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13. SUPPLEMENTARY NOTES

14. ABSTRACT 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, and 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 (66 hours total) and 2 full nights of recovery sleep on cognitive performance and brain function. 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. These data will provide a rich amount of information concerning the effects of prolonged total sleep deprivation and recovery sleep on cognitive performance and the cerebral underpinnings of that performance. Preliminary analyses (n=30) are revealing the course of deterioration and recovery in cognitive performance and the specific component processes of cognition affected by sleep deprivation. We have also initially reported distinct patterns of recovery for different sleep parameters after sleep deprivation, and the possibility of using the FMRI measures to identify neural correlates of vulnerability and resilience to sleep deprivation.

15. SUBJECT TERMS
Sleep, sleep deprivation, functional magnetic resonance imaging, cognition, performance

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Table of Contents

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 (about 66 hours total) 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. Together, these data will provide a rich amount of information concerning the effects of prolonged total sleep deprivation and recovery sleep on cognitive performance and the cerebral underpinnings of that performance. In addition to the 40 individuals in the sleep deprivation protocol, we will recruit 10 separate individuals to serve as control subjects who will participate only in the FMRI portion of the protocol, not the sleep or sleep deprivation portions. 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. Preliminary analyses of the sleep deprivation data are revealing the course of deterioration and recovery in cognitive performance and the specific component processes of cognition affected by sleep deprivation. We have also initially reported distinct patterns of recovery for different sleep parameters after sleep deprivation, and the possibility of using the FMRI measures to identify neural correlates of vulnerability and resilience to sleep deprivation.

BODY:

As of the end of Year 3 of this project, July 15 2005, approximately 500 individuals have been initially screened for the main sleep deprivation study. Thirty-nine (39) were determined to be preliminarily eligible and signed informed consent to participate in the main sleep deprivation protocol. Of those, 30 (15 females) have fully completed the study. Of those who did not complete, 4 voluntarily withdrew for personal reasons prior to the first experimental night, 4 were withdrawn due to further screening determining they were ineligible, and 1 subject voluntarily withdrew because he was unwilling to remain awake after approximately 20 hours of sleep deprivation. The 30 completed subjects match our goal for the end of Year 3 as outlined in the Statement of Work.

Additionally, 3 subjects have completed the control arm of this study. In recruiting subjects for the control arm, we have found that the majority of individuals prefer to participate in the main sleep deprivation protocol, because 1) the compensation is considerably greater, and 2) it requires less travel (since participants live in the lab rather than appear for two separate appointments each day). Thus, we have decided to complete all 40 subjects in the sleep deprivation protocol prior to enrolling anyone else in the control arm.

The 30 subjects who have completed the sleep deprivation protocol represent 900 separate functional MRI scans (10 sessions/subject x 3 cognitive task scans/session) and 300 anatomical MRI scans. Each functional scan requires approximately 10-12 hours to fully process and prepare the data for group level analyses. We are currently analyzing this enormous volume of data and hope to begin reporting the findings in the coming year. Nonetheless, in the past year,

we made 9 presentations of preliminary analyses, largely from the cognitive testing and sleep data (see Reportable Outcomes, References, and appendix). These reports exceed our goals as listed in the Statement of Work. These presentations include 7 published abstracts by team members (3 of which also received platform presentations at the Associated Professional Sleep Societies meeting in June 2005) and two invited international presentations by Dr. Drummond (the PI). Some of these abstracts are currently under preparation for submission as peer reviewed manuscripts.

Evidence of the importance of this project and the quality of the work comes from the fact that two of the published abstracts won major awards at this year's Associated Professional Sleep Societies meeting and four were awarded other merit-based awards. One abstract (Ref 5) was awarded the American Academy of Sleep Medicine award as the Outstanding Sleep Deprivation abstract. This abstract reports very strong findings showing that sleep deprivation affects only a very specific component of working memory performance (i.e., rehearsal span), and not other components. This is the first study to attempt to evaluate the effects of sleep loss on the individual component processes of working memory rather than just total scores. These data will improve our understanding of the deficits seen in the performance of complex tasks during sleep loss and may help us better avoid problems when duty assignments necessitate sleep loss. The other honored report (Ref 4) was awarded the Sleep Research Society's Bill Gruen Memorial Award for outstanding Instrumentation abstract. This abstract reported the validity of the Psychomotor Vigilance Task (PVT) within the MRI environment. This is important because the PVT is one of the most widely utilized performance tests within DoD sleep and sleep deprivation research efforts. Our data show that administration of the PVT within the MRI is valid, and thus our imaging data can be compared and contrasted with the plethora of behavioral studies already published with this task. Other reports described the pattern of recovery seen in sleep following 66 hours of sleep deprivation and the extent to which normal patterns of sleep can predict cognitive function while well rested. The two invited presentations by Dr. Drummond discussed preliminary findings from the brain imaging data suggesting that we may be able to identify the neural patterns that demonstrate whether someone is vulnerable or resilient to the adverse effects of sleep loss. This would be the first step in then predicting such individual differences and testing whether we can alter someone's inherent vulnerability.

