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TITLE: Resilience to Sleep Loss and Stress:
A Framework for Investigation and Intervention

PRINCIPAL INVESTIGATOR: Hans P.A. Van Dongen, PhD

CONTRACTING ORGANIZATION: Washington State University, Pullman, WA

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14. ABSTRACT Sleep loss and acute stress often occur simultaneously during military operations, their combined effect on cognition – and therefore how to protect against any adverse effects – remain under-investigated. In this research project, we seek to develop a framework in which resilience to sleep loss and stress can be investigated separately and jointly. In a laboratory-based study, healthy young adults are assigned to one of four conditions: a sleep deprivation only condition, a stress only condition, a combined sleep deprivation and stress condition, or a control (no sleep deprivation or stress) condition. The subjects are tested on performance tasks specifically developed for this study twice: once while at well-rested baseline and without stress and again 24 hours later, after either 38 hours of sleep deprivation or equivalent well-rested control and stress or equivalent no stress control. By providing a framework for systematic investigation of the effect of sleep loss and stress on military operations, this research project will enable the development of targeted interventions that increase resilience against operational performance impairment. Further, this research project will help to improve the safety and success of millions of Americans, including US military personnel, who are frequently exposed to sleep loss and stress.					
15. SUBJECT TERMS sleep deprivation, stress, performance impairment, attentional control, cognitive flexibility, mission success, resilience					
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1. INTRODUCTION

Sleep loss and acute stress are common during military operations, resulting in impaired situational awareness and decision making. Performance deficits due to sleep loss are increasingly understood to be the result of changes in the ability to adjust attentional control in fast-paced, dynamically changing circumstances. In contrast, less is known about the effect of stress on cognition or its combined effect with sleep loss. Despite the fact sleep loss and stress often co-occur during military operations, their combined effect on cognition – and therefore how to protect against any adverse effects – remain under-investigated. In this research project, we seek to develop a framework in which resilience to sleep loss and stress can be investigated separately and jointly. In a laboratory-based study, healthy young adults are assigned to one of four conditions: a sleep deprivation only condition, a stress only condition, a combined sleep deprivation and stress condition, or a control (no sleep deprivation or stress) condition. The subjects are tested on performance tasks specifically developed for this study twice: once while at well-rested baseline and without stress and again 24 hours later, after either 38 hours of sleep deprivation or equivalent well-rested control and stress or equivalent no stress control. By providing a framework for systematic investigation of the effect of sleep loss and stress on military operations, this research project will enable the development of targeted interventions that increase resilience against operational performance impairment. Further, this research project will help to improve the safety and success of millions of Americans, including US military personnel, who are frequently exposed to sleep loss and stress.

2. KEYWORDS

Sleep deprivation, stress, performance impairment, attentional control, cognitive flexibility, mission success, resilience

3. ACCOMPLISHMENTS

What were the major goals of the project?

Specific Aim 1: Test the prediction of the Dynamic Attention Control (DAC) framework that sleep deprivation (SD) without stress induction spares working memory (WM) capacity, but compromises (a) the establishment of choice outcome associations and (b) the binding and interference management processes needed for cognitive flexibility (CF).	Timeline	Completed
Study Preparations	Months	
Milestone(s) Achieved: Procedures documented and IRB/HRPO approvals obtained	1-3	1 Jul 2021
Data Collection		
Milestone(s) Achieved: Aim 1 data collection completed from 32 subjects (16 in a sleep deprivation condition and 16 in a no sleep deprivation and no stress condition)	4-30	in progress (delay incurred by COVID-19 laboratory closure)
Data Analysis		
Milestone(s) Achieved: Aim 1 analyses completed	5-33	n/a
Specific Aim 2: Test how the attentional control processes specified in the DAC framework are affected by stress induction without SD.		
Data Collection		
Milestone(s) Achieved: Aim 2 data collection completed from 32 subjects (16 in a stress condition and 16 in a no sleep deprivation and no stress condition)	4-30	in progress (delay incurred by COVID-19 laboratory closure)
Data Analysis		
Milestone(s) Achieved: Aim 2 analyses completed	5-33	n/a
Specific Aim 3: Determine how the joint effects of acute stress and SD impact attentional control, CF, and risky decision making.		
Data Collection		
Milestone(s) Achieved: Aim 3 data collection completed from 48 subjects (16 in a sleep deprivation condition; 16 in a stress condition; and 16 in a combined sleep deprivation and stress condition)	4-30	in progress (delay incurred by COVID-19 laboratory closure)
Data Analysis		
Milestone(s) Achieved: Aim 3 analyses completed	5-33	n/a

Final Report Preparation		
Compilation of analyses from aims 1–3 and drafting of report and briefing	34-36	n/a
Presentation of study results to the DoD	36	n/a
Milestone(s) Achieved: study completed	36	in progress

What was accomplished under these goals?

