Simulated Space Radiation Exposure Effects on Switch Task Performance in Rats

Samuel Stephenson; Richard Britten

BACKGROUND: Astronauts on the mission to Mars will be subjected to galactic cosmic radiation (GCR) exposures. While ground-based studies suggest that simulated GCR (GCRsim) exposure impairs performance in multiple cognitive tasks, the impact of such exposures on task switching performance (an important skill for all aviators) has not yet been determined.

METHODS: Male Wistar rats previously exposed to 10 cGy of ^{4}He ions or GCRsim and their sham littermates were trained to perform a touchscreen-based switch task designed to mimic warning light response tests used to evaluate pilots' response times.

RESULTS: Irradiated rats failed to complete a high cognitive task load training task threefold more frequently than shams. There were 18 (4 Sham, 7 He-, and 7 GCR-exposed) rats that successfully completed initial training and underwent switch task testing. Relative to the sham rats in the switch task, the GCRsim-exposed rats had significantly slower response times in switch but not repeat trials. The GCRsim-exposed rats had significantly ($P < 0.01$) higher switch response ratios (switch/repeat trial response time) and absolute switch costs (switch minus repeat trial response time) than either the sham or He-exposed rats.

DISCUSSION: Rats exposed to GCRsim have significantly impaired performance in the switch task manifested as an absolute switch cost of ~700 ms. The operational significance of such an increase requires further investigation, but a 1000-ms switch cost results in a twofold increase in cockpit error rates in pilots. If exposure to GCR in space results in similar effects in humans, the operational performance of astronauts on the Mars mission may be suboptimal.

KEYWORDS: space radiation, switch task switching, switch cost, cognitive task load.

Stephenson S, Britten R. *Simulated space radiation exposure effects on switch task performance in rats*. Aerosp Med Hum Perform. 2022; 93(9):673–680.

Elite individuals can perform at a superior level when under forms of stress loading (time constraints or situations where multiple issues occur at the same time). Astronauts and commercial and military pilots routinely train in a variety of flight simulator-based or real-life exercises to increase their ability to resolve complex, potentially catastrophic scenarios. These situation awareness exercises train individuals to determine the optimal way to resolve a complex problem. Key components of complex problem solving are: 1) the generation of a risk/threat assessment to identify the individual issues; 2) assign some measure of their relative importance; and 3) choose the most appropriate measure to mitigate those risks. In some instances, solving individual tasks in sequential order (in descending risk weighting) may be the optimal approach; however, when multiple high-risk issues are present, the optimal strategy may be to resolve these issues "simultaneously" by alternating attention between the tasks (i.e., task switching).

Situation training exercises have improved the decision-making skills of pilots in high-pressure situations (i.e., combat or adverse landing conditions), yet human errors still account for a high proportion of accidents. Of accidents related to runway approach and landing (which account for 2/3 of all

From Eastern Virginia Medical School, Norfolk, VA, USA.

This manuscript was received for review in October 2021. It was accepted for publication in June 2022.

Address correspondence to: Prof. Richard Britten, Ph.D., Radiation Oncology, Eastern Virginia Medical School, 700 W. Olney Drive, Norfolk, VA 23462, USA; brittera@evms.edu.

DOI: https://doi.org/10.3357/AMHP.6017.2022

commercial aircraft accidents), 83% could have been prevented if the landing was aborted for a go-around.[2] Go-around maneuver procedures are frequently not initiated due to cognitive lockup, as observed with the Eastern Airlines Flight 401 disaster.[22] Cognitive lockup is the tendency to deal with disturbances sequentially,[21] where operators continue to focus on the current task and are reluctant to switch to another task, even if it has a higher priority.[12] Although time pressure and task completion bias are involved in cognitive lockup, frequently it is the result of the individual's decision making bias,[27] such that people decide to switch or not to switch to another task when triggered. Cognitive lockup is an underlying cause of human errors in aviation accidents sufficient to warrant changes in future flight safety computer programs (www.human.aero).

Task switching is a complex executive function that requires multiple brain regions to be activated in a highly coordinated manner. At least 11 brain regions are involved in human task switching: left inferior frontal junction, bilateral superior posterior parietal cortex, left precuneus, bilateral inferior parietal lobule, right middle frontal gyrus, bilateral pre-supplementary motor area, and bilateral middle occipital gyrus.[34] The left inferior frontal junction serves as the center for coordinating task switching behavior.[11,34] Switching attention from one set of cognitive rules to another requires a large amount of distributed neural activation within the frontoparietal cortical network.[24,26] The behavioral outcome of task switching is a "switch cost", manifested as a slower and/or more error prone response than when repeating or continuing the same task.[26] Switch tasks have been used extensively to monitor the neurocognitive performance changes in numerous medical conditions, including age-related cognitive decline[31] and chemobrain.[10] Performance on switch tasks has also been shown to be impacted by stress[23] and sleep disturbances.[14,18,33]

NASA is on the verge of its second and most challenging phase of space exploration, returning to the Moon and then onto Mars. Astronauts on these deep space missions will have to act more autonomously than on previous missions due to the radio delay of 8–42 min roundtrip, depending on planet positions.[1] In the event of an emergency, astronauts will have to manage the situation themselves, so any potential stressors that reduce their cognitive function may potentially be life threatening. Astronauts will have to contend with several physical and psychological challenges, including stress, inadequate sleep, and galactic cosmic radiation (GCR), which is currently estimated to be ~30 cGy for the mission to Mars.[6,28] Stress,[23] sleep loss,[3,20,33] and exposure to < 25 cGy of several of the particles that are constituents of GCR (i.e., protons, ^{4}He, ^{16}O, ^{28}Si, ^{48}Ti, and ^{56}Fe) have all been demonstrated to impair various aspects of executive function.[5,16,32]

