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The degree of radiation-induced DNA strand breaks is altered by acute sleep deprivation and psychological stress and is associated with cognitive performance in humans FREE

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Abstract

Study Objectives

Sleep deprivation is associated with impaired immune responses, cancer, and morbidity and mortality, and can degrade cognitive performance, although individual differences exist in such responses. Sleep deprivation induces DNA strand breaks and DNA base oxidation in animals, and psychological stress is associated with increased DNA damage in humans. It remains unknown whether sleep deprivation or psychological stress in humans affects DNA damage response from environmental stressors, and whether these responses predict cognitive performance during sleep deprivation.

Methods

Sixteen healthy adults (ages 29–52 years; mean age ± *SD*, 36.4 ± 7.1 years; seven women) participated in a 5-day experiment involving two 8 hr time-in-bed (TIB) baseline nights, followed by 39 hr total sleep deprivation (TSD), and two 8–10 hr TIB recovery nights. A modified Trier Social Stress Test was conducted on the day after TSD. The Psychomotor Vigilance Test measured behavioral attention. DNA damage was assessed in blood cells collected at 5 time points, and blood cells were irradiated ex vivo.

Results

TSD, alone or in combination with psychological stress, did not induce significant increases in DNA damage. By contrast, radiation-induced DNA damage decreased significantly in response to TSD, but increased back to baseline when combined with psychological stress. Cognitively vulnerable individuals had more radiation-induced DNA strand breaks before TSD, indicating their greater sensitivity to DNA damage from environmental stressors.

Conclusions

Our results provide novel insights into the molecular consequences of sleep deprivation, psychological stress, and performance vulnerability. They are important for fields involving sleep loss, radiation exposure, and cognitive deficits, including cancer therapy, environmental toxicology, and space medicine.

DNA strand breaks, Psychomotor Vigilance Test performance, sleep deprivation, psychological stress, individual differences, biomarkers, radiation, Trier Social Stress Test

Statement of Significance

Although sleep loss, by itself or in combination with psychological stress, does not increase DNA damage in human blood cells, DNA strand break levels from ex vivo cell irradiation are lower than baseline when participants are sleep deprived, and increase back to baseline levels when participants are sleep deprived and psychologically stressed. The level of radiation-induced DNA strand breaks is higher in the cells of individuals who are cognitively vulnerable to sleep loss, indicating that they are more sensitive to cellular DNA damage from environmental stressors. These results provide novel insights into the molecular processes induced by sleep deprivation, psychological stress, and cognitive performance deficits, and are significant for identifying biomarkers to predict vulnerability to sleep deprivation and for developing effective countermeasures.

Introduction

Chronic sleep deprivation is a significant public health issue and is associated with an increased risk of cardiovascular disease, obesity, diabetes, cancer, and overall morbidity and mortality [1–7]. For most individuals, sleep loss increases fatigue, sleepiness, and sleep propensity, and produces marked deficits in mood and neurobehavioral functions including decreases in sustained attention, cognitive processing speed, working memory, and executive functioning [8–11]. However, large, highly replicable, phenotypic individual differences occur in the magnitude of neurobehavioral vulnerability to sleep deprivation [12], whereby some individuals are vulnerable and others are resistant to sleep deprivation [13, 14]; notably, this phenotypic stability is maintained across months and years [15]. The underlying reasons for such differential neurobehavioral vulnerability to sleep loss are largely unknown and are not reliably explained by demographic and other factors [16]. Candidate gene and various "omics" approaches have been used to identify biomarkers that may relate to such responses [12], although more work is needed, including investigation of molecular mechanisms such as DNA strand break formation.

Single strand DNA breaks are the most frequent type of DNA damage but they are normally rapidly repaired. However, unrepaired single strand DNA breaks can be converted into double strand DNA breaks that could result in chromosome rearrangements and instability [17], and this process may drive cancer development. Reactive free radicals formed during normal aerobic metabolism (causing endogenous DNA strand breaks, ESB) and water radiolysis induced by ionizing radiation (causing induced DNA strand breaks, ISB) are major contributors to the formation of single strand DNA breaks. Sleep loss has been shown to affect DNA integrity. In rats, sleep loss, especially acute total sleep deprivation (TSD), induces DNA strand breaks in both blood and brain cells [18, 19]. Furthermore, the level of 8-Oxoguanine (8-oxoG), a marker for oxidative DNA damage, also increases in rats who are partially sleep deprived [20]. In mice, sleep deprivation induces DNA double strand breaks and delays DNA repair [21]. However, in humans, partial sleep deprivation increases expression of genes involved in the DNA damage response [22].