During Year 1, the major activities to be completed to achieve the goal milestones were:

- Ethical review of the study procedures by the Washington State University IRB and the DoD’s HRPO – completed.
- Development of standard operating procedures for participant screening and enrollment, which have been reviewed and approved by the Washington State University IRB and HRPO, including standard materials for advertising the study, conducting telephone and in-person screening, eligibility requirements for participants, consent form, and COVID-19 screening procedures and questionnaires (Aims 1–3) – completed.
- Development of a cognitive battery to assess elements of the DAC framework. This cognitive battery includes the Delayed Matching to Sample task (DMS), the Go/No Go Reversal Learning task (GNGr), the Situational Awareness of Risk Dynamics task (SARD), and the Psychomotor Vigilance Test (PVT). The DMS requires participants to maintain 2–4 visual patterns (depending on load condition) in working memory, with some trials showing additional stimuli that need to either be ignored or updated in working memory. Additionally, on some trials participants will need to switch between attending the color or shape of the visual patterns. With this one task, we can obtain an index of working memory maintenance, flexible updating, and switch costs, a commonly used measure of cognitive flexibility. The GNGr, which was developed in our previous research and implemented as part of the original PRMRP award, requires participants to learn, from feedback, which stimuli are associated with a “go” response (button press) or a “no go” response (no button press).

Approximately halfway through the task and unannounced to participants, the contingencies reverse, such that stimuli that were associated with a “go” response are now associated with a “no go” response and vice versa. This task serves as a measure of how well participants can form the stimuli-responses associations, as well as interference control (pre-reversal), and cognitive flexibility (post-reversal). The SARD, which was developed for the original PRMRP award, requires participants to learn from feedback which of three zones is associated with more advantageous outcomes, which is associated with more disadvantageous outcomes, and which has an equal likelihood of advantageous or disadvantageous outcomes (neutral zone). Partway through the task, the zones switch, and participants must learn the new associations for each zone. The SARD provides a more realistic test of dynamic risk awareness. Finally, the PVT requires subjects to respond as quickly as possible to a stimulus presented at random inter-stimulus intervals of 2–10 seconds. The PVT is a measure of vigilant attention and is particularly sensitive to sleep loss. (Aims 1-3) – completed.

- Development of new standard protocols for operating the laboratory during the COVID-19 pandemic, with additional health and safety precautions to commence data collection while protecting participants, staff, and students. These protocols include instructions for disinfecting equipment and office supplies, safety guidelines for participants, staff, and students while in the laboratory, and procedures for handling potential exposures to COVID-19 – completed.

Summary of the laboratory study protocol:

Carefully screened, healthy young adults will be randomized to one of four conditions (n = 16 in each condition): a sleep deprivation only condition; a stress only condition; a combined sleep deprivation and stress condition; or a control (no sleep deprivation and no stress) condition. Subjects will be in the laboratory for four days / three nights continuously, under constant observation and physiological monitoring. In either of the two sleep deprivation conditions (sleep deprivation only or combined sleep deprivation and stress), subjects will have one night with 10 hours time in bed for baseline sleep, then will undergo 38 hours of total sleep deprivation (equivalent to missing one night of

sleep), and then will be given one recovery night with 10 hours time in bed for sleep. Those in the stress only or control conditions will have 10 hours in bed for sleep on all three nights. Subjects will be tested on a range of cognitive performance tasks at baseline, and 24 hours later after sleep deprivation (or well-rested control). At baseline, all subjects will complete the battery of tasks following a sham version of a stress test. Following the night of either sleep deprivation or rest, those in the two stress conditions (stress only or combined sleep deprivation and stress) will complete the battery of tasks following a stress test. Those in the other two conditions will again complete the battery following the sham version of the stress test. The cognitive tests and physiological measures obtained during the study will serve to test the prediction of the Dynamic Attention Control (DAC) framework that sleep deprivation without stress induction spares working memory capacity, but compromises (a) the establishment of choice outcome associations and (b) the binding and interference management processes needed for cognitive flexibility; test how the attentional control processes specified in the DAC framework are affected by stress induction without sleep deprivation; and determine how the joint effects of acute stress and sleep deprivation impact attentional control, cognitive flexibility, and risky decision making.

