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Award Number: DAMD17-02-1-0201

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

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

REPORT DATE: August 2007

TYPE OF REPORT: Final

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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<b>REPORT DOCUMENTATION PAGE</b>				<i>Form Approved</i> <b>OMB No. 0704-0188</b>	
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<b>1. REPORT DATE (DD-MM-YYYY)</b> 01-08-2007		<b>2. REPORT TYPE</b> Final		<b>3. DATES COVERED (From - To)</b> 15 Jul 2002 – 15 Jul 2007	
<b>4. TITLE AND SUBTITLE</b>  The Effects of Total Sleep Deprivation and Recovery Sleep on Cognitive Performance and Brain Function				<b>5a. CONTRACT NUMBER</b>	
				<b>5b. GRANT NUMBER</b> DAMD17-02-1-0201	
				<b>5c. PROGRAM ELEMENT NUMBER</b>	
<b>6. AUTHOR(S)</b>  Sean P.A. Drummond, Ph.D.  E-Mail: <a href="mailto:drummond@ucsd.edu">drummond@ucsd.edu</a>				<b>5d. PROJECT NUMBER</b>	
				<b>5e. TASK NUMBER</b>	
				<b>5f. WORK UNIT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b>  Veterans Medical Research Foundation San Diego, CA 92161				<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b> U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				<b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>	
				<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>	
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b> Approved for Public Release; Distribution Unlimited					
<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b>  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 have studied 40 individuals for 6 nights and 6 days. Over the course of this period, subjects received 4 polysomnograms and 10 functional magnetic resonance imaging (fMRI) sessions. During the fMRI sessions, functional brain imaging data was collected while subjects performed each of 3 cognitive tasks. These data 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. The initial manuscripts from this study have shown: a) the course of deterioration and recovery in cognitive inhibitory processes; b) changes during sleep deprivation in brain networks responsible for new learning; c) changes in risk taking during sleep deprivation; and d) the specific components of working memory impaired by sleep deprivation and individual differences in vulnerability to working memory deficits during sleep deprivation.					
<b>15. SUBJECT TERMS</b> Sleep, sleep deprivation, functional magnetic resonance imaging, cognition, performance					
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>  UU	<b>18. NUMBER OF PAGES</b>  37	<b>19a. NAME OF RESPONSIBLE PERSON</b> USAMRMC
<b>a. REPORT</b> U	<b>b. ABSTRACT</b> U	<b>c. THIS PAGE</b> U			<b>19b. TELEPHONE NUMBER (include area code)</b>

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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 (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 this report, we are completely finished with data collection for the study. By the end of Year 4, we had completed the main sleep deprivation portion of the study. In Year 5, we finished data collection for the control arm of the study. Furthermore, we continued to analyze data and submit peer-reviewed manuscripts for publication. Thus, we have completed all tasks on the Statement of Work. Since this is the final report, we briefly present information from the entire project, below.

For the main sleep deprivation portion of the protocol, approximately 700 individuals were initially screened for the main sleep deprivation study. Fifty-one (51) were determined to be preliminarily eligible and signed informed consent to participate in the main sleep deprivation protocol. Of those, 40 (18 females) fully completed the study. Of those who did not complete, 6 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. Additionally, 11 subjects signed informed consent for the control arm of this study, with 10 (6 females) completing the study. The one who did not complete was screened out based on exclusion criteria.

The 50 subjects who have completed the both arms of this study represent 1500 separate functional MRI scans (10 sessions/subject x 3 cognitive task scans/session) and 500 anatomical MRI scans. Each functional scan requires approximately 10-12 hours to fully process and prepare for group level analyses.

Thus far, we have published or have in-press 4 manuscripts from this study. In addition, there are 2 others currently under review. The results of these 4 manuscripts are summarized under Key Research Accomplishments. We also have presented 14 abstracts at national scientific conferences. Some of these abstracts evolved into the four manuscripts and we anticipate others will become manuscripts, as well. Additionally, Dr. Drummond (study PI) has made 9 invited presentations, both nationally and internationally, that have included data from this study. Finally, we were recently notified that the National Science Foundation will fund a 3-year project that is based, in large part, on the findings in reference 3, below.