Psychological stress contributes to cancer development, and increased DNA damage from exposure to stress and stress hormones has been suggested as the possible mechanism [23–25]. A number of studies in animals and humans have shown a relationship between acute stressors and DNA damage. For example, students had more oxidative DNA damage in their lymphocytes when they were undergoing psychological stress induced by examinations than they did during a nonstress period [26]. Clinical studies have also demonstrated that some psychiatric disorders are associated with DNA damage [27]; for example, patients with recurrent depression had more single and double strand DNA breaks and impaired DNA repair compared with healthy controls [28]. Similarly, patients with posttraumatic stress disorder had more DNA strand breaks in their immune cells than a nonstressed matched control group [29]. In addition, greater DNA damage was found in the prefrontal cortex and hippocampus of rats subjected to stress than in control rats [30]. Furthermore, alteration of stress-induced DNA damage response renders cells more vulnerable to environmental stressors such as radiation. For instance, after lymphocytes were irradiated with 0.8, 2.5, and 4.2 Gy γ-rays, immediate DNA damage and residual DNA damage, measured 2 hr after radiation, were both significantly higher in lymphocytes from chronically stressed individuals than in lymphocytes from a nonstressed population [31]. Psychological factors such as depressed mood or certain personality traits can also influence the yield of radiation-induced DNA damage [32].

Thus, both sleep deprivation and psychological stress can affect DNA damage response, leading to changes in radiosensitivity. Although the effects of sleep deprivation and psychological stress on cellular functions and DNA have been investigated, previous research is mostly limited to animal models. To the best of our knowledge, no one has reported the effects of acute sleep deprivation or a combination of sleep deprivation and psychological stress on endogenous DNA strand breaks or radiosensitivity in humans. Given that sleep deprivation amplifies the biological and physiological responses to psychological stress including increasing cortisol, systolic blood pressure, heart rate, and skin conductance [33–36], it is possible that the combination of sleep loss and psychological stress may increase the number of endogenous or radiation-induced DNA strand breaks. In this study, we determined whether sleep loss, alone or in combination with psychological stress, affects DNA integrity and/or the level of radiation-

induced DNA damage in peripheral blood cells from healthy individuals.

Furthermore, in patients with mild cognitive impairment and/or Alzheimer's disease, the loss of general cognitive and functional abilities has been associated with higher DNA damage and poorer DNA repair [37, 38]. In addition, a recent exploratory study reported that genetic variation in the oxidative stress and DNA repair pathways plays an important role in cognitive performance in women with breast cancer prior to initiation of adjuvant therapy, suggesting that oxidative stress and DNA repair genetic polymorphisms are predictors of poorer cognitive function in breast cancer survivors [39]. Therefore, we also determined whether the baseline level of DNA strand breaks and/or the amount of radiation-induced DNA strand breaks in these individuals could predict cognitive performance after sleep deprivation.

Methods

Participants

The Human Research Program Human Exploration Research Analog (HERA) is a high-fidelity space analog isolation facility located in Johnson Space Center in Houston, TX. We studied 16 healthy men and women (ages 29–52 years; mean age ± *SD*, 36.4 ± 7.1 years; 7 women, 13 Caucasians, 1 Hispanic, 1 Asian, and 1 African American). Groups of four volunteers participated in each of the four HERA 30-day missions. These participants were thoroughly screened by the National Aeronautics and Space Administration (NASA), were required to pass drug screening and a physical exam, and were in good health with no history of cardiovascular, neurological, gastrointestinal, or musculoskeletal problems. The study was approved by the Institutional Review Boards of NASA and of the University of Pennsylvania, and all protocol methods were carried out in accordance with approved guidelines and regulations. Participants provided written informed consent, which was in accordance with the Declaration of Helsinki. Participants received compensation for their participation in the protocol.