Despite the documented importance of task switching performance in the aviation world, there have been no studies on the impact of space radiation on task switching. Rodent switch tasks[18] that require switching between two perceptual dimensions (a visual cue and an auditory cue) are close analogs to the switch tasks used clinically. However, it is currently unknown at either the population or individual level whether space radiation exposure differentially impacts a rodent's ability to respond to visual or auditory stimuli. Thus, we developed a switch task that uses only visual stimuli, designed to mimic the warning light response test (used to evaluate pilots' response times[33]) to assess the impact of low doses (10 cGy) of simulated space radiation on task switching ability. If performance in a single perceptive domain version of the switch task is reduced in irradiated rats, then performance in two domain versions of switch tasks, i.e., like those employed in humans, would most likely be impacted to the same and possibly higher extent.

METHODS

Animals and Materials

This study was conducted in accordance with the National Research Council's "Guide for the Care and Use of Laboratory Rats (8th Edition)" at the animal care facilities of Eastern Virginia Medical School (EVMS) and Brookhaven National Laboratory (BNL), both of which are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International. All procedures were approved by the Institutional Animal Care and Use Committees of EVMS and BNL. The animals were under the surveillance of a licensed veterinarian throughout their entire stay at EVMS.

Male Wistar rats [Hla®(WI)CVF®; Hilltop Lab Animals, Inc., Scottsdale, PA, USA] were used in this study. The average age of the rats upon arrival at EVMS was 2 mo, with an average weight of 265 g. After arrival at EVMS, the rats were maintained on a reversed 12:12 light/dark cycle and given ad libitum access to Teklad 2014 chow (Envigo, Cumberland, VA, USA) and municipal water. After 1 wk of acclimatization, the rats were implanted with ID-100us RFID transponders (Trovan Ltd, Douglas, Isle of Man) to facilitate identification of individual rats and weighed.

A week later, the rats were placed on a treadmill exercise regimen (Day 1: 30 min at 20 m · min^{-1}, thereafter 30 min at 25 m · min^{-1}) three times a week for 2 wk; subsequently, the rats were exercised for 30 min at 25 m · min^{-1} twice a week for the entire duration of the study except when the rats were housed at BNL. Such a protocol is claimed to correspond to a mild aerobic exercise regimen.[30]

The rats were single-housed and switched from ad libitum rat chow to a restricted diet 2 wk after the rats started the maintenance exercise regime. The rats received a daily allowance of ~6 g of Cheerios™ (General Mills, Minneapolis, MN, USA), but the exact amount was varied daily to maintain an individual rat's weight at ~85% of its pre-food restriction weight. To increase the comparability in cognitive reserve of the rats in the present study (on switch task performance) with the rats in our previous studies on attentional set-shifting (ATSET) performance, the rats were put through an ATSET prescreening task after 10 d on food restriction.

ATSET Prescreening Procedure

Testing was conducted during the dark cycle, with the first rat being tested at ~2 h into the 12-h dark cycle (Zeitgeber T+2).

The time at which testing was commenced was kept constant for an individual rat. The ambient light within the testing room was only bright enough [4 lx as determined by a Digital Lux Meter LX1330B (Kaysan Electronics, Mountain View, CA, USA)] for the observation of the rats. The rats were prescreened for performance in the ATSET test in accordance with our previously published protocols.[4,15] Only rats that passed all five stages of the prescreening protocol [Food Foraging (FF) to Intradimensional shifting (IDS)] were considered for further study; moreover, any rat that took two attempts to pass two or more stages was also excluded from further study. Rats that satisfied these inclusion criteria (typically only 50–60% of rats are classified as "vetted" rats) were paired-housed, given ad libitum access to Teklad 2014 chow, and then sent to BNL to be irradiated.

Irradiation Procedure

A total of 66 vetted rats were shipped to BNL, where they continued to be pair housed, maintained on a reversed 12:12 light/dark cycle, and given ad libitum access to Teklad 2014 chow and municipal water by bottle. After at least 1 wk of acclimatization, the rats were randomly assigned to one of three cohorts, two of which were exposed to whole-body irradiation with 10 cGy 250 MeV/n ^{4}He (LET = 1.6 keV · μm^{-1}) particles or 10 cGy "Simplified" simulated GCR (GCRsim) at the NASA Space Radiation Laboratory (Ref). At the time of irradiation, the rats were ~7 mo old.

The rats were placed in a well-ventilated custom-made "rat hotel" irradiation jig and exposed to the ^{4}He ion beam at a dose rate of 2–5 cGy/min (< 2 min exposure) and to the GCRsim beam sequence at an overall dose rate of 0.5 cGy · min^{-1} (10 cGy/22 min exposure). Dose calibration was performed as previously described.[17] Sham rats were placed in identical irradiation jigs that remained in the preparation room, while their counterparts were taken into the radiation vault. The total number of rats exposed to each dose point was as follows: Sham: 21; 10 cGy GCRsim: 23; 10 cGy ^{4}He: 22.

