RESEARCH ARTICLE

Fine motor deficits exhibited in rat string-pulling behavior following exposure to sleep fragmentation and deep space radiation

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Abstract
Deep space flight missions will expose astronauts to multiple stressors, including sleep fragmentation and space radiation. There is debate over whether sleep disruptions are an issue in deep space. While these stressors independently impair sensorimotor function, the combined effects on performance are currently unknown. String-pulling behavior involves highly organized bimanual reach-to-grasp and withdraw movements. This behavior was examined under rested wakeful conditions and immediately following one session of sleep fragmentation in Sham and irradiated rats 3 months after exposure (10 cGy [4]Helium or 5-ion simulated Galactic Cosmic Radiation). Sleep fragmentation disrupted several aspects of string-pulling behavior, such that rats' ability to grasp the string was reduced, reach endpoint concentration was more variable, and distance traveled by the nose increased in the Y-range compared to rested wakeful performance. Overall, irradiated rats missed the string more than Sham rats 3 months post-exposure. Irradiated rats also exhibited differential impairments at 3 months, with additional deficits unveiled after sleep fragmentation. [4]Helium-exposed rats took longer to approach the string after sleep fragmentation. Further, rats exposed to [4]Helium traveled shorter withdraw distances 3 months after irradiation, while this only emerged in the other irradiated group after sleep fragmentation. These findings identify sleep fragmentation as a risk for fine motor dysfunction in Sham and irradiated conditions, in addition to radiation exposure. There may be complex temporal alterations in performance that are stressor- and ion-dependent. Thus, it is critical to implement appropriate models of multi-flight stressors and performance assessments in preparation for future deep space flight missions.

Keywords Sleep fragmentation · Space radiation · Fine motor control · Movement accuracy · Kinematics · Motivation

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Introduction

Time spent in space, within low Earth orbit at the International Space Station and deep beyond the Van Allen belt, is frequently associated with significant bouts of sleep disruptions that impair subsequent performance (Berry 1969; Evans-Flynn et al. 2015; Basner et al. 2013; Pandi-Perumal and Gonfalone 2016; for review, see Britten et al. 2021a, b). A single night of sleep reduced by 2 h is sufficient to impair performance in a psychomotor vigilance task as well as influence cortical regions that are involved in motor function (Stojanoski et al. 2018). In addition, sleep quality is impacted while in space, with a 27–50% reduction in the rapid eye movement stage of sleep (Stickgold and Hobson 1999; Whitmire et al. 2013; Barger et al. 2012; Evans-Flynn et al. 2015), which is important for learning and maintaining sensorimotor function and cognitive skills (Deak and Stickgold 2010; Peever and Fuller

2016). The operational effects of these sleep loss-related changes in performance can be significant, with aviation pilots experiencing a twofold increase in error rate during a relatively simple alarm response task (Wilson et al. 2007).

Although various operational changes have been implemented to minimize sleep disruptions on deep space missions and at the International Space Station, astronauts still experience more waking periods and shorter overall sleep durations, commonly known as sleep fragmentation (Roth et al. 1980; Rosenthal et al. 1984; Carskadon et al. 1982; Stepanski et al. 1984; Stepanski 2002). The high prevalence of sleep fragmentation in space is a consequence of many factors, including circadian alterations, mission-related stress, and social isolation. Astronauts adhere to a strict circadian schedule, with regimented sleep as one countermeasure to mitigate potential deficits, yet sleep fragmentation still occurs (Barger et al. 2014). Even with the use of pharmaceutical agents, sleep remains disrupted in space, and most sleep aids do not enhance sleep quality.

During the mission to Mars, astronauts will be exposed to ~40 cGy of space radiation (SR) in the form of galactic cosmic radiation (GCR). The GCR spectrum in deep space is composed of 90% protons, 9% ^{4}Helium (^{4}He), and 1% heavier ions (^{16}Oxygen, ^{28}Silicon (^{28}Si), and ^{56}Iron) (Cucinotta et al. 2014). Due to the modulating effect of the space craft structure, astronauts will be exposed to a different GCR ion spectrum than seen in free space. From a health risk perspective, the impact of the SR spectrum that the internal organs of astronauts will receive within the spacecraft (i.e., local-field spectrum), which is calculated using the current spacecraft design specifications, needs to be considered. Thus, NASA developed the technical ability to generate simulated GCR spectrum (GCRSim) that mimic the linear energy transfer characteristics of the local-field spectrum (Slaba et al. 2016; Simonsen et al. 2019; Huff et al. 2022). Strikingly, exposure to <25 cGy of a single ion or the 5-ion GCRsim paradigm impacts multiple aspects of neural function, which likely contribute to altered performance (reviewed in Britten et al. 2021a, b, 2022). Regardless of the SR type or dose, similar cognitive deficits emerge across independent studies. Most SR work to date has focused on single-ion exposure models and cognitive dysfunction, with deficits observed in a range of tasks assessing attention, working memory, and spatial navigation. Research has recently advanced to multi-ion exposure models that demonstrate similar cognitive deficits. Yet, only one study has examined the effects of multi-ion exposure models on sensorimotor function (Blackwell et al. 2022). Since these space flight stressors have been shown to impair both cognitive and sensorimotor function independently, it is imperative to implement tasks that have the potential to evaluate both aspects of performance quickly and easily.

Fine motor control is important for many space flight activities that must be completed with high levels of accuracy, consistency, and speed of movement, including manipulating tools or space craft controls and seat egress. Rodents quickly engage in string-pulling behavior with minimal training, eliciting highly organized bilateral reach and withdraw hand movements to pull in a string to retrieve a food reward. This behavior has been used extensively to evaluate cognition (for review see Jacobs and Osvath 2015) and recently was developed to provide objective quantifiable metrics to characterize fine motor skills (Blackwell et al. 2018a, b). The organization of string-pulling behavior depends on hand dexterity (i.e., ability to contact and grasp the string) and the estimation of distance and direction (i.e., aim and target) of movement. Humans organize string-pulling behavior similarly (Singh et al. 2019) to rats, providing a translational assessment of fine motor control between species.

SR impairs fine motor skills during rat string-pulling (Blackwell et al. 2021, 2022), disrupting several aspects of performance. Decreased hand-target accuracy as demonstrated by increased misses and decreased contacts when attempting to grasp the string and reduced reach endpoint concentration is observed in rats 7 months after exposure to 5 cGy ^{28}Si (Blackwell et al. 2021). Similar deficits are observed acutely (72 h) after irradiation in rats exposed to either 10 cGy ^{4}He or 5-ion GCRsim (Blackwell et al. 2022). Thus far, regardless of SR exposure type or dose, rats' ability to grasp the string is impaired after irradiation. This may have high operational significance if similar changes occur in astronauts after exposure to SR.

Sleep loss is known to impact similar aspects of performance in many sensorimotor tasks. Inadequate sleep may have a significant effect on string-pulling behavior, although this has yet to be determined in either humans or rats. Thus, it is unclear whether the incidence and magnitude of SR-induced deficits would compare to performance when astronauts have experienced sub-optimal sleep. Furthermore, it is unknown whether SR effects on string-pulling behavior would be independent of, or interact synergistically with, the sleep fragmented-related performance decrements. Therefore, the current experiment characterized Sham and irradiated rats' performance under normally rested conditions and after sleep fragmentation in a bilateral fine motor task. String-pulling behavior was used to assess fine motor control by quantifying contacts and misses as well as the kinematics of both hands and the nose while pulling in the string to retrieve a food reward.

Methods

Ethical statements

This study was conducted in accordance with the National Research Council's "Guide for the Care and Use of Laboratory Animals (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 the procedures were approved by the Institutional Animal Care and Use Committees at EVMS and BNL.

Subjects

A total of 59 male Wistar rats (HlaR(WI)CVFR; Hilltop animals, Inc., Scottsdale, PA, USA) were used in the current study. After 1 week of acclimation at EVMS, the weight and age (approximately 5 months old on arrival) of rats were recorded. Then, rats were implanted with ID-1000us RFID transponders (Trovan Ltd, United States) just under the skin between the shoulder blades for easy identification with travel between facilities throughout this study. Rats remained in consistent vivarium temperature (20–21 °C) and humidity (30–60%) controlled environments on reversed 12-h light/dark cycles with lights on at 2230 (Zeitgeber Time (ZT) 0), throughout the entire study regardless of location. Rats were provided food and water ad libitum throughout the study, except for during string-pulling behavior, during which they were food restricted.