#### **KEY RESEARCH ACCOMPLISHMENTS:**

As little as 23 hours of sleep deprivation significantly impairs the ability to stop oneself from performing an action, even when that action is inappropriate (i.e. to inhibit an automatic behavior). However, a single night of recovery sleep restores this ability. This has implications for operational settings where a war fighter may need to withhold what is an otherwise over-trained automatic response. See reference 1.

Communication among brain regions responsible for learning new information is altered by sleep deprivation. That is, the way the brain processes the learning of new information changes during sleep deprivation. Some of these alterations appear to allow individuals to continue to learn despite sleep loss, although they likely represent less efficient use of the cerebral networks responsible for learning. The net result is a relatively intact ability to learn new information and remember it for at least 20-30 minutes. See reference 2.

Sleep deprivation significantly alters individuals' willingness to take risks when making decisions by blunting our sensitivity to risk. Interestingly, whether this results in an increase or a decrease in risk taking depends on how the decision is framed. If an individual is seeking to maximize a gain, s/he will take more risk when sleep deprived than s/he would well-rested. If an individual is seeking to minimize losses, s/he will take less risk when sleep deprived than s/he would well-rested. This suggests we may be able to develop training paradigms to help war fighters make more consistent decisions about risk when they are sleep deprived. See reference 3.

Working memory is a "higher order" cognitive function that is involved in many other aspects of performance. Working memory allows individuals to keep information "on-line" for further manipulation or use. Sleep deprivation does not impair all aspects of working memory equally. On average, the amount of information someone can keep on-line at one time decreases during sleep deprivation. Attention to incoming information also decreases, but not as much. Once information makes it into working memory, though, individuals are equally likely to memorize it when sleep deprived as when well-rested. However, there are individual differences in the impact of sleep deprivation on working memory such that some individuals are resilient or vulnerable only one specific aspect of working memory and not the others. See reference 4.

#### **REPORTABLE OUTCOMES:**

1. Four peer-reviewed manuscripts (references 1-4)
2. Fifteen abstract presentations at the Associated Professional Sleep Societies meeting in June 2005 (references 5-19)
  - a. Eight earned platform presentations
  - b. Seven were awarded merit-based awards from the Sleep Research Society

- c. Reference 7 was awarded the Academy of Sleep Medicine award as the Outstanding Sleep Deprivation abstract
  - d. Reference 12 was awarded the Sleep Research Society's Bill Gruen Memorial Award for outstanding Instrumentation abstract
- 3. Nine invited presentations at national and international scientific meetings and institutions, including the 2006 Military Health Research forum (references 20-29)
- 4. Granted funded by the National Science Foundation (proposal #0729021). "Collaborative Research: DRU: Behavioral and Neural Effects of Sleep Deprivation on Specific Components of Decision Making" This is a 3-year grant based, in part, on the results of reference 3. Dr. Drummond is the PI of this grant.

### **CONCLUSIONS:**

Overall, we have completed all of the items in the Statement of Work related to both the sleep deprivation portion of this study and the control condition. This represents 1500 individual functional magnetic resonance imaging scans. Over the four years of the study, we have produced 4 published manuscripts, 15 conference abstracts (8 were platform presentations and 7 received merit-based awards), 9 invited presentations at international meetings, and 1 successful grant application.

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#### Conference Abstracts

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#### Invited Presentations

20. "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.

21. "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. Drummond, SPA, Salamat, JS, Yanagi, MA, Stiller, C, Chen, T, Orff, HJ. Sleep Deprivation Affects Inhibitory Ability. Sleep 2005 28(Suppl 1):A132.
23. "The Impact of Sleep Loss on Brain Function: Evidence from FMRI Studies." Colloquium presented in the Department of Psychology, University of Arizona. October 28, 2005.
24. "Consequences of Sleep Deprivation." Presentation given at the NIH Neuroimaging in Sleep Research workgroup. March 29, 2006.
25. "Effects of Sleep Deprivation and Recovery Sleep on Cognitive Performance and Brain Function." Presentation given at the 2006 Military Health Research Forum. San Juan, Puerto Rico. May 2, 2006
26. "Functional MRI Investigations of Cognitive Performance in Experimental Sleep Deprivation and Obstructive Sleep Apnea: Similarities and Differences." Invited presentation to the Respiratory, Neurobiology, and Sleep dinner at the annual American Thoracic Society Meeting. San Diego, California. May 2006
27. "Sleep Deprivation/Restriction: Human Studies" Invited presentation at the Associated Professional Sleep Societies meeting. Salt Lake City, Utah June 2006; CME lecture
28. "Sleep, Sleep Loss, Brain Function and Cognition" Invited presentation at the International Neuropsychological Society Meeting. Portland, Oregon, February 2007
29. "Sleep Deprivation/Restriction: Effects on Brain, Behavior, Health, and Safety" Invited presentation at the 21st annual Associated Professional Sleep Societies meeting. Minneapolis, Minnesota, June 2007