A week after irradiation, the rats were transported back to EVMS, where they were pair-housed, maintained on a reversed 12:12 light/dark cycle, and given ad libitum access to autoclaved Teklad 2014 chow and municipal water. At 14 ± 2 wk postirradiation, at ~10 mo of age, the rats were again placed on food restriction prior to being tested in the Switch Task. Each rat was allocated to a specific touchscreen chamber and was tested in the same chamber at the same time each day throughout experimentation.

Touchscreen Chamber Habituation Procedure

The Habituation (Hab) task involves habituating the rats to the touchscreen chamber [Bussey-Saksida rat touch screen (Model 80,604), Lafayette Instruments, Lafayette, IN, USA] and recognizing that there are food rewards (sugar pellets) in the food dispenser tray. The chamber is trapezoidal in shape with a length of 332 mm, a width of 126 mm at the end with the food dispenser, a width of 240 mm at the end with the touchscreen, and a height of 300 mm. The rats were placed in the chamber (light off) for 30 min with five sugar pellet "rewards" in the food dispensing tray. If a rat ate all five pellets during the 30-min period it progressed to the first stimulus response (STR) training stage. Rats were given 3 d to reach criterion in the Hab task, after which they were eliminated from any further testing.

The STR15 involves the rats learning that a food reward is dispensed when any of the "holes" within a three-row × five-column grid [top row: holes numbered 1–5 (L to R); middle row: holes numbered 6–10 (L to R); bottom row: holes numbered 11–15 (L to R)] are touched. The holes are 35-mm diameter holes drilled into the touchscreen protection shield that is placed adjacent to the screen itself, which serves to minimize incidental touching of the screen. All holes are lit in the STR15 stage. Any rat that did not reach criterion in STR15 was rested overnight and retested the following day. If after eight sessions a rat did not reached criterion, it was eliminated from any further testing. Once the rats reached criterion in the STR15 stage (at least 30 rewarded responses from 50 trials during a 30-min, period with no time limit for a response), they advanced to the STR4 task.

During the STR4 task, the rats had to refine their stimulus response skills to recognize that the food reward was only dispensed when only lit holes were touched. The rats were presented with a 2 × 2 block of lit holes that were randomly located within the 3 row × 5 column grid. The position of the lit block of four holes was changed after any response (i.e., correct selection of a lit hole, or incorrect selection of an unlit hole). Any rat that did not reach criterion in STR4 was rested overnight and retested the following day. If after eight sessions a rat did not reached criterion, it was eliminated from any further testing. Once the rats reached criterion in STR4 (a minimum of 30 correct responses out of the possible 50 trials within the 30-min period on 2 consecutive days), they were moved onto the STR1 task.

In the STR1 stage, rats had to further refine their stimulus response skills to recognize that the food reward was only dispensed when the single illuminated hole (randomly selected from the entire 15 grid positions) was selected. An incorrect choice in the STR1 task resulted in a punishment (aversive stimuli—chamber light switched on) and a time out for 10 s. If a rat failed to reach criterion (75% accuracy and > 30 trials completed for 2 consecutive days) in the STR1 task, it was rested overnight and presented with the task the following day. Each rat was given a maximum of 17 attempts to reach criterion in the STR1 task. Any rat that failed to reach criterion in 17 attempts or did not get ≥ 10 rewards during a testing session by day 8 of training was also eliminated (because experience has shown that such rats never complete the STR1 task). There were 18 rats (4 Sham, 7 He-, and 7 GCR-exposed) that reached criterion in the STR1 stage allocated to perform in the switch task; the remaining rats were allocated to a different touchscreen-based assay (the results of which are not reported here).

Switch Task Training Procedure

During the first stage of the Switch Task Training procedure, designated "Left 1", the rat had to learn that a food reward was

only awarded if the "response" 1GR (a green light in position 1, **Fig. 1A**) hole was touched after the "stimulus" 7WS hole (a white light in position 7, Fig. 1A) was illuminated. If a rat failed to reach criterion, it was rested overnight and presented with the task again the next day. Once a rat had correctly selected the 1GR hole 50 times during a session it progressed to the "Right 1" stage of the training. The "Right 1" stage was conceptually identical to the "Left 1" stage, but now the "response" hole was a green light in position 5 (5GR), and the stimulus light was a white light in position 9 (9WS) (**Fig. 1B**).

The next stage of testing, designated "Discrimination", required the rats to learn that a food reward was only awarded if the specific "paired" response light was selected (from a choice of 1GR and 5GR) when a single stimulus light was illuminated. Firstly, only the 9WS light switched on (**Fig. 1D**); if the rat selected the 5GR hole it received a food reward, if hole 1GR was selected it received a 5-s punishment (overhead light switched on), and the rat was presented with the problem again. Each rat was given an unlimited amount of time to select a response. Once the rat reached criterion (> 75% accuracy within a 50-trial session with a max time of 30 min), it was then presented with the opposite scenario (7WS hole illuminated, 1GR selection gaining a food reward, whereas 5GR selection received a punishment) (**Fig. 1C**). Once the rats reached criterion (> 75% accuracy within a 50-trial session with a max time of 30 min), it progressed to the next stage of training.

