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14. ABSTRACT This is an annual progress report for the funding period between 03/09/2012 to 02/27/2013. The study start-up period was completed within the expected timeframe, and recruitment was open in July 2012. Recruitment goals for Year 1 have been met, and enrollment remains ongoing. All SOPs have been completed and implemented. Data monitoring, management, review, and processing are conducted on an ongoing basis, and reviewed weekly.					
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Table of Contents

	<u>Page</u>
Introduction.....	1
Body.....	1
Key Research Accomplishments.....	5
Reportable Outcomes.....	5
Conclusion.....	6
References.....	6
Appendices.....	8

ANNUAL PROGRESS REPORT

W81XWH-12-2-0024

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

Progress Period: March 9, 2012 to February 26th, 2013

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.

This progress report covers the performance period between March 9th, 2012 and February 26th, 2013.

II. BODY

Research accomplishments associated with each task outlined in the approved Statement of Work. The tasks and timeline initially proposed and approved in the approved Statement of Work are provided below. Progress and outcomes on each of the tasks listed are detailed for this review period.

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 HRPO approvals and order study supplies.	DONE									
2. Hire and train new personnel (2)	DONE									
3. Recruit, screen, and randomize, and test 198 subjects		(Completed 18 in Y1) ONGOING								
4. Perform genetics procedures		ONGOING								
5. Data review, quality control /insurance, processing, scoring, and storage		ONGOING								
6. Perform exploratory and confirmation analysis and reports										

Task 1: Secure IRB and HRPO approvals (Months 1-4, NCTRC) and order study supplies. In this first year of performance, we have secured all approvals for human research from the University of Pittsburgh Institutional Review Board (IRB), and USAMRMC Human Research Protection Office (HRPO) prior to initiating recruitment. All start-up supplies and materials have been received, tested and calibrated. All data acquisition, pre-processing, and processing protocols have been finalized and implemented, and we have updated our manual of operations accordingly.

Task 2: Hire and train new personnel (Months 1-4, NCTRC). All newly hired staff has completed necessary trainings, and our team is fully operational.

Task 3: Recruit, screen, randomize, and test 198 healthy young adults (Months 5 – 54; NCTRC). We have been successful at developing low-costs advertisement strategies to achieve and sustain the flow of incoming contacts by interested individuals, using web-based media and flyers posted around campuses in Pittsburgh. As of February 26, 2013, we have been contacted by 575 individuals, and 116 were invited for an in-person screening

consent visit. Of these 102 have completed the Childhood Trauma Questionnaire (CTQ) and 102 have provided blood samples for genotyping. We have randomized 24 eligible participants to one of the 3 experimental sleep conditions, and will have completed the full experimental protocol with 19 individuals between August 2012 and March 2, 2013. These procedures include behavioral and fMRI tasks to assess the dose-dependent effects of sleep disruption on fear acquisition, fear extinction, fear extinction recall, and reward processing. Thus, we are proud to report that we have achieved our Year 1 target for completed studies (i.e., $n = 18$ completed through the experimental protocol).

Dr. Edward Pace-Schott and Dr. Mohammed Milad from the Massachusetts General Hospital (MGH) have visited Dr. Germain and her team at the University of Pittsburgh in August and November 2012 to review all pilot and study data collection and analysis protocols, and to certify the pre-processing and data analysis plans in place. The preliminary analyses conducted on subjects enrolled in the experimental phase of the study are consistent with the expected fMRI and psychophysiological signals. All data review by external experts has now been completed. Drs. Germain, Pace-Schott and Milad are scheduled to meet again in March or April 2013 to review preliminary findings, and determine whether novel data analysis methods can be applied to the dataset in the coming year.

Participants' safety is monitored continuously while participants are in our offices or in the sleep lab (NCTRC). New literature that may affect the risk/benefit ratio of the study is discussed in weekly data and safety monitoring meeting. All fMRI pre-processing and processing protocols are in place, and procedures are completed on a regular basis, and as soon as data becomes available.

Task 4: Store venous blood samples, extract genomic DNA and perform molecular genetic analyses (Months 5 – 54; Western Psychiatric Institute). As of 2/26/2013, we have collected 102 samples for genetic analyses, and randomized 24 subjects.

Task 5: Conduct data integrity and safety review, quality control /insurance, monitor and review data processing, scoring, and storage protocols. (Months 5-60; NCTRC). Dr. Germain and her team have held weekly data and safety monitoring and review meetings. We conducted monthly data review and summary, as well as quarterly progress assessment. As we reported previously, we experienced one unanticipated event in September 2012. This event was immediately reported to the University IRB and HRPO. The University IRB reviewed the event in October 2012, and determined that the event had been handled appropriately. No further action was required. The IRB review letter and report from the independent monitor were forwarded to HRPO in October 2012, which determined that no further action was required.

III. KEY RESEARCH ACCOMPLISHMENTS

- None to report at this time.

