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TITLE: Effects of Dose-Dependent Sleep Disruption on Fear and Reward Responses

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14. ABSTRACT This is an annual progress report for the funding period between 03/01/2013 to 02/27/2014. We have met our enrollment targets for Year 2, although some participants cancelled experimental procedures or were unable to tolerate the sleep manipulation. We have initiated preliminary and ancillary data analyses, and 2 abstracts have been prepared to submission to national scientific meetings. Data monitoring, management, review, and processing are conducted on an ongoing basis, and reviewed weekly.					
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Type of report: Annual Technical Progress Report
Progress Period: March 1 2013 to February 25 2014

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I. INTRODUCTION

The goal of this research study is to evaluate the effects of different doses of sleep deprivation on psychophysiological and neural responses to threat and reward stimuli in healthy young adults between the ages of 18 and 30. Exploratory aims will assess whether genotype and childhood exposure to adversity influence the effects of dose-dependent sleep disruption on fear and reward responses. The current report summarizes progress made in the past 12 months of performance.

II. BODY

Research accomplishments associated with each task outlined in the approved Statement of Work for this period of performance are detailed below.

Table 1. Summary of tasks and timelines for each study-related task.										
	Year 1		Year 2		Year 3		Year 4		Year 5	
	Months 1-4	Months 5-12	Months 13-18	Months 19-24	Months 25-30	Months 31-36	Months 37-42	Months 43-48	Months 49-54	Months 55-60
Task										
1. Secure IRB and HROP approvals and order study supplies.	DONE									
2. Hire and train new personnel (2)	DONE									
3. Recruit, screen, and randomize, and test 198 subjects		DONE	ONGOING							
4. Perform genetics procedures		DONE	ONGOING							
5. Data review, quality control /insurance, processing, scoring, and storage		DONE	ONGOING							
6. Perform exploratory and confirmation analysis and reports			Initiated							

Summary of progress in the second year of performance. Our efforts in the past year have focused primarily on continuing to enroll research participants and conducting the experimental phase of the protocol. We have and continue to closely monitor enrollment in the study, and to refine our recruitment efforts to optimize the rate of conversion from screening to completed experimental procedures. We have continued to hold weekly meetings to review progress and address any procedural questions that have arisen. Dr. Germain continues to hold weekly meetings multiple meetings with staff and co-investigators to review the different research procedures that compose the study protocol, as well as participants' eligibility, data integrity, and quality insurance reviews. We have also initiated bi-weekly data analysis meetings in order to further refine the data analytical plan, and make sure we are well positioned to complete all confirmatory data analyses in a timely manner at the end of the award.

We are now conducting experimental procedures at the expected rate of one to two participant(s) per week. We have also significantly reduced the mean time from screening to completion of the study from an average of 69 days to an average of 32 days in the past year. As of 2/25/2014, we have randomized a total of 67 participants to one of the three sleep conditions, and 56 have completed all experimental procedures. One more participant is scheduled to complete the experimental protocols by March 7th 2014. Ten participants who were randomized cancelled their study, or were found ineligible one the first study night, or did not tolerate the sleep manipulations and withdrew from the study. To date, our recruitment and enrollment is on target, but the rate of cancellations or

withdrawal due to inability to tolerate sleep disruption is slightly higher than anticipated. Therefore, we will increase our recruitment and target the completion of 5 participants per month on average (we have the ability to complete up to 7 per month) in the coming period of performance. We are confident we will rapidly achieve our targeted number of completed study in Year 3.

Genotype analysis procedures have been revised and improved to allow for rapid genotyping and randomization of participants into the experimental phase of the study. We are now able to receive genotyping information within 14 days of blood sampling (compared to 60 days last year). We are very pleased with this development, and this new approach has further facilitated our enrollment target in Year 3 (March 2014 – March 2015).

Detailed description of effort expended during the last period of performance: The tasks and timeline listed in the approved Statement of Work (summarized in Table 1) are provided below. Progress and outcomes on each of the tasks listed are detailed for this review period.

Task 1: Secure IRB and HRPO approvals (Months 1-4, NCTRC) and order study supplies.

- Secure approvals for human research from the University of Pittsburgh Institutional Review Board (IRB), and USAMRMC Human Research Protection Office (HRPO) prior to initiating recruitment.

Progress: This sub-task has been completed. The University of Pittsburgh IRB first reviewed and approved the protocol on 8/16/2011. Renewal has been granted on February 2, 2014, and will be due for renewal on February 3, 2015.