Prescreening regimen

Executive function and physical fitness are critical for astronauts on deep space flight missions. As such, rats were pre-screened for engagement in an exercise regimen as well at an Attentional Set-Shifting (ATSET) task which evaluates aspects of executive function (as previously described by Britten et al. 2020). Briefly, rats were exercised on a treadmill twice per week, except for when at BNL. Further, rats were tested in ATSET which was used as the basis for further inclusion in the rest of this study.

Procedures

Irradiation exposure paradigm

Following pre-screening in ATSET, rats were randomly assigned to one of three groups: Sham ($n=11$), 10 cGy ^{4}He ($n=24$), or 10 cGy 5-ion GCRsim ($n=24$) and sent to BNL for irradiation exposure. After approximately 2 weeks of acclimation at BNL when rats were approximately 7 months of age, they were placed in well-ventilated custom-made irradiation jigs, constructed of red plastic, and exposed to the ^{4}He ion beam at a dose rate of <1 cGy/min (~12 min exposure) or to the GCRsim beam sequence at an overall dose rate of 0.5 cGy/min (~20 min exposure) at NASA Space Radiation Laboratory (NSRL) (bnl.gov). Dose calibration was performed as previously described (La Tessa et al. 2016). Control rats were placed in identical irradiation jigs that remained in the preparation room, while their counterparts were taken into the radiation vault. Radiation exposure occurred during the rats' dark, wakeful, cycle.

String-pulling behavior

String-pulling behavior was evaluated approximately 3 months post-irradiation exposure before and after sleep fragmentation during the rats' dark, wakeful, cycle. Rats were first habituated to strings (black, 0.2 cm diameter, 100% cotton) and HoneyNut Cheerios as previously described (Blackwell et al. 2021) ~7 months of age prior to radiation exposure. A subset of rats used in the current study were also assessed in a separate experiment (Blackwell et al. 2022) 72 h after SR exposure. Consistent engagement by rats in string-pulling behavior is facilitated by mild food restriction to ~85% of rats the free-feeding baseline weight. Therefore, rats were food restricted for approximately 1 week before pre-sleep fragmentation string-pulling behavior was assessed. Mild food restriction is used commonly in food-motivated tasks to consistently maintain rats' motivation to perform in the task.

During a string-pulling session, rats were individually placed in a small (28×14 cm $\times 26$ cm) clear Plexiglas apparatus where they remained for six trials. The apparatus was thoroughly cleaned between each rat. A trial consisted of one 59-cm-long string being placed into the front of the apparatus that draped back to provide a clear view of the rat. The string had half of a Cheerio tied to the end to reinforce performance in the task. Rats approached the string, initiated pulling, and pulled to the end of the string to retrieve a food reward. Disengagement over a consecutive 20-min period terminated the session, and the rat was tested the subsequent day. The string-pulling apparatus was placed on a table located ~1.5 m above the floor. A HD camera (model #: XA30) with 1/1000 shutter speed and 59.98 frames per second was placed on a tripod perpendicular to the front wall of the apparatus. Lights were positioned on both sides of the apparatus/camera to illuminate the fine motor movements of rats during video recording. Recorded videos were used for offline analysis, including general measures of performance, frame-by-frame contact and miss quantification, and kinematic analyses.

Sleep fragmentation

Rats were placed individually in clear Plexiglas chambers (Lafayette Instruments, Lafayette, IN, USA), Sleep Fragmentation Chamber, model 80391) that contained bedding on the floor for sleep fragmentation. A single episode (13.25 h) of a mild sleep fragmentation paradigm was used starting at ZT − 1.25. This does not reduce overall sleep, impact sleep architecture, or increase measurable stress hormones but results in cognitive performance losses (McCoy et al. 2007; Nair et al. 2011; Ramesh et al. 2012; Hakim et al. 2014). This level of sleep fragmentation has been previously shown to allow for the non-rapid eye movement stage of sleep while preventing the rapid eye movement stage sleep. During this paradigm, rats were placed in electronically controlled chambers with a mobile bar that swept across the floor every 2 min. Rats continued food restriction during sleep fragmentation but were provided water ad libitum. Rats were reassessed in six trials of string-pulling behavior exactly as described above immediately after one night of sleep fragmentation.

Characterization of rat string-pulling behavior

Approach time and pull duration

After a string is placed into the apparatus, the rat will approach the string to begin reach and withdraw string-pulling behavior. The amount of time it takes rats to first approach the string to initiate pulling was quantified as approach time. Once string-pulling behavior is initiated, rats may consecutively cycle through reach and withdraw movements or pause to break from pulling and then re-engage; the amount of time it takes rats to fully pull in the string to reach the Cheerio tied at the end was quantified as pull duration.

Frame-by-frame contact and miss analysis

While engaging in string-pulling behavior, rats contact the string by grasping it with both hands and the mouth to pull it into the apparatus. The number of string contacts made during this behavior was quantified across testing. Rats may miss the string while pulling it into the apparatus, or fail to contact (i.e., Grasp) the string with the hands or the mouth. Therefore, the number of misses made with both the hands and the mouth were characterized across testing. To investigate the nature of contacts and misses, the percent of total misses and contacts were calculated relative to total attempts (i.e., hand and mouth contacts + hand and mouth misses = total attempts) to grasp the string.

Kinematic nose component analysis

XY data generated from the nose was not segmented into reach and withdraw components like the hands. Instead, nose movement was quantified across the entire bout of string-pulling behavior to evaluate peak speed (cm/s) and the range of maximum and minimum *XY* movement. This range of movement was used as a proxy for changes in posture as the rat is pulling in the string. Typically, rats remain upright with the nose engaging in minimal changes in *XY* movement.

Kinematic reach and withdraw components

Markerless pose estimation was conducted with the open-source machine learning program DeepLabCut (DLC) (v2.1 Mathis et al. 2018). DLC was used to label both the hands and the nose on each image that composed a video of rat string-pulling behavior. Twenty random video frames from one video per rat were extracted via *k*-means using DLC. These frames were manually labeled and used to train a network. The trained network was then used to label the remaining frames from three videos per rat for 174 videos. After these videos were labeled with the DLC network, the data was screened frame-by-frame for errors using the free Tracker program (https://physlets.org/tracker/). Errors were corrected by averaging the data before and after the incorrect data, unless too many errors occurred, in which case the data was split into two separate bouts of pulling and then averaged across measures.

After videos and corresponding *XY* data were screened, several kinematic and topographic measures of performance were derived using a custom-macro. The macro was used to segment bouts of string-pulling behavior into upward reaches to grasp the string and downward withdraws to advance the string into the apparatus. Once the data were segmented, the following measures were calculated for reaches and withdraws, respectively.

Parameter of concentration Circular statistics (Batschelet 1981) were used to quantify the parameter of concentration (first order R) and heading direction (second order R) of reach and withdraw movement components. To do this, the *XY* starting point from reaches and withdraws was transformed to have an origin of 0, 0. The endpoint angle (i.e., heading direction) of reach and withdraw paths was then calculated relative to a polar coordinate system (0°: right, 90°: up, 180°: left, 270°: down). The parameter of concentration represents the clustering strength of these headings with values close to zero denoting weak clustering in varying directions and values approaching one representing strong clustering in one direction.

Heading direction (degrees (°)) Circular statistics were also used to evaluate the average heading direction of reach and withdraw endpoints from 0° to 360°. Typically, reaches are directed upward toward 90°, and withdraws are oriented downward toward 270°.

Peak speed (cm/s) The peak speed of movement was calculated for both hands during reaches and withdraws per string-pulling bout. The peak speeds were averaged across three string-pulling trials for the left and right hands.

Distance (cm) The distance traveled with each hand was calculated for all reaches and withdraws during a pulling bout. Then, the average distance the hands traveled was calculated across string-pulling bouts from three trials.

Path circuity The circuity of paths was calculated by dividing the Euclidean distance by the total distance traveled for all reaches and withdraws for three trials. Path circuity ranges from zero (most circuitous) to one (direct, straight line).

Statistical analyses

Several measures violated statistical assumptions, including approach time, pull duration, and the miss-to-contact ratio, under certain conditions. As such, non-parametric analyses were implemented for group comparisons, including Kruskal–Wallis (KW) and Mann–Whitney (MW) tests ($p < 0.05$). Kernel density estimation (KDE) was also conducted via Free Statistics Software (v1.2.1) (Wessa 2022) to generate probability density profiles that established the 5th worst percentile performance metrics of Sham rats. This provided a basis of comparison to determine how sleep fragmentation and SR exposure altered performance metrics from Sham-level performance. Fisher's exact test ($p < 0.050$) was used to assess group differences between both SR groups and Sham rats. Grubbs' test was used to identify and remove outliers, which was only necessary for analyses of approach time and pull duration.

