

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

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# REPORT DOCUMENTATION PAGE

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<b>14. ABSTRACT</b> This report covers Year 4 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 proposed to complete 15 participants (60 in total with year 1 and 2). Progress was slowed due to difficulty recruiting subjects during staffing shortages.					
<b>15. SUBJECT TERMS</b> Sleep restriction, circadian disruption, fear conditioning, extinction, safety, PTSD					
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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?

Activities listed in the SOW for this performance period:

Subtask 3: Due to COVID19 there was significant disruption to timelines. In Year 4, we altered our goals in the NCE period to complete recruitment and finalize analyses. This includes initial data cleaning and processing and adding data to the master database.

**What was accomplished under these goals?**

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 61 subjects and completed 25 CTRLs, 28 REM fragmentation, and 8 SWS fragmentation participants. We are adding to the SWS fragmentation arm to increase power. We have also created all scripting required for data entry into the database, which is now occurring after each person is completed thus we expect analysis to be completed rapidly. 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 January 2023 as well as finalize analysis.

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

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?**

The preliminary results of this study were presented at the San Antonio Brain Health Symposium on PTSD on October 14<sup>th</sup>, 2022 by Dr. Risbrough. “Biomarkers of Risk for PTSD in Military Populations: what we have learned from the Marine Resiliency Study (MRS)”. Hosted by Dr. David Morilak, UT, San Antonio, TX.

**What do you plan to do during the period to accomplish the goals?**

The next reporting period will focus on completing research participants as well as finalizing the database for final analysis.

**4. IMPACT:****What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report

**What was the impact on other disciplines?**

Nothing to report

**What was the impact on technology transfer?**

Nothing to report

**What was the impact on society beyond science and technology?**

Nothing to report

**5. CHANGES/PROBLEMS:**

No changes to report

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

Our main problem is continued staffing shortages.

**Changes that had a significant impact on expenditures**

Given staffing shortages (medical leave) during this reporting period, our expenses were reduced and allowed for a few additional months of carry forward for a second NCE to finalize recruitment and data analysis.

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

**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**

### **Journal publications.**

Christopher Hunt, Daniel M. Stout, Ziyun Tie, Dean Acheson, Peter J. Colvonen, Caroline M. Nievergelt, Kate A. Yurgil, Dewleen G. Baker, Victoria B. Risbrough, Pre-deployment threat learning predicts increased risk for post-deployment insomnia: Evidence from the Marine Resiliency Study, Behaviour Research and Therapy, 2022, in press

### **Books or other non-periodical, one-time publications.**

Nothing to report

### **Other publications, conference papers and presentations.**

The preliminary results of this study were presented at the San Antonio Brain Health Symposium on PTSD on October 14<sup>th</sup>, 2022 by Dr. Risbrough. “Biomarkers of Risk for PTSD in Military Populations: what we have learned from the Marine Resiliency Study (MRS)”. Hosted by Dr. David Morilak, UT San Antonio, San Antonio, Tx.

- **Website(s) or other Internet site(s)**

Nothing to report

- **Technologies or techniques**

Nothing to report

- **Inventions, patent applications, and/or licenses**

*r any other invention reporting required under the terms and conditions of an award.*

Nothing to report

- **Other Products**

Nothing to report

## **7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

**What individuals have worked on the project?**

Name: Victoria Risbrough, Ph.D.

Project Role: Principal Investigator

Nearest person month worked: 1.8

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: Bruna Cuccurazzu, Ph.D.

Project Role: Study Coordinator

Nearest person month worked: 3.0

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: Anjana Patel

Nearest person month: 5.5

Contribution to project: Supervises staff, conducts regulatory document submission and responses, supervised data base management.

Name: Yevgenya Stulov, B.S.

Project Role: Respiratory Therapist/Sleep Technician

Nearest person month worked: 5.2

Contribution to project: Ms. Stulov is a trained sleep technician, he was trained on study equipment (PSG) and protocols, 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: Erin Natale, Research Associate

Nearest person months: 4.5

Contribution to project: Aided in cognitive testing and handling subject meals and wait times

Name: Shakia Mobley, Research Associate

Nearest person months: 3.4

Contribution to project: Aided in cognitive testing and handling subject meals and wait times

Name: Dana Pensegera, Research Associate

Nearest person months: 0.6

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?**

Nothing to report

**What other organizations were involved as partners?**

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:**

**QUAD CHARTS:**

**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

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**Research Area(s):** 1199/1499

**Award Status:** 9/30/2018-01/29/2023\*in 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. in press

**Patents:** none to date

**Funding Obtained:** none to date