- Order start-up supplies and materials.

Progress: This sub-task is completed.

- Test and calibrate instrumentation (e.g., fMRI tasks programming and test run, calibrate MR-compatible shock- and skin conductance sensors), data acquisition and data management protocols.

Progress: This sub-task has been completed in July 2012.

- Update manuals of operations already in place for Dr. Germain's and others' research protocols to include all procedures related to the Specific Aims of this project.

Progress: This subtask has been completed.

Task 2: Hire and train new personnel (Months 1-4, NCTRC).

Progress: This task has been completed.

Task 3: Recruit, screen, randomize, and test 198 healthy young adults (Months 5 – 54; NCTRC).

- Develop advertisement material and disseminate information about this study.

Progress: This subtask is ongoing. As of 27 Feb, 2014, we have consented 225 individuals, and 175 completed all screening procedures. Eighty-nine remained eligible after completing all screening procedures, and completed an apnea sleep screen study. Sixty-seven individuals have been randomized to one of the 3 experimental conditions. Of these, 56 have completed all experimental procedures, and 10 withdrew or were withdrawn after randomization because they 1) could not tolerate the sleep deprivation procedures; or 2) screened positive on a urine drug test, or 3) were found to have significant sleep disorder; or 4) cancelled their study due to illness or other unexpected circumstances. Thus, we have achieved our cumulative goal of randomizing 67 individuals in year 1 and year 2, but because of subject loss post-randomization, we have a shortage of 10 subjects in our targeted goal initiating and completing all experimental procedures in 67 subjects. This will be redressed in Year 3 by increasing the throughput for recruitment in order to achieve the recruitment target of 48 subjects in Year 3 and recruit 10 more participants to meet our cumulative recruitment target of 114 participants.

- Recruit and conduct diagnostic, physical and sleep screenings procedures and genotype participants (Appendix I, Recruitment Flow Chart)

Progress: From July 9th 2012 (opening of recruitment) to 2/27/14, we have been contacted by a total of 1522 individuals, and have obtained written informed consent for the screening procedures from 225 of them. The screening procedures include 3 segments. Visit #1 is the consent visit, and participants complete self-report screening questionnaires and the genetic blood draw. After providing written informed consent, 225 remained eligible. Visit #2 involves clinician-administered psychiatric and sleep interviews, and the physical examination. One-hundred and seventy-five participants have completed these procedures, and 90 remained eligible after completing this second visit. Visit #3 refers to the overnight sleep screening study. Of these, 89 completed the in-home sleep screening, and 80 were found eligible to enter the experimental phase of the study. Sixty-seven have been randomized to one of the sleep condition (normal sleep vs. sleep restriction vs. sleep deprivation), and 10 withdrew from the study prior to randomization. Of the 67 randomized, 56 have completed all study procedures, and one more is on schedule to complete these procedures by March 7, 2014.

- Using the Childhood Trauma Questionnaire (CTQ), obtain a history of adverse childhood experiences (i.e., neglect, abuse, other traumas) in order to carefully characterize the sample, enhance the ability for generalizability / comparisons with military samples of young adults, and explore the suspected moderating effects of ACEs (like 5HTTP) on neural fear and reward responses following dose-dependent sleep disruption.

Progress: Since the beginning of recruitment, 201 of the 225 participants who provided written consent for the screening procedures have also completed the CTQ and genetic blood draw. One individual was unable to complete the CTQ at Visit #1, and did not return to subsequent appointment. One individual requested that we destroy the genetic sample and related data after finding out that s/he was not eligible for the study due to clinically significant and current anxiety and mood disorders.

- Randomize eligible participants to one of the three experimental sleep conditions Conduct behavioral and fMRI tasks to assess the dose-dependent effects of sleep disruption on fear acquisition, fear extinction, fear extinction recall, and reward processing.

Progress: Sixty-seven participants have been randomized to one of the 3 experimental conditions (normal sleep (n = 18), sleep restriction (n = 24), total sleep deprivation (n = 24 + 1 in March). Of these 67, 56 have completed all experimental procedures as of 2/27/2014 and 1 more is currently in the process of completing these conditions and will be done by 3/7/2014. Ten participants who initiated the experimental procedures withdrew or were withdrawn due to positive drug screens, nausea following sleep deprivation, or headaches following sleep restriction, were found to have significant sleep disordered, or cancelled their study due to illness or other unexpected circumstances.

- Monitor participants' safety, adverse study events, and new literature that may affect the risk/benefit ratio.