Statistical assumptions were met for kinematic measures. Thus, repeated measures ANOVAs with Hand (Left and Right) were used for statistical analyses to evaluate the effects of SR (^{4}He and GCRsim) and sleep fragmentation (pre and post) as well as their interactions on performance measures derived from the string-pulling task ($\alpha = 0.050$). Linear trend analysis and Tukey's HSD post hoc tests were used to evaluate significant effects and interactions ($\alpha = 0.050$). JASP 0.14.0.0 open-source statistical software was used to conduct these analyses.

Results

Approach time

SR exposure selectively increased the amount of time necessary for rats to approach the string under rested wakeful conditions (Fig. 1A). Rats exposed to GCRsim [MW: $p = 0.008$, CI 0.872–6.338%] took significantly longer amounts of time to approach the string relative to Sham rats. Whereas no significant differences were observed between Sham and ^{4}He-exposed [MW: $p = 0.066$, CI -0.233 to 5.133%] or the two SR groups [MW: $p = 0.389$, CI -1.417 to 3.408%]. Due to within group variability, KDE analysis was used to calculate the 5th worst percentile performance of Sham rats to be 8.35 s; 30% of ^{4}He- and 33% of GCRsim-exposed rats took longer than 8.35 s to approach the string (Fig. 1B). Fisher's exact tests conducted on the probability density profiles generated from the KDE analysis revealed that Sham and ^{4}He-exposed rats [$p < 0.001$] and Sham and GCRsim-exposed rats [$p < 0.001$] significantly differed in approach time. Thus, both SR groups exhibited longer approach times relative to the 5th worst percentile performance of Sham rats.

After one night of sleep fragmentation, rats exposed to ^{4}He exhibited differences in approach time [KW $p = 0.002$]
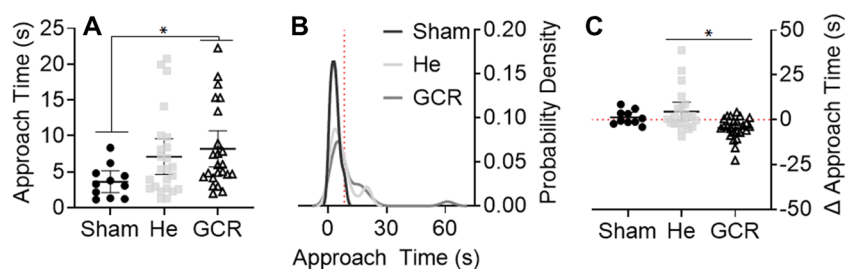

Fig. 1 Rats exposed to SR exhibited a significant increase in approach time 3 months after exposure relative to Sham rats (**A**). Kernel estimation generated probability density identified the 5th worst percentile performance of Sham rats to be 8.35 s which was significantly exceeded ($p < 0.050$) by 30% of ^{4}He- and 33% of GCR-sim-exposed rats approach time (**B**). After one session of sleep fragmentation, ^{4}He-exposed rats took a significantly longer amount of time to approach the string relative to rats exposed to GCRsim (**C**). *$p < 0.050$

(Fig. 1C), taking a significantly longer amount of time to approach the string relative to GCRsim-exposed rats [Tukey $p < 0.050$]. Approach time was selectively influenced by sleep in [4]He-exposed rats only.

Pull duration.

While select changes were observed in approach time 3 months after irradiation and after one night of sleep fragmentation, pull duration was not influenced similarly. Both [4]He- [MW: $p = 0.605$, CI -1.955–0.965%] and GCRsim-exposed [MW: $p = 0.532$, CI -2.065 to 0.840%] groups failed to differ from Sham rats or one another [MW: $p = 0.955$, CI -1.013 to 0.842%] 3 months post-radiation exposure. Lastly, an ANOVA conducted on the difference in pull duration from post- to pre-sleep fragmentation failed to reveal group differences [$F(2, 56) = 0.170$, $p = 0.844$, $\eta_p^2 = 0.006$]. Pull duration was organized similarly between groups 3 months after irradiation, and one night of sleep fragmentation did not significantly influence pull duration between the groups.

Contacts and misses

Rats engaged in both misses (Fig. 2A) and contacts (Fig. 2B) with the hands and mouth while pulling in the string. Exposure to SR resulted in more misses and less contacts relative to Sham rats [$F(2, 56) = 14.487$, $p < 0.001$, $\eta_p^2 = 0.341$] (Fig. 2C). This work suggests that
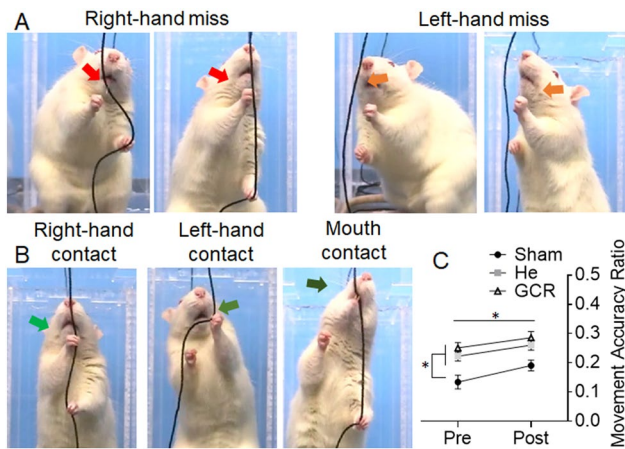
issues grasping the string are present 3 months following exposure to [4]He or GCRsim.

Sleep fragmentation also reduced the rats' ability to contact a string (Fig. 2C). Relative to rested wakeful performance, all rats (Sham and SR-exposed) exhibited an increase in misses and a decrease in contacts after sleep fragmentation [$F(1, 56) = 8.757$, $p = 0.005$, $\eta_p^2 = 0.135$]. This suggests that there is an additive effect of these space flight stressors impairing rats' ability to contact and grasp a string.

Nose component

A select change in upward nose movement was observed after sleep fragmentation by all rats (Table 1). Compared to rested wakeful performance (Fig. 3A), the maximum Y-position of the nose significantly increased after sleep fragmentation (Fig. 3B), indicating that rats reached higher with their nose during string-pulling behavior (Fig. 3C). Other effects and interactions were non-significant for the maximum Y-position or for other measures (minimum Y-position and maximum/minimum X-positions) of the nose (Table 1). Thus, the nose traveled higher within the apparatus during string-pulling without exhibiting significant changes in downward or horizontal movement.

Reach component

Kinematic aspects of hand movements were impaired after sleep fragmentation in the string-pulling task (Table 2).

Fig. 2 Frame-by-frame photos display misses, or failure to contact the string by grasping, for two different rats (**A**, top row). Three different representative contacts, with the right-hand, left-hand, and mouth are displayed for a rat (**B**). Arrows are highlighting the hand position relative to the string. The percent of contacts and misses are depicted across testing by group (**C**). Three months after irradiation, both [4]He- and GCRsim-exposed rats engaged in more misses and less contacts than Sham rats. However, one night of sleep fragmentation resulted in an increase in misses and a decrease in contacts for all rats, regardless of group. *$p < 0.050$

Table 1 Statistical data are shown for nose kinematics between groups pre- versus post-sleep fragmentation

|	F	df	p	η_p^2
Maximum Y-range				
Sleep	7.365	1, 56	0.009*	0.116
Sleep × group	0.096	2, 56	0.908	0.003
Group	1.086	2, 56	0.345	0.037
Minimum Y-range				
Sleep	1.750	1, 56	0.191	0.030
Sleep × group	2.354	2, 56	0.104	0.078
Group	0.515	1, 56	0.600	0.018
Maximum X-range				
Sleep	3.506	1, 56	0.066	0.059
Sleep × group	2.372	2, 56	0.103	0.078
Group	0.770	1, 56	0.468	0.027
Minimum X-range				
Sleep	0.024	1, 56	0.877	4.334e−4
Sleep × group	0.710	2, 56	0.496	0.025
Group	0.197	1, 56	0.822	0.007