The third stage of the training, designated "Activation", required the rats to learn to "activate" a trial, i.e., the rat had to press a green light located at position 8 (G8A) to initiate the test. This activation step served to increase the accuracy of the response time by removing potential behavioral time confounders, such as the rats self-grooming midtrial, being unaware of stimulus presentation, and the time needed to move from the food dispenser to the touchscreen. Once the rats touched the G8A light, it was turned off, and the rats were presented with one of the "discrimination" configurations (Fig. 1C or Fig. 1D). While the reward/punishment conditions remained the same as before, once the trial was activated, the rat had 5 s to respond, or the system turned off (all lights are turned off and G8A is turned on) and the trial was omitted. The rats were initially presented with the "Left" configuration (**Fig. 1E**) of the task and once the rats reached criterion (> 75% correct choices within a 50-trial session with a max time of 30 min), they were then presented with the "Right" configuration (**Fig. 1F**). Each rat was given 10 d to pass the "activation stage", and any rat that failed was removed from the study.

Once a rat reached criterion in the activation stage, the rat was then trained to repeatedly make a correct selection before receiving a reward. Each individual rat was assigned either of the configurations shown in Fig. 1E or Fig. 1F, but a food reward was now only dispensed after two consecutive correct choices. Once the rat reached criterion (> 75% accuracy within 64 trials during a 30-min session) it was then presented with the opposite configuration. This alternating process was repeated: first, requiring four consecutive correct selections to gain a food reward and then eight consecutive correct selections. If a rat failed any stage, it was rested overnight and then presented with the task again the following day. Each rat was given a maximum

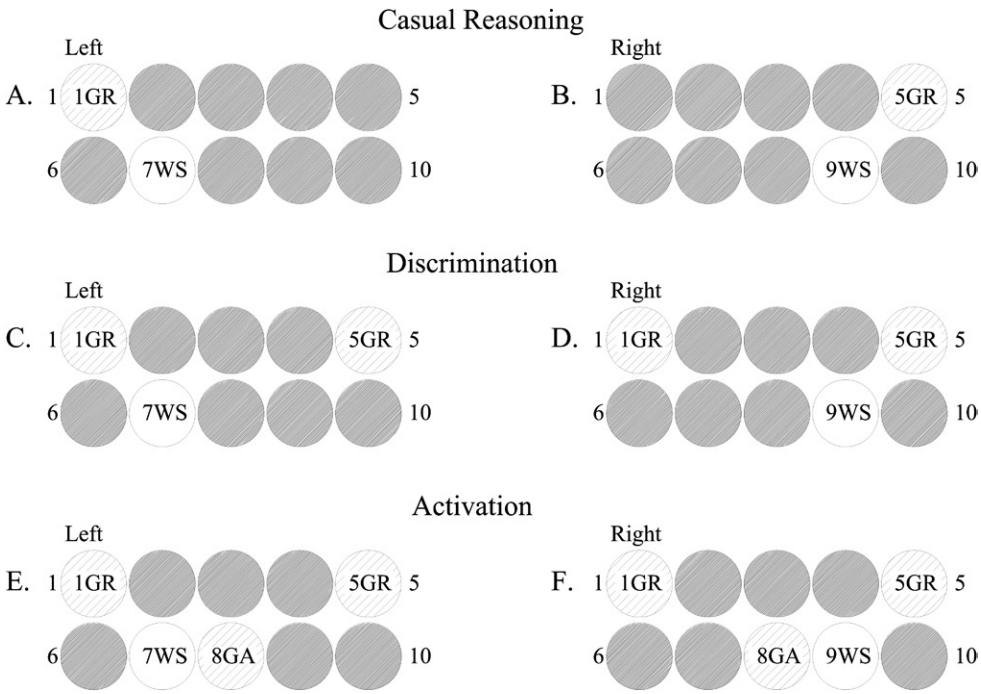

Fig. 1. Schematic representation of the light configurations used in the switch task. Causal reasoning training: A) left configuration, B) right configuration; discrimination training: C) left configuration, D) right configuration; activation training: E) left configuration, F) right configuration. The white circles represent the stimulus (7WS or 9WS) lights. The hashed circles represent the green response (IGR or 5GR) or activation (8GA) lights. The dark circles represent background lights that were unlit.

Table I. Switch Trial Training.

LEVEL	MAX NUMBER OF TRIALS	MAX TIME	TRIAL BLOCK SIZE	PASSING CRITERIA
Specific Stimulus Response				
Left or Right	50	30 min	1	50 trials completed
Discrimination				
Right or Left	50	30 min	1	50 Trials completed and > 75% accuracy
Activated				
Right or Left	64	30 min	1–8	64 Trials completed and > 75% accuracy
Switch Task				
Random	64	30 min	1–8	De facto

of 5 d to pass each stage. Any rat that failed to do so was removed from the study. For the activation trials, the criterion was changed from 50 trials max to 64 trials, so that the rats could participate in blocks (up to 8) of trials between food rewards. The completion criterion for each stage is listed in **Table I**.

Switch Task Test Procedure

During each testing session, the rats were presented with a maximum of 64 total trials grouped in strings of 3–7 consecutive trials for each of the two stimuli (either 7WS or 9WS as shown in Fig. 1E and Fig. 1F), resulting in ~11 switches between blocks. The number of trials in which each stimulus was presented before switching to the other stimuli was randomized to prevent any predictability, both within and between sessions. Within each session, the first trial on the new stimulus was classified as a switch trial. An example of a switch task session is shown in **Fig. 2**.