#### **APPENDICES:**

Previously, we submitted the page proofs from references 1-2. We have enclosed the final reprints in this report. In addition, we have enclosed the page proofs of references 3-4.

# Effects of two nights sleep deprivation and two nights recovery sleep on response inhibition

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Accepted in revised form 19 May 2006; received 9 December 2005

**SUMMARY** This study examined the effects of two nights of total sleep deprivation (TSD) and two nights of recovery sleep on response inhibition. Thirty-eight young, healthy adults performed a Go-NoGo task at 14 : 00 after: (1) a normal night of sleep; (2) each of two consecutive nights of TSD; and (3) each of two consecutive nights of recovery sleep; they also performed the task at 05 : 00 during the first night of sleep deprivation. We hypothesized that TSD would lead to an impaired ability to withhold a response that would be reversed with recovery sleep. Subjects did experience a significant increase in false positive responses throughout all of TSD, errors of omission (i.e. missed 'go' targets) were not significant until after the second night of TSD. Both components (withholding a response and automatic responding) of the task returned to baseline levels after one night of recovery sleep. These data suggest that individuals experience difficulty in withholding an inappropriate response during TSD, even when they are able to attend to the incoming stimuli and respond accurately to appropriate stimuli.

**KEYWORDS** attention, inhibition, NoGo, recovery sleep, sleep deprivation

## INTRODUCTION

Response inhibition is the cognitive process necessary to stop oneself from engaging in a prepotent response when that reaction is not appropriate. Response inhibition involves two cognitive components: attention to incoming stimuli and prevention of an automatic response (Lezak *et al.*, 2004). Poor response inhibition has been reported as one of the cognitive symptoms of a variety of conditions, such as schizophrenia (Weisbrod *et al.*, 2000), substance use disorders (Fillmore, 2003), and attention deficit/hyperactivity disorder (Willcutt *et al.*, 2005).

Response inhibition is often measured with a Go–NoGo task. Such a task requires frequent automatic responding to stimuli interspersed with the need to withhold a response from a specific, less frequently occurring, stimulus. It is well established that sleep deprivation can affect performance such that automatic responding is slowed and more variable during sleep deprivation (Doran *et al.*, 2001; Dorrian *et al.*, 2005).

The effect of sleep deprivation on withholding a prepotent or automatic response, though, has not been extensively studied. The few published studies in this area have reported inconsistent results. One reason for the inconsistency is that most studies have used fairly complex cognitive tasks involving a number of demands beyond withholding a response. For example, some studies have employed stimulus-response incompatibility paradigms that required not only inhibition of an automatic response but also initiation of a less salient response (Harrison and Horne, 1998; Jennings *et al.*, 2003; Smulders *et al.*, 1997). Studies have also used complex choice reaction time tasks (Jennings *et al.*, 2003; Smulders *et al.*, 1997), negative priming (Harrison and Espelid, 2004), or tasks with vague inhibitory demands (Fallone *et al.*, 2001). Another reason for the inconsistent findings is that with a few exceptions, the aims of these studies were not specifically to examine response inhibition. Rather, withholding a response was but one part of a larger set of cognitive demands, all of which influenced the behavioral outcome.

Thus, it remains unclear whether total sleep deprivation (TSD) affects the ability to withhold a response specifically or whether errors of commission result from deficits in other task demands. Here, we used a Go–NoGo task to address this issue.