*$p < 0.050$
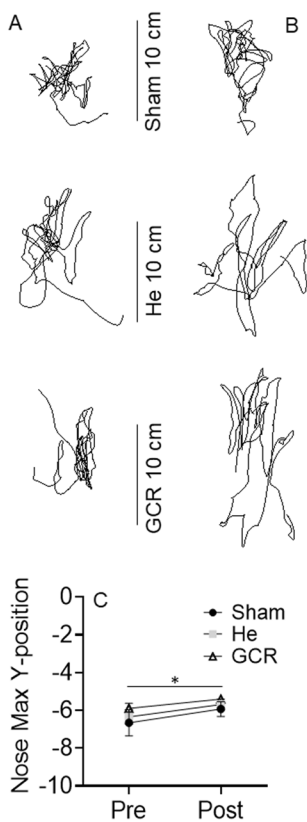
Fig. 3 Topographic paths traveled by the nose while string-pulling is shown for one rat per group under rested wakeful (**A**) and sleep fragmented (**B**) conditions. Quantification of the maximum (**C**) *Y*-position selectively revealed differences that the nose traveled, such that an increase in the maximum *Y*-position traveled was observed by all rats after sleep fragmentation. *$p < 0.050$

Table 2 Statistical data are displayed for left- and right-hand reach kinematics between groups pre- versus post-sleep fragmentation

	F	df	p	η_{p}^2
Distance traveled				
Sleep	0.422	1, 56	0.518	0.007
Sleep × group	1.524	2, 56	0.227	0.052
Hand	0.698	1, 56	0.407	0.012
Hand × group	1.997	2, 56	0.145	0.067
Group	0.794	2, 56	0.457	0.028
Sleep × hand	0.388	1, 56	0.536	0.007
Sleep × hand × group	0.356	2, 56	0.702	0.013
Peak speed				
Sleep	1.540	1, 56	0.220	0.029
Sleep × group	0.049	2, 56	0.952	0.002
Hand	1.640	1, 56	0.206	0.031
Hand × group	1.040	2, 56	0.361	0.038
Group	0.305	2, 56	0.738	0.012
Sleep × hand	0.740	1, 56	0.394	0.014
Sleep × hand × group	1.122	2, 56	0.333	0.041
Path circuity				
Sleep	0.025	1, 56	0.876	4.418e−4
Sleep × group	0.264	2, 56	0.769	0.009
Hand	0.228	1, 56	0.635	0.004
Hand × group	3.976	2, 56	0.024*	0.124
Group	0.160	2, 56	0.160	0.063
Sleep × hand	0.379	1, 56	0.541	0.007
Sleep × hand × group	0.272	2, 56	0.763	0.010
Endpoint concentration				
Sleep	4.540	1, 56	0.038*	0.075
Sleep × group	0.059	2, 56	0.943	0.002
Hand	6.526	1, 56	0.013*	0.104
Hand × group	0.714	2, 56	0.494	0.025
Group	1.841	2, 56	0.168	0.062
Sleep × hand	0.933	1, 56	0.338	0.016
Sleep × hand × group	0.157	2, 56	0.855	0.006

*$p < 0.050$

Under rested wakeful conditions, the endpoints of reach paths are tightly clustered (Fig. 4A). However, after sleep fragmentation, reach endpoints were less concentrated than previously (Fig. 4B). Both the left (Fig. 4C) and right (Fig. 4D) hands elicited more variable reach endpoint concentrations for all rats.

In addition, comparisons of left- and right-hand reaches provided a kinematic analysis of lateralization during the aim, target, and grasp components of string-pulling behavior (Table 2). ⁴He-exposed rats exhibited differences in path circuity between the left (Fig. 5A) and right (Fig. 5B) hands during reaches, such that more circuitous paths were traveled with the left- (Fig. 5C) than the right-hand (Fig. 5D). Further, the endpoints of reach paths were less concentrated for rats left-hand (Fig. 5C) versus their right-hand (Fig. 5D). No other kinematic differences (distance, peak speed) were observed during the reach component (Table 2).

Withdraw component

Varying SR exposure and sleep fragmentation effects were observed on withdraw distance traveled (Table 3). First, select SR effects on distance traveled were observed 3 months after exposure to ⁴He. Sham rats traveled longer distances during withdraws with their left hand (Fig. 6A) relative to ⁴He-exposed rats (Fig. 6B) before sleep fragmentation (Fig. 6E). Second, sleep fragmentation revealed specific group changes in withdraw distance traveled. Exclusively GCRsim-exposed rats traveled significantly longer withdraw distances pre- (Fig. 6C) versus post- (Fig. 6D) sleep fragmentation [Tukey $p < 0.050$] (Fig. 6E and F).
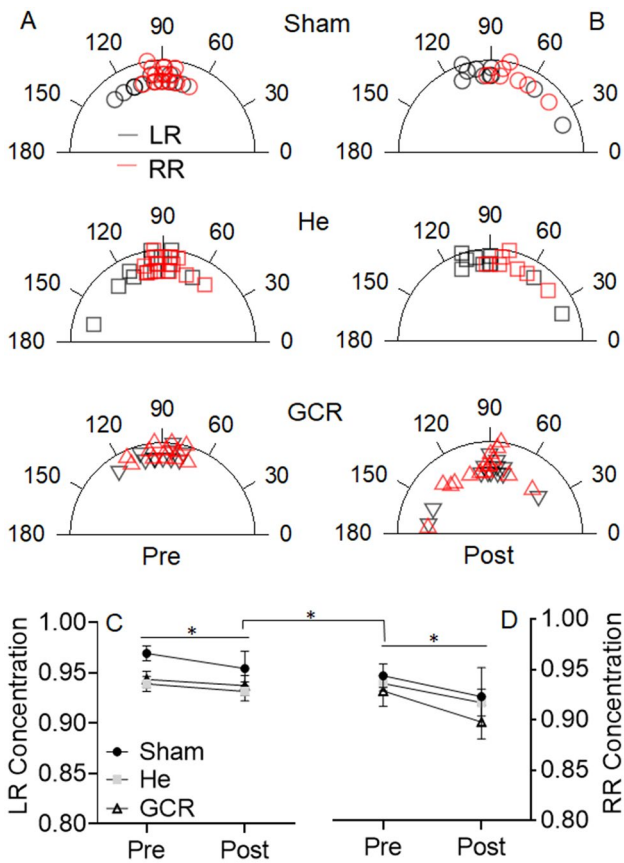
Fig. 4 Representative reach endpoints are shown on circular plots for one rat from each group under normally rested (**A**) and sleep fragmented (**B**) conditions. All rats exhibited more variable reach endpoints with both the left- (**C**) and right-hand (**D**) after sleep fragmentation relative to rested wakeful performance. In addition, overall, reach endpoints were more concentrated for rats left-hand (**C**) versus their right-hand (**D**). *$p < 0.050$

Fig. 5 Representative left (**A**) and right (**B**) reach paths are shown for a ^{4}He-exposed rat. Rats exposed to ^{4}He exclusively demonstrated more circuitous reach paths with their left hands (**C**) relative to their right hands (**D**) across testing. *$p < 0.050$

Left- and right-hand comparisons of withdraw heading revealed differences between the hands (Table 3). Overall, rats ended left-hand withdraws closer to 265°, while right-hand withdraws ended near 275°. No other differences were observed in kinematic measures (peak speed, path circuity, concentration) of the withdraw component (Table 3).

Discussion

Sleep fragmentation and simulated space radiation influenced the organization of rat string-pulling behavior. Each of these space flight stressors was found to independently disrupt rats' ability to contact and grasp a string. Overall, sleep fragmentation led to greater impairments in kinematic measures of performance during the string-pulling task than SR alone. Still, distinct aspects of performance were influenced by these space flight stressors.
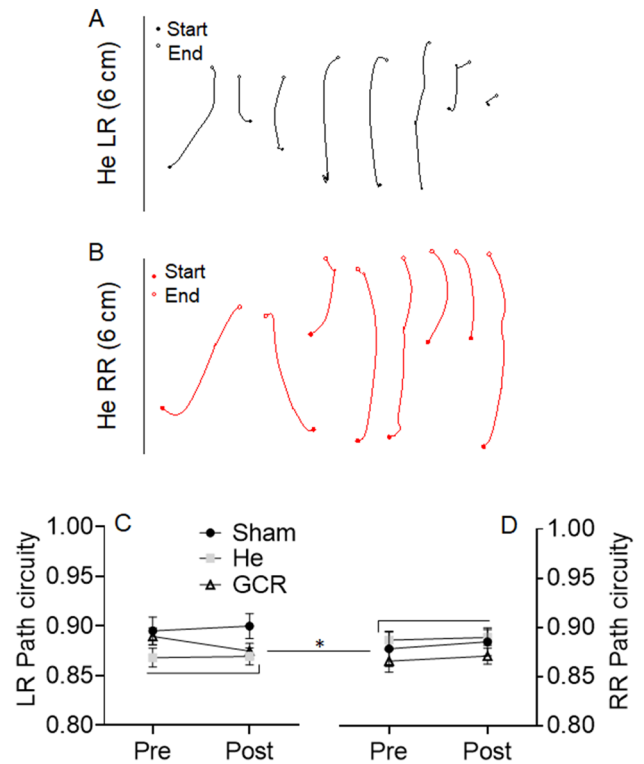
SR-induced disruptions were observed in performance, resulting in increased misses and decreased contacts by both irradiated groups relative to Sham rats. Second, SR-exposed rats took more time to approach the string than Sham rats 3 months after irradiation. The ^{4}He-exposed group also traveled shorter left-hand withdraw distances compared to Sham rats. Lastly, evidence of lateralization was present with ^{4}He-exposed rats engaging in more circuitous reach paths with their left- versus right-hand. These findings support the emergence of latent deficits 3 months after ^{4}He or GCRsim exposure that were not present acutely after irradiation at 72 h and persistent impairments in rats' ability to grasp the string (Blackwell et al. 2022).