Data were acquired from rats performing in the switch task for 3 consecutive days. Omitted trials (where the rats did not select a response within 5 s) were removed from the analysis as they did not allow accuracy analysis since no response was chosen. These omitted trials made up less than 1% of the trials in each of the three cohorts. Accuracy and response times for the repeat (intrablock) and switch (interblock) trials were calculated for each session. The trials immediately after a miss or an omitted trial were excluded as these are neither repeat nor switch trials.

Statistical Analysis

A number of direct performance metrics were obtained during the study: total number of trials completed (sum of both repeat and switch trials); response frequency (percentage of trials presented that elicited a response from a rat); correct frequency (percentage of responses that were correct); trials presented that elicited a response from a rat; and response time (time rat took to make a selection, calculated for repeat and switch trials separately). These direct performance measures were further analyzed to generate two additional performance metrics: the switch response ratio (switch/repeat trial response time) and the absolute switch cost (switch trial response time minus repeat trial response time). These derivative metrics were calculated for each individual rat. All statistical calculations (Mann-Whitney) were performed using the appropriate software program within Prism 9.1 (Graphpad Software, San Diego, CA, USA).

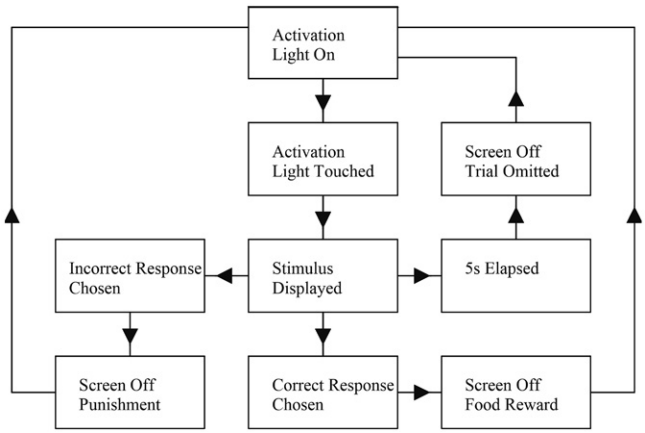

Fig. 2. Flowchart of functional organization of the switch task.

RESULTS

None of the rats used in this study demonstrated any physical impairments that required veterinarian intervention over the course of the study, nor were there any obvious signs of motor deficits during the study. A total of 66 rats started the Hab task; 17/21 (80.9%) of Shams reached criterion in the STR1 task, while only 8/22 (36.4.2%) of the He- and 7/23 (30.4%) of the GCR-exposed rats reached criterion in the STR1 stage. Moreover, the irradiated rats that did reach criterion in STR1 took significantly more attempts to do so than did the Shams (Shams: 7.41 ± 0.78; He: 10.75 ± 0.64, $P = 0.011$, Mann-Whitney; GCR: 10.40 ± 0.68, $P = 0.014$, Mann Whitney). The 18 (4 Sham, 7 He-, and 7 GCR-exposed) rats that successfully completed the STR1 stage were then randomly selected for switch task training.

All rats passed the Left 1 and Right 1 stages on the first day and reached criterion in the Discrimination stage in two sessions (days) or less. However, 2 rats (1 He and 1 GCR-exposed) failed to reach criterion in the activation stage of training, with the other 16 (4 Sham, 6 He-, and 6 GCR-exposed) rats passing the activation stage in 4 d or less. There were no significant intercohort differences in the number of sessions it took to complete the switch task training (16.25–16.83 sessions).

Across the 3 d of performing the switch task test, there were no significant differences in average number of daily trials (Sham: 45.4, He: 39, and GCR: 42.7) or total response accuracy [number of correct responses (touches)/total number of trials] between the various cohorts (Shams: 76.7%, GCR-exposed: 72.4%, and He-exposed: 72.7%).

The Sham rats chose the correct option in repeat trials with a significantly higher accuracy (80%) than either the GCR- (70%; $P = 0.006$, Mann-Whitney) or He- (70%, $P = 0.009$, Mann- Whitney) exposed rats. Sham rats also responded faster than He exposed rats in the repeat trials (Sham: 1.76 ± 0.08 s; He: 2.09 ± 0.11 s) (**Fig. 3A**), although this just failed to reach statistical significance ($P = 0.056$, Mann-Whitney).

During the switch trials, the Sham rats averaged 50.8 ± 0.082.% correct, whereas the He and GCR rats averaged 72.2 ± 0.047% and 75.1 ± 0.057%, respectively, the latter being significantly ($P = 0.029$, Mann-Whitney) higher than the Shams. The average response time of the Sham rats in the switch trials was significantly faster (1.68 ± 0.11 s, $P = 0.0056$, Mann-Whitney: **Fig. 3B**) than the GCRsim exposed rats (2.71 ± 0.36 s). While the He-exposed rats had slower response time (2.11 ± 0.13 s) than the Shams, this did not reach statistical significance.

The response times in the switch and repeat trials for individual rats were used to calculate the Switch Response ratio and the absolute Switch Cost. The Switch Response ratio (switch trial response time/repeat trial response time) for GCR-exposed rats was significantly ($P < 0.008$, Mann-Whitney; **Fig. 3C**) higher than either the Sham or He-exposed rats, which were close to unity. Similarly, the absolute Switch Cost (switch trial response time minus repeat trial response time) was significantly ($P < 0.005$, Mann-Whitney; **Fig. 3D**) higher (700 ms) in the GCR-exposed rats than in either the Sham or He-exposed rats (−0.1 and 0.0 ms, respectively).

