has already identified a number of possible cognitive processes that could be sensitive to SR exposure, and prior to the start of the mission to Mars, additional information on more advanced "primate specific" processes are likely required to fully characterize this risk. The additional impacts of psychological and other flight stressors should also be known at that time. NASA ground based neurocognitive studies should thus be considered a great success.

NASA's HRP has initiated an integrated research strategy to use the vast body of data from the rodent studies to both identify operationally-relevant brain performance pathways along with a robust focus on developing appropriate countermeasures (to include nutritional, intelligent systems, etc), in the expectation that some level of cognitive impairment could occur in astronauts. The prevailing approach to developing countermeasures is to employ pharmacological agents that are either "traditional" radioprotective agents or some form of biological response modifiers (e.g., anti-inflammatory agents). The choice of these agents may be driven by mechanistic studies on the effect of SR on neurological function or may be "off-the shelf" compounds used to treat neurodegenerative disorders or nuclear weapons related radiation exposure. However, pharmacological countermeasures may not be as easily implemented in space as they would be on Earth. Whether such compounds can be stored appropriately during a deep space mission, and whether they will retain the same pharmacological biodistribution and effect in prolonged microgravity will need to be determined. This may be especially problematic for drugs that target the brain, with the pronounced cephalic fluid shifts and altered perfusion and possible glymphatic clearance issues in space. The long-term health (physical and psychological) issues arising from prolonged use of neuromodulatory drugs may bring additional performance problems for the mission.

Dr Rabin and colleagues have argued for the last 30 years that food-based radioprotection may be a useful strategy to combat SR-induced cognitive impairments, an approach that may be even more justified from the increasing body of data that suggest the microbiome impacts neurological function (Rabin et al., 2005a, 2005b; Poulose et al., 2014, 2017).

Despite the tremendous advances that have been made in establishing the impact of SR on neurocognitive function, all studies to date have been in systems with a fixed (frequently low) level of cognitive reserve/training. Even those studies which have used pretrained rats have been passive scenarios, where the irradiated subjects receive no further behavioral training experience either before or after performance assessment. Astronauts will continue to train/learn/compensate during the mission, which will probably allow astronauts to compensate for any loss of neurocognitive function arising from SR. As such the

development of complicated pharmacological countermeasures maybe unwarranted. Ground based rodent studies have or will identify several cognitive processes that have a high sensitivity to SR-induced impairment, it should be possible to develop training exercises/games that specifically target these vulnerable processes, allowing the astronauts to continuously hone their skills in these operationally-relevant cognitive domains during the mission. Such an approach would allow for the astronauts to compensate for any SR-induced loss of performance on a daily basis, which may prove far more beneficial than passive, non-targeted pharmaceutical approaches. The Defense Health Agency is actively using cognitive rehabilitation protocols (ideally tailored to the individual patients symptomatic condition) to improve many cognitive processes in active or former military personnel who have suffered traumatic brain injuries (https://dvbic.dcoe.mil/cogrehab/index.html). Similar cognitive rehabilitation approaches have been shown to improve cognitive performance (especially processing speed and working memory) in patients with multiple sclerosis (Rilo et al., 2018). NASA's HRP Human Factors and Behavioral Performance Element's research approach entitled, Mars Adaptive Training Information System (MATRIKS) is conceptualized to build on these initiatives.

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