KEY RESEARCH ACCOMPLISHMENTS:

- Thirty (30) subjects have completed the sleep deprivation protocol
- Three (3) have subjects completed the control arm of the protocol

REPORTABLE OUTCOMES:

1. Oral presentation entitled, "Evidence for Cerebral Compensation after Sleep Deprivation." Grounds Rounds presented at the Max Planck Institute for Psychiatry, Munich Germany. October 19, 2004.
2. Oral presentation entitled, "Neuroimaging of Sleep Debt and Its Effect on Cerebral Responses to Cognitive Performance." Invited presentation at the 2005 Organization for Human Brain Mapping annual conference. Toronto, Ontario. June 15, 2005.

3. Seven (7) abstract presentations at the Associated Professional Sleep Societies meeting in June 2005
   a. Three (3) earned platform presentations (Ref 3,5,6)
   b. Four (4) were awarded merit-based awards from the Sleep Research Society (refs 5-7,9)
   c. Reference 5 was awarded the Academy of Sleep Medicine award as the Outstanding Sleep Deprivation abstract
   d. Reference 4 was awarded the Sleep Research Society's Bill Gruen Memorial Award for outstanding Instrumentation abstract

CONCLUSIONS:

In Year 3 of this project, we met our goal of a total of 30 subjects completed through the main sleep deprivation portion of the protocol. Additionally, 3 subjects completed the control arm of the study. We are confident we will meet our entire enrollment goal as planned by the end of Year 4. We have begun to report preliminary results from this study, particularly from the cognitive and sleep data. Analyses of the functional brain imaging data are considerably more time consuming, and we are currently working on those. Our hope is that we will present the initial reports from the imaging data during the coming year, but it is likely these data will require additional time to reach peer-reviewed publication status. In the end, this project will provide rich and wide ranging data concerning the effects of sleep loss on brain function and cognitive performance on the rate of recovery of those functions, and increase knowledge of the individual differences in the response to sleep loss.

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1. "Evidence for Cerebral Compensation After Sleep Deprivation." Grounds Rounds presented by Dr. Drummond at the Max Planck Institute for Psychiatry, Munich Germany. October 19, 2004.

2. "Neuroimaging of Sleep Debt and Its Effect on Cerebral Responses to Cognitive Performance." Invited presentation by Dr. Drummond given at the 2005 Organization for Human Brain Mapping annual conference. Toronto, Ontario. June 15, 2005.

3. Drummond, SPA, Salamat, JS, Yanagi, MA, Stiller, C, Chen, T, Orff, HJ. Sleep Deprivation Affects Inhibitory Ability. Sleep 2005 28(Suppl 1):A132.

4. Carr, WC, Yanagi, MA, Salamat, JS, Drummond, SPA. PVT During MRI. Sleep 2005 28(Suppl 1):A326.

5. Turner, T, Yanagi, MA, Brown, GG, Drummond, SPA. The Effects of Sleep Deprivation on Component Processes in Working Memory. Sleep 2005 28(Suppl 1):A129-130.

6. Salamat, JS, Chen, T, Stiller, CS, Lopez,C, Drummond, SPA. Subjective Sleep Measures Predict Sustained Attention but not Performance on other Cognitive Tasks. Sleep 2005 28(Suppl 1):A353.

7. Chen, T, Salamat, JS, Yanagi, MA, Stiller, CS, Drummond, SPA. Actigraphy Measures vs. Cognitive Performance in Normal Sleepers. Sleep 2005 28(Suppl 1):A357.

8. Wong, RT, Salamat, JS, Schlosser, AM, Perrine, WF, Wetherell, LA, Yanagi, MA, Chen, T, Orff, HJ. Drummond, SPA. REM Rebound Following 64 Hours TSD. Sleep 2005 28(Suppl 1):A148.

