

AWARD NUMBER: W81XWH-16-1-0259

TITLE: When Sleep Isn't Perfect: Risk and Resilience for Cognitive Consequences of Imperfect Sleep Duration and Suboptimal Timing of Tasks in Circadian Rhythm

PRINCIPAL INVESTIGATOR: Anne Richards

CONTRACTING ORGANIZATION: Northern California Institute for Research and Education, San Francisco CA 94121

REPORT DATE: July 2018

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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|--|------------------------------------|-------------------------------------|-----------------------------------|---|--|
| 1. REPORT DATE July 2018 | | 2. REPORT TYPE Annual | | 3. DATES COVERED 1 Jul 2017 - 30 Jun 2018 | |
| 4. TITLE AND SUBTITLE When Sleep Isn't Perfect: Risk and Resilience for Cognitive Consequences of Imperfect Sleep Duration and Suboptimal Timing of Tasks in Circadian Rhythm | | | | 5a. CONTRACT NUMBER | |
| | | | | 5b. GRANT NUMBER W81XWH-16-1-0259 | |
| | | | | 5c. PROGRAM ELEMENT NUMBER | |
| 6. AUTHOR(S) Anne Richards 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 4150 Clement St 151NC San Francisco CA 94121-1545 | | | | 8. PERFORMING ORGANIZATION REPORT NUMBER | |
| 9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012 | | | | 10. SPONSOR/MONITOR'S ACRONYM(S) | |
| | | | | 11. SPONSOR/MONITOR'S REPORT NUMBER(S) | |
| 12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited | | | | | |
| 13. SUPPLEMENTARY NOTES | | | | | |
| 14. ABSTRACT We have made significant progress since our last Annual Report. In addition to our 2017 published work, we have performed analyses on tasks assessing cognitive domains of selective attention, response inhibition, cognitive flexibility and task switching. We have replicated our published findings with respect to sleep duration using different tasks, have found that chronotype and task-time aligned with chronotype do <i>not</i> appear to markedly impact performance but that time-of-day has a strong relationship with performance level, and have identified compelling interactions between sleep duration, time-of-day and chronotype variables on cognitive performance. We have also found some interesting preliminary findings with respect to sleep and mood. We are preparing a follow-up manuscript based on new findings and are continuing to perform analyses on additional tasks for which our industry collaborator has collected datasets large enough for addressing our research questions. While continuing to analyze data on task performance, we are progressing to our analyses with respect to the relationship of sleep and chronotype effects on change in performance (i.e.learning). We are also currently preparing a DoD grant submission based on our findings to date. | | | | | |
| 15. SUBJECT TERMS Sleep Duration, Chronotype, Cognitive Performance, Learning | | | | | |
| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
| a. REPORT Unclassified | b. ABSTRACT Unclassified | c. THIS PAGE Unclassified | Unclassified | 10 | USAMRMC |
| | | | | | 19b. TELEPHONE NUMBER (include area code) |

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1. INTRODUCTION:

Our DoD Discovery Award study uses large-scale internet-based cognitive performance data of adult men and women to examine how sleep and chronotype affect cognitive performance, and to uncover non-sleep factors contributing to cognitive risk and resilience in the setting of deviations from habitual sleep duration as well as misalignment of task timing with participants' endogenous circadian rhythmicity. The primary aims of this proposal are to examine the relationship of habitual sleep duration (HSD), deviations from habitual sleep duration, self-reported chronotype, and the degree to which task performance is aligned with chronotype (task-timing alignment to chronotype, (TTAC)) with cognitive performance and improvement in performance (i.e.: learning) of cognitive tasks in adult male and female users of an internet-based cognitive training program. The design will involve both cross-sectional and longitudinal assessment of cognitive performance on internet cognitive training tasks in adult men and women to examine the contributions of sleep, chronotype, demographic, lifestyle, and mood variables to cognitive performance and improvement in cognitive performance (i.e. learning) in adult male and female users of an internet cognitive training program

2. KEYWORDS:

Sleep Duration
Chronotype
Cognitive Performance
Learning

3. ACCOMPLISHMENTS:

Major Goals of Project: The primary scientific aims of our study are as follows:

Primary Aim 1: To assess the effects of habitual sleep duration (HSD), as defined by average sleep duration over a period of 4 months, and naturalistic deviation from habitual sleep duration, as determined by sleep duration immediately prior to task performance, on performance score and/or improvement in performance (i.e. learning) in tasks of working memory, task-shifting, response inhibition and verbal memory in adult male and female users of an internet cognitive training program.