Procedures

During the 30 days of confinement in HERA, volunteers participated in a 5-day experiment designed to create stress and induce sleep deprivation, and to measure cognitive performance. This experiment consisted of two baseline nights (B1 and B2; 8 hr time-in-bed [TIB], 2300–0700 hr), followed by a night of acute TSD during which participants remained awake all night. A modified Trier Social Stress Test (TSST) was conducted between 1500 and 1730 hr on the day after the TSD night to induce psychosocial stress (described below). The TSD night was followed by a 10 hr TIB night of recovery (R1; 2200–0800 hr), and a second 8 hr TIB night of recovery (R2; 2300–0700 hr). Napping was prohibited during the experiment. Sleep–wake episodes were verified by wrist actigraphy (Philips Respironics Healthcare, Bend, OR).

Cognitive performance

Each participant completed a total of 11 cognitive testing sessions during the study. Testing sessions occurred at 1130 and 1730 hr each day of the experiment, with an additional test at 0400 hr after TSD. The cognitive sessions included an objective behavioral attention test measuring reaction time, the 10-min Psychomotor Vigilance Test (PVT) [40, 41].

Trier social stress test

The TSST is a commonly used validated test to experimentally induce psychosocial stress [42–44]. It has been successfully modified and validated using a virtual, rather than a physical, audience [45, 46]. The TSST has been shown to affect a range of biological markers of stress, including cortisol, heart rate, blood pressure, and blood catecholamines [42, 44, 47–49]. Our 30-min TSST consisted of a number of challenging interview questions regarding responses to TSD, including those relating to performance, motivation, aptitude, and interactions with others. The TSST also had several difficult cognitive tests demanding both accuracy and speed, including a 3-min Stroop task and a 5-min calculation task requiring participants to count backwards aloud in 13-step sequences. The TSST was conducted with participants remotely via audio and a one-way video camera.

Blood samples for DNA strand breaks

ESB and ISB were measured in DNA from blood samples that were collected from each participant at the following six time points: (1) immediately before the HERA mission (prestudy); (2) during the experiment after two nights of fully rested conditions (baseline); (3) on the day after a night of TSD and before stress was induced (TSD [AM]); (4) on the day after TSD and immediately after stress was induced (TSD [PM]); (5) after two

nights of fully rested conditions (recovery); and (6) 5 days after the study (poststudy). Blood was drawn at the same time each day (0800 hr before eating), except for the poststress assessment, which was drawn at 1730 hr.

Blood collection and peripheral blood mononuclear cell storage

Human peripheral blood mononuclear cells (PBMCs) were isolated from 4 mL of whole blood that was collected in BD Vacutainer CPT Mononuclear Cell Preparation Tubes (BD Biosciences, USA). Isolated cells were suspended in 1 mL of freezing medium containing 20 per cent Roswell Park Memorial Institute medium (RPMI-1640) medium, 10 per cent dimethyl sulfoxide (DMSO), and 70 per cent fetal calf serum (FCS), and stored overnight at −80°C in a Mr. Frosty Freezing Container (Thermo Fisher Scientific, USA). The cells were then transferred to a liquid nitrogen tank at −180°C until they were shipped overnight on dry ice to Konstanz, Germany. In Konstanz, the cells were kept in a liquid nitrogen tank at −180°C until they were analyzed.

Cell thawing procedure

The cells were thawed using the same procedure described previously [50]. Briefly, the cryovial containing the cells was carefully immersed in a water bath at 37°C until a small amount of ice remained in the cryovial. Next, 1 mL of thawing medium containing 90 per cent RPMI and 10 per cent FCS was added to the cryovial and gently mixed; after 1 min the cell suspension was transferred into a polypropylene 15 mL tube. The thawing medium was added stepwise as follows: 1 mL was added 1 min later, an additional 2 mL was added another 1 min later, and an additional 4 mL was added after another minute. After an additional minute, the tube was centrifuged at 300 × *g* for 10 min. The cell pellet was gently resuspended in 1 mL RPMI medium, and the cell concentration and viability (determined by electric current exclusion) were assessed using CASY cell counter technology (Innovatis, Switzerland).