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This task is ideal for focusing on withholding of an automatic response because of the simplicity of the design. Subjects performed the task at baseline, three times during TSD, and after each of two nights of recovery sleep. We hypothesized that (a) TSD would impair response withholding; (b) this impairment would be greater than that seen for automatic responding; and (c) recovery sleep would reverse the expected performance decrements.

## METHODS

### Subjects and conditions

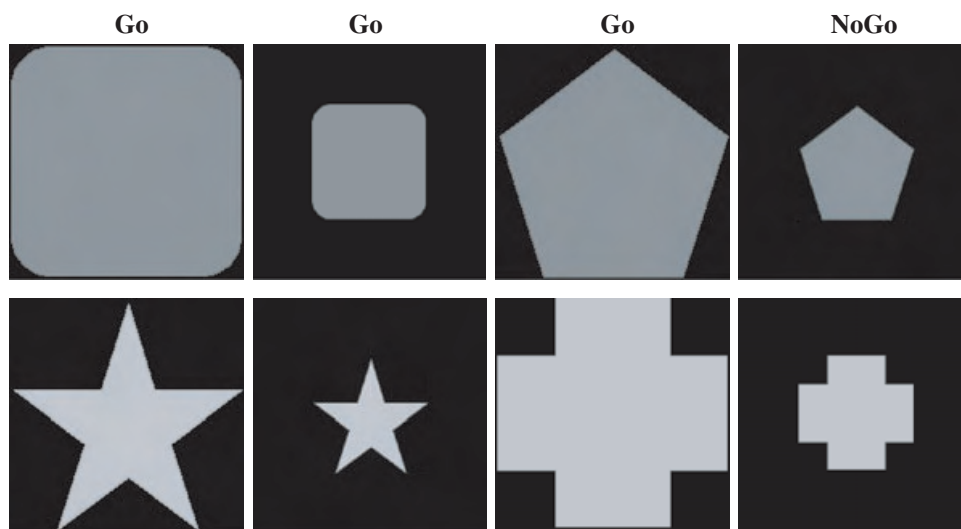
Thirty-eight young healthy adults (18 females; age:  $24.1 \pm 5.0$ ; education:  $15.3 \pm 1.6$ ) free of medical and psychiatric disorders participated in this study after providing written informed consent. All subjects reported habitually obtaining 7–9 h of sleep. They completed sleep diaries and wore actigraphs for 1 week before the study to verify adherence to a regular sleep–wake schedule. After an adaptation night in the laboratory, subjects returned the next night and were then sequestered in the laboratory until completion of the study. The subjects slept according to their normal schedule on night 2, underwent TSD for the next two nights (about 64 h total), and then were given two nights of recovery sleep (again, according to their habitual sleep–wake schedule).

### Testing procedures

At 14 : 00 on each day starting after night 2, plus at 05 : 00 during the first TSD night, subjects performed a Go–NoGo task. Thus, the task was administered at an average of 21.75,

30.75 and 54.75 h TSD (standard deviation of each = 0.44 h), as well as  $6.75 \pm 0.44$  h after waking on the baseline day and after each recovery night. The computer-administered task involved viewing stimuli presented individually in the center of the screen in a semi-random order for 200 ms with a 1300 ms interstimulus interval. A total of 181 stimuli were shown during the 4.5 min task. Stimuli consisted of two geometric shapes in each of two sizes (see Fig. 1 for examples). Subjects were instructed to respond ‘as fast as possible’ with a button press on the keyboard to all shapes *except* the target shape and to withhold a response for the target shape. The task directions emphasized both speed and accuracy of responding. To develop a prepotent tendency to respond positively with a button press, the need to respond quickly was emphasized repeatedly in the directions, 68.5% of the stimuli were ‘go’ stimuli, and the ‘NoGo’ stimulus shared a perceptual feature in common with two of the Go shapes (size or geometric shape, respectively).

