

AWARD NUMBER: W81XWH-20-1-0307

TITLE: Using an Ambulatory Technology Approach to Understand Nightmares, Nightmare Enactment, and Sleep-Related Violent Behavior: Toward Precision Diagnosis in PTSD

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CONTRACTING ORGANIZATION: Northern California Institute for Research and Education

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14. ABSTRACT PTSD occurs in 8% to 10% of civilians, and 20% to 30% of combat veterans. Sleep problems, including distressing nightmares, are present in nearly all individuals with PTSD. The goal of this study is to characterize the sleep physiological background and clinical factors which contribute to trauma nightmares, nightmare enactment during sleep, and sleep-related violent behaviors in trauma-exposed male and female U.S. military veterans. The primary scientific aims of our study are as follows: (1) To use an ambulatory, participant-administered multi-modal approach including sleep encephalogram (EEG), sleep diary app, standard wristband actigraphy with event marker, and video-recording of sleep, to examine the sleep architectural background of nightmares, nightmare enactment, and sleep-related violent behaviors; (2) To use an ambulatory, participant-administered approach including EEG, pulse oximetry, and respiratory belts, to examine the relationship between respiratory events during sleep and nightmares, nightmare enactment, and non-nightmare distressed awakenings; (3) To use a machine learning approach, utilize the full range of demographic, clinical, trauma, sleep/wake activity, sleep architectural and sleep-associated physiological data in the sample to identify independent and interacting predictors of the target sleep disturbances in the sample.					
15. SUBJECT TERMS Sleep disturbance, Nightmares, Post-Traumatic Stress, Nightmare Enactment					
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1. INTRODUCTION:

We are aiming to characterize the sleep physiological background and clinical factors which contribute to trauma nightmares, nightmare enactment during sleep, and sleep-related violent behaviors in trauma-exposed male and female U.S. military veterans. The primary aims will be (1) to use a multi-modal approach to examine the sleep architectural background of nightmares, nightmare enactment, and sleep-related violent behaviors, (2) to examine the relationship between respiratory events during sleep and nightmares, nightmare enactment, and non-nightmare distressed awakenings, and (3) to identify independent and interacting predictors of the target sleep disturbances in the sample. Trauma-exposed male and female veterans aged 18-80, and their available and consenting bed partners, will complete a two-phase study involving 3 weeks of mobile app plus actigraphy data collection (Phase 1), followed by 1-2 weeks of multi-modal assessments (Phase 2, involving sleep diary, actigraphy, EEG recordings, and video recordings) for those meeting symptom and adherence criteria in Phase 1. In combination with physiological data obtained in Phases 1 and 2, self-report surveys and chart review will provide data on multiple clinical and demographic characteristics that will contribute to analyses for Aim 3. The sample size objective is eighty (80) veteran participant completers of multi-modal assessments (Phase 2).

2. KEYWORDS:

Sleep disturbance
Nightmares
Post-Traumatic Stress
Nightmare Enactment

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Goals of the Project: The Primary scientific aims of our study are as follows:
Specific Aims: (1) Using an ambulatory, participant-administered multi-modal approach including sleep EEG, sleep diary app, standard wristband actigraphy with event markers, and video-recording of sleep activity, to examine the sleep architectural background of nightmares, nightmare enactment, and sleep-related violent behaviors; (2) Using an ambulatory, participant-administered approach including EEG, pulse oximetry, and respiratory belts, to examine the relationship between respiratory events during sleep and nightmares, nightmare enactment, and non-nightmare distressed awakenings; (3) Using a machine learning approach, utilize the full range of demographic (e.g., age, sex), clinical (e.g., overweight, medication use, medical history), trauma (e.g., type of trauma; time since trauma), sleep/wake activity, sleep architectural and sleep associated physiological data in the sample to identify independent and interacting predictors of the target sleep disturbances, as well as predictors of diary-reported sleep quality characteristics (e.g., sleep efficiency, total sleep time, wake after sleep onset, subjective sleep quality) in the sample.

