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TITLE: Impact of Operational Sleep Disruption on PTSD-Relevant Fear Learning Processes

PRINCIPAL INVESTIGATOR: Victoria Risbrough

CONTRACTING ORGANIZATION: Veterans Medical Research Foundation

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This report covers Year 5 of the project. This project examines the impact of disturbances in normal sleep and circadian regulation on mechanisms underlying vulnerability to, and maintenance of, posttraumatic stress disorder (PTSD). The goal of Year 3 was continued data collection and harmonization with Monash. We have now recruited 93 total subjects (67 completing the full data collection period).

15. SUBJECT TERMS

Sleep restriction, circadian disruption, fear conditioning, extinction, safety, PTSD

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
U	U	U	UU	16	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

This project examines the impact of disturbances in normal sleep and circadian regulation on mechanisms underlying vulnerability to, and maintenance of, posttraumatic stress disorder (PTSD). Specifically, we will focus on the role REM sleep plays in fear extinction and safety signal learning. The overarching Aim of this project is to determine if two operationally valid models of REM disruption impair fear inhibition processes in ways consistent with impairments seen in PTSD. We will test REM Fragmentation (Aim 1: Veterans Medical Research Foundation) and Circadian Misalignment (Aim 2: Monash University) methods of disrupting REM sleep. We predict each method of REM disruption will lead to decreased quantity and/or quality of REM sleep, and this will, in turn, impair the specific fear inhibition processes of extinction learning and recall, as well as safety recall. We believe the underlying mechanism for both types of disruption is reduced REM Consolidation, and we will test this hypothesis in Aim 3.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Sleep restriction, circadian disruption, fear conditioning, extinction, safety, PTSD

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Activities listed in the SOW for this performance period:

Subtask 3: In Year 5, we altered our goals in the NCE period to complete recruitment to allow for REM fragmentation vs. Normal sleep to ensure publication of primary outcome findings. This includes initial data cleaning and processing and finalizing the master data base.

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Our primary task was to finalize recruitment for the study in year 4, our NCE period. Unfortunately due to staffing shortages (2 staff members went on medical leave for over 2 months during this period) we are still slightly behind in our recruitment goals, although we have managed to enroll a total of 93 subjects and completed 67 total subjects, N=29 REM fragmentation, 11=X SWS fragmentation and N=27 Normal sleep. All data has been entered into the database and cleaned and is now undergoing analyses. We have also conducted preliminary analyses of our primary outcome (fear potentiated startle). Initial analyses indicate that REM fragmentation is associated with significantly increased cued fear recall compared to normal sleep, as well as reduced fear extinction recall. These preliminary data were presented by Dr. Risbrough at the San Antonio Brain Health Symposium on PTSD in October of 2022. We are using a limited NCE to continue filling out our subject groups until December 2022 as well as finalize analysis.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

The NCE year of the project has provided training and professional development opportunities:

Dr. Patrick Vizeli, a post-doctoral researcher has had training opportunities in data collection and data analysis for this project. He was trained in EMG and GSR collection, data processing and analysis.

Dr. Christopher Hunt, a post-doctoral researcher had training opportunities in data analysis of insomnia and cued fear learning in a secondary analysis on a completed data set, which offered training in longitudinal analysis of sleep and cued fear outcomes in military populations.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report." Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

The preliminary results of this study were presented at the May 10th, San Diego VA Research Week Poster Session by Dr. Bruna Cuccurazzu. "The effect of fragmented sleep on configural fear learning in healthy volunteers". Hosted by Dr. Victoria Risbrough. We also disseminated a secondary analysis of our past DOD-funded study of sleep deprivation effects on prepulse inhibition, another form of startle inhibition. This paper was published in Behavioral Brain Research (Vizeli P, Cuccurazzu B, Drummond SPA, Acheson DT, Risbrough VB. Effects of total sleep deprivation on sensorimotor gating in humans. Behav Brain Res. 2023 May 9;449:114487. doi: 10.1016/j.bbr.2023.114487. Epub ahead of print. PMID: 37169130.)

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Nothing to report

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

No changes to report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to report.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

We also disseminated a secondary analysis of our past DOD-funded study of sleep deprivation effects on prepulse inhibition, another form of startle inhibition. This paper was published in Behavioral Brain Research (Vizeli P, Cuccurazzu B, Drummond SPA, Acheson DT, Risbrough VB. Effects of total sleep deprivation on sensorimotor gating in humans. Behav Brain Res. 2023 May 9;449:114487. doi: 10.1016/j.bbr.2023.114487. Epub ahead of print. PMID: 37169130.)

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

The preliminary results of this study were presented at the May 10th, San Diego VA Research Week Poster Session by Dr. Bruna Cuccurazzu. "The effect of fragmented sleep on configural fear learning in healthy volunteers". Hosted by Dr. Victoria Risbrough.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Victoria Risbrough, Ph.D.
Project Role: Principal Investigator
Nearest person month worked: .04
Contribution to Project: Dr. Risbrough has obtained and maintained regulatory approval for the study, supervised laboratory set up, equipment calibration and purchase, staff hiring, data collection, quality control assessments, development of testing and screening SOPs and staff management.

Dr. Dean Acheson, Ph.D. (unpaid)
Project Role: Co-Investigator
Nearest person month worked: 1.0
Note: Contribution to project: Supervised EMG laboratory and trained staff and maintained quality control for clinical assessments.

Name: Erin Natale, Research Associate
Nearest person months: 1.04
Contribution to project: Aided in cognitive testing and handling subject meals and wait times

Name: Patrick Vizlei: Post Doctoral Associate (Unpaid, he is on fellowship)
Nearest person months: 6.0
Contribution to projects: Aided in cognitive testing and handling subject meals and wait times, data processing, cleaning and set up of scripting for database entry and data processing.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*

- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

The only partner is Monash University, the second site on this collaborative grant. Monash has submitted an independent report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

W81XWH1810761: Impact of Operational Sleep Disruption on PTSD-Relevant Fear Learning Processes

PI: Victoria Risbrough, VMRF, CA

Budget: $1,061,660.00

Topic Area: Sleep Disorders

Mechanism: W81XWH-17-PRMRP-IIRA

Research Area(s): 1199/1499

Award Status: 9/30/2018-01/29/2023 NCE

Study Goals:

This project examines the impact of disturbances in REM sleep on fear inhibition mechanisms which underlie vulnerability to, and maintenance of, posttraumatic stress disorder (PTSD). Operationally, if our hypotheses are borne out, we will identify sleep-related elements of the operational environment increasing the risk of development and maintenance of PTSD as well as identify a countermeasure designed to mitigate the negative effects of REM disruption on PTSD-related mechanisms.

Specific Aims:

Aim 1: Examine the effect of REM fragmentation on extinction learning and recall and safety signal recall compared to normal sleep and non-REM sleep fragmentation.

Aim 2: Examine the effect of an 8-hour phase advance with placebo administration, relative to an 85-hour phase advance with melatonin agonist administration and to no circadian disruption, on extinction learning and recall and safety signal recall

Aim 3: Combining participants from both sites, examine the effects of REM Consolidation on extinction learning and recall and safety signal recall.

Key Accomplishments and Outcomes:

Publications: Winston et al. 2019, Acheson et al. 2019, Vaughn et al. 2021, Hunt et al. 2023; Vizeli et al. in press

Patents: none to date

Funding Obtained: none to date