Progress: This subtask is ongoing, and addressed in weekly team meetings. In the past year, there has been no issues affecting participants' safety, adverse study events, or new literature that may affect the risk/benefit ratio of the study. We have experienced an unanticipated event. One participant developed marked bruising following the blood draw on 9/20/2013, and sought medical attention for soreness to his arm prior to contact the research team on 9/23/2013. On 9/26, the study physician met with the participant to assess the situation, and determined that the bruising was indeed larger than usual. A management plan was discussed with the participant, and follow-up was arranged. A telephone follow was also conducted by the study physician on 10/1/2013, at which point the participant report no concern or discomfort. As per the IRB review, this unanticipated event did not represent serious or continuing noncompliance nor does it meet the definition of an unanticipated problem involving risk to study participants or others. No additional follow up was required.

- Pre-process MR data.

Progress: This subtask is ongoing, and data quality is reviewed in monthly data review meetings.

Task 4: Store venous blood samples, extract genomic DNA and perform molecular genetic analyses (Months 5 – 54; Western Psychiatric Institute).

- Prescreen ~500 participants by genotyping a functional insertion/deletion polymorphism in the promoter region of *HTT* called 5HTTLPR.

- Genotype a functional A→G polymorphism in the 'L' allele carriers of 5-HTTLPR.

Progress: As described above, these subtasks are ongoing. Co-investigators specialized in genetics have also recently identified a new method to be able to analyze samples more rapidly, without any cost increase.

Task 5: Conduct data integrity and safety review, quality control /insurance, monitor and review data processing, scoring, and storage protocols. (Months 5-60; NCTRC).

- Monitor data integrity, safety, and unexpected/adverse events, conduct regulatory reviews, and report all necessary events including deviations as required.

Progress: This subtask is ongoing. Weekly study meetings are the primary forum to conduct these tasks. We have also conducted 2 meetings with all co-investigators in the past year (August and November 2013).

- Perform bi-monthly and quarterly data review.

Progress: This subtask is ongoing. Data review is now conducted on a monthly basis, as well as during investigators meetings.

Task 6: Perform exploratory and confirmation analysis and prepare/submit progress and research reports (Months 25-60; NCTRC).

- Conduct preliminary statistical analyses with SPM-8 for MR data and relevant statistical packages for behavioral data to evaluate the impact of sleep disruption on fear acquisition, extinction, extinction recall and reward processing.
- Conduct confirmatory statistical analyses with SPM-8 for MR data with relevant statistical packages for behavioral data to evaluate the impact of sleep disruption on fear extinction recall and reward processing.

Progress: We have initiated a bi-monthly data meeting to start reviewing and refining our data analysis plan and to consider additional exploratory analytical methods. Preliminary findings are also reviewed during these meetings in preparation for manuscripts. On a monthly basis, we review data integrity and perform re-entry of 30% of the data cumulated in the prior months, in order to detect possible data entry error. fMRI analyses are regularly updated and reviewed to verify that our data analyses protocols are consistent, and yield to expected patterns, at least in a preliminary manner. We also have initiated a number of ancillary data analyses aimed to 1) the impact of sleep deprivation on neural responses to losses; and 2) evaluate the effect of sleep manipulations on skin conductance response to fear learning. The former effort has led to a research abstract that will be presented as an oral presentation at the 2014 SLEEP meeting. The latter results will be submitted as an abstract for the 2014 annual meeting of the International Society for Traumatic Stress Studies (ISTSS).

Task 5. Prepare and submit research reports (NCTRC) (Months 32-48; NCTRC).

Progress: This task is not relevant for this past period of performance.

III. KEY RESEARCH ACCOMPLISHMENTS

- None to report at this time.

IV. REPORTABLE OUTCOMES

Award secured in the past year:

- PT130572: Uncovering Physiological Markers Linking Sleep and PTSD. PI: Reifman. Department of Defense (DoD) office of the Congressionally Directed Medical Research Programs (CDMRP), Psychological Health/Traumatic Brain Injury Research Program (PH/TBI) Basic and Applied Psychological Health Award - Applied/Combined Research.