Major Task 1 (Months 1-5): Prepare Protocol and Perform Regulatory Procedures for Study: Complete

Milestone: Local IRB approval at UCSF and VA (Target timeline: Months 1-3)

Current status: Complete as of 6/4/2020

Milestone: HRPO approval (Target timeline: Months 2-5)

Current status: Complete as of 12/15/2020

Major Task 2 (Months 1-4): Coordinate Study Staff for Study: Complete

Milestone: Research staff hired and trained (Target timeline: Months 3-4)

Current status: Complete as of December 2020

Major Task 3 (Months 5-30): Data Collection: In Progress

Milestone: Study begins (Target timeline: Month 5)

Current status: Complete as of 5/15/2021

Milestone: 1st participant consented, screened and enrolled (Target timeline: Month 5)

Current status: Complete as of 6/18/2021

Milestone: Study data collection complete (Target timeline: Month 30)

Current status: In Progress

Major Task 4 (Months 5-36): Data Analysis and Dissemination of Findings: Pending

Milestone: Data analysis complete (Target timeline: Month 35)

Current status: Pending

Milestone: Results Disseminated (Target timeline: Month 36)

Current status: Pending

What was accomplished under these goals?

1. Major activities: During the past reporting period, we have continued study recruitment and enrollment, consenting a total of 109 participants, and completing a total of 72 Part 1 participants and 21 Part 2 participants. Additionally, at the end of the reporting period, we had 5 participants enrolled in Part 1 and 5 participants enrolled in or ready to start Part 2 of the study. We successfully initiated a Trialfacts recruitment contract and continued work with UCSF's Participant Recruitment Program (PRP) and ResearchMatch to contact individuals interested in participating in research.
2. Specific objectives: Our specific objectives remained consistent with our major activities. During Months 25-36, we focused on study recruitment and enrollment of participants.
3. Significant results or key outcomes: Our primary aims are focused on data acquired in Part 2 of the study, but our Part 1 data as well as preliminary analysis of Part 2 data are yielding important findings regarding the characteristics of distressing dreams and nightmares in trauma survivors and their relationship to clinical outcomes, regarding the relationship of sleep apnea to nightmare experiences, and regarding the relationship of mood and affect regulation to trauma distressing dreams and nightmares. We have presented 2 posters and 1 oral presentation on our work and were invited to present another poster and symposium oral presentation at the fall 2023 International Society for Traumatic Stress Studies international meeting.
4. Other achievements: None to report.

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

Given COVID-related reductions in in-person training opportunities, funds were not used for this purpose during the past year.

How were the results disseminated to communities of interest?

Poster presentation at the 2/2023 ASCS (Advances in Sleep and Circadian Sciences; Clearwater Beach, FL) meeting and poster and oral presentations at SLEEP annual meeting 6/2023 (Indianapolis, IN).

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

We will continue to focus on Major Task 3 by continuing our recruitment and data collection efforts. We will continue to use the recruitment methods that have been proven to be effective (for example, the ResearchMatch recruitment service, social media recruitment, and Trialfacts recruitment). Additionally, we plan to enhance our recruitment of individuals experiencing nightmare enactment by collaborating with neurodegenerative clinics at UCSF and the San Francisco VA. We will continue to reach out to other nightmare researchers across the nation as well to receive participant referrals and advertise our study in other treatment facilities.

4. IMPACT:

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

We are preparing several manuscripts based on our initial data analysis and recent posters, including a manuscript that provides both excellent validation of our DOD-supported sleep diary mobile app as well as findings demonstrating relationships between nightmares and clinical outcomes and a manuscript highlighting the link between sleep apnea and nightmare events using physiological data.

We recently published initial findings from the pilot project leading up to the current study. Our findings on cardiovascular activity preceding a nightmare awakening in a small sample are already providing compelling preliminary information about the sleep physiology of nightmare sleep. We are seeing that our approach allows us to closely examine assumptions about the sleep physiology of nightmares and nightmare enactment that have not been previously examined. The published report can be found here:
<https://doi.org/10.1111/jsr.13639>

What was the impact on other disciplines?

Our recent published work highlights the feasibility and potential of at-home measurement of events that are difficult to capture in the sleep lab. We believe this is highly relevant to non-PTSD researchers who are interested in sleep disorders and parasomnias.

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:

Changes in approach and reasons for change

To help improve recruitment we have initiated a contract with Trialfacts (approved 2/21/2023). In addition, we added an additional optional EEG device for Part 2 procedures (approved 6/22/2023). This device provides a less bulky and burdensome alternative for participants. It can be used in occasional cases where participants would otherwise drop out of the study due to the discomfort wearing the Sleep Profiler device during sleep.