Induction of DNA strand breaks

Cells (0.5–1 × 10^6/mL) in suspension buffer (0.25 M meso-inositol; 10 mM sodium phosphate, pH 7.4; 1 mM magnesium chloride) were irradiated (Biological X-ray Irradiator X-RAD 225 iX from Precision X-Ray, Inc., North Branford, USA) on ice for 380 s at a dose rate of 0.59 Gy/min (70 kV, 30 mA, 70 cm distance, 1.25mm Al filter) resulting in a total dose of 3.73 Gy. After radiation, cells were placed in the pipetting robot to assess DNA strand breaks.

Detection of DNA strand breaks

DNA strand breaks were detected using the automated version of the "Fluorimetric detection of Alkaline DNA Unwinding" (FADU) assay [51, 52], which has been successfully used in a number of prior studies [29, 53–64]. This assay is based on controlled DNA unwinding that starts at DNA strand breaks. SybrGreen (MoBiTec, Germany) was used as the marker for double stranded DNA. A decrease in the fluorescence intensity indicates an increase of DNA unwinding and consequently a greater number of strand breaks. The fluorescence signal was expressed as a measure of radiation dose (Gy-equivalent) using a published mathematical transformation [65].

Statistical analyses

The poststudy time point was not included in any statistical analyses because one participant's blood sample was not collected at this time point, and the cell viability after thawing was compromised for 7 of the 15 remaining participants. Mixed-model regression analysis was used to estimate the change in means of endogenous and induced DNA strand breaks (expressed as an equivalent radiation dose in Gy-equivalent) between each time point and prestudy to account for the repeated-measures design. After estimation, analysis of variance (ANOVA)-based approximate degrees of freedom were used to construct 95% confidence limits (CLs) for all changes from the prestudy values.

Repeated measures ANOVA, using multivariate models, with resistant/vulnerable cognitive performance as a between-participants factor was used to assess ESB and ISB measures across the five time points. Cognitively resistant ($n = 8$) and cognitively vulnerable ($n = 8$) groups were defined by a median split on TSD 10-min PVT performance [66], defined by total lapses (>500 ms response time) and errors performance (range: 1.33–33.33 PVT lapses and errors; mean ± *SD*, resistant: 3.63 ± 2.15 PVT lapses and errors; vulnerable: 12.00 ± 8.71 PVT lapses and errors); these groups were not significantly different in terms of sex or age ($p > .05$). After ANOVAs, post hoc comparisons corrected for multiple testing were used to assess differences in ESB and ISB measures for the cognitively resistant versus cognitively vulnerable groups at each time point. Repeated measures ANOVA examined sleep variables across nights, and examined cognitive performance across the baseline, TSD, and recovery assessments.

Results

Cognitive performance

After sleep loss, participants had significantly more PVT lapses and errors (mean ± *SD*, 7.81 ± 7.50) than during their baseline PVT performance (mean ± *SD*, 3.81 ± 6.47; $t(15) = -4.92$, $p < .001$). PVT performance returned to baseline levels after one night of recovery sleep (mean ± *SD*, 4.31 ± 8.99 lapses and errors; $p > .05$).

Actigraphic sleep–wake

Participants were highly compliant to the sleep–wake schedule, as indicated by total sleep time (TST) during the experiment (Table 1). TST and other sleep variables, including sleep onset latency, sleep efficiency, and wake after sleep onset, were not significantly different on the B2 and R2 nights, the nights before the baseline and the recovery blood draws, respectively ($p > .05$; Table 1). No significant differences were found between the cognitively resistant and cognitively vulnerable groups for TST or any other sleep variables on any of the experiment nights ($p > .05$), and sex or age had no significant effect on any sleep variables.

Table 1.