A single exposure to a mild sleep fragmentation paradigm impaired several aspects of rat string-pulling behavior. Sleep fragmentation resulted in increased misses and decreased contacts with less concentrated reach endpoints by both hands in Sham and irradiated rats. This suggests reduced aim-to-target and grasp movement accuracy and additive effects of sleep fragmentation. Increases in the maximum Y-range that the nose traveled in the apparatus while pulling was also influenced by one night of sleep fragmentation. Disruptions in the reach-to-grasp movement accuracy may be related to neural dysfunction, such as reduced efficiency,

Table 3 Statistical data are shown for left- and right-hand withdraw kinematics between groups pre- versus post-sleep fragmentation

	F	df	p	η_{p}^{2}
Distance traveled				
Sleep	3.028	1, 56	0.087	0.051
Sleep × group	4.226	2, 56	0.020*	0.131
Hand	0.364	1, 56	0.111	0.045
Hand × group	2.622	2, 56	0.013*	0.143
Radiation	1.300	2, 56	0.281	0.044
Sleep × hand	0.934	1, 56	0.338	0.016
Sleep × hand × group	0.105	2, 56	0.900	0.004
Peak speed				
Sleep	0.013	1, 56	0.911	2.406e−4
Sleep × group	0.048	2, 56	0.953	0.002
Hand	1.020	1, 56	0.317	0.019
Hand × group	1.585	2, 56	0.215	0.057
Group	0.380	2, 56	0.686	0.014
Sleep × hand	1.453	1, 56	0.233	0.027
Sleep × hand × group	0.088	2, 56	0.916	0.003
Path circuity				
Sleep	3.553	1, 56	0.065	0.060
Sleep × group	2.566	2, 56	0.086	0.084
Hand	0.264	1, 56	0.610	0.005
Hand × group	0.130	2, 56	0.878	0.005
Group	0.655	2, 56	0.524	0.023
Sleep × hand	0.500	1, 56	0.483	0.009
Sleep × hand × group	0.621	2, 56	0.541	0.022
Endpoint concentration				
Sleep	1.145	1, 56	0.289	0.020
Sleep × group	1.879	2, 56	0.162	0.063
Hand	1.059	1, 56	0.308	0.019
Hand × group	0.219	2, 56	0.804	0.008
Group	0.550	2, 56	0.580	0.019
Sleep × hand	0.275	1, 56	0.602	0.005
Sleep × hand × group	0.005	2, 56	0.995	1.705e−4
Heading direction				
Sleep	0.016	1, 56	0.900	2.870e−4
Sleep × group	0.046	2, 56	0.955	0.002
Hand	9.991	1, 56	0.003*	0.151
Hand × group	1.840	2, 56	0.168	0.062
Group	1.238	2, 56	0.298	0.042
Sleep × hand	0.321	1, 56	0.574	0.006
Sleep × hand × group	0.499	2, 56	0.610	0.018

*$p < 0.050$

while neural compensation involved in the coordination of fine motor skills may contribute to changes in nose kinematics.

Sleep fragmentation interacted with SR to influence distinct aspects of performance. This is the first study to examine the combined effects of these space flight stressors on
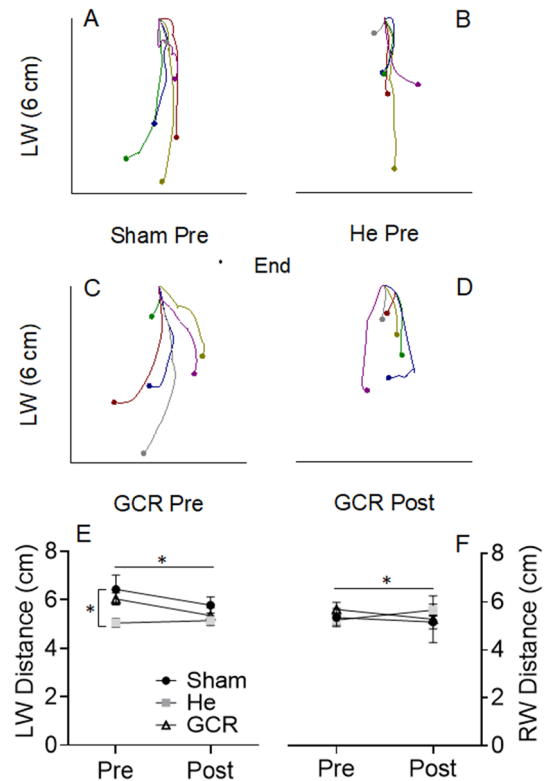

Fig. 6 Representative left withdraw (LW) trajectories transformed to begin at a 0, 0 origin for a Sham (**A**) and ⁴He-exposed (**B**) rat. ⁴He-exposed rats traveled shorter withdraw distances with their left-hand relative to Sham rats across testing (**E**). Further representative left withdraw trajectories are depicted for one bout of string-pulling behavior for one GCRsim-exposed rat pre- (**C**) versus post- (**D**) sleep fragmentation. After one night of sleep fragmentation, GCRsim-exposed rats traveled shorter withdraw distances with both the left (**E**) and right (**F**) hands relative to pre-sleep fragmentation. *$p < 0.050$

fine motor control. ⁴He-exposed rats took a longer amount of time to approach the string compared to GCRsim-exposed rats, and GCRsim-exposed rats traveled shorter withdraw distances following sleep fragmentation relative to their rested wakeful performance, neither of which were apparent under normally rested conditions. These results may suggest that there are specific temporal profiles of neuropathology that emerge following different types of SR exposure (i.e., single vs multi-ion) alone and when combined with sleep fragmentation. These observed changes in performance are characterized in relation to the functions of sleep and its role in processing sensorimotor information, as well as to SR exposure.

Sleep fragmentation

It is well established that sleep disruptions impair cognitive (McCoy et al. 2007; Nair et al. 2011; Ramesh et al. 2012) and sensorimotor function (Varga et al. 2014; Pettibone et al.

2019; Wang et al. 2021), with speed and accuracy of movement particularly sensitive to these disruptions regardless of task across species from rodent models and non-human primates to humans. Even acute sleep issues are sufficient to impair subsequent performance after engaging in both fine (skilled reaching: Varga et al. 2014) and gross (rotarod: Yang et al. 2014) motor tasks. The present findings from the string-pulling task add to this growing body of the literature demonstrating sleep disruption-induced motor deficits that influence accuracy of movement, including increased misses and reach endpoint concentration variability. The ability to detect performance deficits that are both novel and consistent with previous work following one session of sleep fragmentation may be attributed to the sensitivity of the complex rhythmic bilateral movements elicited when pulling in a string following neural injury (Blackwell et al. 2018a, b; 2021, 2022; Hart*, Blackwell* et al. 2022; Saadat*, Blackwell* et al. 2022).

Reductions in the speed of movement without changes in movement accuracy would support a speed/accuracy trade-off phenomenon (for review, see Heitz 2014). Yet, only the accuracy component was influenced by one session of sleep fragmentation in the current study in both Sham and irradiated rats, while the speed of movement was not altered after sleep fragmentation. Thus, rats failed to reduce speed to increase movement accuracy (i.e., more string contacts, consistent reach endpoints). This may suggest an inability to alter the reach component in an online fashion to improve performance within a test session. Further, the increased maximum Y-nose range that rats exhibited may be compensation for these performance deficits. Rats use tactile information generated from the face (vibrissae, nose) to guide string-pulling behavior, and reaching up higher likely provides more tactile information about the spatial position of the string to aid in guiding performance.