Awards submitted based on data collected in this award

- *Sleep and Neural Circuitry Underlying Psychological Resilience in Combat Exposed Military Returnees.* Submitted to the USAMRMC, November 5, 2013. PI: Germain, Anne

Research abstracts submitted or to be submitted to scientific conferences

- Conrad TS, McNamee R, Banihashemi L, Forbes E, Germain A. Loss anticipation and outcome following total sleep deprivation and normal sleep. Research abstract to be presented as an oral presentation at the 2014 SLEEP Meeting, Minneapolis, MN. June 2014.
- Lynch G, McNamee R, Pace-Schott E, Milad MR, Germain A. Decrease in Skin Conductance Level Response Following Total Sleep Deprivation in Healthy Subjects. Research Abstract to be submitted for peer review for presentation at the 2014 ISTSS meeting.

Research training activities conducted under this award in the past year.

Undergraduate training

- **Brook M. Sims, B.A. Post-baccalaureate Fellow.** Ms Sims is a fellow of the Hot Metal Bridge Program (HMBP) at the University of Pittsburgh, who has joined Dr. Germain team for the academic year. The HMBP is a program that aims to enhance diversity in Arts and Sciences, and that aims to preparing trainees to compete successfully for admission into top-tier graduate programs in Psychology. Ms. Sims has been trained to assist the research assistant and coordinator in screening and consent research participants, and will receive training in fMRI tasks and data processing.
- **Gavin Lynch** is an undergraduate student in Neuroscience at the University of Pittsburgh and research intern who joined the team in August 2013. His responsibilities include the revamping of our study website and online advertisement, which are some of the primary methods of recruitment for the study.
- **Casey Snyder**, is an undergraduate student in psychology at the University of Pittsburgh who has joined Dr. Germain's team in August 2013. Ms Snyder is also a flight medic in the US Air Force. Her responsibility will include assisting the study physician and nurse in preparing reports from the medical reviews and evaluations conducted with consented participants in the study.
- **Elisabeth Beaudoin**, is an undergraduate student in psychology at the University of Pittsburgh, and has joined the team in August 2013. Her responsibilities include assisting the research assistant and coordinator in preparing consent and assessment visits, monitor research participants while they are in the sleep laboratory in the evening and in the morning.

Post-doctoral training

- **Layla Banihashemi, Ph.D.** is a postdoctoral fellow co-mentored by Dr. Germain. Dr. Banihashemi's interests are on the effects of early adversity on pre-autonomic brain structures and functions. She has submitted a K award to NIMH in February 2013, and proposes to obtain additional training in advanced neuroimaging methods (DTI, DSI) and clinical research under Dr. Germain's mentorship. It is expected that the research project she will conduct for her K award will leverage the high-throughput recruitment platform offered by the current award for her study recruitment. The review of her submission is expected imminently.
- **Salvatore Insana Ph.D.** is a 3rd year post-doctoral fellow. His interests focus on the impact of exposure to early life adversity on brain development and resilience across the life span. He submitted a K-award to NICHD in October 2012, to study the impact of physical maltreatment on brain and sleep development in pre-adolescents. Through the current award, Dr. Insana has initiated his training in conducting fMRI studies targeting the neural fear and reward circuits.

CONCLUSION

In the first 24 months of this award, we have met initial milestones regarding required approvals and staff training, and have sustained high recruitment and enrollment rates. We have also developed extensive SOPs specific to this project. By 3/8/2014, we expect to have met 100% of our planned enrollment, and have completed all

experimental procedures in > 85% of the targeted samples. We have plans to ensure that we meet 100% of our enrollment goal by the end of Year 3 (March 2014). We have also successfully screened 225 young adults in the study, and have been successful at advertising our study to the population of interest, as indicated by the high number of contacts to date. Data management and MR data processing is conducted in a timely fashion. We have initiated regular data review and analyses, as well as undertaken a number of ancillary data analysis projects.

In the coming period of performance, we will continue to randomize eligible participants to one of the 3 sleep conditions and conduct experimental procedures at an average rate of 5 subjects per month.

- **REFERENCES**

None applicable.

- **APPENDIX**

I. Recruitment flow charts (July 2012 to Feb 27, 2014).

II. Enrollment demographics

SUPPORTING DATA

None provided at this time.