Mean ± *SD* actigraphic sleep measures for the five experimental nights (*N* = 16 participants)

Study night	Sleep onset latency (min)	Sleep efficiency (%)	Wake after sleep onset (min)	Wake time (%)	Sleep time (%)	Total sleep time (min)
Night 1 (B1)	16.38 ± 23.50	87.49 ± 6.76	32.75 ± 13.91	7.48 ± 3.25	92.52 ± 3.25	407.00 ± 37.46
Night 2 (B2)	13.31 ± 34.19	87.77 ± 8.39	34.88 ± 19.98	8.03 ± 4.46	91.97 ± 4.46	402.88 ± 40.72
Night 3 (TSD)	N/A	N/A	N/A	N/A	N/A	N/A
Night 4 (R1)	1.19 ± 2.07	91.19 ± 6.36	44.81 ± 38.00	7.52 ± 6.16	92.48 ± 6.16	546.31 ± 33.38
Night 5 (R2)	10.88 ± 9.61	83.99 ± 9.46	53.94 ± 46.57	11.95 ± 10.02	88.05 ± 10.02	393.88 ± 48.39

B1 = Baseline night 1; B2 = Baseline night 2; TSD = Total sleep deprivation; R1 = Recovery night 1; R2 = Recovery night 2; N/A = Not applicable.

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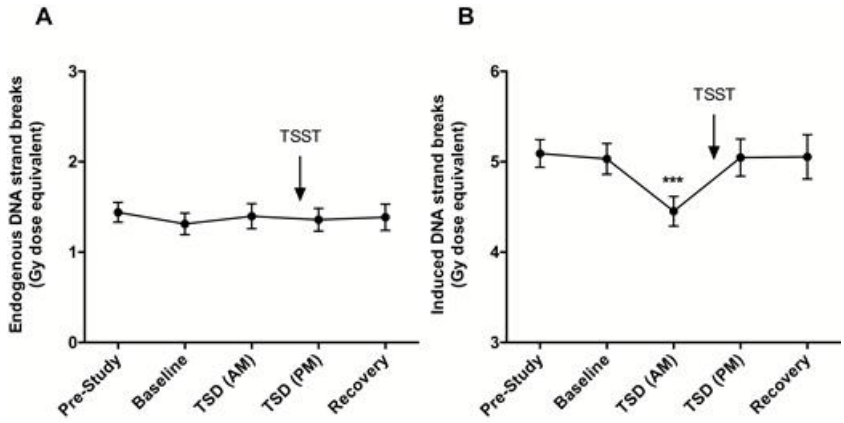
Endogenous and radiation-induced DNA strand breaks

In our study, no significant differences were found for the level of endogenous DNA strand breaks for any of the time points, including those that involved the sleep loss and psychological stress conditions (Figure 1A; $p > .05$). Before exposure to radiation, the average of DNA strand breaks for all participants for the five time points studied was 1.38 ± 0.09 (SEM) in units equivalent to radiation dose in Gy (Figure 1A). After ex vivo exposure of 3.73 Gy of x-rays, the corresponding DNA strand breaks increased to an average of 4.94 ± 0.16 (SEM). The difference of 4.94 − 1.38 = 3.56 agrees well with the dose of 3.73 Gy as predicted by the Gy-equivalent dose model [65] (Figure 1B). However, there was a significant effect of time point on the degree to which radiation-induced DNA strand breaks ($F(4, 60) = 5.81$; $p < .001$). In particular, we found that radiation induced significantly fewer DNA strand breaks in the blood collected the morning after sleep loss (TSD [AM]), (estimated change compared with prestudy = −0.64, 95% CL = (−0.96, −0.32) in equivalent units of dose in Gy) ($t(60) = -4.02$; post-hoc Bonferroni-corrected, $p < .001$). After the TSST, average radiation–induced DNA strand breaks measured at TSD (PM) were greater than at TSD (AM) and did not differ significantly from the level of ISBs detected prestudy (Figure 1B). Sex and age did not significantly affect these data.

Figure 1.