IV. REPORTABLE OUTCOMES

Funding secured based on work supported by this award in the last year:

- *University of Pittsburgh Pilot Imaging Program: Sleep and Neural Circuitry Underlying Psychological Resilience in Combat Exposed Military Returnees.* Awarded in August 2012. Pilot award to cover the costs of 10 hours of fMRI scanning sessions. This pilot project aims to collect preliminary data to evaluate the effects of a brief behavioral treatment of insomnia on neural responses to threat and reward in 10 combat-exposed OEF/OIF/OND Veterans with chronic insomnia. These preliminary results will provide the building block for an anticipated full grant proposal to be submitted to the CMDRP or to NIMH.

Funding applied for based on work supported by this award

- *NARSAD Independent Investigator Award: Brain circuits underlying risk and resilience: A study of children of combat-exposed military veterans.* Submitted November 15, 2012 to the Brain and Behavior Research Foundation (formerly NARSAD) PI: Germain, Anne.
- *Family Ties: Social Rhythm Stability and Affective Security as Pathways of Risk or Resilience in Military Families* (R01 submitted to NIMH, PI: Troxel; Co-I: Germain). Under peer-review.
- *PM&R-cmTBI Consortium: Mental and Sleep Health Program.* Application submitted January 4th 2013 DoD CMDRP, Consortium on the Chronic Effects of Neurotrauma. PI: Wagner, Co-I: Germain.

- *Sleep and Neuroplasticity in Sub-acute and Chronic Mild Traumatic Brain Injury: Mechanisms and Treatment.* PI: Germain. Pre-proposal submitted February 27th, 2013, in response to W81XWH-13-PHTBI-TBIRA.

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

Undergraduate training

- **John Skicki** is a Psychology Honors Student at University of Pittsburgh who is currently doing a research internship on this study. He is involved in a number of tasks, including the creation of study binders for participants, organizing materials collected from participants during the study, and assisting sleep technicians with the monitoring of wakefulness during sleep deprivation and sleep restriction studies. He has initiated the training to be able to assist the research assistant in conducting telephone script and telephone screens with individuals who expressed interest in the study. He will continue his research internship next semester, and throughout the summer of 2013. He is expected to go on to graduate school after July 2013.

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.
- **Melynda Casement, Ph.D.** is a clinical psychologist and post-doctoral fellow co-mentored by Drs. Erica Forbes (co-investigator on the present award) and Germain. Her research interests are on the impact of stress exposure on the brain reward circuitry in adolescence. Dr. Casement also has extensive experience in conducting psychiatric and sleep evaluations. On the present study, she has completed the training to conduct clinical evaluations with the CAPS, SCID, and SLED, and has achieved the high inter-rater reliability necessary to contribute to the assessment of participants evaluated on this study.
- **Nataria Joseph, Ph.D.** is a clinical psychologist and post-doctoral fellow co-mentored by Dr. Karen Matthews in the Behavioral Medicine Program. Dr. Joseph has extensive experience in conducting psychiatric evaluations in military veterans. On the present study, she has completed the training to conduct clinical evaluations with the CAPS, SCID, and SLED, and has achieved the high inter-rater reliability necessary to be able to conduct psychiatric and sleep evaluations with enrolled participants.
- **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.

VI. CONCLUSIONS

We have met all the tasks and milestones anticipated for Year 1 of the award. We have met our enrollment and retention targets, and all SOPs are in place and certified. Data and safety monitoring is conducted weekly. This award provides a unique platform of training for new investigators, and has provided building blocks for a number of funding applications. We do not anticipate any challenges in the upcoming period of performance.

VII. REFERENCES

None applicable.

VIII. APPENDICES

I. Recruitment flow charts for total period of performance to date (Recruitment initiated in July 2012 through February 26, 2013).

II. Enrollment Tables for (a) all participants consented to date, and (b) participants who completed the in-lab experimental procedures.

SUPPORTING DATA

None to provide at this time.

APPENDICES

I. Recruitment flow chart for total period of performance to date
(Year 1 recruitment initiated in July 2012 through February 26th, 2013).

