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W81XWH-18-1-0762

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

PRINCIPAL INVESTIGATOR: Sean Drummond

CONTRACTING ORGANIZATION: Monash University

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<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 significant unexpected hardware and software issues requiring us to return our primary data collection equipment to the manufacturer twice. Despite these hurdles, we completed 7 participants (46.7% 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.					
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**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. 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:** *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; expected completion date: 30 March 2019

*Subtask 1:* Obtain regulatory approval. Completed: 17 January 2019

*Subtask 2:* Hire and train all study staff. Completed 15 April 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

46.7% (7/15) 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, expect the completion of 15 participants.

The majority of our efforts during this first year were focused on overcoming technical difficulties originally reported in the semi-annual report dated 30 April, 2019. At that time, we believed we were close to solving the problems. Unfortunately, the problems continued, as discussed in Section 5: CHANGES/PROBLEMS. The result was 2 additional periods of down time, related to trouble shooting and repairing hardware. The equipment is currently fully functional, and we now believe all problems have been solved. As of this report, we have completed 7 participants (46.7% of this task). We have another 15 participants scheduled before the end of 2019. Given typical screen-out/drop-out rates, we anticipate 12 of those will provide complete data.

### **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. Kate Porcheret was hired as the Postdoctoral Fellow and project coordinator. Prof Drummond meets with Kate on a weekly basis to discuss both project issues and career development issues. Kate has learned specific technical skills (e.g., fear potentiated startle), as well as project management and personnel supervision skills.

Jacob Clark is a PhD student working on the project. He has learned several technical skills, as well. Jake’s thesis involves not only this project, but also a parallel project in mouse models (funded through a different source). Thus, he is learning valuable research translation methods as part of his work on this project.;

Eleni Kavaliotis was hired as a full time research assistant. Eleni recently graduated with a Bachelors degree from Monash University, and this is her first post-degree job. She is learning a variety of skills related to conducting a high level research project. I have also had multiple career development discussions with Eleni, including how she can leverage her work on this project to continue her studies into the PhD level.

*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.*

We experienced significant hardware and software issues with the Fear Potentiated Startle (FPS) equipment purchased for this study. This equipment collected data related to our primary outcomes, and thus, these issues halted data collection on two occasions. Here is a brief description of the issues.

- Our original goal was to begin data collection in January 2019 (month 4 of the grant year).
- In January 2019, significant noise in the EMG signal produced by the equipment was noted. EMG is the primary data signal.
- For the next 6 weeks, we attempted to determine the source of the noise through a series of calls and experiments with our colleagues in San Diego (the other grant site), the manufacturer of the equipment, and Monash Bioengineering. None of this work discovered the problem.
- In March 2019, we returned the equipment to the manufacturer for replacement.
- In April 2019, new equipment was received and testing commenced.
- June 2019, we completed our first 2 participants, and 1 more in July.
- July 2019, a new issue was discovered that ultimately required we again send the equipment back to the manufacturer.
- September 2019, the new/repared equipment returned to Monash University. After extensive testing, we determine it was now fully functional and we began data collection. We have since completed 4 participants in the study.

**Plans moving forward**

- We are carefully monitoring data produced by the FPS equipment and conduct ongoing QA/QC. So far, we are satisfied with the data generated on the most recent participants.
- We plan to bring more research assistant staff on board in Year 2 to increase our pace of participant recruitment and completion. This will result in greater personnel and participant expenses than originally budgeted in Year 2, but we will utilise savings from Year 1 for this.

**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: Sean P.A. Drummond  
Project Role: PI  
Researcher Identifier: ORCID ID 0000-0002-9815-626X  
Nearest person month worked: 1.2  
Contribution to Project: Prof Drummond has led all aspects of the project

Name: Prof Shantha Rajaratnam  
Project Role: co-investigator  
Researcher Identifier: 0000-0001-7527-8558  
Nearest person month worked: 0.6  
Contribution to Project: Prof Rajaratnam has led development of the circadian manipulation protocol, including selection of timing of the manipulation and selection of drug and dosage to use in the protocol.

Name: Dr. Kate Porcheret  
Project Role: Postdoctoral Fellow  
Researcher Identifier: 0000-0001-7832-9269  
Nearest person month worked: 5.5  
Contribution to Project: Dr. Porcheret serves as the project coordinator, overseeing data-to-day operations. Dr. Porcheret started later than originally planned in the grant proposal, due to needing to finish her prior work commitment and delays in her work visa to Australia.

Name: Eleni Kavaliotis  
Project Role: Research Assistant  
Researcher Identifier: n/a  
Nearest person month worked: 9.0  
Contribution to Project: Ms. Kavaliotis has been involved in the development of SOPs, has built our master database template, and contributed to development of recruitment materials. She has also trained other staff in sleep lab procedures.

Name: David Litewka  
Project Role: Sleep Technician  
Researcher Identifier: n/a  
Nearest person month worked: 6.0  
Contribution to Project: Mr. Litewka has developed our sleep study related SOPs and is training other staff in sleep study procedures.

Name: Jacob Clark (unpaid)  
Project Role: Graduate student  
Researcher Identifier: 0000-0002-9412-3356  
Nearest person month worked: 6.0  
Contribution to Project: Mr. Clark served as the project coordinator prior to Dr. Porcheret arriving. Currently, he leads develop of SOPs and training on our main fear conditioning psychophysiological measures. He also maintains the associated equipment.

**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 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:** *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.*