The sleep fragmentation paradigm used in the current study prevents rats from entering the non-rapid eye movement stage of sleep which may have implications for neural activity. The non-rapid eye movement stage of sleep has been shown to be important for corticostriatal plasticity while rats learn a skilled task (Lemke et al. 2021). Further, improvements in motor skills have been shown to positively correlate with amounts of the non-rapid eye movement stage of sleep (Genzel & Robertson 2015). Much of the precedential literature has focused on the impact that sleep disruptions have in off- and online processing of sensorimotor skills during sleep and wakeful resting periods, respectively. Performance gains, which are only evident after a night of sleep, typically occur through replay, or the reactivation of specific neural ensembles that occurred during task engagement, with greater motor learning gains typically observed as task complexity increases (Kuriyama et al. 2004). Historically research has focused on replay

within the hippocampus related to cognitive function; yet, over the last few years, novel work has demonstrated a role for the human motor cortex in the replay of skilled motor activity during periods of rest (Eichenlaub et al. 2020) and sleep (Rubin et al. 2022). Yet, this continued improvement is not associated with additional training (Fischer et al. 2022; Walker et al. 2022), demonstrating the importance of sleep for skilled fine motor performance. Thus, disruptions to the processes that are involved in solidifying and strengthening previous sensorimotor experiences have the potential to be deleterious to performance. Whether the sleep fragmented rats retained previous experience in the string-pulling task during sleep and the post-test session is unknown at this time. Future work is needed to determine if processing of fine motor skills is compromised at the neuronal level following sleep fragmentation.

Simulated space radiation exposure models

The radiation qualities of ^{4}He and the 5-ion GCRsim paradigm on biological systems seem to be distinct. For example, it is estimated that approximately 15 ions traverse a single cell with exposure to ^{4}He, compared to ∼ 250 ions that traverse a single cell with exposure to protons which mainly comprise the 5-ion GCRsim spectrum (Huff et al. 2022). ^{4}He contributes to 9% of the total 5-ion GCRsim beam, while protons make up 90%; it may thus be beneficial to examine the contribution of proton exposure to fine motor control to determine independent and synergistic effects of the major components of 5-ion GCRsim on performance. However, work that has characterized behavioral disruptions after irradiation to single ions or GCRsim thus far have failed to support this differentiation at the cellular level. Instead, similar behavioral deficits are generally observed that seem to be task or modality dependent (Britten et al. 2022). Further, exposure to single ions or GCRsim has been shown to produce disruptions in neuronal function and neuroinflammation (Cekanaviciute et al. 2018; Rosi 2018; Klein et al. 2021; Krukowski et al. 2021; Ton et al. 2022). Yet, no work to date has directly compared this within the same study.

Most work characterizing the effects of SR on performance have focused on cognitive function (for review see Britten et al. 2021a, b) and gross motor control (Philpott and Miquel 1986; Joseph et al. 1998; Pecaut et al. 2004; Whoolery et al. 2017). Yet, recent work has identified fine motor deficits that, if were to occur in astronauts, may compromise mission success. Impairments in fine motor control during string-pulling behavior were recently identified in SR exposure models at multiple time points following irradiation. Approximately, 7 months after exposure to 5 cGy ^{28}Si disruptions in fine motor control were identified in a string-pulling task, some of which were transient (pull duration) and others persistent (string misses, kinematics)

over subsequent test days (Blackwell et al. 2021). Recent work observed that rat string-pulling behavior is also impaired at an acute timepoint, 72 h after SR exposure with more pronounced deficits in rats exposed to 10 cGy [4]He than a separate group of rats exposed to the same dose of 5-ion GCRsim (Blackwell et al. 2022), which likely has implications for in-flight performance if astronauts were to experience similar impairments. However, most effects of radiation are characterized approximately 3 months after exposure, given the relevance to post-mission health and livelihood. Now, the current study provides evidence for persistent issues in rats ability to contact the string 3 months post-irradiation, further supporting protracted deficits in fine motor control following exposure to SR. In addition, this work also demonstrates the emergence of protracted deficits in [4]He- (withdraw distance) and GCR-sim-exposed (approach time) rats 3 months after irradiation that were not apparent 72 h following exposure.

Exposure to SR has been shown to elicit premature senescence (Suman et al. 2013). Thus, aging alone after irradiation (Joseph et al. 1992) or age and additional SR exposure(s) may lead to further performance disruptions. For example, [28]Si-exposed rats, which were assessed in the string-pulling task later in life around 15 months of age, exhibited greater fine motor impairments relative to the rats in the current study, including reduced reach distance traveled and endpoint concentration in addition to increased misses when trying to grasp the string. Thus, there may be an age by SR interaction influencing fine motor control. Further, SR may induce changes in plasticity and adaptation inhibiting rats to compensate in string-pulling behavior when exposed to an additional space flight stressor (i.e., sleep fragmentation).

Another potentially impactful observation from this work is that rats exposed to single ions seem to develop lateralized deficits in some performance metrics. For example, [28]Si-exposed rats engaged in shorter reach distances and less concentrated reach endpoints with the left-hand relative to Sham rats, while no differences were observed between groups with the right-hand. In the present study, [4]He-exposed rats exhibited differential path circuity between the hands with the left hand traveling more circuitous paths than the right hand, while no evidence of lateralization was observed in the GCRsim-exposed rats. Further work is needed to determine the consistency and persistence of lateralized changes in fine motor control at protracted time points following SR exposure. Taken together, this work may suggest that there are specific temporal profiles of neuropathology that emerge following different types of SR exposure (i.e., single vs multi-ion). Yet, regardless of the exposure type (10 cGy [4]He, 5 cGy [28]Si, and 10 cGy GCRsim) or post-irradiation assessment time point (72 h, 3 months, 7 months),

movement inaccuracies are consistently observed during the string-pulling task.

Mechanistic basis for deficits

Numerous studies have reported decreased neural processing speed and/or reduced neural efficiency following sleep fragmentation (for review, see Brewster et al. 2015). Many disorders, including sleep apnea and idiopathic rapid eye movement sleep behavior disorder, that involve fragmented sleep and have been shown to disrupt fine motor control (Ayalon et al. 2006; Djonlagic et al. 2012; Landry et al. 2014; Li et al. 2019), may provide insight into the neural processes that are influenced by sleep fragmentation and the associated effects on performance. Using functional magnetic resonance imaging, previous work has also shown that individuals with sleep apnea exhibit similar levels of performance in a verbal learning task, yet with greater brain activation than controls when doing so (Ayalon et al. 2006). After sleep disruptions, healthy control subjects also elicit greater brain activation as indicated by functional magnetic resonance imaging while performing cognitive tasks (Drummond et al. 2005). During idiopathic rapid eye movement sleep behavior disorder, sleep fragmentation and striatal dopamine deficiency are strongly positively associated in patients exhibiting fine motor deficits (Li et al. 2019). This evidence supports that sleep fragmentation impacts both performance and neural function at transmitter and system (intensity, speed, efficiency) levels. Therefore, the impairments observed by sleep fragmented rats in the current study may be attributed to neural disruptions leading to an inability to efficiently process information and/or rapidly compensate during the reach-to-grasp component in the string-pulling task.

The impact of SR on neural function underlying fine motor control is under studied. While future work is needed to evaluate ion-specific changes in sensorimotor performance and corresponding neural function after SR exposure to fill this gap, some previous work may provide a starting foundation. Given that SR-ions typically travel along a primary path causing destruction and fragmenting into multiple secondary paths after contact with an object (i.e., skull and brain), it may be likely that SR also produces cortical damage. While little research currently exists on the neural basis of bimanual fine motor control or on cortical contributions to SR-induced deficits, exposure to SR has been shown to negatively impact neurotransmission that is involved in fine motor control. For example, evidence of striatal dopaminergic dysfunction was first reported from 3 days after iron irradiation that persisted until several months later (Joseph et al. 1992); this change was also associated with reduced performance in a wire suspension task. Other work identified dopaminergic dysfunction that was associated with deficits in a psychomotor vigilance

task which assesses correct responses, impulsivity, and attention (Davis et al. 2014, 2015). Reductions in dopamine are sufficient to impair skilled reaching behavior, including the decreased ability to grasp a food pellet (Whishaw et al. 1986; Hyland et al. 2019). Therefore, disruptions to this system may be sufficient to impair rat behavior in the string-pulling task after SR exposure.