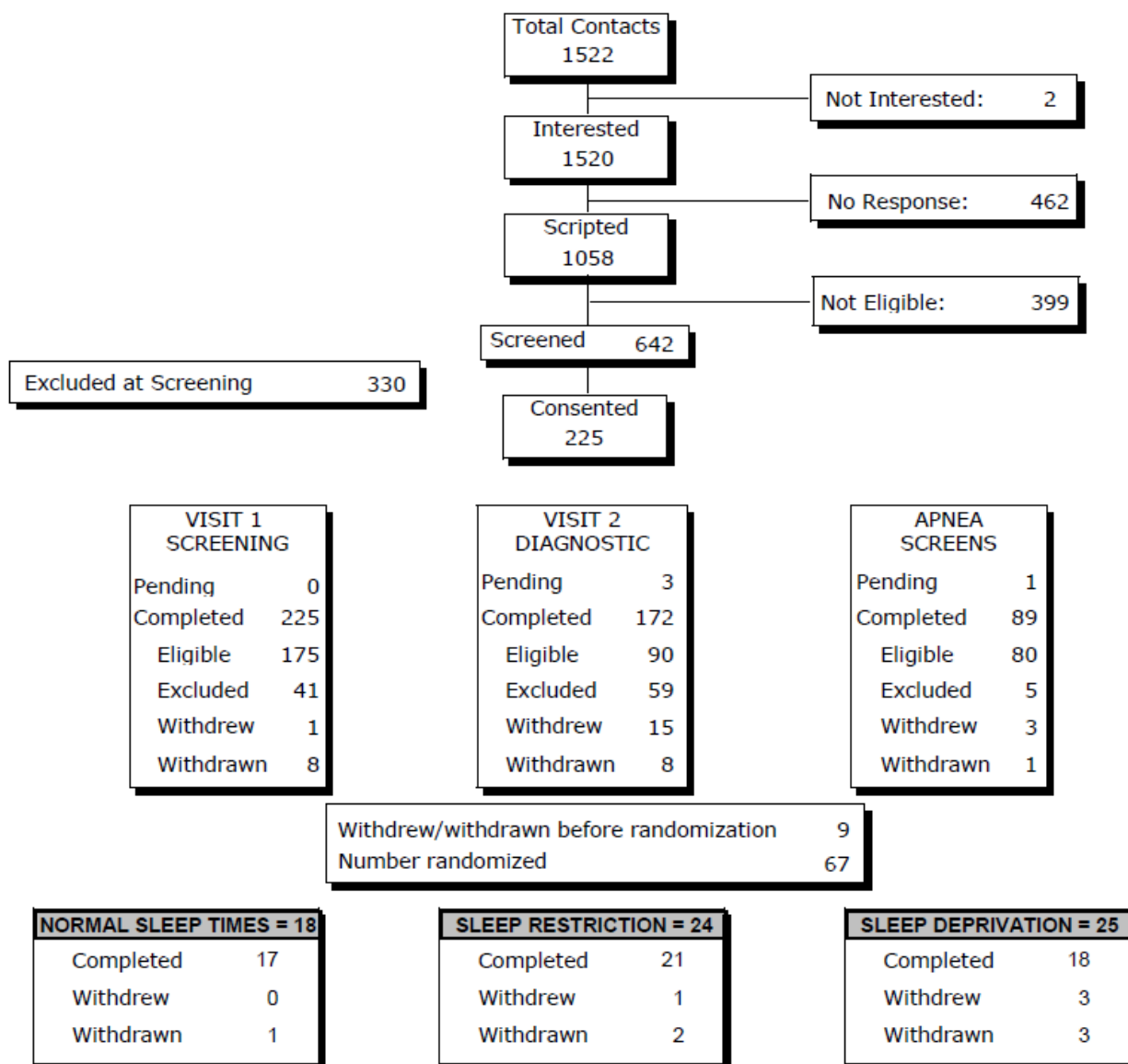
Appendix I

Recruitment Flow Chart For the first 21 months of performance

(18 months of recruitment: 7/2012 to 2/27/2014)

Participant Flow Report for SFERE

Thursday, February 27, 2014



Scheduled - 3/4/2014

I.

Appendix II

Enrollment demographics

(18 months of recruitment: 7/2012 to 2/27/2014)

SFERE ENROLLMENT TO 2/27/14 ALL PARTICIPANTS CONSENTED TO SCREENING			
ETHNIC CATEGORY	FEMALES	MALES	TOTAL
HISPANIC OR LATINO	5	4	9
NOT HISPANIC OR LATINO	113	102	215
UNDISCLOSED	1	0	1
<i>ETHNIC CATEGORY: TOTAL OF ALL SUBJECTS</i>	<i>119</i>	<i>106</i>	<i>225</i>
RACIAL CATEGORIES			
AMERICAN INDIAN/ALASKA NATIVE	1	0	1
ASIAN	15	13	28
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0
BLACK OR AFRICAN AMERICAN	24	15	39
WHITE	74	75	149
MULTIRACIAL	2	2	4
UNDISCLOSED	3	1	4
<i>RACIAL CATEGORIES: TOTAL OF ALL SUBJECTS</i>	<i>119</i>	<i>106</i>	<i>225</i>