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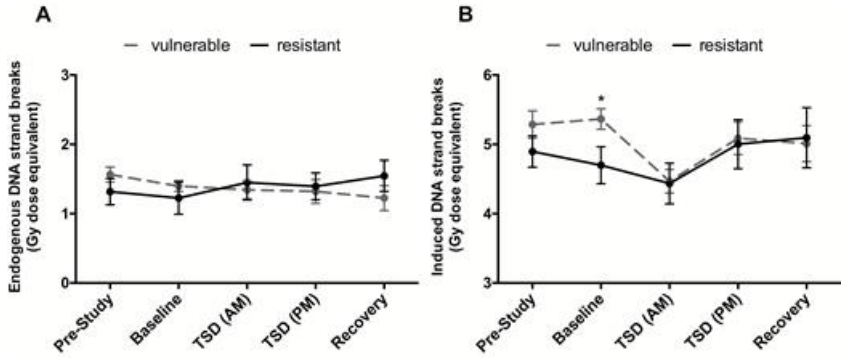
Mean ± SEM DNA strand breaks for $N = 16$ participants undergoing total sleep deprivation and psychological stress. DNA strand breaks were quantified at prestudy, baseline, total sleep deprivation in the morning (TSD [AM]), total sleep deprivation after psychological stress (TSD [PM]), and recovery. TSST indicates the time when induced psychological stress via a modified Trier Social Stress Test (TSST) occurred. **(A)** Levels of endogenous DNA strand breaks did not change at different time points and were unaffected by sleep deprivation and/or psychological stress. **(B)** By contrast, levels of radiation-induced DNA strand breaks significantly decreased after TSD (AM) ($t(60) = -4.02$; post-hoc Bonferroni-corrected, $^{***}p < .001$). After TSST, levels of radiation-induced DNA strand breaks increased compared with TSD (AM) but did not differ significantly from the level of ISBs detected prestudy.

Endogenous and radiation-induced DNA strand breaks in cognitively vulnerable and cognitively resistant individuals

No significant time point × group interactions or group differences were detected in ESBs for the cognitively vulnerable and cognitively resistant groups (Figure 2A; $p > .05$). In addition, the cognitively vulnerable and cognitively resistant groups did not differ significantly for ESBs at any individual time point ($p > .05$).

Figure 2.



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Mean ± SEM DNA strand breaks for $N = 16$ participants undergoing total sleep deprivation and psychological stress, separated into cognitively vulnerable ($n = 8$) and cognitively resistant ($n = 8$) individuals. DNA strand breaks were quantified at prestudy, baseline, total sleep deprivation in the morning (TSD [AM]), total sleep deprivation after psychological stress (TSD [PM]), and recovery. **(A)** There were no significant time point × group interactions or group differences in ESBs between the cognitively vulnerable and cognitively resistant performance groups. **(B)** There was an overall significant time point × group interaction between the cognitively vulnerable and cognitively resistant performance groups ($F(4, 11) = 3.78$; $p < .05$). In addition, sleep-deprived cognitively vulnerable individuals were more affected by radiation than sleep-deprived cognitively resistant individuals, evidenced by significantly more radiation-induced DNA strand breaks at baseline before TSD ($F(1, 14) = 4.76$; $^{*}p < .05$).

For ISBs, there was an overall significant time point × group interaction between the cognitively vulnerable and cognitively resistant performance groups ($F(4, 11) = 3.78$; $p < .05$; Figure 2B). In addition, ISB values were significantly higher in the cognitively vulnerable group at baseline than they were in the cognitively resistant group ($F(1, 14) = 4.76$; $p < .05$; Figure 2B). No other significant time point × group interactions or group differences

between the cognitively vulnerable and cognitively resistant performance groups were detected for ISBs ($p > .05$; Figure 2B).

Discussion

Previous studies have reported an association between sleep loss and stress, and DNA damage and/or DNA repair. We determined whether acute sleep deprivation and/or psychosocial stress induced by the TSST affected endogenous DNA strand breaks and/or radiation-induced DNA strand breaks, and whether DNA strand breaks predict cognitive performance during sleep deprivation. We found that endogenous DNA strand breaks did not change with time, and levels were not affected by TSD or psychological stress. By contrast, radiation-induced DNA strand breaks decreased after TSD but increased back to baseline following psychological stress. Furthermore, based on PVT performance, cognitively vulnerable individuals were more sensitive than cognitively resistant individuals to induction of radiation strand breaks at baseline, but levels of DNA strand breaks were the same for these two groups after sleep deprivation.

