AWARD NUMBER: W81XWH-18-1-0761

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

PRINCIPAL INVESTIGATOR: Victoria Risbrough

CONTRACTING ORGANIZATION: Veterans Medical Research Foundation
San Diego, CA 92161

REPORT DATE: October 2020

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Oct 2020	Annual	30 Sept 2019 – 29 Sept 2020

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-18-1-0761

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This report covers Year 2 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 2 was data collection and initial validation of data collection procedures and harmonization with Monash. We proposed to complete 30 participants (45 in total with year 1). Progress was slowed due to COVID19, which prompted our VA facility to shut down all human research the fall. Our study, which requires a hospital stay, was finally approved for collection in October with mitigation procedures in place. We have completed 18 subjects (30% of target). However we do have 6 weeks now booked for collection and a large list of applicants for the study. During the COVID period we examined data for errors and trained and harmonized sleep scoring across the study. We have seen exceptional interest in the study since recruitment opened and hope to make up for lost time this year.

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			USAMRMC
U	U	U	UU	16	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

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:

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

3. ACCOMPLISHMENTS:

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 2: In Year 2, complete approximately 30 participants at each site. This includes initial data cleaning and processing and adding data to 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.

We have successfully completed all tasks from year 1 except the completion of 30 participants in year 2. During the facility shut down due to COVID19 (we trained our new sleep technician on the protocol, established new PSG equipment and conducted extensive data audits with the Monash team. All sleep data across both study sites was double scored and interclass correlations were established between scorers. We reconfigured our testing suites to allow for subject testing to be separate at all times to mitigate COVID19 risk. We also amassed a large recruitment list in preparation for study opening, and once we received approval for data collection we have scheduled the next 6 weeks with subjects. We will need an aggressive testing schedule 4-6 participants/month to make up for lost time, however we think it is feasible given the high volume of interested participants, which is much higher than before COVID19 perhaps due to a weak labor market. PROBLEMS. COVID19 forced facility shut down has been the primary problem.

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 second year of the project has provided several training and professional development opportunities:

Dr. Daniel Stout is a PhD in clinical psychology and has participated in study design, set up and development of cognitive tasks. Prof Risbrough met with Dr. Stout on a weekly basis to discuss both project issues and career development issues. Dr. Stout learned specific technical skills (e.g., psychophysiological measures), as well as project management and personnel supervision skills.

Cindy Napan is an undergraduate student at University of California San Diego, and is a first generation college student in her family. Cindy is assisting with proctoring of cognitive tasks as well as subject screening and recruitment through a work study agreement. Dr. Risbrough meets with Cindy biweekly to monitor study progress and her training in data collection, record keeping and cognitive assessments.

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.

Nothing to report

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

The next reporting period will focus on enrolling and completing research participants. We will work hard to make up as much of the lost ground due to COVID19 related closures this past year as possible.

4. IMPACT

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: *T*

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.

Our main problem was inability to conduct data collection due to facility mandated halt of human research studies due to COVID19. We have been approved to reopen our data collection (October 15, 2020) and have begun screening 10/26/2020 and have our first subject since the closure on Nov 2nd. We are booked out for 6 weeks thus we expect with aggressive data collection we will be able to make up for lost time, barring any further COVID19-related halts to data collection.

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.

Given we were unable to enroll participants for the majority of this reporting period, our expenses were reduced. However, we did make the decision to retain all main personnel on the study. This allowed us to work on the data we had already collected, as well as our interrater reliability with the San Diego site. It also allowed us be ready to start as soon as we were allowed to do so.

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:

- **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).*

Published: Acheson DT, Kwan B, Maihofer AX, Risbrough VB, Nievergelt CM, Clark JW, Tu
XM, Irwin MR, Baker DG. Sleep disturbance at pre-deployment is a significant predictor of post-deployment re-experiencing symptoms. Eur J Psychotraumatol. 2019 Oct 29;10(1):1679964. doi: 10.1080/20008198.2019.1679964. PMID: 31723377; PMCID: PMC6830277.

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.*

Risbrough (2020) Keynote Speaker, Physiological Biomarkers in Stress-related Disorders: From Animal Models to Clinic. *Annual Meeting for American Physiological Society*, San Diego, CA, April 6th

Risbrough (2020) Symposium Chair, Inflammation as a Risk Factor for Psychiatric Illness, *Winter Conference on Brain Research,* Big Sky Montana, January 29th

- **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: 2
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.

Name: Sonya Norman, Ph.D.
Project Role: Co-Investigator
Nearest person month worked: 1
Contribution to project: Dr. Norman consulted on IRB regulatory issues, and also supervises mental health screening and has trained study staff to conduct screening over the telephone and in person and develop screening SOPs. She is also the on-call clinician for this study at the VA in case of mental health emergency.

Dr. Dean Acheson, Ph.D. (unpaid)
Project Role: Co-Investigator
Nearest person month worked: 1
Note: Contribution to project: Supervised EMG laboratory and trained staff and maintained quality control for clinical assessments.

Name: Bruna Cuccurazzu, Ph.D.
Project Role: Study Coordinator
Nearest person month worked: 3
Contribution to project: Dr. Cuccurazzu has performed work in the area of laboratory set up, equipment maintenance, hiring and supervising of staff and students, pilot data collection and analysis, and assistance with regulatory documents.

Name: Michele Eaton, B.S.
Project Role: Respiratory Therapist/Sleep Technician
Nearest person month worked: 7
Contribution to project: Ms. Eaton is a trained sleep technician, she was trained on study equipment (PSG), she developed sleep assessment protocols, calibrated equipment, set up the sleep rooms for assessments, supervised purchase of all required consumables for sleep measurement, developed and revised sleep assessment and sleep phase fragmentation protocols.

Name: Nicholas Kelley, B.S.
Project Role: Respiratory Therapist/Sleep Technician
Nearest person month worked: 3
Contribution to project: Mr. Kelley is a trained sleep technician, he was trained on study equipment (PSG) and protocols, developed the COVID-19 SOP for sleep assessments, supervised purchase of all required consumables for COVID-19 safety procedures, revised sleep assessment and sleep phase fragmentation protocols and scored all PSG data collected thus far and analyzed it for interrater reliability with Monash.

Name: Karina Campos
Project Role: Research Assistant
Nearest person month: 1
Contribution to project: monitored participant during morning and evening hours before and after testing.

Name: Albert Chiu
Project Role: Database setup and management
Nearest person month worked: 7
Contribution to project: Developed and maintained database

Name: Nathan Klein, Undergraduate (unpaid)
Nearest person month 2
Contribution to project: Aided in piloting equipment recording and data collection

Name: Zackary Yeh, Undergraduate
Nearest person month: 1
Contribution to project: Study recruitment, screening and data management

Name: Cindy Napan, Undergraduate
Nearest person month: 1
Contribution to project: Aided in cognitive testing and recruitment

Name: Anjana Patel
Nearest person month: 1
Contribution to project: Aided in regulatory document preparation

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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:

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: 9/30/2019-9/29/2020

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: Acheson et al. 2019

Patents: none to date

Funding Obtained: none to date