Several lines of converging evidence suggest that sleep fragmentation and SR influence similar neural mechanisms which have the potential to disrupt performance during fine motor skills. It is well established that these space flight stressors lead to cognitive dysfunction and related neuropathology. However, the effects on fine motor control and relative neural regions and systems are less understood. Yet, the synchronization of neural activity between cortical and subcortical regions is important for the organization of fine motor skills (Penhune and Doyon 2002; Boutin et al. 2018). Since focal cortical damage is sufficient to impair rat string-pulling (Blackwell et al. 2018a), cortical dysfunction may contribute to the observed deficits in this task following sleep fragmentation and SR exposure. Further, disruptions to a neural structure or regions within sensorimotor networks that support fine motor control may also have the potential to impair behavior in the string-pulling task.

Data availability Data will be made available on reasonable request.

Declarations

Conflict of interest The authors do not have any non-financial conflicts of interest.

References

Ayalon L, Ancoli-Israel S, Klemfuss Z, Shalauta MD, Drummond SP (2006) Increased brain activation during verbal learning in obstructive sleep apnea. Neuroimage 31:1817–1825

Barger L, Sullivan JP, Vincent AS, Fiedler ER, McKenna LM, Flynn-Evans EE, Gilliland K, Sipes WE, Smith PH, Brainard GC, Lockley SW (2012) Learning to live on a Mars day: fatigue countermeasures during the Phoenix Mars Lander mission. Sleep 35(10):1423–1435

Barger LK, Flynn-Evans EE, Kubey A, Walsh L, Ronda JM, Wang W, Wright KP Jr, Czeisler CA (2014) Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study. Lancet Neurol 13:904–912

Basner M, Dinges DF, Mollicone D, Ecker A, Jones CW, Hyder EC, Di Antonio A, Savelev I, Kan K, Goel N, Morukov BV, Sutton JP (2013) Mars 520-d mission simulation reveals protracted crew hypokinesis and alterations of sleep duration and timing. Proc Natl Acad Sci USA 110(7):2635–2640

Batschelet E (1981) Circular statistics in biology. Academic Press, New York

Berry CA (1969) Preliminary clinical report of the medical aspects of Apollos VII and VIII. Aerosp Med 40:245–254

Blackwell AA, Widick WL, Cheatwood JL, Whishaw IQ, Wallace DG (2018a) Unilateral forelimb sensorimotor cortex devascularization disrupts the topographic and kinematic characteristics of hand movements while string-pulling for food in the rat. Behav Brain Res 338:88–100

Blackwell AA, Banovetz MT, Qandeel WIQ, Wallace DG (2018b) The structure of arm and hand movements in a spontaneous and food rewarded on-line string-pulling task by the mouse. Behav Brain Res 345:49–58

Blackwell AA, Schell BD, Osterlund Oltmanns JR, Whishaw IQ, Ton ST, Adamczyk NS, Kartje GL, Britten RA, Wallace DG (2021) Skilled movement and posture deficits in rat string-pulling behavior following low dose space radiation (^{28}Si) exposure. Behav Brain Res 400:113010

Blackwell AA, Fesshye A, Tidmore A, Lake RI, Wallace DG, Britten RA (2022) Rapid loss of sensorimotor function after low dose space radiation. Behav Brain Res 430:113907

Boutin A, Pinsard B, Boré A, Carrier J, Fogel SM, Doyon J (2018) Transient synchronization of hippocampo-striato-thalamo-cortical networks during sleep spindle oscillations induces motor memory consolidation. Neuroimage 169:419–430

Brewster GS, Varrasse M, Rowe M (2015) Sleep and cognition in community-dwelling older adults: a review of literature. Healthcare (basel) 3(4):1243–1270

Britten RA, Fesshaye AS, Duncan VD, Wellman LL, Sanford LD (2020) Sleep fragmentation exacerbates executive function impairments induced by low doses of Si ions. Radiat Res 194(2):116–123

Britten RA, Duncan VD, Fesshaye AS, Wellman LL, Fallgren CM, Sanford LD (2021a) Sleep fragmentation exacerbates executive function impairments induced by protracted low dose rate neutron exposure. Int J Radiat Biol 97(8):1077–1087

Britten RA, Wellman LL, Sanford LD (2021b) Progressive increase in the complexity and translatability of rodent testing to assess space-radiation induced cognitive impairment. Neurosci Biobehav Rev 126:159–174

Britten RA, Fesshaye A, Ihle P, Wheeler A, Baulch JE, Limoli CL, Stark CE (2022) Dissecting differential complex behavioral responses to simulated space radiation exposures. Radiat Res 197(3):289–297. https://doi.org/10.1667/RADE-21-00068.1

Carskadon MA, Brown E, Dement WC (1982) Sleep fragmentation in the elderly: relationship to daytime sleep tendency. Neurobiol Aging 3:321–327

Cekanaviciute E, Rosi S, Costes SV (2018) Central nervous system responses to simulated galactic cosmic rays. Int J Mol Sci 19(11):3669

Cucinotta FA, Alp M, Sulzman FM, Wang M (2014) Space radiation risks to the central nervous system. Life Sci Space Res 2:54–69

Davis CM, DeCicco-Skinner KL, Roma PG, Hienz RD (2014) Individual differences in attentional deficits and dopaminergic protein levels following exposure to proton radiation. Radiat Res 181:258–271

Davis CM, DeCicco-Skinner KL, Hienz RD (2015) Deficits in sustained attention and changes in dopaminergic protein levels following exposure to proton radiation are related to basal dopaminergic function. PLoS One 10:e0144556

Deak MC, Stickgold R (2010) Sleep and cognition. Wiley Interdiscip Rev Cogn Sci 1(4):491–500

Djonlagic I, Saboisky J, Carusona A, Stickgold R, Malhotra A (2012) Increased sleep fragmentation leads to impaired off-line consolidation of motor memories in humans. PLoS One 7(3):e34106

Drummond SP, Bischoff-Grethe A, Dinges DF, Ayalon L, Mednick SC, Meloy MJ (2005) The neural basis of the psychomotor vigilance task. Sleep 28:1059–1068

Eichenlaub JB, Jarosiewicz B, Saab J, Franco B, Kelemen J, Halgren E, Hochberg LR, Cash SS (2020) Replay of learned neural firing sequences during rest in human motor cortex. Cell Rep 31(5):107581

Evans-Flynn E, Gregory K, Arsintescu L, Whitmire A, Leveton L, Vessey W (2015) Risk of performance decrements and adverse health outcomes resulting from sleep loss, circadian desynchronization, and work overload, NASA. Johnson Space Center, Houston

Fischer S, Hallschmid M, Elsner AL, Born J (2022) Sleep forms memory for finger skills. Proc Natl Acad Sci USA 99:11987–11991

Genzel L, Robertson EM (2015) To replay, perchance to consolidate. PLoS Biol 13(10):e1002285

Hart ML, Blackwell AA, Whishaw IQ, Wallace DG, Cheatwood JL (2022) Use of string-pulling as a behavioral measure of skilled hand motor function in a middle cerebral artery occlusion model in rats. Biorxv

Hakim F, Wang Y, Zhang SXL, Zheng J, Yolcu ES, Carreras A, Khalyfa A, Shirwan H, Almendros I, Gozal D (2014) Fragmented sleep accelerates tumor growth and progression through recruitment of tumor-associated macrophages and TLR4 signaling. Cancer Res 74:1329–1337

Heitz RP (2014) The speed-accuracy tradeoff: history, physiology, methodology, and behavior. Front Neurosci 8:150

Huff JL, Poignant F, Rahmanian S, Khan N, Blakely EA, Britten RA, Chang P, Fornace AJ, Hada M, Kronenberg A, Norman RB, Patel ZS, Shay JW, Weil MM, Simonsen LC, Slaba TC (2022) Galactic cosmic ray simulation at the NASA space radiation laboratory—progress, challenges and recommendations on mixed-field effects. Life Sci Space Res. https://doi.org/10.1016/j.lssr.2022.09.001

Hyland BI, Seeger-Armbruster S, Smither RA, Parr-Brownlie LC (2019) Altered recruitment of motor cortex neuronal activity during the grasping phase of skilled reaching in a chronic rat model of unilateral parkinsonism. J Neurosci 39:9660–9672

Jacobs IF, Osvath M (2015) The string-pulling paradigm in comparative psychology. J Comp Psychol 129(2):89–120. https://doi.org/10.1037/a0038746

Joseph JA, Hunt WA, Rabin BM, Dalton TK (1992) Possible "accelerated striatal aging" induced by ^{56}Fe heavy-particle irradiation: Implications for manned space flights. Radiat Res 130:88–93

Joseph J, Erat S, Rabin B (1998) CNS effects of heavy particle irradiation in space: behavioral implications. Adv Space Res 22(2):209–216