Six different versions of the test were constructed. A previous pilot study, not designed as a direct control for this study, with 21 subjects from the same demographic as those reported here examined the practice effects and comparability of task versions. In that pilot, each subject took five of the six different versions of the Go–NoGo task, once each on five separate days after normal sleep. These test administration days were either consecutive or included two non-testing days (i.e. Saturday and Sunday) when the 5-day testing period included a weekend. Briefly, with respect to practice effects, only false positive rate showed a main effect of time ( $P = 0.018$ ), with an improvement from test 1 to test 2, and no significant changes thereafter. Overall, these data suggest that the practice effects for this task are



**Figure 1.** Examples of task stimuli. Each row shows the stimuli from 1 of the 6 matched versions of the task. In each case, the first three shapes represented ‘go’ stimuli where subjects were required to press a button as quickly as possible when they appeared. The far right shape was the ‘NoGo’ stimulus where subjects were required to withhold a response. Note that to increase the tendency to respond with a button press, the NoGo shape shared a perceptual feature with each of two Go shapes (size or geometric shapes, respectively). While the shapes are shown in gray scale here, the actual stimuli were in color (all shapes of a given version were the same color).

**Table 1** Practice effects from a previous pilot study

	Time 1	Time 2	Time 3	Time 4	Time 5
Hit rate	0.97	0.99	0.99	0.99	0.99
	0.07	0.01	0.01	0.03	0.02
False + rate	0.14	0.10	0.09	0.09	0.10
	0.08	0.08	0.08	0.07	0.07
Hit RT (ms)	602.18	614.30	622.75	589.54	589.08
	50.46	84.42	98.14	62.08	49.76

Data for each variable are presented as mean (top) and standard deviation (bottom).

modest and largely resolved after the first administration (Table 1). With respect to version compatibility, analyzes showed no differences in any version of the task on any variable (Table 2).

### Data analysis

The outcome variables for task performance included (1) hit rate (correct button press for Go stimuli); (2) response time (RT) for correct hits; and (3) false positive rate (error of commission for NoGo stimuli). Automatic responding was measured with hit rate and RT for hits, while response withholding was measured with false positive rate (i.e. errors of commission). All variables were analyzed with one-way repeated measures ANOVA. *Posthoc* follow-up tests were done with Dunnett's test corrections using the baseline scores as the comparator. Hit RT data for six subjects was lost due to technical errors, so  $n = 32$  for that analysis.