9. Orff, HJ, Salamat, JS, Chen, T, Yanagi, MA, Wong, RT, Schlosser, AM, Perrine, WF, Wetherell, L, Drummond, SPA. Three Patterns of Recovery in Sleep Parameters Following 64-hour TSD. Sleep 2005 28(Suppl 1):A149.

APPENDICES:

Copies of the published abstracts for references 3-9 are provided. Please note, these abstracts were scanned from the published journal. There are multiple abstract per page in this journal.

0387

Sleep Deprivation Affects Inhibitory Ability

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Introduction: Total sleep deprivation (TSD) affects both attention and
executive processes. The ability to inhibit responses lies at the intersec-
tion of these two domains. Here, we examined performance changes on
an inhibition task across 2 nights TSD and 2 nights of recovery sleep
(REC).

Methods: 23 subjects (age 23.9 ±4.0 years; 13F) participated. The proto-
col involved one night baseline sleep (BL), 64hrs TSD, and 2 nights
recovery sleep (REC). We administered a go-nogo test every day at 14:00
(7, 31, 55hrs TSD) and 05:00 on TSD1 (22hrs TSD). We used MANOVA
and planned contrasts to analyze d' (the ability to discriminate among tar-
gets and non-targets) and response bias. Further analyses of hits and
false+ responses helped elucidate the source of errors.

Results: All variables showed a significant effect of Time. d' decreased
linearly throughout TSD. 22hrs, 31hrs, and 55hrs TSD had significantly
worse d' than BL. Subjects showed a significantly bias towards greater
responding at 22hrs TSD and after REC1 with a similar trend at 31hrs
TSD. Hit rate showed a significant decline at 55hrs TSD and a significant
increase after REC2. False+ responses were significantly greater at 22hrs,
31hrs, and 55hrs TSD.

Conclusion: TSD leads to impaired inhibitory abilities. Subjects showed
diminished ability to effectively discriminate targets and non-targets
throughout TSD. At 22hrs and 31hrs TSD, this inability was due to disin-
hibition generating increased false+ responses. At 55hrs of TSD, it result-
ed from a bias to underrespond. Circadian influences may underlie the
bias to overrespond, as it was strongest at 05:00. These results suggest
errors in operational settings during TSD may result from a decreasing
ability to quickly judge whether to take or withhold action. Furthermore,
they suggest that the mechanisms underlying this inability may differ
depending on both the length of TSD and the time of night.

0964
PVT During MRI

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Introduction: The Psychomotor Vigilance Test (PVT) is an established measure in fatigue and sleepiness assessment. Its effectiveness has led to its widespread use in research, including research protocols supporting development of Department of Defense fatigue performance prediction models. Here, we examined PVT performance in a functional magnetic resonance imaging (FMRI) environment relative to more typical sleep lab administration.

Methods: Eighteen people completed the PVT in each of 4 conditions: seated in a lab environment and supine during FMRI, both with and without 36 hours sleep deprivation. Four PVT response time variables, their reciprocals, and missed responses (i.e., lapses) were compared.

Results: As is typically seen, across PVT variables, subject responses were slower and lapses more frequent after sleep deprivation than when well rested. However, it was also the case that subject responses were slower and lapses more frequent during FMRI than lab environment testing. Interestingly, there was an interaction between sleep and test environment conditions, in that the slowing of PVT responses and increase in frequency of lapses with sleep deprivation occurred to a greater degree during FMRI than lab environment testing.

Conclusion: Generally, the PVT retains its value as a measure of the effects of sleep deprivation in the FMRI environment even though PVT performance during FMRI appears to be slower overall than in a lab environment. However, given the nature of the FMRI physical environment (e.g., supine posture, confinement, noise), effects of sleep deprivation may be magnified in FMRI relative to sleep lab, as we see in the more sensitive PVT measures of lapses and slowest 10% of responses. This finding has implications for fatigue research conducted with FMRI and for generalization of fatigue research to development of fatigue-performance prediction models, which, when applied, may be used to predict performance with variable posture and other immediate environmental parameters.

0381
The Effects Of Sleep Deprivation On Component Processes In Working Memory

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Introduction: Many studies have reported that total sleep deprivation (TSD) alters working memory (WM) performance, although the nature of alteration is not consistent across studies. One possible reason for this inconsistency is that overall performance is typically measured, with little consideration for specific components of WM. Here, we utilized a verbal WM task that allowed us to tease apart the effects of TSD on different cognitive processes involved.