Primary Aim 2: To assess the effects of chronotype, based on self-reported evening and morning preference, as well as degree of task-timing alignment to chronotype (TTAC score), as determined by chronotype and time-of-day of task performance, on performance score and/or improvement in performance (i.e. learning) in tasks of working memory, task shifting, response inhibition and verbal memory in adult male and female users of an internet cognitive training program.

Primary Aim 3: To assess the interaction of habitual sleep duration and degree of task-timing alignment to chronotype (TTAC score) on performance in tasks of working memory, task shifting, response inhibition and verbal memory in adult male and female users of an internet cognitive training program.

Primary Aim 4: To determine whether age moderates the effects of habitual sleep duration (HSD), deviations from habitual sleep duration, and degree of task-timing alignment with chronotype (TTAC score) on task performance and improvement in task performance (i.e. learning).

We described our major tasks and target dates of achievement of these tasks as follows:

Major Task 1 (Months 1-3): Study Start-Up and Approvals: Completed

We obtained required approvals for the study and established a strong working relationship with collaborators at Lumos Labs, who are committed to continue working with us in future projects.

Major Task 2 (Months 1-6): Obtain Data and Prepare Data for Analysis: In Progress

While we have already obtained and analyzed large data sets for tasks assessing cognitive domains of selective attention, response inhibition, cognitive flexibility and task switching, we are continuing to work with Lumos Labs to obtain additional datasets on different cognitive tasks to perform analyses consistent with our primary aims. Each dataset, once obtained, requires thorough review and trouble-shooting of data cleaning challenges that are inherent in internet-based datasets. Our work to date has provided us with the experience and skill to work effectively with data from our industry collaborators to generate satisfactory data quality for analysis.

Major Task 3: Data Analysis (Months 7-13): In Progress

We have made significant progress in addressing Primary Aims 1, 2, 3 and 4. We have found significant effects of sleep duration on cognitive performance and age-by-sleep-duration interaction effects on cognitive performance across multiple tasks. We have also identified compelling findings with respect to deviations from usual sleep duration. Interestingly, we did *not* find evidence for our hypotheses regarding chronotype effects on cognitive performance in two different tasks, nor did we find that alignment of task timing to chronotype improved performance, at least for evening chronotypes. Instead, we found an interesting time-of-day effect on performance which we plan to study further. While we did not observe a simple chronotype effect on performance, we *did* identify an interaction effect for chronotype and deviation from usual sleep duration, providing evidence that research to unravel the complex relationships between sleep, chronotype, circadian and other variables in the prediction of cognitive performance is crucial. We are also now initiating our analysis of sleep and chronotype effects on learning. We plan to request an additional no-cost extension to continue to obtain and analyze data for our primary aims on learning and our exploratory aims during an additional year.

Major Task 4 (Months 14-18): Dissemination of Findings and Preparation of Follow-Up Grants: In Progress

We have already published findings from an initial analysis on the relationship between sleep duration and cognitive performance. These results are compelling and success in publication demonstrates that findings are of relevance and interest to the sleep and broader scientific research community. We are preparing a manuscript with our findings on sleep, chronotype and time-of-day effects on cognitive performance at this time and expect to submit these in the coming month.

Thanks to our initial analyses and ongoing work using large-scale internet data acquired from Lumos Labs, we have established a collaboration with colleagues collecting large-scale data through the Brain Health Registry, an internet-based registry containing cognitive performance and health data from over 50,000 participants in the community, the goal of which is to understand the risk factors and causes of dementia and simultaneously to generate a pool of potential candidates for clinical trials. We intend to grow the collaboration with the BHR researchers to continue to advance large-scale data research to better understand the contribution of sleep and chronotype to cognitive performance.