DISCUSSION

On a deep space mission to Mars, astronauts may need to make extremely complicated decisions, often rapidly, to ensure both their survival and the success of the mission. In situations where initial risk assessments identify multiple high-risk issues, the optimal strategy may be to resolve these issues "simultaneously" by alternating attention between the tasks, i.e., task switching. This study has established that exposure to 10 cGy of either GCRsim or ^{4}He ions (which account for ~35% of the dose within "Local-Field" GCR spectrum[29]) significantly reduces the ability of rats to perform in the STR1 [high cognitive task load (CTL)] training task. The threefold increase in the failure rate in the high CTL STR1 stage may have more profound consequences for operational success. Emergencies are almost by definition multifactorial in nature, requiring multiple responses to be made in a very short time. The STR1 stage of training, in contrast to the previous STR4 stage, required the rat to contend with a reduced number of rewarded options and a penalty for incorrect choices. Whatever the underlying causes are for the reduced ability of SR-exposed rats to perform in this high CTL test, e.g., slower processing speed and/or an inability to maintain attention possibly due to reduced interference, the inability to complete high CTL tasks is extremely problematical as it would impact performance in multiple cognitive tasks/situations.

Furthermore, rats exposed to 10 cGy GCRsim (but not to 10 cGy of He ions) took 700 ms longer to respond in switch trials than did the Shams. The differential sensitivity of switch task performance to isodoses of the complex [multi-ion, -energetic, and -linear energy transfer (-LET)] GCRsim vs. the relatively low LET, monoenergetic He ion beam suggests that switch task performance may be more sensitive to the higher LET (Z > 8, i.e., O, Si, and Fe) components of the GCRsim beam. However, the current paucity of data on the effect of ionizing radiation in general on switch task performance prevents any firm conclusions to be made on the LET dependency of switch task performance decrements.

This is the first study to demonstrate that exposure to GCRsim results in longer switch response times, an increase in the switch/repeat response time ratio, and thus a higher switch cost (700 ms)

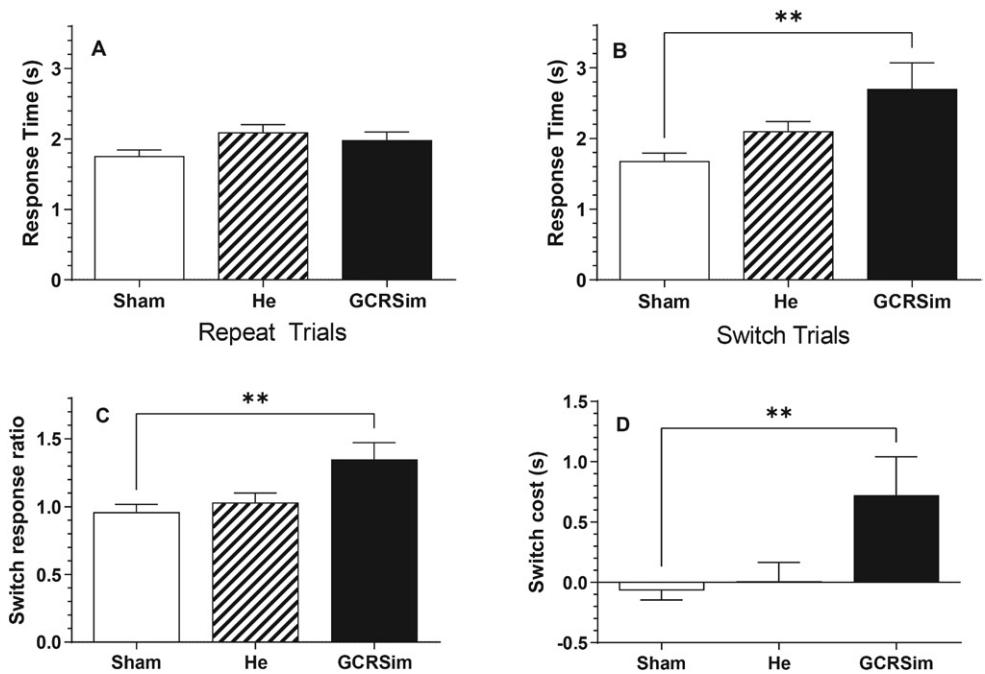

Fig. 3. Relative performance of sham and simulated space radiation-exposed rats in the switch task. A) Response time in repeat trials; B) response time in switch trials; C) switch response ratio (switch/repeat trial response times); D) absolute switch cost. Bars denote mean and SEM for sham (white bar), He-exposed (striped bar), and GCRsim-exposed (black bar) rats. ** Represents significance at the $P < 0.05$ level (Mann Whitney).

than that seen in Sham rats. When sleep-deprived pilots had to perform a similar task, there was a 1000-ms increase in their reaction times to warning lights being switched on which was associated with double the errors made in cockpit simulations.[33] Increased response times in the rodent psychomotor vigilance test (rPVT) have been observed previously following exposure to ≥ 25 cGy protons.[7,8] However, the structure of the rPVT more resembles the repeat trials used in this study, which were not significantly impacted by either He or GCR exposure.