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

During the past reporting period, we have experienced a couple of minor delays in participant completion. June and July 2022 had a slight decrease of enrollment throughout the month as we shifted focus to train a new coordinator. Study staff also hired two new research assistants to help lead night visits with participants and manage volunteers.

At this point we have recruited fewer participants with nightmare enactment than predicted. Currently we are further exploring recruitment options, and plan to initiate a nightmare-enactment focused recruitment campaign through one of our specialized participant recruitment services.

Changes that had a significant impact on expenditures

Nothing to Report.

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.

Nothing to Report.

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

Nothing to Report.

Other publications, conference papers and presentations.

Poster presented at Advances in Sleep and Circadian Science 2023:
Stuewe, E., Malcolm, K., Woodward, S., Yack, L., Metzler T., Neylan T., Richards., A. (2023, February).
The Interrelationships Between Insomnia, Sleep Apnea, and Nightmares in Veterans with Psychological Trauma.

Poster presented at SLEEP:
Kennedy, E., Malcolm, K., Woodward, S., Yack, L., Metzler T., Neylan T., Richards., A. (2023, June).

Evaluating the Interrelationship Between Insomnia, Sleep Apnea, and Nightmares in Veterans with Posttraumatic Stress Disorder.

Oral Presentation at SLEEP:

Kennedy E., and Malcolm, K. (2023, June). *Evaluating the Interrelationship Between Insomnia, Sleep Apnea, and Nightmares in Veterans with Posttraumatic Stress Disorder.*

ISTSS (2023, November): Accepted during this reporting period.

Poster to be presented at the 39th Annual Meeting of the International Society for Traumatic Stress Studies:

Malek, N., Kovnick, M., Santistevan, A., Richards, A. (2023, November). *Exploring the Relationship Between Difficulties with Affect Regulation, Nightmares, and Mood.*

Exploring the Relationship Between Affect Regulation, Nightmares, and Mood in Trauma-Exposed Individuals.

ISTSS (2023, November): Accepted during this reporting period.

Oral symposium presentation at the 39th Annual Meeting of ISTSS:

Richards, A., Neylan, T., Santistevan, A., Woodward, S., *Distressing Dreams and Memory in PTSD: An App-Based Study Examining Nightmare Characteristics and Next Day Distress and Intrusions in Trauma-Exposed Subjects with and without PTSD.*

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?

<i>Name:</i> <i>Project Role:</i> <i>Research Identifier:</i> <i>Nearest person month worked:</i> <i>Contribution to project:</i>	Anne Richards Principal Investigator 1 No change from previous report.
<i>Name:</i> <i>Project Role:</i> <i>Research Identifier:</i> <i>Nearest person month worked:</i> <i>Contribution to project:</i>	David Baquirin Co-Coordinator 3 No change from previous report.
<i>Name:</i> <i>Project Role:</i> <i>Research Identifier:</i> <i>Nearest person month worked:</i> <i>Contribution to project:</i>	Nikhila Udupa Co-Coordinator 2 No change from previous report.
<i>Name:</i> <i>Project Role:</i> <i>Research Identifier:</i> <i>Nearest person month worked:</i> <i>Contribution to project:</i>	Miles Kovnick Coordinator 10 No change from previous report.
<i>Name:</i> <i>Project Role:</i> <i>Research Identifier:</i> <i>Nearest person month worked:</i> <i>Contribution to project:</i>	Polina Orlova Research Assistant 2 No change from previous report.
<i>Name:</i> <i>Project Role:</i> <i>Research Identifier:</i> <i>Nearest person month worked:</i> <i>Contribution to project:</i>	Shane Pracar Research Assistant 1 Ms. Pracar is responsible for managing participants wearing the ambulatory EEG device for data collection. She will also assist with recruitment, managing volunteers, downloading data of participant sleep/wake patterns, and data entry.
<i>Name:</i> <i>Project Role:</i> <i>Research Identifier:</i> <i>Nearest person month worked:</i>	Anthony Santistevan Biostatistician 1

Contribution to project:

Dr. Santistevan will take the lead with reviewing data quality, running statistical analyses, and preparing results for abstracts, manuscripts, and presentations.

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

COLLABORATIVE AWARDS: Nothing to Report.

QUAD CHARTS: See attached.