SFERE ENROLLMENT TO 2/27/14 COMPLETED EXPERIMENTAL PHASE PARTICIPANTS			
ETHNIC CATEGORY	FEMALES	MALES	TOTAL
HISPANIC OR LATINO	2	1	3
NOT HISPANIC OR LATINO	24	29	53
<i>ETHNIC CATEGORY: TOTAL OF ALL SUBJECTS</i>	<i>26</i>	<i>30</i>	<i>56</i>
RACIAL CATEGORIES			
AMERICAN INDIAN/ALASKA NATIVE	0	0	0
ASIAN	4	3	7
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0
BLACK OR AFRICAN AMERICAN	2	2	4
WHITE	19	25	44
UNDISCLOSED	1	0	1
<i>RACIAL CATEGORIES: TOTAL OF ALL SUBJECTS</i>	<i>26</i>	<i>30</i>	<i>56</i>

Title: Dose-dependent effects of sleep disruption of fear responses and reward processing

Proposal ID: Log Number 11293006

Funding Source: CDMRP



DMRDP

PI: Anne Germain

Org: University Of Pittsburgh

Award Amount: \$4,995,975

Study Aim(s)

Objective: To study and probe the relationship between sleep disruption and neural networks underlying fear responses and reward processing that contribute to psychological resilience or poor stress-related psychological outcomes that are highly prevalent and comorbid in combat-exposed warfighters, such as posttraumatic stress disorder, anxiety, depression, suicidality, and addictions.

Objective 1: To study and probe the effects of dose-dependent sleep disruption on behavioral and neural correlates of fear acquisition, fear extinction, and extinction recall.

Objective 2: To study and probe the dose-dependent effect of sleep disruption on neural correlates of reward processing.

Exploratory Objective: To explore the moderating effects of early exposure to adversity and a genetic variant known to affect fear responses and reward processing following dose-dependent sleep disruption.

Approach: 500 subjects will be screened, and 180 will complete the experimental approach as depicted in the study timeline and procedures.

Study timeline and procedures: Dose-dependent effect of sleep disruption on fear responses and reward processing.

Evening 1 Report to NCTRC	Evening 2 (20:00) Reports to NCTRC	Evening 3 (20:00- 22:00) Reward Processing Task Fear Extinction Recall
Night 1 Adaptation & Screening Sleep Study	Night 2: Randomization •Sleep Deprivation •Sleep Restriction (4 h) •Normal Sleep	Night 3: Sleep Recovery
Morning 1: Discharge from NCTRC	Morning 2 (8:00-10:00) Fear Acquisition/Extinction Protocol	Morning 3 (08:00-10:00) Fear Extinction Recall Retest Reward Processing Retest
	Day 2: All-day monitoring in the N-CTRC sleep laboratory	Day 3: Discharge from NCTRC

As of 27 February 2014, we have consented 225 participants for the study. Fifty-six have been completed all experimental procedures, and 1 participant is scheduled for experimental procedures by March 8, 2014.

Timeline and Cost

Activities FY	12	13	14	15	16
Secure required approvals and train personnel	Done				
Probe the sleep-fear relationships		Ongoing			
Probe the sleep-reward relationships		Ongoing			
Explore effects of adverse childhood events and genotypes		Ongoing			
Final data analyses, reports submission/publication					
Estimated Budget (\$K)	800	1,028	1,126	1,142	1,000

Goals/Milestones

CY12 Goal – Study start up and recruitment

- ☒ Hire/train personnel; secure approvals
- ☒ Initiate recruitment: Year 1 goals: 90 in screening and 18 in experimental protocol
- ☒ Conduct pilot studies to verify data acquisition and analyses protocols

CY13 through CY 16 Goals

- ☒ Enroll subjects and conduct study procedures
- ☒ Conduct preliminary analyses
- CY16-CY17 Goal – Preliminary and confirmatory analyses and report**
 - ☐ Conduct analyses for primary and exploratory study aims.
 - ☐ Submit progress reports and manuscripts to peer-reviewed journals.

Comments/Challenges/Issues/Concerns

- No anticipated challenge at this time.

Budget Expenditure to date

Projected Expenditure: 4,995,975

Actual Expenditure: \$ 1,345,567* (with encumbrances through 6/30/2014)

Updated: (February 27, 2014)