Stated goals not met:

Following the spread of COVID-19 in the United States in early 2020, Washington State University by order of the Governor closed the majority of its facilities, including our laboratory. As a result, we were unable to screen or enroll participants for any study, including the project described here. Staff and students were finally permitted to return to the facility in July 2021, and the remaining 2 months of year 1 of this project were used to reopen and clean the laboratory, maintain and check the equipment and computer infrastructure, update manuals and SOPs and post signage to implement IRB-approved COVID-19 precautions, rehire and train staff, and prepare to commence recruitment for the study. These important steps forward notwithstanding, due to the COVID-19 pandemic we are behind schedule for studying subjects in the laboratory (Aims 1–3).

What opportunities for training and professional development has the project provided?

The project provides significant opportunities for postdoctoral and graduate education and professional development:

- A postdoctoral researcher in the Department of Psychology at Washington State University, Courtney Kurinec, is intensively involved in the memory aspects of the research of this project and more generally provides assistance regarding study management. She receives training in the management and development of sleep deprivation studies; preparing reports for government stakeholders; programming of cognitive performance tasks in E-Prime software; and data reduction and statistical analysis. The postdoctoral researcher is involved in the project under the mentorship of the PI and Co-PIs of the project. During Year 1, she has presented her work at a national conference on sleep science and published two papers related to the project.
- A Ph.D. student in the Experimental Psychology graduate program at Washington State University, Amanda Hudson, is involved in this project to develop and program novel cognitive tasks to assess performance changes during sleep deprivation and/or stress. She is receiving training in recording of sleep (polysomnography); recording and processing of galvanic skin conductance; developing and programming of cognitive performance tasks in E-Prime software; and data reduction and statistical analysis. The graduate student is involved in the project under the direct mentorship of the PI, and training and experience has been gained on a daily basis. During Year 1, the graduate student worked with the investigators to develop study procedures and tasks for the study.
- A Ph.D. student in the Experimental Psychology graduate program at Washington State University, Anthony Stenson, is involved in the development of several of the cognitive performance tests in this project. He is receiving training on the programming of cognitive performance tasks in E-Prime software; data reduction

and statistical analysis; cognitive model development; and manuscript writing. The graduate student is involved in the project under the direct mentorship of two Co-PIs of the project, Drs. Paul Whitney and John Hinson. During Year 1, the graduate student published a paper related to the project.

How were the results disseminated to communities of interest?

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?

Year 2 will be focused on subject recruitment and screening and studying subjects and data collection in the laboratory experiment. Our goal will be to have completed at least 16 subjects by the end of Year 2. As described above, due to the COVID-19 pandemic our laboratory was closed until July 2021 and we are therefore behind on our schedule for studying subjects. We will attempt to accelerate the pace of subject recruitment, but because another DoD-supported study in our laboratory was likewise suspended we expect a high level of strain on subject recruitment and limited availability of the laboratory. At least in Year 2, this will constrain us in our ability to make up fully for the time lost in Year 1 due to the pandemic.

We expect that some of the data collected during the study will be amenable for preliminary analyses, which will be used in training opportunities for graduate students and post-baccalaureate students and presented at national conferences.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Because our facility was closed due to the COVID-19 pandemic, we could not study participants in the laboratory. However, we were scientifically productive by writing and contributing to papers that moved the needle on the theoretical underpinnings of the present project, using data from earlier studies supported by the DoD and unlocking new insights through novel analyses of these data. We published four peer-reviewed journal articles related to this project; see under the Appendices.

Briefly, in a paper in the journal *Sleep*, we report that sleep deprivation impairs the ability to associate (or bind) new information together in memory, which is particularly relevant for interpretation of data sets that will result from the present project. In a paper in *PLoS ONE*, we showed that even though sleep deprivation does not appear to influence bottom-up processing of affective stimuli, it does impair emotion regulation, likely due to its effect on cognitive control processes. In a paper published in *Nature Communications*, we elucidated the role of the circadian system in the autonomic nervous system as reflected in cardiovascular function. And in a paper in *Clocks & Sleep*, we quantified the magnitude of the impact of sleep inertia on sleepiness.

What was the impact on other disciplines?