9. APPENDICES: No appendices relevant to project status attached.

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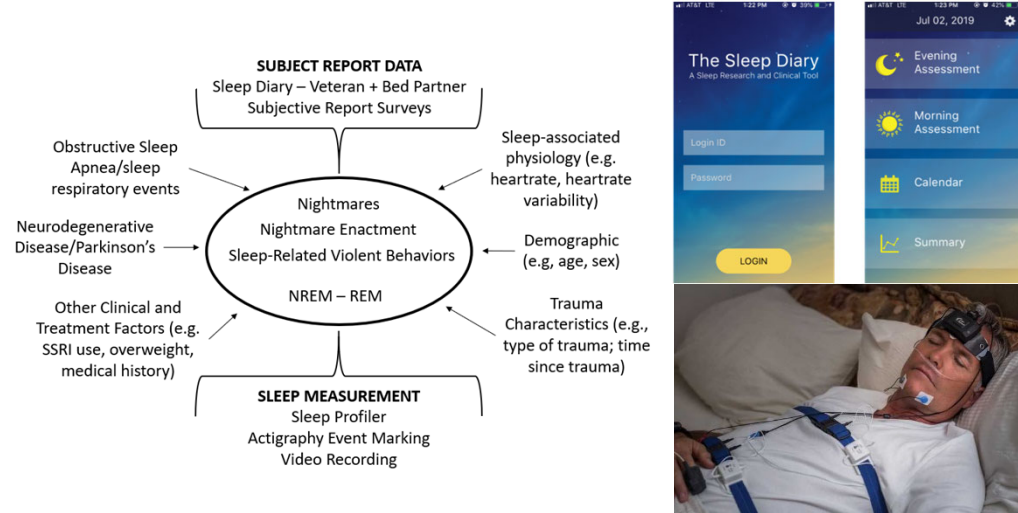
PI: Anne Richards, MD, MPH Org: Northern California Institute for Research and Education (NCIRE) Award Amount: \$1,816,437.00 (directs + F&A)

Study Aims

- Using an ambulatory, participant-administered multi-modal approach including sleep EEG, sleep diary app, standard wristband actigraphy with event markers, and video-recording of sleep activity, to examine the sleep architectural background of nightmares, nightmare enactment, and sleep-related violent behaviors.
- Using an ambulatory, participant-administered approach including EEG, pulse oximetry, and respiratory belts, to examine the relationship between respiratory events during sleep and nightmares, nightmare enactment, and non-nightmare distressed awakenings.
- Using a machine learning approach, utilize the full range of in the sample to identify independent and interacting predictors of the target sleep disturbances in the sample.

Approach

Trauma-exposed male and female veterans aged 18-80, and their available and consenting bed partners, will complete a two-phase study involving 3 weeks of mobile app plus actigraphy data collection (Phase 1), followed by 1-2 weeks of multi-modal assessments (Phase 2, involving sleep diary, actigraphy, EEG recordings, and video recordings) for those meeting symptom and adherence criteria in Phase 1. In combination with physiological data obtained in Phases 1 and 2, self-report surveys and chart review will provide data on multiple clinical and demographic characteristics that will contribute to analyses for Aim 3.



Pilot work has optimized our sleep diary mobile app for collection of data on the sleep events of interest. Analysis of pilot data provides support for our primary hypothesis and compelling physiological data that will be pursued further in the current study.

Timeline and Cost

Activities	CY	20-21	21-22	22-23
Prepare Protocol and Perform Regulatory Procedures		█		
Coordinate Study Staff for Study		█		
Data Collection			█	
Data Analysis and Dissemination of Findings			█	
Estimated Budget (\$K)		\$622,797	\$629,534	\$564,106

Goals/Milestones

CY20 Goal – Perform Regulatory Procedures for Study

- Local IRB approval at UCSF and VA
- HRPO approval

CY20 – Coordinate Study Staff for Study

- Research staff hired and trained

CY21-23 – Data Collection

- Study begins
- First participant consented, screened, and enrolled
- Study data collection complete

CY21-23 – Data Analysis and Dissemination of Findings

- Data analysis complete
- Results disseminated

Budget Expenditure to Date (as of 05/14/23)

Projected Expenditure: \$1,816,437 (directs + F&A)

Actual Expenditure: \$734,924 (directs + F&A)

Updated: (08/04/2023)