Klein PM, Parihar VK, Szabo GG, Zöldi M, Angulo MC, Allen BD, Amin AN, Nguyen QA, Katona I, Baulch JE, Limoli CL, Soltesz I (2021) Detrimental impacts of mixed-ion radiation on nervous system function. Neurobiol Dis 151:105252

Krukowski K, Grue K, Becker M, Elizarraras E, Frias ES, Halvorsen A, Koenig-Zanoff M, Frattini V, Nimmagadda H, Feng X, Jones T, Nelson G, Ferguson AR, Rosi S (2021) The impact of deep space radiation on cognitive performance: From biological sex to biomarkers to countermeasures. Sci Adv 7(42):eabg6702

Kuriyama K, Stickgold R, Walker MP (2004) Sleep-dependent learning and motor-skill complexity. Learn Mem 11:705–713

La Tessa C, Sivertz M, Chiang I-H, Lowenstein D, Rusek A (2016) Overview of the NASA space radiation laboratory. Life Sci Space Res (amst) 11:18–23

Landry S, Anderson C, Andrewartha P, Sasse A, Conduit R (2014) The impact of obstructive sleep apnea on motor skill acquisition and consolidation. J Clin Sleep Med 10(5):491–496

Lemke SM, Ramanathan DS, Darevksy D, Egert D, Berke JD, Ganguly K (2021) Coupling between motor cortex and striatum increases during sleep over long-term skill learning. Elife 10:e64303

Li Y, Zhang H, Mao W, Liu X, Hao S, Zhou Y, Ma J, Gu Z, Chan P (2019) Visual dysfunction in patients with idiopathic rapid eye movement sleep behavior disorder. Neurosci Lett 709:134360

Mathis A, Mamidanna P, Cury KM, Abe T, Murthy VN, Mathis MW, Bethge M (2018) DeepLabCut: markerless pose estimation of user-defined body parts with deep learning. Nat Neurosci 21(9):1281–1289

McCoy JG, Tartar JL, Bebis AC, Ward CP, McKenna JT, Baxter MG et al (2007) Experimental sleep fragmentation impairs attentional set-shifting in rats. Sleep 30:52–60

Nair D, Zhang SX, Ramesh V, Hakim F, Kaushal N, Wang Y et al (2011) Sleep fragmentation induces cognitive deficits via nicotinamide adenine dinucleotide phosphate oxidase-dependent pathways in mouse. Am J Respir Crit Care Med 184:1305–1312

Pandi-Perumal SR, Gonfalone AA (2016) Sleep in space as a new medical frontier: the challenge of preserving normal sleep in the abnormal environment of space missions. Sleep Sci 9(1):1–4

Pecaut MJ et al (2004) The effects of low-dose, high-LET radiation exposure on three models of behavior in C57BL/6 mice. Radiat Res 162(2):148–156

Peever J, Fuller PM (2016) Neuroscience: a distributed neural network controls REM sleep. Curr Biol CB 26(1):R34–R35

Penhune VB, Doyon J (2002) Dynamic cortical and subcortical networks in learning and delayed recall of timed motor sequences. J Neurosci 22(4):1397–1406

Pettibone WD, Kam K, Chen RK, Varga AW (2019) Necessity of sleep for motor gist learning in mice. Front Neurosci 13:293

Philpott DE, Miquel J (1986) Long term effects of low doses of ^{56}Fe ions on the brain and retina of the mouse: ultrastructural and behavioral studies. Adv Space Res 6(11):233–242

Ramesh V, Nair D, Zhang SXL, Hakim F, Kaushal N, Kayali F, Wang Y, Li RC, Carreras A, Gozal D (2012) Disrupted sleep without sleep curtailment induces sleepiness and cognitive dysfunction via the tumor necrosis factor-alpha pathway. J Neuroinflam 9:91

Rosenthal L, Roehrs T, Sicklesteel J, Zorick F, Wittig R, Roth T (1984) Periodic leg movements during sleep. Sleep 7:326–330

Rosi S (2018) The final frontier: Transient microglia reduction after cosmic radiation exposure mitigates cognitive impairments and modulates phagocytic activity. Brain Circ 4(3):109–113

Roth T, Hartse KM, Zorick F, Conway W (1980) Multiple naps and the evaluation of daytime sleepiness in patients with upper airway sleep apnea. Sleep 3:425–439

Rubin DB, Hosman T, Kelemen JN, Kapitonava A, Willett FR, Coughlin BF, Halgren E, Kimchi EY, Williams ZM, Simeral JD, Hochberg LR, Cash SS (2022) Learned motor patterns are replayed in human motor cortex during sleep. J Neurosci 42(25):5007–5020. https://doi.org/10.1523/JNEUROSCI.2074-21.2022

Saadat A, Blackwell AA, Kazowski C, Pallera H, Owens D, Lattanzio F, Tushar S (2022) Therapeutic hypothermia demonstrates

sex-dependent improvement in motor function in a rat model of neonatal hypoxicischemic encephalopathy. Exp Brain Res

Simonsen LC, Slaba TC, Guida PM, Rusek A (2019) 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

Singh S, Mandziak A, Barr K, Blackwell AA, Mohajerani MH, Wallace DG, Whishaw IQ (2019) Reach and grasp altered in pantomime string-pulling: A test of the action/perception theory in a bilateral reaching task. Exp Brain Res 237:3431–3447

Slaba TC, Blattnig SR, Norbury JW, Rusek A, La Tessa C (2016) Reference field specification and preliminary beam selection strategy for accelerator-based GCR simulation. Life Sci Space Res 8:52–67

Stepanski EJ (2002) The effect of sleep fragmentation on daytime function. Sleep 25(3):268–276

Stepanski E, Lamphere J, Badia P, Zorick F, Roth T (1984) Sleep fragmentation and daytime sleepiness. Sleep 7:18–26

Stickgold R, Hobson JA (1999) REM sleep and sleep efficiency are reduced during space flight. Sleep 22(Suppl):S82

Stojanoski B, Benoit A, Van Den Berg N, Ray LB, Owen AM, Shahidi Zandi A, Quddus A, Comeau FJE, Fogel SM (2018) Sustained vigilance is negatively impacted by mild and acute sleep loss reflected by reduced capacity for decision making, motor preparation and execution. Sleep. https://doi.org/10.1093/sleep/zsy200

Suman S, Rodriguez OC, Winters TA, Fornace AJ Jr, Albanese C, Datta K (2013) Therapeutic and space radiation exposure of mouse brain causes impaired DNA repair response and premature senescence by chronic oxidant production. Aging (Albany NY) 5:607–622

Ton ST, Laghi JR, Tsai SY, Blackwell AA, Adamczyk NS, Osterlund Oltmanns JR, Britten RA, Wallace DG, Kartje GL (2022) Exposure to 5 cGy 28Si particles induces long-term microglial activation in the striatum and subventricular zone and concomitant neurogenic suppression. Radiat Res 198(1):28–39

Varga AW, Kang M, Ramesh PV, Klann E (2014) Effects of acute sleep deprivation on motor and reversal learning in mice. Neurobiol Learn Mem 114:217–222

Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R (2022) Practice with sleep makes perfect: sleep-dependent motor skill learning. Neuron 35:205–211

Wang H, Yu K, Yang T, Zeng L, Li J, Dai C, Peng Z, Shao Y, Fu W, Qi J (2021) Altered functional connectivity in the resting state neostriatum after complete sleep deprivation: impairment of motor control and regulatory network. Front Neurosci 15:665687

Wessa P (2022) Free Statistics Software, Office for Research Development and Education, version 1.2.1. https://www.wessa.net/

Whishaw IQ, O'Connor WT, Dunnett SB (1986) The contributions of motor cortex, nigrostriatal dopamine and caudate-putamen to skilled forelimb use in the rat. Brain 109:805–843

Whitmire A, Slack K, Locke J, Keeton K, Patterson H, Faulk J, Leveton L (2013) Sleep quality questionnaire short-duration flyers. National Aeronautics and Space Administration, Washington, DC

Whooley CW et al (2017) Whole-body exposure to 28Si-radiation dose-dependently disrupts dentate gyrus neurogenesis and proliferation in the short term and new neuron survival and contextual fear conditioning in the long term. Radiat Res 188(5):612–631

Wilson GF, Caldwell JA, Russell CA (2007) Performance and psychophysiological measures of fatigue effects on aviation related tasks of varying difficulty. Int J Aviat Psychol 17(2):219–247

Yang G, Lai CS, Cichon J, Ma L, Li W, Gan WB et al (2014) Sleep promotes branch-specific formation of dendritic spines after learning. Science 344:1173–1178