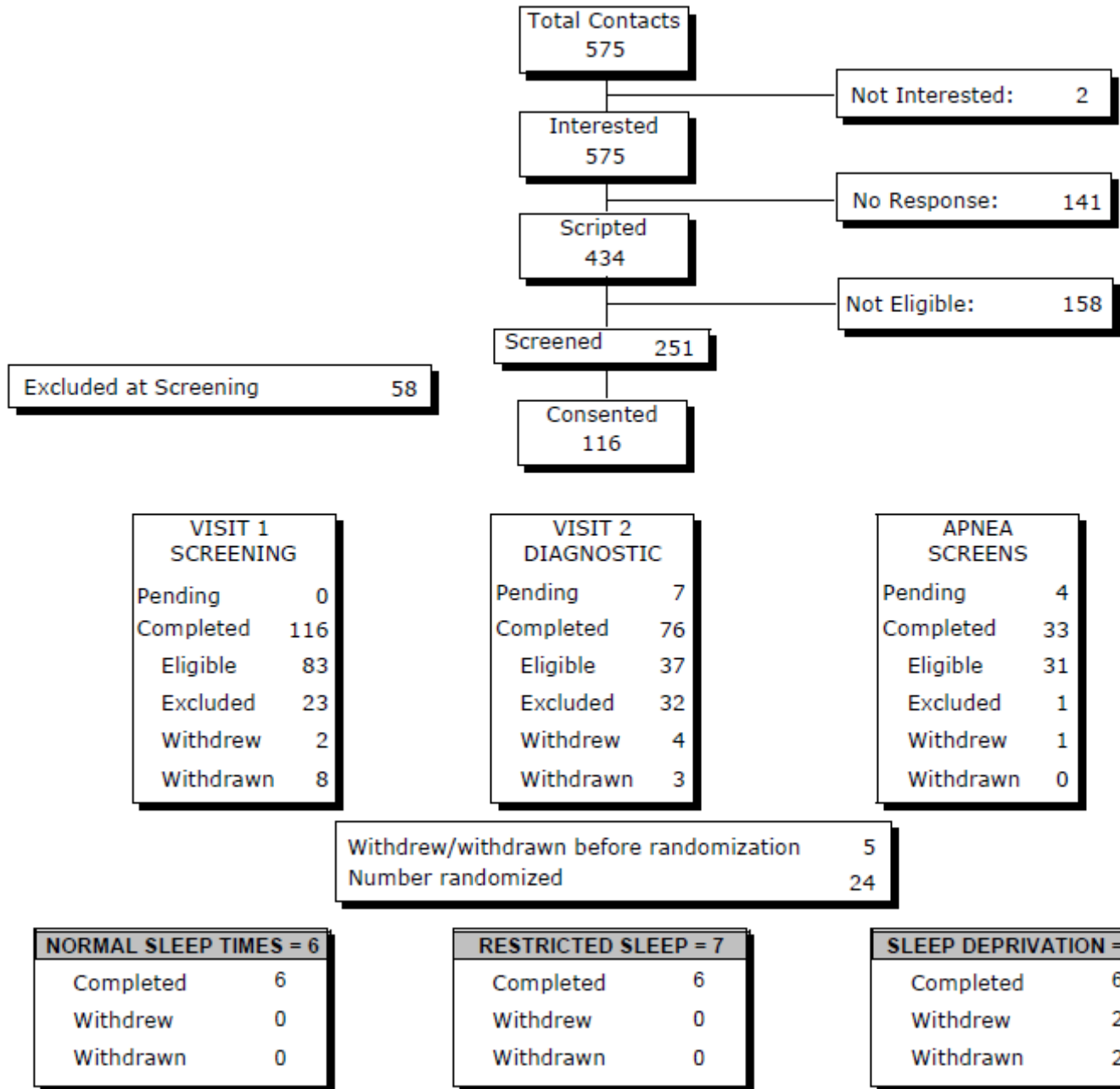
II. Enrollment Tables for (a) all participants consented to date, and (b) participants who completed the in-lab experimental procedures.

Appendix I

Year 1 recruitment initiated in July 2012 through February 26, 2013

Participant Flow Report for SFERE

Tuesday, February 26, 2013



Note: Two more participants are scheduled to complete the experimental procedures, starting 2/27/2013 and 3/5/2013, respectively.

Appendix II

SFERE ENROLLMENT TO From 7/12/212 to 2/26/13 ALL CONSENTED PARTICIPANTS			
ETHNIC CATEGORY	FEMALES	MALES	TOTAL
HISPANIC OR LATINO	2	2	4
NOT HISPANIC OR LATINO	54	57	111
UNDISCLOSED	1	0	1
<i>ETHNIC CATEGORY: TOTAL OF ALL SUBJECTS</i>	<i>57</i>	<i>59</i>	<i>116</i>
RACIAL CATEGORIES			
AMERICAN INDIAN/ALASKA NATIVE	1	0	1
ASIAN	4	5	9
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0
BLACK OR AFRICAN AMERICAN	12	7	19
WHITE	39	47	86
UNDISCLOSED	1	0	1
<i>RACIAL CATEGORIES: TOTAL OF ALL SUBJECTS</i>	<i>57</i>	<i>59</i>	<i>116</i>

SFERE ENROLLMENT FROM 7/12/2012 to 2/26/13 EXPERIMENTAL PHASE			
ETHNIC CATEGORY	FEMALES	MALES	TOTAL
HISPANIC OR LATINO	0	0	0
NOT HISPANIC OR LATINO	8	10	18
<i>ETHNIC CATEGORY: TOTAL OF ALL SUBJECTS</i>	<i>8</i>	<i>10</i>	<i>18</i>
RACIAL CATEGORIES			
AMERICAN INDIAN/ALASKA NATIVE	0	0	0
ASIAN	0	0	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0
BLACK OR AFRICAN AMERICAN	1	0	1
WHITE	7	10	17
<i>RACIAL CATEGORIES: TOTAL OF ALL SUBJECTS</i>	<i>8</i>	<i>10</i>	<i>18</i>