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

PRINCIPAL INVESTIGATOR: Dr. Anne Richards, MD, MPH

CONTRACTING ORGANIZATION: Northern California Institute for Research and Education
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PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

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4. TITLE AND SUBTITLE Using an Ambulatory Technology Approach to Understand Nightmares, Nightmare Enactment, and Sleep-Related Violent Behavior: Toward Precision Diagnosis in PTSD			**5a. CONTRACT NUMBER** **5b. GRANT NUMBER** W81XWH-20-1-0307 **5c. PROGRAM ELEMENT NUMBER**
6. AUTHOR(S) **A**nne Richards, MD, MPH E-Mail: anne.richards@ucsf.edu			**5d. PROJECT NUMBER** **5e. TASK NUMBER** **5f. WORK UNIT NUMBER**
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Northern California Institute for Research and Education, Inc. 4150 Clement St 151NC San Francisco, CA 94121-1545			**8. PERFORMING ORGANIZATION REPORT NUMBER**
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12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited			
13. SUPPLEMENTARY NOTES			
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			
16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT** Unclassified
18. NUMBER OF PAGES 12	**19a. NAME OF RESPONSIBLE PERSON** USAMRDC		
a. REPORT Unclassified	**b. ABSTRACT** Unclassified	**c. THIS PAGE** Unclassified	**19b. TELEPHONE NUMBER** *(include area code)*

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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 36 participants and completing a total of 21 part 1 participants and 9 part 2 participants. At the end of the reporting period, we additionally had 9 participants enrolled in part 1 and 4 participants enrolled in or ready to start part 2 of the study. We additionally explored new recruitment methods including social media advertisements via UCSF's Participant Recruitment Program (PRP) and use of ResearchMatch to contact individuals interested in participating in research. The UCSF PRP social media advertisements were especially effective, giving us over 200 potential participants to screen in the past year. Finally, we opened recruitment to individuals residing anywhere in the United States to expand our recruitment pool. In March of this past year, we also opened recruitment to civilians, though our focus remains on recruiting Veteran participants.
2. Specific objectives: Our specific objectives remained consistent with our major activities. During Months 19-24, we focused on study recruitment and enrollment of participants.
3. Significant results or key outcomes: No results to date.
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?

Nothing to Report.

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 efforts. We will continue to use the recruitment methods that have been proven to be effective (for example, the ResearchMatch recruitment service and social media recruitment). We will continue to explore the different recruitment services offered by Trialfacts.
Additionally, we plan to specifically enhance our recruitment of individuals experiencing nightmare enactment by using Trialfacts and by collaborating with neurodegenerative clinics at UCSF and the San Francisco VA. Finally, we will reach out to other nightmare researchers across the nation as well to receive participant referrals and advertise our study in other treatment facilities. Finally, we will collaborate with neurodegenerative clinics at UCSF to find eligible patients who have nightmare enactment.

4. IMPACT:

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

We just 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 publication 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 mitigate recruitment challenges we have made the following changes to widen our enrollment pool:

- Expanding nationally (approved 6/23/2021).
- Including civilians (approved 3/18/2022). Our goal remains to enhance our recruitment of veterans while also accelerating our overall recruitment through addition of civilian participants.
- Began using ResearchMatch (approved 3/18/2022). ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University as an IRB-approved data repository that UCSF researchers have access to.
- Decreased the minimum number of nightmares required in inclusion criteria from 2 to 1 (approved 6/23/2021). Of note, these new criteria are in line with commonly used standards of nightmare frequency for nightmare experiencers and individuals with PTSD.

To reduce burden on study participants and study staff, we requested and were approved for use of VA DocuSign (approved 3/18/2022); this has reduced the amount of time involved with consenting and has reduced the number of documents that staff and participants must mail.

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

During the past reporting period, we have experienced a few delays in participant completion. During the surge in COVID cases in January of 2022, the San Francisco VA changed its guidelines on in-person research activity. To keep up with the new guidelines and ensure study staff safety, all clinical interviews were conducted remotely for a period of a month, which took longer to schedule and complete than before.

There were also intermittent slow-downs with mailing equipment and documents to participant as the VA UPS system switched to using new softwares.

