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

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14. ABSTRACT This project will examine 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 examine the effects of disturbances in REM sleep on fear extinction and safety signal learning. These emotional learning processes are critical for trauma recovery and contribute to the efficacy of PTSD treatments such as exposure therapy. Disturbances in REM sleep and circadian dysregulation are common in serving military populations as well as veterans and civilian populations such as shift workers and rescue service personnel. These are also common disturbances reported in as many as 70-90% of Veterans with PTSD. However, to date research using both animal and human studies have all either been correlational in nature or have deprived subjects of REM sleep entirely. Neither of those methodologies are accurate models of the REM sleep disruption seen in military personnel at risk for PTSD. The proposed study will be the first to use ecologically valid models of sleep disruption (that mirror the types of disruption common in military missions and among Veterans with PTSD) to understand the mechanistic role sleep plays in the types impaired extinction and safety processes seen in PTSD.					
15. SUBJECT TERMS None listed.					
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TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	7
5. Changes/Problems	8
6. Products	9
7. Participants & Other Collaborating Organizations	12
8. Special Reporting Requirements	13
9. Appendices	13

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. To further explore the contribution of circadian misalignment to REM disruption, we will administer melatonin to rapidly reverse the REM disruption effects of circadian misalignment. 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?

Major tasks as stated in the SOW are:

Major Task 1: Study Set-up

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

Major Task 3: Data analysis and manuscript preparation

What was accomplished under these goals?

We successfully accomplished Major Task 1 (study set-up) during Year 1. As detailed in our Semi-annual and Annual reports that year, we experienced significant and unexpected technical difficulties with the equipment required to collect our primary outcome data (Fear Potentiated Startle). Given the vendor for the equipment is located in San Diego, California and we are in Melbourne, Australia, diagnosis of the problems and repairs took considerable time. We did finally resolve the issues late in the year. In the end, we completed only 50% of our target number of participants in that year (Oct 2018 - Sept 2019).

Major Task 2 (completion of study participants), especially in Years 2-3 of the grant (Oct 2019 – Sept 2021), was extensively negatively impacted by the COVID-19 pandemic. Melbourne, Australia experienced severe lockdowns throughout this 2-year period. We established the world record for the most number of days in lockdown during the pandemic. We experienced 6 separate lockdowns for a total of 262 days between March 2020 and October 2021. In addition, Monash University remained on Work From Home orders for extended periods of time, even when the city was not officially in lockdown. In Year 2, our research facilities were closed for 7 full months. In Year 3, our facilities was closed for 137 days (4.5 months).

Each time we existed lockdown, our team had to ramp up recruitment efforts, which involved a minimum of 2 weeks lead time for screening prior to any given participant commencing the experimental part of the study. Moreover, on at least two occasions, we had multiple participants lined up to admit into our facilities on a Sunday night, only to have a snap lockdown announced on the prior Thursday or Friday. Typically, we were not able to retain these participants once the lockdown eventually lifted. Finally, we and others experienced a notable drop in healthy controls willingness to participate in research even after all the lockdown ended. Unfortunately, this dynamic impacted Year 4 of this project.

In an effort to adapt to the new realities we faced once our lockdowns ended, we made a decision at the start of our NCE year, in consultation with our partnering site and our Science Officer, to drop one of the three arms in the study. This was initially mentioned in our Year 3 Annual Report (October 2021) and implemented in January of 2022. This allowed us to focus on collecting data to addressed our fundamental, novel aim in the grant.

Our final numbers for participants are as follows:

2200 expressions of interest (EOI)

1083 initial screening conducted

72 participants consented

42 participants started the experimental portion of the study

36 participants completed the study

We are currently working on Major Task 3 (data analysis and manuscript preparation). Our grant ended on 29 September 2022. We are in the process of cleaning and scoring the data collected from the final few participants. We are also in discussions with our partnering site (whose study will end in December 2022) to plan the specific manuscripts we believe we can produce, based on the data collected. We anticipate data analysis beginning in January 2023.

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

Despite the challenges faced by the project, we provided opportunity for training and professional development for the following numbers of trainees:

Postdoctoral Fellows: 3

PhD Students: 1

Honours: 4

Research Assistants (RA): 2

The Postdocs served as project coordinators. They gained experience in new research skills, as well as leadership and mentoring skills managing the study staff. The PhD student, Honours students (a research specialised 4th year of undergraduate), and the RAs had a variety of responsibilities, including recruitment and screening of participants, working with participants while they were in the lab, processing and scoring data, and writing theses with preliminary data from the grant. Both the RAs (who were fulltime employees) continued their careers in research after working on this project.

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?

Nothing to Report

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:

Nothing to report

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

Nothing to report

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.

Nothing to report

- **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?

The following information reflects the period since the NCE Semi-Annual report was submitted (i.e., 1 April 2022 – 29 Sept 2022).

Name: Sean P.A. Drummond
No change

Name: Prof Shantha Rajaratnam
No change

Name: David Litewka
No change

Name: Johanna Boardman
Project Role: Postdoctoral Fellow
Researcher Identifier: 0000-0002-0353-5639
Nearest person month worked: 1.0
Contribution to Project: Dr. Boardman served as project coordinator (part time) over the last few months of this project.

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 Veterans Medical Research Foundation (VMRF), who is the lead site on this collaborative grant. VMRF has submitted an independent report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: