Award Number: DAMD17-02-1-0201

TITLE: The Effects of Total Sleep Deprivation and Recovery Sleep on Cognitive Performance and Brain Function

PRINCIPAL INVESTIGATOR: Sean P.A. Drummond, Ph.D.

CONTRACTING ORGANIZATION: Veterans Medical Research Foundation
San Diego, California 92161

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Fort Detrick, Maryland 21702-5012

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An ever-increasing number of military personnel and civilians alike must work daily without adequate sleep. Although considerable data show that sleep deprivation alters many aspects of behavior, little is known about changes in the brain substrate underlying the behavioral effects. Even less is known about the cerebral effects of recovery sleep. The overarching objective of this study is to investigate the effects of 2 full nights of sleep loss and 2 full nights of recovery sleep on cognitive performance and brain function. We will study 40 individuals for 6 nights and 6 days. Subjects will receive 4 polysomnograms and 10 functional magnetic resonance imaging (fMRI) sessions. During the fMRI sessions, functional brain imaging data will be collected while subjects perform each of 3 cognitive tasks: sustained attention, arithmetic working memory, and verbal learning. Thus far, 17 subjects have completed the protocol. While these data are preliminary, there are indications that this study will help identify the rate at which performance on different cognitive tasks deteriorates with sleep loss and recovers with subsequent sleep. Furthermore, we may be able to advance our understanding of the brain function correlates of individual differences in vulnerability and resilience to sleep deprivation.
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INTRODUCTION:
An ever-increasing number of military personnel and civilians alike must work daily without adequate sleep. Although considerable data show that sleep deprivation alters many aspects of behavior, including motor skills and cognitive performance, little is known about changes in the brain substrate underlying the behavioral effects. Even less is known about the cerebral effects of recovery sleep. The overarching objective of this study is to investigate the effects of 2 full nights of sleep loss and 2 full nights of recovery sleep on cognitive performance and brain function. To accomplish this goal we will study 40 individuals for 6 nights and 6 days. Over the course of this period, subjects will receive 4 polysomnograms and 10 functional magnetic resonance imaging (FMRI) sessions. During the FMRI sessions, functional brain imaging data will be collected while subjects perform each of 3 cognitive tasks: sustained attention, arithmetic working memory, and verbal learning. In addition to these 40 individuals in the sleep deprivation protocol, we will recruit 10 separate individuals who will participate only in the FMRI portion of the protocol, not the sleep or sleep deprivation portions (the “Aim 5” portion of the protocol). These data will allow us to determine the effects on FMRI measures of brain activation due to repeated measurements, independent of any sleep or sleep deprivation-related effects.

BODY:
As of July 15, 2004, the end of Year 2 of this award, we have enrolled 21 subjects in this study. Of these 21, 17 (10 females) have fully completed the study. Three of the remaining four individuals voluntarily withdrew from the study. Two withdrew prior to any of the experimental nights in the laboratory, while one withdrew due to an unwillingness to remain awake after approximately 20 hours of the sleep deprivation portion of the study. The fourth individual was withdrawn from the study prior to the experimental nights because he underwent dental work after signing informed consent that made him ineligible for the MRI portion of the study (i.e., he had a permanent retainer fitted). Overall, we accomplished the main goals in our Statement of Work for Year 2.

As reported in our Year 1 annual report, we originally experienced a delay in starting the study due to technical difficulties with the magnetic resonance imaging (MRI) machines we planned to use. At the end of April 2003, the Directors of the UCSD Center for Functional Magnetic Resonance Imaging decided to replace the MRI machines due to these difficulties. At that time, we decided to enroll subjects prior to the replacement of the magnets. Six subjects were subsequently enrolled and completed the study. In December 2003 the Center closed for about 4 months to replace the MRI machines with different models. The Center reopened in late March 2004 and we immediately began enrolling subjects again. However, due to this gap in enrollment, we decided to delay enrolling subjects in Aim 5 of the study until Year 3. We did this in order to enroll as many subjects as possible in the main study.

