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CONTRACTING ORGANIZATION: Monash University

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14. ABSTRACT This report covers Year 3 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 to complete 15 participants in the study (60 total across all years), including processing and cleaning of all data. Not surprisingly, the coronavirus pandemic continued to significantly impact those plans. Our sleep lab was shut down for a total of 137 days, across 4 separate local lockdowns over the year. Nonetheless, during Year 3, 27 participants signed consent and 12 of them completed the study. At the end of this grant year, we requested a No Cost Extension. We anticipate we will not ultimately be able to meet our original recruitment goals. Thus, our plan is to drop one of our 3 conditions to allow us to focus enrollment on the other two conditions and still address key aims of the grant. This will maximize the efficiency of our remaining time for recruitment.					
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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 2: Recruit, enroll, and run study participants

Subtask 3: In Year 3, complete approximately 15 participants at each site. This includes initial data cleaning and processing and adding data to the master data base.

Subtask 4: Maintain coordination, calibration, and common procedures across sites

Major Task 3: Data analysis and manuscript preparation

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.

Given the severe lockdowns in Melbourne, Australia (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). In Year 3, specifically, the sleep lab was closed for 137 days over 4 separate lockdowns. That severely affected our ability to enrol participants into the study. Nonetheless, during Year 3, 27 participants signed consent and 12 of them completed the study. While this is very close to the SOW work goal for completed participants in Year 3, we remain behind schedule due to 2020 and 2021 being severely impacted by the pandemic. In total, 68 participants have signed consent and 32 have fully completed the study. Of those not completing the study, 33 were either excluded or dropped out after signing consent and before starting the experimental week in the lab. While this is a higher proportion than we typically see in this kind of experimental study, much of the increase can likely be attributed to the pandemic. Specifically, a number of participants signed consent while the sleep lab was open and were then unable to participate because the sleep lab was again shut down due to local lockdowns. Typically, those individuals were no longer available or no longer interesting in participating. In addition, a larger than normal proportion of people were excluded because they did not follow the agreed-upon sleep wake schedule during the baseline week. This is consistent with multiple studies that have reported sleep has become both later and more irregular during the pandemic (especially in young adults). Those features are exclusionary for this study.

Given the reduced rate of recruitment, we were able to manage our budget such that we requested a No Cost Extension at the end of Year 3. Our goal is to enrol as many participants as possible prior to exhausting the grant funds.

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.

Despite the challenges associated with Year 3, we trained two Honours students (i.e., 4th year Psychology students involved in a research training year) on this project throughout the year. Each student worked on the study 2 days/week. Their responsibilities included recruitment and screening of participants, working with participants while they were in the lab, processing and scoring data, and writing an Honours thesis with preliminary data from the grant. We anticipate at least one of these theses will convert into a peer reviewed manuscript during the coming year.

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state “Nothing to Report.” 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

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

If this is the final report, state “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 do not anticipate meeting our original enrolment goals. Thus, the investigator team (including from our partnering site) are currently developing a strategy to maximise the value of the participants we can recruitment. Specifically, we are conducting preliminary analyses to determine the best strategy for dropping one of our current conditions, and focusing on enrolling into the other two conditions. This will allow us to achieve sufficient statistical power to answer a subset of the key questions posed in the grant. For example, one option is to drop the circadian misalignment+melatonin group. We would then focus on the normal sleep and circadian misalignment+placebo groups, allowing us to address the critical question of whether circadian disruption (e.g., operationally caused by jet lag or night missions) creates the kind of sleep disturbances that impair fear extinction. Currently, no human study has addressed that question. Thus, the aim alone would make a significant contribution to the literature. We anticipate making this decision prior to restarting data collection after the holiday period, so the remaining (approximately) 6 months of data collection can focus on those conditions most likely to answer one of the study aims.

- 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.

Please see discussion above about potentially dropping one study condition to allow more focused data collection with the remaining time on the grant. Our government has a stated policy of not imposing additional lockdowns. So, we are cautiously optimistic we will be able to enrol participants continuously between now and the end of the project. We currently project the budget to allow us to continue data collection through June 2022.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Given we were unable to enrol participants for a large portion of this reporting period, our expenses were reduced. However, I did make the decision to retain all main personnel on the study. This allowed us to work on the data we had already collected, as well as ramp back up as soon as feasible following each lockdown period.

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”.

Name: Sean P.A. Drummond
No change

Name: Prof Shantha Rajaratnam
No change

Name: David Litewka
Project Role: Sleep Technician
Researcher Identifier: n/a
Nearest person month worked: 8.2

Contribution to Project: Mr. Litewka developed our sleep study related SOPs, trained other staff in sleep study procedures, ran our sleep studies, scored all sleep records and played the major role in establishing interrater reliability with the San Diego site.

Name: Jacob Clark
Project Role: Postdoctoral Fellow
Researcher Identifier: 0000-0002-9412-3356
Nearest person month worked: 10.4

Contribution to Project: Dr. Clark started as project coordinator in February 2021. Prior to that, he served in a research assistant role while finishing his PhD. Dr. Clark led the in-lab component of the study and oversaw the research assistants and volunteers working on the study.

Name: Ms. Kiandra Tomlinson
Project Role: Research Assistant
Researcher Identifier: n/a
Nearest person month worked: 5.2

Contribution to Project: Ms. Tomlinson served as the recruitment officer on the project starting in January 2021. She also helped run the in-lab component of the study and oversaw data processing of data from the baseline week of sleep.

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*

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.*