Our findings regarding radiation-induced DNA damage are intriguing and unexpected. The levels of radiation-induced DNA strand breaks at prestudy and baseline were in accordance with the expected DNA strand break levels induced when applying 3.73 Gy of x-ray. Interestingly, radiation induced fewer DNA strand breaks after sleep deprivation suggesting that sleep loss causally decreased radiosensitivity. The level of radiosensitivity could depend on the following: (1) DNA repair activity, (2) cell chromatin status, (3) cell cycle status, (4) cell antioxidant status, or (5) cell type. Since cells were irradiated on ice and lysed and analyzed immediately after, any influence of DNA repair mechanisms is unlikely. Cells with relaxed chromatin and cells in the S phase of the cell cycle are more, not less, sensitive to radiation [67, 68]; therefore, cell cycle status can be excluded. Radiation induces the formation of reactive oxidative species (ROS) through water radiolysis. Since antioxidants are radical scavengers, increased antioxidant capacity reduces the radiation-induced DNA damage [69]. Interestingly, acute TSD increases antioxidant responses such as increased glutathione peroxidase (GPx) activity in rats [70]. Furthermore, sleep-deprived mice had higher expression levels of the manganese superoxide dismutase (MnSOD) gene and significantly increased copper-zinc-superoxide dismutase (CuZnSOD) and MnSOD activity compared to a control group [71]. A recent meta-analysis in animals concluded that sleep deprivation has an important antioxidant function, although further studies are needed [72].

Notably, sensitivity to radiation also depends on cell type. In this study, we analyzed DNA strand breaks in PBMCs, a mixed blood cell population including lymphocytes (T cells, B cells, and NK cells), monocytes, and dendritic cells. Sleep deprivation affects blood cell distribution, changing the percentage of different subpopulations [73] such as granulocytes [74], neutrophils [75], and NK cells [76–78]. Additionally, different types of immune cells (T cells and B cells) from mouse splenocytes have different radiosensitivity [79]. A comprehensive review summarized the current knowledge of radiosensitivity of immune cells and concluded that stem cells, T helper cells, cytotoxic T cells, monocytes, neutrophils, and B cells are more radiosensitive, whereas regulatory T cells, macrophages, dendritic cells, and natural killer cells appear to be more radioresistant [80]. Therefore, a sleep-loss-induced shift in the cell subpopulations within the PBMCs could affect the average levels of DNA strand breaks detected after radiation. However, sleep deprivation mostly affects granulocytes, natural killer cells, and monocytes [73–78]. Of these, granulocytes are not mononucleated cells. Natural killer cells, which are more radioresistant, are decreased after sleep deprivation. By contrast, monocytes, which are more radiosensitive, are increased after sleep deprivation, which would result in a higher level of DNA strand breaks. Thus, a shift in the cell subpopulation as an explanation for the lower level of DNA strand breaks observed is unlikely, although further studies are required to determine the extent to which the DNA strand break effects may be due to a change in certain mononuclear cell subpopulations.

By contrast, acute TSD did not influence the level of endogenous DNA strand breaks in our cohort. Several rat studies reported that sleep deprivation affects DNA damage [18–20]. This human-rodent discrepancy could be due to the species, the type of analyzed tissue, and/or the duration and type of sleep deprivation. For example, 6 hr of acute sleep restriction was associated with DNA damage in brain cells but not in peripheral blood cells [19]. Furthermore, another study showed DNA damage in blood and brain cells of rats who were submitted to a long duration of selective sleep stage deprivation (paradoxical sleep deprivation for 96 hr) [18].

Similarly, in our study, psychological stress induced by the TSST also did not affect the level of endogenous DNA strand breaks. This finding was unexpected given there are several studies indicating higher DNA damage in stressed individuals. However, only a few studies have been conducted in healthy populations, and individuals in those studies were exposed to prolonged stress, including students experiencing stress during examination periods [26]. This suggests that increased endogenous DNA damage may be related to psychiatric disorders or chronic psychological stress rather than to acute short-term stress in healthy individuals. Indeed, the effect of chronic, subchronic, and acute restraint stress on DNA damage response has been investigated in the rat brain. Although the expression of genes involved in DNA repair differed depending on the level of stress, endogenous DNA damage was not affected by stress [30].