Should humans exposed to GCR in space experience similar effects on switch response times as observed in this study, there may be quite profound operational consequences. It is important to note the monoperceptual switch task employed in this study is relatively simple, in that there are only two possible stimuli to respond to: illuminated holes in two fixed spatial locations. While this task was designed to resemble the warning-light response task used in aviation medicine,[33] typically, switch tasks interrogate the ability to maintain and switch attention between two different perceptual modalities (visual vs. auditory cues, numbers vs. letters in the Trail Making Task-B test). Since performance in this simple switch task was impacted by GCRsim exposure, it would be reasonable to expect that performance in more complicated switch tasks would be affected to at least a similar, if not to a greater extent. In addition to space radiation exposure, astronauts will also be subjected to other flight stressors that impact task switching, e.g., sleep[14,20,33] and stress.[23] It remains to be determined what impact such flight stressors will have on task switching in GCRsim exposed rats. While a reduced or slowed task switching response can negatively influence performance, an unknown risk is whether combined exposure to flight stressors will lead to more severe cognitive lock-up.

Under normally rested conditions, an inability or reduced willingness to execute attentional switching has been found to be a major factor leading to cognitive lockup.[27] While significantly longer switch response times were observed in the GCRsim exposed rats, mining all the switch task data revealed a nonsignificant trend toward reduced overall accuracy in the GCRsim and He irradiated rats compared to the Shams. More specifically, the irradiated rats selected significantly fewer correct responses in the repeat trials while both irradiated cohorts selected more correct responses in the switch trials while taking longer to do so, both of which were significant for the GCRsim cohort. Simulated space radiation-induced increases in a dentate gyrus-reliant pattern separation task have recently been reported, where irradiated mice learned faster and were more accurate than controls.[32] Two possible explanations were proposed for the simulated space radiation-induced increase in pattern separation ability. The first may be "specific" for pattern separation involving a hyperactive entorhinal cortex and hypoactive dentate gyrus/CA3.[13,25] The second possibility, which may be more applicable to the current switch task data, is that simulated space radiation exposure results in conditions in the dentate gyrus that favor "sparse encoding" of entorhinal cortical input. Sparse encoding in dentate gyrus granule cell neurons is critical for pattern separation, as it minimizes interference between memory representations of similar but not identical experiences.[9,19] The superior performance of the Sham rats in the repeat trials, but worst performance in the switch trials, would be consistent with a high level of memory representation in the repeat trials, with such memories leading to interference when the novel response light was illuminated. i.e., the rats expected the same light to be lit. Enhanced level of sparse encoding in the simulated space radiation exposed rats would be consistent with a reduced memory representation (worse repeat performance), but an apparently superior switch performance due to reduced interference, i.e., the rats had no expectation of the previously rewarded light being lit.

In summary, this experiment is the first to establish that exposure to a low (10 cGy) level of GCRsim impacts performance in a warning light selection type switch task. GCRsim exposed rats exhibited longer switch response times and a higher switch cost relative to those seen in Sham rats. Moreover, rats exposed to both He and GCRsim were threefold less able to pass the STR1 (high CTL) training stage than Sham rats. Overall, this work suggests that exposure to GCR may result in a reduced ability to respond in emergencies. Given the sensitivity of task switching to a wide range of in-flight stressors that astronauts will have to contend with on the mission to Mars, it is surprising that switch task performance is not part of the standard cognitive surveillance program for astronauts.

ACKNOWLEDGMENTS

The authors are indebted to Dr. Adam Rusek and his staff for their help with the irradiation of the rats and animal husbandry at Brookhaven National Laboratories. This study would not have been possible without their help.

Financial Disclosure Statement: This work was funded by NASA grant support NNX15AI22G and NNX14AE73G. The authors have no conflict of interests to report for this study.

Authors and Affiliation: Samuel Stephenson, B.S., and Richard Britten, Ph.D., Professor, Eastern Virginia Medical School, Norfolk, VA, USA.

REFERENCES

1. Bajracharya M, Maimone MW, Helmick D. Autonomy for Mars Rovers: Past, present, and future. Computer. 2008; 41(12):44–50.
2. Blajev T. Go-around decision-making & execution project report. 62nd Annual Business Aviation Safety Summit, BASS 2017; 4–5 May 2017; Phoenix, AZ, USA. Red Hook (NY): Curran Associates, Inc.; 2017:45–62.
3. Bratzke D, Rolke B, Steinborn MB, Ulrich R. The effect of 40 h constant wakefulness on task-switching efficiency. J Sleep Res. 2009; 18(2):167–172.
4. Britten RA, Duncan VD, Fesshaye AS, Wellman LL, Fallgren CM, Sanford LD. Sleep fragmentation exacerbates executive function impairments induced by protracted low dose rate neutron exposure. Int J Radiat Biol. 2021; 97(8):1077–1087.
5. Britten RA, Wellman LL, Sanford LD. Progressive increase in the complexity and translatability of rodent testing to assess space-radiation induced cognitive impairment. Neurosci Biobehav Rev. 2021; 126:159–174.
6. Cucinotta FA, Alp M, Sulzman FM, Wang M. Space radiation risks to the central nervous system. Life Sci Space Res (Amst). 2014; 2:54–69.
7. Davis CM, DeCicco-Skinner KL, Hienz RD. Deficits in sustained attention and changes in dopaminergic protein levels following exposure to