What was accomplished under these goals?

- 1) Major Activities: Obtained all approvals for performance of research; publication of results of a preliminary cross-sectional analysis of sleep duration and cognitive performance in a sample of nearly 500,000 participants in high-impact journal; establishment of collaboration with new Lumos data scientists; data analysis for Primary Aims 1-4 (cognitive performance, but not learning) on 2 separate datasets comprised of approximately 50,000 participants with over 2 million test scores each for tasks assessing multiple cognitive domains; development of strategy for obtaining larger datasets in collaboration with Lumos collaborators and developing plans for partnership in a new DoD research proposal.
- 2) Specific Objectives: Our specific objectives were consistent with our major activities. Due to data scientist changes at our industry partner, we were delayed in obtaining target datasets until 2017 but are now analyzing data smoothly and consistently with our objectives.
- 3) Significant results/Key outcomes: Both published and preliminary analyses are yielding compelling simple and interaction effects for the key predictors of interest (see Major Tasks 2 and 3 above).

See: Richards A, Inslicht SS, Metzler TJ, Mohlenhoff BS, Rao MN, O'Donovan A, Neylan TC. Sleep and Cognitive Performance From Teens To Old Age: More Is Not Better. *Sleep*. 2017 Jan 1;40(1) PMID: 28364476

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

This project provided Dr. Richards (PI) with several professional development opportunities:

- 1) Attendance at the Associated Professional Sleep Societies June 2018 Annual Meeting. This annual meeting provides a forum for researchers and clinicians in sleep medicine to learn about the latest developments in sleep science and to network with other scientists.

How were the results disseminated to communities of interest?

The results were disseminated to communities of interest through the published manuscript of preliminary analysis, as above, and through informal discussions with research colleagues to inform next steps in our project.

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

1. Continue to collaborate actively with Lumos collaborators to obtain datasets of size and scope required to accomplish our objectives primary, as well as exploratory, objectives
2. Continue analyses to accomplish primary aims with respect to cognitive performance for a task of verbal memory and perform analyses to accomplish primary aims with respect to improvements in performance (i.e. learning)
3. Perform analyses to accomplish exploratory aims
4. Publish and disseminate findings on cognitive performance as well as learning
5. Advance our collaboration with UCSF colleagues who founded the Brain Health Network to expand our sources of large-scale data to understand the relationship between sleep, chronotype and cognitive performance.

4. IMPACT:

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

Preliminary findings from analysis of data from our industry collaborator have been published and well-received. Our findings raise compelling questions about sleep need and optimal sleep duration with respect to cognitive functioning at different ages. These findings highlight the importance of further research on the relationship between sleep duration and cognitive performance across the full range of the age spectrum. They demonstrate the potential of large-scale internet data for gaining knowledge in this area. We are confident that our new findings will also be impactful.

What was the impact on other disciplines?

We expect findings from our research to have an impact on disciplines focused on cognition, learning and neurodegenerative diseases, such as neurology and geriatric medicine. We expect our findings to be relevant in non-research and non-medical arenas in which there may be barriers to normal sleep durations and job schedules and in which optimizing cognitive performance in the context of unusual work hours is critical, such as the military.

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:

Nothing to report.

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

As described above, delays due to data scientist turnover at Lumos Labs initially created a barrier to achievement of Major Task 2 until spring 2017. In May 2017 we obtained a preliminary dataset which allowed us to identify and trouble-shoot data cleaning challenges that are inherent in internet-based datasets. We have now made major progress towards accomplishing our primary objectives, and have multiple important findings to report. We plan to request an additional no-cost extension to complete our primary objectives and advance our exploratory aims. We are actively preparing a DoD grant with objectives that are distinct from our current study's objectives, but which objectives are based directly on new and compelling findings that emerged from the current study.