Additionally, we are currently in the process of hiring staff and anticipate a slight decrease of enrollment throughout the month of July as we temporarily shift focus to train a new coordinator.

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

Nothing to Report.

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.

A paper was submitted and accepted using data from the UCSF-funded pilot study that was conducted prior to the current study receiving funding. These findings enhance our enthusiasm about the added insights that the current study will provide us.
Authors: Richards, A., Woodward, S.H., Baquirin, D.P.G., Yack, L.M., Metzler, T.J., Udupa, N.S., Staggs,

E.J. and Neylan, T.C.
Title: The sleep physiology of nightmares in veterans with psychological trauma: Evaluation of a dominant model using participant-applied electroencephalography in the home environment.
Journal: Journal of Sleep Research
Volume: 2022;1-6
Status: Published

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

Nothing to Report.

Other publications, conference papers and presentations.

Poster presented at the 37th Annual Meeting of the International Society for Traumatic Stress Studies: Richards, A., Woodward, S., Baquirin, D., Yack, L., Udupa, N., Metzler, T., Neylan, T. (2021, November). *A Pilot Study of the Sleep Physiology of PTSD Nightmares Using Participant-Applied Devices in the Home Environment.*
NOTE: This poster presentation was paid for using funds from award number W81XWH-17-1-0234 (also conducted by PI Dr. Anne Richards). However, the content of the poster presentation is very relevant to the current study, and staff working on the poster were paid using funds from the current award. Therefore, we felt it was reasonable to include here.

☐ **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?

Name:	Anne Richards
Project Role:	Principal Investigator
Research Identifier:	
Nearest person month worked:	2
Contribution to project:	No change from previous report.
Name:	David Baquirin
Project Role:	Co-Coordinator
Research Identifier:	
Nearest person month worked:	12
Contribution to project:	No change from previous report.
Name:	Nikhila Udupa
Project Role:	Co-Coordinator
Research Identifier:	
Nearest person month worked:	12
Contribution to project:	No change from previous report.

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.

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

PR191120

W81XWH-20-1-0307

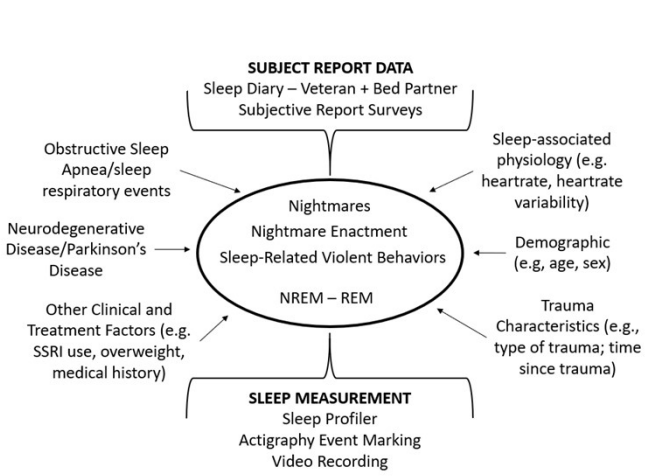
PI: Anne Richards, MD, MPH **Org:** Northern California Institute for Research and Education (NCIRE) **Award Amount: $1,816,437.00** (directs + F&A)

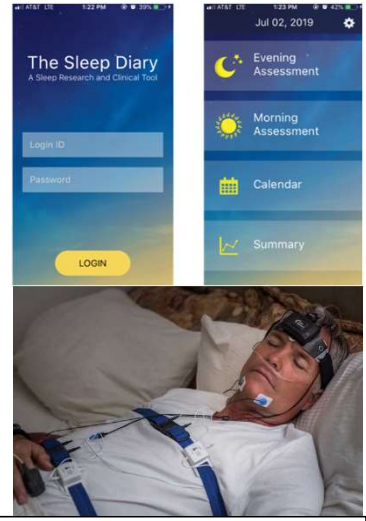
Study Aims

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 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	$564,107

Updated: (05/14/2022)

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 05/14/22)

Projected Expenditure: $1,252,331 (directs + F&A)

Actual Expenditure: $420,762 (directs + F&A)