Our four peer-reviewed journal articles (described above) also contributed to disciplines beyond those directly related to the current project. For instance, our contribution to the paper in *Nature Communications* helped to shed light on how changes in sleep timing and behavior may influence susceptibility to cardiac events such as arrhythmias. Our paper in *Sleep* revealed how sleep loss effects on binding information in memory could have real-world impact, e.g., in eyewitness memory. And our sleep inertia findings reported in *Clocks & Sleep* have direct relevance in on-call and emergency response operations including those commonly encountered in the military.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Errors, accidents, and safety risks due to sleep loss and stress increase the chances of mission failure and lead to injury and death in military and civilian environments. Although how sleep loss affects situational awareness and decision making is increasingly well understood, the mechanisms underlying the impact of stress on these abilities, as well as the joint effect of stress and sleep loss, remain areas for investigation. This project will provide a single framework for explaining the separate and joint effects of sleep loss and stress on decision making in dynamic environments, which will serve to guide the development of future countermeasures.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

Due to the impact of COVID-19 and the associated closure of our facility through to July 2021, we are currently behind schedule with regard to studying subjects in the laboratory. Now that we have been able to reopen our laboratory and resume research that had been suspended due to the pandemic, we have intensified our efforts to conduct this study.

We will attempt to accelerate the pace of subject recruitment, but because another DoD-supported study in our laboratory was likewise suspended during the pandemic (as were other studies in other laboratories dependent on human subject recruitment) we expect a high level of strain on our subject pool for recruitment. Combined with constraints in the availability of the laboratory, this means that at least in Year 2, we will be limited in our ability to make up fully for the time lost in Year 1 due to the pandemic. We expect to be able to further accelerate study completion in Year 3.

Changes that had a significant impact on expenditures

Due to the impact of COVID-19 and the associated closure of our facility through to July 2021, we are currently behind schedule with regard to studying subjects in the laboratory. Expenditures are therefore lagging compared to the original budget. We expect that the difference will dissipate as we accelerate the pace of the study in Years 2 and 3 to complete data collection.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals.

Nothing to Report (Not Applicable).

Significant changes in use of biohazards and/or select agents

Nothing to Report (Not Applicable).

6. PRODUCTS

Publications, conference papers, and presentations

Journal publications

Hayter, E. A., Wehrens, S. M., Van Dongen, H. P. A., Stangherlin, A., Gaddameedhi, S., Crooks, E., Barron, N. J., Venetucci, L. A., O'Neill, J. S., Brown, T. M., Skene, D. J., Trafford, A. W., & Bechtold, D. A. Distinct circadian mechanisms govern cardiac rhythms and susceptibility to arrhythmia. *Nature Communications*, 2021; 12: 1-13, published. Acknowledgement of federal support: yes.

Kurinec, C. A., Whitney, P., Hinson, J. M., Hansen, D. A., & Van Dongen, H. P. A. Sleep deprivation impairs binding of information with its context. *Sleep*, 2021; 44: zsab113, published. Acknowledgement of federal support: yes.

Lundholm, K. R., Honn, K. A., Skeiky, L., Muck, R. A., & Van Dongen, H. P. A. Trait Interindividual Differences in the Magnitude of Subjective Sleepiness from Sleep Inertia. *Clocks & Sleep*, 2021; 3: 298-311, published. Acknowledgement of federal support: yes.

Stenson, A. R., Kurinec, C. A., Hinson, J. M., Whitney, P., & Van Dongen, H. P. A. Total sleep deprivation reduces top-down regulation of emotion without altering bottom-up affective processing. *PLoS One*, 2021; 16: e0256983, published. Acknowledgement of federal support: yes.

Books or other non-periodical, one-time publications

Ph.D. dissertations:

Nothing to Report.

Conference abstracts:

Kurinec, C. A., Stenson, A., Hinson, J. M., Whitney, P., Honn, K. A., & Van Dongen, H. P. A. Investigating the role of fluid intelligence in task-specific, inter-individual differences in resilience to sleep deprivation. MHSRS, 2021, published.
Acknowledgement of federal support: yes.

Kurinec, C. A., Whitney, P., Hinson, J. M., Hansen, D. A., & Van Dongen, H. P. A. Sleep deprivation disrupts binding of information with its context. *Sleep*, 2021; 44 (Abstract Suppl.): A17-A18, published. Acknowledgement of federal support: yes.