While the data generated from the study thus far must still be considered preliminary, we have made three presentations based on this work. One data-driven poster was presented at the Military Health Research Forum held in San Juan, Puerto Rico, in April 2004. At that same meeting, Dr. Drummond (the PI) gave an oral presentation covering issues in human subjects protection that arise in sleep deprivation research. Finally, we gave a second poster presentation at the Associated Professional Sleep Societies (APSS) annual meeting in June 2004. This last presentation was published in a special supplement to the journal SLEEP (see
references below). In addition, Dr. Drummond has presented preliminary brain imaging data from this study as an example of studying individual differences in vulnerability to sleep deprivation, as part of three larger invited oral presentations to international audiences.

KEY RESEARCH ACCOMPLISHMENTS:
- Enrolled 21 subjects into the study
- Completed 17 subjects throughout the entire protocol

REPORTABLE OUTCOMES:
3. Poster presentation at the Associated Professional Sleep Societies (APSS) annual meeting, June 2004 (see references, below).
4. Data presented as part of 3 larger international presentations:

CONCLUSIONS:
Despite additional delays in data collection due to infrastructure issues beyond our control, we accomplished the main goals set forth for Year 2. We anticipate continuing to successfully meet the goals set forth in the Statement of Work for subsequent years. While our data analysis at this point is quite preliminary, there are indications that this study will help identify the rate at which performance on different cognitive tasks deteriorates with sleep loss and recovers with subsequent sleep. Furthermore, we may be able to advance our understanding of the brain function correlates of individual differences in vulnerability and resilience to sleep deprivation.

REFERENCES:

APPENDICES:
1. Copy of poster presentation from APSS meeting, June 2004 (reference #1 above).
EFFECTS OF 62-HOUR TOTAL SLEEP DEPRIVATION AND RECOVERY SLEEP ON COGNITIVE PERFORMANCE

Henry J. Orff, Tiffany Chen, Jennifer Salamat, Matthew A. Yanagi, Carina Lopez, Sean P. A. Drummond
UCSD Laboratory for Sleep and Behavioral Neurosciences & Veterans Affairs San Diego Healthcare System

**Background/Purpose**

Military personnel and civilians alike often work with little or no sleep
- The effects of sleep loss on cognitive performance and brain function are not fully known
- Importantly, the process of recovery from extended sleep loss is not well understood
- We are assessing the effects of extended Total Sleep Deprivation (TSD) and Recovery sleep on brain function
- We are examining several factors related to brain function under these conditions
  - Different cognitive processes
  - Individual differences in vulnerability/resilience to TSD
  - Cognitive performance & Functional Magnetic Resonance Imaging (fMRI) measures of brain function

**Methods**

**Subjects**
- 11 healthy, normal sleeping adults
- 4 M, 7 F
- age: 24.9 ± 4.8 years
- education: 15.6 ± 1.7 years

**Study Schedule**
- 2 nights of Normal Sleep
- 62-hours Total Sleep Deprivation
- 2 nights of Recovery Sleep
- 2 fMRI scans each day for 5 days
- Cognitive testing every 2 hours for 5 days

**FMRI Cognitive Testing**
- AM & PM sessions each day
- Normal Sleep 2: 2 & 12 hours awake
- TSD1: 26 & 36 hours awake
- TSD2: 50 & 62 hours awake
- Recovery 1: 2 & 12 hours awake
- Recovery 2: 2 & 12 hours awake
- 3 Tests at each session
- Verbal learning (VL)
- Arithmetic working memory (Math)
- Sustained attention task (FVT: psychomotor vigilance task)

**Laboratory Cognitive Testing**
- Tests here given in afternoon (14:00–16:00)
  - Normal Sleep 2: 8-10 hours awake
  - TSD1: 32-34 hours awake
  - TSD2: 56-58 hours awake
  - Recovery 1: 8-10 hours awake
  - Recovery 2: 8-10 hours awake
  - 3 tests at each session
  - Behavioral inhibition (NoGo)
  - Spatial working memory (SWM: attention vs 2-back)
  - Verbal working memory (N-Back, 0,1,2 back)

**Results: Group Laboratory Cognitive Testing**
- **Attention Lapses**
  - Day effect (p < 0.001): TSD1 & TSD2 vs Normal Sleep. Recovery was complete after 1 night of sleep.
  - Day x AMPA effect (p = 0.05): AM testing showed greater decline with TSD.