Changes that had a significant impact on expenditures

Due to prior personnel changes at our Industry collaborator's institution, we were delayed in addressing our project objectives (previously reported in 2017). Our collaboration has gone smoothly this year and we have made significant progress in achieving our objectives, but have not recovered the delays in expenditures. Our plan is to request a second no-cost extension to continue to be able to complete all components of our objectives, including analyses on the relationship of sleep duration and chronotype to learning.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

6. PRODUCTS:

Richards A, Inslicht SS, Metzler TJ, Mohlenhoff BS, Rao MN, O'Donovan A, Neylan TC. Sleep and Cognitive Performance From Teens To Old Age: More Is Not Better. Sleep. 2017 Jan 1;40(1) PMID: 28364476

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

What individuals have worked on the project?

| | |
|-------------------------------------|--|
| <i>Name:</i> | Anne Richards, MD, MPH |
| <i>Project Role:</i> | Principal Investigator |
| <i>Researcher Identifier:</i> | |
| <i>Nearest Person Month Worked:</i> | 1.5 |
| <i>Contribution to Project:</i> | Dr. Richards is the initiating investigator and has assumed the overall scientific and administrative responsibility for the project. She is taking the lead on study design, data quality control, data analysis, and preparation of results for dissemination. |
| <i>Name:</i> | Thomas Neylan, MD |
| <i>Project Role:</i> | Co-Investigator |
| <i>Researcher Identifier:</i> | |
| <i>Nearest Person Month Worked:</i> | .36 |
| <i>Contribution to Project:</i> | Dr. Neylan has collaborated closely with Dr. Richards to ensure data quality and integrity. He has provided expertise in sleep and cognitive data analysis and interpretation. |

| | |
|-------------------------------------|---|
| <i>Name:</i> | Thomas Metzler, M.S. |
| <i>Project Role:</i> | Statistician |
| <i>Researcher Identifier:</i> | |
| <i>Nearest Person Month Worked:</i> | .5 |
| <i>Contribution to Project:</i> | Mr. Metzler has played a lead role in working with Lumos Labs data scientists to identify the appropriate datasets and prepare datasets for analysis via data quality examination and cleaning. Mr. Metzler is actively involved in grant preparation for a study building on our current findings. |
| <i>Name:</i> | Russell Huie |
| <i>Project Role:</i> | Statistician |
| <i>Researcher Identifier:</i> | N/A |
| <i>Nearest Person Month Worked:</i> | 2.4 |
| <i>Contribution to Project:</i> | Dr. Huie has taken on the leading statistician role for the project, based on his extensive experience working with large-scale data. He has taken a lead role in writing code and implementing complex data analytic procedures for this project. |
| <i>Name:</i> | Christen Chapman |
| <i>Project Role:</i> | Lab Manager |
| <i>Researcher Identifier:</i> | N/A |
| <i>Nearest Person Month Worked:</i> | 0.75 |
| <i>Contribution to Project:</i> | Ms. Chapman has provided general lab management support for Dr. Richards and preparation of grants, manuscripts and technical report and supervision of other research staff, such as Ms. Emery. She has expertise in lab management and regulatory issues but is currently off-site therefore collaborates with on-site staff to support the study team. |
| <i>Name:</i> | Alaisa Emery |
| <i>Project Role:</i> | Research Assistant |
| <i>Researcher Identifier:</i> | N/A |
| <i>Nearest Person Month Worked:</i> | 1 |
| <i>Contribution to Project:</i> | Ms. Emery has provided work in the area of data cleaning and data management support for the study, with supervision of PI and statistician, as well as support of Dr. Richards and Ms. Chapman in preparation of grant, manuscript and technical report preparation. |
| <i>Name:</i> | Sijing Ye |
| <i>Project Role:</i> | Research Assistant |
| <i>Researcher Identifier:</i> | N/A |
| <i>Nearest Person Month Worked:</i> | .5 |
| <i>Contribution to Project:</i> | Ms. Ye has provided work in the area of data cleaning and data management support for the study, with supervision of PI and statistician, as well as support of Dr. Richards and Ms. Chapman in preparation of grant, manuscript and technical report preparation. |

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?

Lumos Labs, for provision of data. There is no change to report.

8. SPECIAL REPORTING REQUIREMENTS:

COLLABORATIVE AWARDS:

Not applicable.

QUAD CHART:

Not applicable.

9. APPENDICES: None