Methods: Twenty-two adults (age 19-32, 9M) performed a parametric n-back test after normal sleep (NORM) and after 42 hours TSD. Tests were composed of continuous sets with alternating conditions: study of target nonsense words to be remembered, and selection of a previously studied target from amongst 3 foils. Lag, defined as the number of intervening study-selection sets before testing of a target, varied between 0 and 4. Eight trials were given for each level of lag (0,1,2,3,4 back).

Results: Multivariate ANOVA revealed significantly worse overall performance after TSD. A priori repeated contrasts revealed a significant interaction between sleep condition and lag. The performance drop from lag 0 to lag 1 was greater after TSD than NORM. All other contrasts and paired-sample t-tests for levels of lag between sleep conditions were not significantly different.

Conclusion: Prior research suggests TSD impacts basic attention processes, reflected here as the ability to identify stimuli immediately after presentation (lag 0). Our results suggest that sleep deprivation does not impact basic attention to verbal material, but rather impairs maintenance of information in WM. Importantly, the effect manifests at lag 1 and then remains constant across greater lags, suggesting that encoding and retrieval processes remain relatively preserved. In sum, these data suggest that 42 hours TSD adversely affects the verbal WM rehearsal buffer, but not attention to stimuli or encoding and retrieval processes.

1041

Subjective Sleep Measures Predict Sustained Attention But Not Performance On Other Cognitive Tasks

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Introduction: Significantly restricting or extending sleep (e.g., 4-5hrs or 10-12hrs TIB) can influence cognitive performance. It is unclear if variations within a normal TIB range can influence performance. Here we examined whether subjective sleep parameters predicted performance on several cognitive tasks.

Methods: Fifty-five normal control subjects (30M, age=26.6±5.8, education=15.6±1.7) completed sleep diaries for 7 days prior to a night of sleep in the lab. Partial correlation analysis, controlling for education, was used to assess the relationship between averaged diary variables (TIB, TST, SL, SE, WASO and a 7-point Likert scale asking about how refreshed subjects felt upon awakening) and cognitive performance on three tasks: the PVT, arithmetic working memory, and verbal learning. Tasks were performed 12 hours after awakening.

Results: There were no significant relationships between subjective sleep measures and arithmetic or verbal learning performance. Subjective reports of how refreshed a person felt predicted some PVT performance variables. Specifically, how refreshed a person felt was associated with faster mean reaction time (RT), faster slowest 10% RT, and lower standard deviation of RT (p<.02, p<.003, and p<.002, respectively). The number of awakenings during the night was also negatively correlated with the same PVT variables, plus lapses. No other subjective sleep parameters predicted PVT performance.

Conclusion: Subjective sleep measures can predict sustained attention. Overall, the more refreshed a person felt upon awakening, the faster the RTs and the more ability to consistently sustain attention. It is unclear why a greater number of reported awakenings would also predict better PVT performance. Interestingly, none of the subjective sleep measures predicted performance on more complex cognitive tasks. This suggests that while variations within a relatively normal range of sleep times can influence attention, the effect is not strong enough to influence other cognitive processes that do not rely exclusively on sustained attention.

1052

Actigraphy Measures Vs. Cognitive Performance In Normal Sleepers

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Introduction: Previous studies have shown that either a restricted or extended amount of sleep can influence cognitive performance. However, it is unclear whether variability within a "normal sleepers" population can also influence performance. Here we examined whether actigraphy measures of prior sleep in a sample of "normal sleepers" predicted cognitive performance.

Methods: A total of 17 (11F, 6M) normal control subjects with a mean age of 24.4 ± 4.2 years and a mean education of 15.8 ± 1.7 years participated in this study. Subjects wore actigraph watches continuously for 4-13 days (10.2 ± 3.0 days) and nights while maintaining their normal sleep and wake times. After the last night of sleep, we administered the Psychomotor Vigilance Task (PVT), an arithmetic working memory task (MATH), and a verbal learning task (VL) at both 2 and 12 hours post awakening. Correlation analyses were used to assess the relationship between actigraphy measures (TIB, TST, SE, SL, and WASO) and performance variables at each time point.