**Results: Individual Differences**
- Some individuals showed resilience to TSD, while others appeared more vulnerable
  - The following graphs show the extent of individual differences in the response to 50 hours TSD. The 1st shows RT slowing on TSD2 and the next 2 compare the AM fMRI scan session after Normal sleep to the AM session after TSD (i.e., 50 hours TSD).

**Results: Group FMRI Cognitive Testing**
- **Response Time**
  - Day effect (p < 0.001): TSD1 & TSD2 had worse recall vs Normal Sleep. Recovery was complete after 1 night of sleep.
  - Day x Speed effect (p = 0.002): Fastest responses maintained during TSD, but slowest responses become

**Conclusions**

1. Different cognitive tasks are impacted at different rates by TSD and Recovery Sleep
   - Verbal Learning (e.g., ability to hear and remember orders) was typical: VL declined about 40% after TSD1, but showed no further decline with TSD2
   - Attention lapes and arithmetic working memory (FVT: psychomotor vigilance task) continued to decline with TSD2
   - While most tasks recovered after only 1 night of sleep, subjects showed a poor ability to inhibit responses until after 2 full nights of recovery sleep.

2. Individuals showed different levels of resiliency or vulnerability to acute TSD, as measured with cognitive performance
   - Some subjects appeared globally resilient to TSD (e.g., #8)
   - Some subjects appeared globally vulnerable to TSD (e.g., #6)
   - Some subjects were resilient on some tests, but vulnerable on others (e.g., #7, #10)

3. These differences in response to TSD were also evident in the fMRI data
   - Some subjects were able to show cerebral compensation after 50 hours TSD and this allowed them to maintain near normal performance levels
CURRICULUM VITAE
Update 8/04

NAME: Sean Patrick Andrews Drummond, PhD

ADDRESS: Department of Psychiatry, 9116A
UCSD / San Diego VAMC
3350 La Jolla Village Drive
San Diego, CA 92161
858 642 1274 (phone); 858 458 4201 (fax)
email: drummond@ucsd.edu

BIRTH DATE: April 15, 1969

EDUCATION:

6/00 Doctor of Philosophy in Clinical Psychology
San Diego State University/University of California, San Diego
Joint Doctoral Program in Clinical Psychology (JDP)
San Diego, California
Dissertation Committee Chair: J. Christian Gillin, M.D.

5/92 Bachelor of Science degree in Psychology
Summa Cum Laude, Phi Beta Kappa
University of Arizona; Tucson, Arizona

ACADEMIC POSITIONS:

10/02 - Present Assistant Professor In Residence
Department of Psychiatry, 9116A
UCSD / VA San Diego Healthcare System
3350 La Jolla Village Drive
San Diego, California 92161

9/00 - 9/02 Postdoctoral Fellow
Research Health Science Specialist
Biological Psychiatry and Neuroscience Fellowship Program
Department of Psychiatry, 9116A
UCSD / San Diego VAMC
3350 La Jolla Village Drive
San Diego, California 92161
Mentor: Gregory G. Brown, Ph.D.
9/99 – 8/00 Predoctoral Psychology Intern
Southern Arizona VA Health Care System
Mental Health Care Group (4-116B)
Tucson, AZ 85723
Training Director: James Comer, Ph.D.

8/94 – 8/99 NIMH NRSA Predoctoral Fellow
Department of Psychiatry, 9116A
UCSD / San Diego VAMC
3350 La Jolla Village Drive
San Diego, California 92161
Mentor: J. Christian Gillin, M.D.

6/92 – 7/94 Research Associate
Sleep Disorders Center
UC Irvine Medical Center
101 S. City Dr., building 22C, route 23
Orange, California, 92668
Mentor: Sarah Mosko, Ph.D.

4/90 – 5/92 Research Assistant
Sleep Research Laboratory
Psychology Department, University of Arizona
Mentors: Richard Bootzin, Ph.D. and Michael Perlis, Ph.D. (then M.A.)