Interestingly, the average levels of radiation-induced DNA strand breaks measured after inducing stress at TSD (PM) were higher than those measured that morning after sleep deprivation but before the TSST. This finding could be explained by a decreased antioxidative capacity of the cells

after stress. Indeed, there are indications of reduced antioxidative capacity after acute psychological stress, although this seems to depend on the stressor, antioxidative enzymes, and tissue type [81, 82]. Since the participants did not sleep during the 9.5 hr between the TSD (AM) and TSD (PM) time points, the mechanisms underlying the observed increased radiosensitivity after psychological stress are not due to processes related to sleep. However, given emerging evidence for circadian rhythmicity of the cellular antioxidant system [83], DNA repair capacity, cell cycle checkpoints, and apoptosis [84], a time-of-day effect cannot be excluded. For example, splenocytes isolated from mice during the light phase displayed higher DNA repair activity than those isolated during the dark phase [64], and activity levels of 8-Oxoguanine DNA glycosylase (OGG1), which removes oxidative DNA damage, were higher in the morning compared with the evening, and consistently, 8-oxoG levels were lower in the morning than in the evening in humans [85]. In addition, the sensitivity to radiation-induced apoptosis changes throughout the day in cells of small intestinal crypts in mice [86]. However, time-of-day effects on cellular antioxidative and DNA repair capacity are beyond the scope or design of this study, and further experiments are needed to investigate this issue.

We discovered robust individual differences in the molecular consequences of sleep deprivation and psychological stress. Before sleep loss, individuals who are cognitively resistant to sleep deprivation (defined by PVT performance) were more resistant to radiation than individuals who are cognitively compromised by sleep deprivation. Notably, rats also showed individual differences in performance on the validated rodent version of the PVT [87–90] in response to irradiation, with some rats showing performance resistance and others showing vulnerability [91]; the vulnerable rat group had changes in the levels of the dopamine transporter and the D2 receptor, implicating dopamine as a possible biological mechanism of action [91, 92]. Thus, heightened sensitivity to environmental stressors, including radiation, may make the vulnerable subgroup more susceptible to cognitive performance deficits after sleep loss. Thus, tests of sensitivity to radiation or other environmental stressors in a well-rested individual may provide a possible biomarker for predicting individual differences in performance after sleep loss.

Our study has the following limitations. Our participants were healthy, and between the ages of 29–52 years, and thus our results may not apply to other age groups (e.g. adolescents or the elderly), or to nonhealthy individuals. Although our sample size was 16 participants, we assessed biological and cognitive outcomes at multiple time points for each participant, and data were collected under highly controlled conditions, thus capitalizing on a within-participants design with reduced variance. In addition, our study design does not allow for the effects of psychological stress to be completely separated from the effects of TSD on radiosensitivity. Finally, our study was not designed to detect time-of-day effects on cellular antioxidative capacity but rather to focus on the role of sleep deprivation.

In our study, sleep deprivation, alone or in combination with psychological stress, did not significantly induce DNA damage. By contrast, sleep deprivation reduced radiation-induced DNA strand breaks, supporting the idea of an antioxidative function of sleep deprivation. Furthermore, an individual's level of radiosensitivity predicted his/her subsequent cognitive performance. Given that the consequences of sleep deprivation have been investigated in diverse human cohorts, including firefighters [93], astronauts [94, 95], nurses [96], students [97], and physicians [98], it is critical to identify molecular biomarkers to predict individual vulnerability to sleep deprivation and develop effective countermeasures.

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Notes

Conflict of interest statement. None declared.

Work Performed: Data collection was performed at the National Aeronautics and Space Administration, Johnson Space Center, Houston, TX 77058, USA. DNA strand breaks were measured at the Molecular Toxicology Group, Department of Biology, University of Konstanz, Konstanz 78457, Germany. Data analyses were conducted at the National Aeronautics and Space Administration, Johnson Space Center, Houston, TX 77058, USA and the Division of Sleep and Chronobiology, Department of Psychiatry, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA

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