

AWARD NUMBER: W81XWH-18-1-0761  
PR170893P1

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 2019

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

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

<b>REPORT DOCUMENTATION PAGE</b>			<i>Form Approved</i> <i>OMB No. 0704-0188</i>	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. <b>PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.</b>				
<b>1. REPORT DATE</b> OCT 2019		<b>2. REPORT TYPE</b> Annual		<b>3. DATES COVERED</b> 30 Sept 2018 - 29 Sept 2019
<b>4. TITLE AND SUBTITLE</b>  Impact of Operational Sleep Disruption on PTSD-Relevant Fear Learning Processes			<b>5a. CONTRACT NUMBER</b> W81XWH-18-1-0761	
			<b>5b. GRANT NUMBER</b> PR170893	
			<b>5c. PROGRAM ELEMENT NUMBER</b>	
<b>6. AUTHOR(S)</b>  Victoria B. Risbrough  E-Mail: vrisbrough@ucsd.edu			<b>5d. PROJECT NUMBER</b>	
			<b>5e. TASK NUMBER</b>	
			<b>5f. WORK UNIT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) AND ADDRESS(ES)</b>  Veterans Medical Research Foundation 3350 La Jolla Village Dr. San Diego, CA 92161			<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b>  U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012			<b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>	
			<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>	
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b>  Approved for Public Release; Distribution Unlimited				
<b>13. SUPPLEMENTARY NOTES</b>				
<b>14. ABSTRACT</b> This report covers Year 1 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 1 was to set the study up and commence data collection. We proposed to complete 15 participants. Progress was slowed due to experiencing a flood in the VA sleep laboratory requiring new space and equipment to be set up and validated which included additional steps to ensure power conditioning for the PSG system. Despite these hurdles, we completed 6 participants (40% of target), and are now running smoothly. We have plans in place to increase the pace of participant recruitment and completion in Year 2, to make up for lost time in Year 1.				
<b>15. SUBJECT TERMS</b> NONE LISTED				
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>  Unclassified	<b>18. NUMBER OF PAGES</b>  15
<b>a. REPORT</b>  Unclassified	<b>b. ABSTRACT</b>  Unclassified	<b>c. THIS PAGE</b>  Unclassified		
			<b>19b. TELEPHONE NUMBER</b> (include area code)	

**TABLE OF CONTENTS**

	<b><u>Page</u></b>
<b>1. Introduction</b>	<b>4</b>
<b>2. Keywords</b>	<b>4</b>
<b>3. Accomplishments</b>	<b>4-6</b>
<b>4. Impact</b>	<b>6-7</b>
<b>5. Changes/Problems</b>	<b>8-9</b>
<b>6. Products</b>	<b>9-12</b>
<b>7. Participants &amp; Other Collaborating Organizations</b>	<b>12-15</b>
<b>8. Special Reporting Requirements</b>	<b>15</b>
<b>9. Appendices</b>	<b>15-16</b>

**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:

Major Task 1: Study Set-up;

*Subtask 1:* Obtain regulatory approval. Completed: VA Medical Center, San Diego, CA (H180066 IRB APPROVAL DATE: 05/10/2018, continuing renewal approval date 04/11/2019, Date of expiration, 05/05/2020)

*Subtask 2:* Hire and train all study staff. Completed 1 June 2019

*Subtask 3:* Develop and maintain common procedures across sites. Completed: 30 March 2019

Major Task 2: Recruit, enroll, and run study participants

*Subtask 1:* Complete approximately 15 participants; expected completion date: 29 Sept 2019  
40% (6/15) complete as of this report

### **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 successfully completed all tasks, except the completion of 15 participants.

The majority of our efforts during this first year were focused on setting up an entirely new sleep laboratory due to flooding of the original laboratory, harmonizing procedures and aiding the Monash group in overcoming technical difficulties. Hence we began recruitment somewhat later than expected, with our first subject completed August 2<sup>nd</sup> and since then completing 2 subjects/month for a total of 6 as of this report, and with our 7<sup>th</sup> subject currently enrolled during this reporting period, and 5 scheduled for screens. We have now established another sleep room to allow us to complete 2 subjects at once and expect to catch up to 3-4 subjects completed/month to achieve 37 by the next annual reporting period.

**CHANGES/PROBLEMS.** We had set up 2 sleep laboratory beds by June, however one of the PSG systems we discovered had intermittent electrical noise problems caused by unpredictable power usage in the middle of the night at the hospital causing poor quality EEG data. To mitigate this

### **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 first 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 technical difficulties this past year as possible.

**4. IMPACT:** *Describe 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.*

Our sleep laboratory was flooded by pipes bursting and we were required to set up a new location for our sleep laboratory, which caused an unexpected delay as described in the semi-annual report. We also experienced an unexpected delay in getting the PSG system up and running for one of the new sleep rooms because of intermittent electrical noise experienced only during the late night. Our sleep technician and IT specialist identified the problem as intermittent power surges and cycling due to equipment usage late at night in the hospital. We purchased a dual converter power conditioning system to mitigate this problem and the PSG system is now operating correctly with high quality data throughout the night. This will allow us to double our capacity in the following study period.

Plans moving forward

- We are carefully monitoring data produced by the PSG equipment to ensure high signal/noise ratio.
- We have added 3 more part-time research assistant staff to aid in recruitment and screening to increase our pace of participant recruitment and completion.

**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).*

Nothing to report

**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.*

Nothing to report

- **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

ORCID: <https://orcid.org/0000-0001-8347-3820>

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

ORCID: <https://orcid.org/0000-0002-4751-1882>

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:

Note: Dr. Acheson was called to Active Duty in Oct. 2018 and Dr. Risbrough and Dr. Norman took over his staff supervision and data analysis duties. He returns in Oct. 2019 and will take up his study duties at that time.

Name: Bruna Cuccurazzu, Ph.D.

Project Role: Study Coordinator

Nearest person month worked: 5

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: 10

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: Sorana Caldwell, B.S.

Project Role: Research Technician

Nearest person month worked: 6

Contribution to project: Maintained equipment, aided with administrative tasks and regulatory documents, aided staff in maintaining safety and training records.

Name: Albert Chiu

Project Role: Database setup and management

Nearest person month worked: 1

Contribution to project: Developed and maintained database

Name: Nathan Klein, Undergraduate (unpaid)

Nearest person month worked: 2

Contribution to project: Aided in piloting equipment recording and data collection

Name: Karina Campos, Undergraduate (unpaid and paid)

Nearest person month worked: 2

Contribution to project: Aided in piloting actigraph watches and data analysis.

Name: Zackary Yeh, Undergraduate (paid)

Nearest person month worked: 1

Contribution to project: Study recruitment, screening and data management

Name: Cindy Napan, Undergraduate (paid)

Nearest person month worked: 1

Contribution to project: Aided in cognitive testing and recruitment

**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.*

- **See attached Year 1 Award Chart**

# 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:** 9/30/2018-9/29/2019

## **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:** none to date

**Patents:** none to date

**Funding Obtained:** N/A