OTHER PROFESSIONAL POSITIONS:

1991-1992 Polysomnographic Technician
Sleep Disorders Center
University Medical Center, Tucson Arizona
Supervisor: Cathy Cross, R.EEG.T/EP.T/R.PSG.T.

GRANTS/FELLOWSHIPS:

Last 5 years

10/96-12/98 Individual National Research Service Award
NIMH; F31 MH11452
PI: Drummond ($35,214.00)

1998 Dissertation Fellowship ($3,000.00)
Phi Beta Kappa Epsilon Association

9/00-8/02 Institutional Postdoctoral NRSA Fellowship
NIMH; T32 MH18399
Director: Eric Turner, M.D.
9/01-2/04  Young Investigator Grant  $25K/year DC
Sleep Medicine Education & Research Foundation (SMERF) Award #01-01-01
PI: Drummond

7/02 – 12/03  Cephalon, Inc. Investigator-initiated grant  18 months, $140K DC
“The Effects of Modafinil on Behavioral and Cerebral Responses to Total Sleep Deprivation”
PI: Drummond

Active
4/02 – 12/04  Office of Naval Research  2.5 years; $213K/year DC
“Influence of individual differences and task difficulty on cerebral and behavioral responses during cognitive performance following total sleep deprivation.”
Co-PI: Carr; Co-PI: Drummond

7/02 – 7/06  US Army Peer Reviewed Medical Research Program; 4 years, $425K/year DC
“Effects of total sleep deprivation and recovery sleep on cognitive performance and brain function”
PI: Drummond

10/02 – 9/04  UC Center for Medicinal Cannabis Research  2 years; $39K/year DC
“Sleep and Medicinal Cannabis”
PI: Drummond

Pending
7/04 - 6/09  National Institute on Aging 1 R01 AG024506-01  5 years, $1.125M DC
“Sleep Deprivation and Brain Function in Older Adults”
PI: Drummond

HONORS RECEIVED:

1988  Outstanding Freshman Essay Award, Virginia Commonwealth University
1988-1992  Dean's List, University of Arizona
1989  Phi Kappa Phi Certificate of Merit
1989-1992  University Class Scholarship Award, University of Arizona
1991-1992 & Travel Awards for the annual Associated Professional Sleep Societies
1994-1998 conferences
1995  Travel Award for the World Federation of Sleep Research Societies conference
1995-1999  JDP Departmental Travel Awards (intramural)
1995  National Science Foundation Graduate Research Fellowship Program, Honorable Mention
1997  JDP Dorathe Frick Memorial Award for Outstanding Third Year Student
1998  Phi Beta Kappa Society - Epsilon Association Dissertation Fellowship
1998  Blue Ribbon Award Winner for abstract submitted to Division 40 at the 106th Annual Convention of the American Psychological Association
1999  Sleep Research Society Research Merit Award
2001  Sleep Research Society Young Investigator Award

HONORARY SOCIETAL MEMBERSHIPS:

Honors Program, University of Arizona, 1988-1992
Psi Chi National Honor Society, inducted 1989
Phi Eta Sigma National Honor Society, inducted 1989
Golden Key National Honor Society, inducted 1990
Phi Kappa Phi National Honor Society, inducted 1992
Phi Beta Kappa National Honor Society, inducted 1992

PROFESSIONAL SOCIETAL MEMBERSHIPS:

Sleep Research Society, 1991-Present
American Psychological Association, 1991-Present
American Academy of Sleep Medicine, 2000-Present
Cognitive Neuroscience Society, 2001-Present

CLINICAL EXPERIENCES:

Graduate School:
6/95 - 8/95  West Wing Acute Inpatient Unit, UCSD Medical Center
7/95 - 10/96  Smoking Cessation for Depressed Patients, UCSD Department of Psychiatry
8/95 - 8/96  San Diego State University Psychology Clinic, Mood and Anxiety Disorders Clinic
7/96 - 6/97  Alcohol and Drug Treatment Program (ADTP), San Diego VAMC
7/97 - 12/98  Sleep Disorders Clinic, San Diego VAMC