proton radiation are related to basal dopaminergic function. PLoS One. 2015; 10(12):e0144556.
8. Davis CM, Decicco-Skinner KL, Roma PG, Hienz RD. Individual differences in attentional deficits and dopaminergic protein levels following exposure to proton radiation. Radiat Res. 2014; 181(3):258–271.
9. Diamantaki M, Frey M, Berens P, Preston-Ferrer P, Burgalossi A. Sparse activity of identified dentate granule cells during spatial exploration. Elife. 2016; 5:e20252.
10. Ehlers DK, Aguiñaga S, Cosman J, Severson J, Kramer AF, McAuley E. The effects of physical activity and fatigue on cognitive performance in breast cancer survivors. Breast Cancer Res Treat. 2017; 165(3):699–707.
11. Funahashi S. Working memory in the prefrontal cortex. Brain Sci. 2017; 7(5):49.
12. Hollnagel E, editor. Handbook of cognitive task design, 1st ed. Boca Raton (FL): CRC Press; 2003.
13. Ikrar T, Guo N, He K, Besnard A, Levinson S, et al. Adult neurogenesis modifies excitability of the dentate gyrus. Front Neural Circuits. 2013; 7:204.
14. Jennings JR, Monk TH, Van der Molen MW. Sleep deprivation influences some but not all processes of supervisory attention. Psychol Sci. 2003; 14(5):473–486.
15. Jewell JS, Duncan VD, Fesshaye A, Tondin A, Macadat E, Britten RA. Exposure to ≤15 cgy of 600 mev/n 56 fe particles impairs rule acquisition but not long-term memory in the attentional set-shifting assay. Radiat Res. 2018; 190(6):565–575.
16. Kiffer F, Boerma M, Allen A. Behavioral effects of space radiation: a comprehensive review of animal studies. Life Sci Space Res (Amst). 2019; 21:1–21.
17. La Tessa C, Sivertz M, Chiang IH, Lowenstein D, Rusek A. Overview of the NASA space radiation laboratory. Life Sci Space Res (Amst). 2016; 11:18–23.
18. Leenaars CHC, Joosten RNJMA, Zwart A, Sandberg H, Ruimschotel E, et al. Switch-task performance in rats is disturbed by 12 h of sleep deprivation but not by 12 h of sleep fragmentation. Sleep. 2012; 35(2):211–221.
19. Leutgeb JK, Leutgeb S, Moser M-B, Moser EI. Pattern separation in the dentate gyrus and CA3 of the hippocampus. Science. 2007; 315(5814): 961–966.
20. McCoy JG, Tartar JL, Bebis AC, Ward CP, McKenna JT, et al. Experimental sleep fragmentation impairs attentional set-shifting in rats. Sleep. 2007; 30(1):52–60.
21. Moray N, Rotenberg I. Fault management in process control: eye movements and action. Ergonomics. 1989; 32(11):1319–1342.
22. National Transportation Safety Board. Aircraft accident report - Eastern Airlines, Inc. Miami, Florida, December 29, 1972. Washington (DC): NTSB; 1973. Report No.: AAR73-14.
23. Plessow F, Kiesel A, Kirschbaum C. The stressed prefrontal cortex and goal-directed behaviour: acute psychosocial stress impairs the flexible implementation of task goals. Exp Brain Res. 2012; 216(3):397–408.
24. Rubinstein JS, Meyer DE, Evans JE. Executive control of cognitive processes in task switching. J Exp Psychol Hum Percept Perform. 2001; 27(4):763–797.
25. Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, et al. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature. 2011; 472(7344):466–470.
26. Schneider DW, Logan GD. Task switching. In: Encyclopedia of Neuroscience. Cambridge (MA): Academic Press, Elsevier Ltd; 2009:869–874.
27. Schreuder EJA, Mioch T. The effect of time pressure and task completion on the occurrence of cognitive lockup. In: CEUR Workshop Proceedings; 2011 February 10-11; Genoa, Italy. The Hague (Netherlands): TNO; 2011.
28. Simonsen LC, Slaba TC, Guida PM, Rusek A. NASA's galactic cosmic ray simulator at Brookhaven National Laboratory: enabling human exploration missions to the Moon and Mars. In: Proceedings of the International Astronautical Congress, IAC; 2019 Oct. 21–25; Washington, DC. Paris (France): International Astronautical Federation; 2019.
29. Slaba TC, Blattnig SR, Norbury JW, Rusek A, La Tessa C. Reference field specification and preliminary beam selection strategy for accelerator-based GCR simulation. Life Sci Space Res (Amst). 2016; 8:52–67.
30. Véras-Silva AS, Mattos KC, Gava NS, Brum PC, Negrão CE, Krieger EM. Low-intensity exercise training decreases cardiac output and hypertension in spontaneously hypertensive rats. Am J Physiol. 1997; 273(6):H2627–H2631.
31. Wasylyshyn C, Verhaeghen P, Sliwinski MJ. Aging and task switching: a meta-analysis. Psychol Aging. 2011; 26(1):15–20.
32. Whoolery CW, Yun S, Reynolds RP, Lucero MJ, Soler I, et al. Multidomain cognitive assessment of male mice shows space radiation is not harmful to high-level cognition and actually improves pattern separation. Sci Rep. 2020; 10(1):2737.
33. Wilson GF, Caldwell JA, Russell CA. Performance and psychophysiological measures of fatigue effects on aviation related tasks of varying difficulty. Int J Aviat Psychol. 2007; 17(2):219–247.
34. Yin S, Wang T, Pan W, Liu Y, Chen A. Task-switching cost and intrinsic functional connectivity in the human brain: toward understanding individual differences in cognitive flexibility. PLoS One. 2015; 10(12):e0145826.