Results: Subjects obtained a mean of 402.7 ± 40.4 min TST (range 331.0min - 482.5min) and had a mean SE of $87.7\pm7.5\%$ (range 75.9% - 99.0%). No significant relationship was found between any of the actigraphy measures and any performance measure at either testing session.

Conclusion: Overall, actigraphy measures from individuals sleeping what is typically considered a "normal" amount could not predict performance on the PVT, MATH, or VL. Results suggest that these variations within a normal range of sleep, as measured with actigraphy, were not extreme enough to influence cognitive performance. Given that there was still considerable variation among individuals' cognitive performance scores, however, it is likely that factors other than sleep amount and continuity contributed to the differences in individual performance among these normal control subjects.

0438

REM Rebound Following 64 Hours TSD

Wong R,[1] Salamat JS,[1] Schlosser AM,[3] Perrine WF,[3] Wetherell LA,[2] Yanagi MA,[1] Chen T,[1] Orff HJ,[1,4] Drummond S[1,2]

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Introduction: It has been documented that REM sleep recovers later than NREM sleep following TSD. However, it is not clear this pattern is consistent throughout the full night or is specific to early REM periods when the homeostatic drive for SWS is strongest. Here we examined REM sleep recovery across REM periods after TSD.

Methods: 21 subjects (age=23.7 ± 3.7, 11F) participated in a 6-consecutive-night study in the sleep lab. The protocol involved 1 night of baseline sleep (BL), 64 hours total sleep deprivation (TSD), and 2 nights of recovery sleep (REC1 and REC2). Data were analyzed using within-subjects repeated measures ANOVA with planned contrasts.

Results: REM efficiency and REM density (REMD) both showed a significant main effect of Night during all 3 REM periods. REM efficiency in periods 1, 2 and 3 declined significantly from BL to REC1 and increased from REC1 to REC2 (but remained significantly less than BL on REC2). In most subjects, REM was fragmented by the occurrence of Stage 2 during REC nights. REMD showed no difference between BL and REC1, but increased significantly on REC2. The length of REM periods did not change significantly across nights.

Conclusion: Overall, it appears that the lack of recovery in REM sleep on REC1 and the subsequent recovery on REC2 manifests in each of the first 3 REM periods. REM was less efficient and REMD was low throughout the night on REC1, and each increased in all REM periods on REC2. The consistent fragmentation and reduced intensity of REM on REC1 may relate to a need to conserve resources for other recovery processes occurring during SWS. The lack of complete REM recovery in this study suggests that to fully understand the process of recovery sleep, more than 2 recovery nights may be necessary.

0440

Three Patterns Of Recovery In Sleep Parameters Following 64-Hour TSD

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Introduction: Total sleep deprivation (TSD) alters several sleep parameters upon recovery. Sleep is more consolidated and competition between the need to replace slow wave sleep (SWS) and REM sleep appear to alter normal sleep architecture during recovery sleep. Here, we compared sleep parameters on baseline and for two consecutive nights of recovery sleep following 64-hours of TSD.

Methods: 23 subjects (23.94+/-3.99, 13F) participated in this study. The protocol involved one night baseline sleep (BL), 64hrs TSD and 2 nights recovery sleep (REC1, REC2). 11 sleep variables were evaluated, including: TST, TIB, WASO, SE, SL, RL, REMD, Stage1%, Stage2%, Delta%, and REM%. Data were analyzed with within subjects repeated measures ANOVA and planned contrasts.

Results: All variables showed a significant effect of Night, except for TIB which did not differ between nights. Three patterns of recovery emerged in the data. First, TST, SE, and Delta% were all greater on both REC1 and REC2 vs BL, but less on REC2 than REC1. SL, Stage1%, Stage2% showed a similar recovery pattern with BL>REC2>REC1. Second, REMD and REM% showed REC2>BL=REC1. RL showed REC2 **Conclusion:** These data replicate previous findings suggesting that sleep is altered during recovery sleep following 64-hour TSD. Here, three distinct patterns of recovery sleep were observed: complete recovery after 1 night, incomplete recovery with even 2 nights, and no recovery until night 2. WASO fully recovered after 1 night of recovery sleep. NREM and most sleep continuity variables showed strong signs of recovery on REC1 and continued to show recovery even on REC2. REM variables showed no recovery until REC2. Thus, most sleep parameters did not fully recover after 2 nights of sleep, suggesting that it takes longer to recover sleep than to lose it.