Internship:
8/99 - 12/99  Psychological Assessment, Tucson VAMC
8/99 - 12/99  Day Programs for seriously mentally ill, Tucson, VAMC
12/99 - 3/00  Medical Rehabilitation, Tucson VAMC
12/99 - 3/00  Insomnia Clinic, University of Arizona - University Medical Center
3/00 - 5/00  Health Psychology Clinic and Primary Care, Tucson VAMC
6/00 - 8/00  Neuropsychology Clinic, Tucson VAMC
PROFESSIONAL EXPERIENCES:

Teaching Experiences:
Fall 1996  Introduction to Statistics, San Diego State University (SDSU) Psychology Department
Spring 1997  Introduction to Statistics, SDSU Psychology Department

Invited Lectures and Workshops:
1998  “Sleep and Substance Abuse” - ADTP clinical staff inservice
2/00  “Psychotherapy: What it is and When to Refer” - University of Arizona Internal Medicine Residents inservice
2/00  “Assessment and Behavioral Treatment of Insomnia” - Tucson VAMC Psychology Staff inservice
6/00  “The use of FMRI to measure the effects of sleep deprivation on cognitive performance” - Invited presentation during a symposium entitled “The neuroanatomy of sleep: A synthesis of functional neuroimaging, clinical, and behavioral findings” at the 14th annual Associated Professional Sleep Societies conference, June 19, 2000
8/00  “To Compensate or Not To Compensate: That is the Question.” Invited presentation as part of the Young Investigator Seminar Series at the Brown University Sleep and Chronobiology Summer Research Apprenticeship program, August 21, 2000.
06/02  “Cerebral response to experimentally induced sleepiness as measured with FMRI” Invited presentation to be given during symposium entitled “Sleepiness in OSA: mechanisms and consequences” at the 8th Sleep & Breathing Symposium, Reykjavik, Iceland. June 2, 2002
06/02  “Brain function and cognitive performance during sleep deprivation.” Invited seminar at the Center for Sleep and Respiratory Neurobiology in the University of Pennsylvania Medical Center. June 28, 2002


Committee Memberships:
1996, 1997 Associated Professional Sleep Societies (APSS) Trainee Program Committee
1996, 1998 JDP Experimental Psychopathology Track Graduate Student Selection Committee
1996 - 1997 JDP Graduate Student Subcommittee to the Faculty Search Committee
1998 Chair, APSS Trainee Program Committee
1999 - 2003 Member, Sleep Research Society Committee for Animal Research Ethics
2002 - Member, American Academy of Sleep Medicine Research Committee
2003 Member, Sleep Research Society Trainee Education and Advisory Committee
2004- Chair, Sleep Research Society Trainee Education and Advisory Committee

Review Contributions:

Journals
2001 - 2003 Reviewer for Sleep
2001 - 2004  Reviewer for Journal of Sleep Research
2002  Ad Hoc reviewer for American J Respiratory & Critical Care Medicine
2002  Reviewer for Sleep Medicine Reviews
2002  Reviewer for Clinical Neurophysiology
2002  Reviewer for Journal of Studies on Alcohol
2002  Reviewer for Neuropsychology
2002  Reviewer for Journal of Psychosomatic Research
2002  Reviewer for American J Respiratory & Critical Care Medicine
2003  Reviewer for Brain Research
2004  Reviewer for Journal of Neuroscience
2004  Reviewer for International Journal of Psychophysiology

Grants
2003  Reviewer for Sleep Medicine Education & Research Foundation
2004  Reviewer for Netherlands Organization for Scientific Research (NWO)
2004  Reviewer for American Sleep Medicine Foundation

Other Professional Experiences:
1995-1998  Editor of the Sleep Trainee Email Network
1996  Chair, Sleep and Depression Symposia: APSS Conference
1997  Chair, Sleep and Depression II Symposia: APSS Conference
1997  Trainee Member-at-Large on the Sleep Research Society Board of Directors

PUBLICATIONS:
Manuscripts:


Chapters, Manuals, and Unreviewed Contributions:


Abstracts:

# = Oral Conference Presentations (n=15). Others are Poster-only presentations (n=23)


#18) Drummond, S.P.A., Gillin, J.C., Smith, T.L., Demodena, A. Sleep changes and recovery over 27 months in pure primary alcoholic patients. Sleep Research. 1997, 26:289