Lundholm, K. R., Van Dongen, H. P. A., & Honn, K. Systematic individual differences in vulnerability to sleep inertia. *Sleep*, 2021; 44 (Abstract Suppl.): A31-A32, published.
Acknowledgement of federal support: yes.

Muck, R. A., Hudson, A. N., Honn, K. A., Van Dongen, H. P. A. Is the timing of the endogenous circadian rhythm of neurobehavioral functioning inherently task-dependent? MHSRS, 2021, published. Acknowledgement of federal support: yes.

Schneider, B., Honn, K., & Van Dongen, H. P. A. Does extraversion predict subjective ratings of sleepiness and performance during sleep deprivation? *Sleep*, 2021; 44 (Abstract Suppl.): A56-A58, published. Acknowledgement of federal support: yes.

Other publications, conference papers, and presentations

Invited lectures:

Van Dongen, H. P. A. Sleep, sleep deprivation, and human performance. Essential Topics in Translational Sleep Medicine seminar, University of Arizona College of Medicine (via videoconference), September 2021.

Oral presentations at conferences:

Kurinec, C. A. Sleep deprivation disrupts binding of information with its context. Oral presentation at the SLEEP 2021 conference (via videoconference), June 2021.

Website(s) or other Internet site(s)

Nothing to Report.

Technologies or techniques

Nothing to Report.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other Products

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	<i>Hans P.A. Van Dongen, Ph.D.</i>
Project Role:	<i>PI</i>
Researcher Identifier:	<i>ORCID ID: 0000-0002-4678-2971</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Van Dongen oversaw the project and coordinated all personnel activities and tasks.</i>
Funding Support:	

Name:	<i>Kimberly A. Honn, Ph.D.</i>
Project Role:	<i>Co-PI</i>
Researcher Identifier:	<i>ORCID ID: 0000-0001-8911-6277</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Honn developed the study protocol and assisted with obtaining IRB and HRPO approval.</i>
Funding Support:	

Name:	<i>Paul Whitney, Ph.D.</i>
Project Role:	<i>Co-PI</i>
Researcher Identifier:	<i>ORCID ID: 0000-0003-1973-5261</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Whitney contributed key expertise on the development of measures in the cognitive task battery.</i>
Funding Support:	

Name:	<i>John M. Hinson, Ph.D.</i>
Project Role:	<i>Co-PI</i>
Researcher Identifier:	<i>ORCID ID: 0000-0002-5012-5974</i>
Nearest person month worked:	<i>1</i>

Contribution to Project:	<i>Dr. Hinson contributed critical expertise the development of measures in the cognitive task battery.</i>
Funding Support:	

Name:	<i>Courtney A Kurinec, Ph.D.</i>
Project Role:	<i>Postdoctoral Researcher</i>
Researcher Identifier:	<i>ORCID ID: 0000-0001-5800-1610</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Kurinec helped with the study design and IRB and HRPO approvals.</i>
Funding Support:	

Name:	<i>Amanda Hudson, M.A.</i>
Project Role:	<i>Ph.D. Student</i>
Researcher Identifier:	<i>ORCID ID: 0000-0002-1641-1782</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Ms. Hudson developed study procedures and implemented performance testing for the study.</i>
Funding Support:	

Name:	<i>Anthony Stenson, M.A.</i>
Project Role:	<i>Ph.D. Student</i>
Researcher Identifier:	<i>ORCID ID: 0000-0002-2405-0649</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Mr. Stenson assisted with the development of measures in the cognitive task battery.</i>
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report.

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

Award Chart is enclosed (see under Appendices).

9. APPENDICES

The following items are enclosed:

Award Chart for 15 Sept 2020 – 14 Sept 2021

Journal publications

Hayter, E. A., Wehrens, S. M., Van Dongen, H. P. A., Stangherlin, A., Gaddameedhi, S., Crooks, E., Barron, N. J., Venetucci, L. A., O'Neill, J. S., Brown, T. M., Skene, D. J., Trafford, A. W., & Bechtold, D. A. Distinct circadian mechanisms govern cardiac rhythms and susceptibility to arrhythmia. *Nature Communications*, 2021; 12: 1-13, published. Acknowledgement of federal support: yes.

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Conference abstracts

Kurinec, C. A., Stenson, A., Hinson, J. M., Whitney, P., Honn, K. A., & Van Dongen, H. P.A. Investigating the role of fluid intelligence in task-specific, inter-individual differences

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