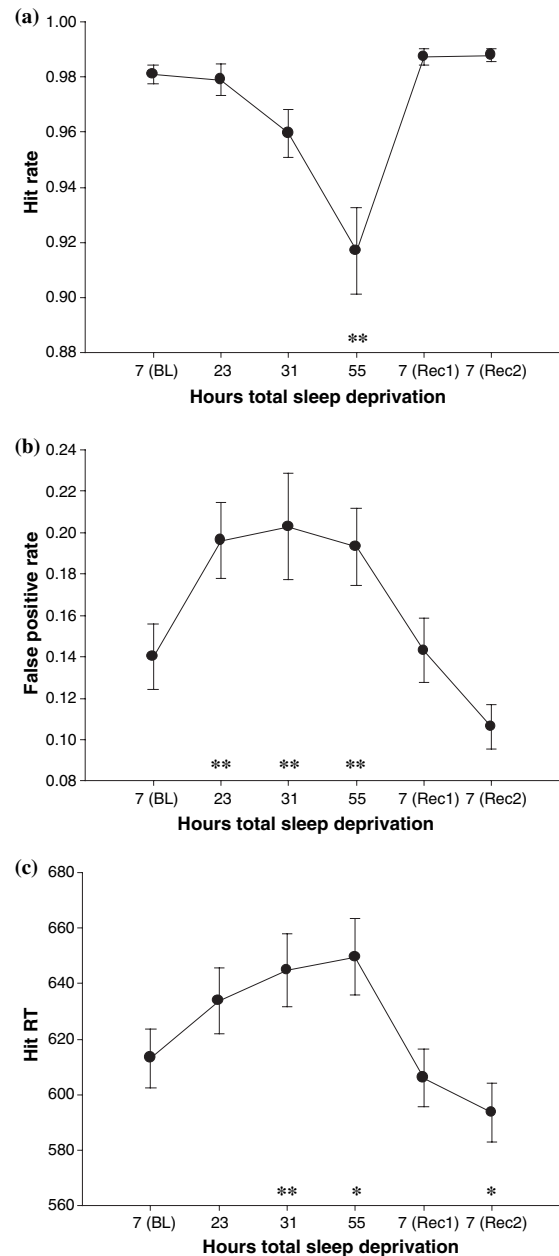
## RESULTS

Figure 2 shows the results of the three outcome variables. Each variable showed a significant effect of Time in the omnibus ANOVA ( $P < 0.001$  with Greenhouse–Geisser correction). Hit rates were significantly different from baseline only after two nights TSD (55.75 h). Hit RT was significantly slower than baseline after both 31.75 and 55.75 h TSD. False positive rates, on the other hand, were elevated during all TSD testing sessions. Each of these variables returned to baseline values after one night of recovery sleep. Hit RT and false positive rates continued to decline after the second recovery night, but this change was significant only for hit RT.

**Table 2** Version comparability from a previous pilot study

	Version 1	Version 2	Version 3	Version 4	Version 5	Version 6
Hit rate	0.98	0.99	0.99	0.99	0.99	0.99
	0.08	0.01	0.01	0.03	0.01	0.02
False +	0.08	0.12	0.14	0.12	0.09	0.09
	0.07	0.08	0.07	0.09	0.07	0.06
Hit RT (ms)	584.25	607.98	601.47	603.39	610.16	615.21
	76.23	52.42	56.09	57.35	69.35	100.93

Data for each variable are presented as mean (top) and standard deviation (bottom).



**Figure 2.** Behavioral performance. Graphs show the five performance measures (mean  $\pm$  SE) across the six testing sessions. All outcome measures showed a significant effect of time ( $P < 0.001$ ). Significance of follow-up analyzes are denoted as \* $P < 0.05$  versus baseline; \*\* $P < 0.01$  versus baseline. All analyzes had  $n = 38$ , except Hit RT which had  $n = 32$  (due to loss of RT data for six subjects).

## DISCUSSION

Here, we report the effects of two nights TSD and two nights of recovery sleep on response inhibition as measured by a Go–NoGo task. Given the simple nature of the task design, we were able to more directly test the effects of TSD on the ability to stop oneself from performing an automatic response than many previous studies examining inhibition during TSD. We found that throughout TSD, subjects showed an impaired ability to withhold an automatic response. In contrast, hit rates remained stable early in TSD and only showed significant declines after the second night of TSD. This pattern suggests that during most of TSD subjects could initiate a response normally when appropriate (although somewhat slower than usual), but the inability to withhold an inappropriate response was impaired. Performance on all outcome variables returned to baseline levels after a single night of recovery sleep.

The main goal of this report was to evaluate whether the ability to withhold a response is impaired by TSD. As stated above, these data suggest that is indeed the case. One possible explanation for why subjects made more errors of commission than errors of omission during TSD may be they sacrificed accuracy in favor of speed. The emphasis on speed in the task directions may have led subjects to emphasize this outcome over the need to not respond during the NoGo stimuli. However, the RT data does not support this hypothesis. Such a focus on speed over accuracy should have favored intact RTs during correct hits with TSD. However, as Fig. 2 shows, that is not the case since RTs actually slowed during TSD.

The fact that both automatic responding and withholding a response were impaired during TSD (albeit at different rates) raises the possibility that both functions rely on the same cognitive processes and/or brain regions. While it is clear that the automatic responding component of this task requires attention, it remains unclear whether withholding a response also relies mainly on the attention system or an inhibitory system independent of attention. Manly and colleagues, through a series of experiments, argue that both task components require endogenous attention (Manly *et al.*, 1999). Evidence for this includes the fact that subjects scoring high on a measure of ‘absent mindedness’, but not those scoring low, showed greater false positive rates when the task was made longer or the proportion of NoGo stimuli was reduced (both manipulations should increase attentional demands). Additionally, they found that faster hit RTs were correlated with increased false positives and suggested this means that ‘inefficient’ use of attention or an ‘inattentive approach to the task’ produces both speeding of responses and errors of commission (Manly *et al.*, 1999). However, given that there are many different types of attention (e.g. sustained, selective, spatial, divided, etc.) that each engage different brain regions (Itti *et al.*, 2005; Posner, 2004), possibly the two very different behaviors of automatic responding and withholding a response rely on distinct aspects of the attention system. Consistent with this idea are the facts that (a) during TSD our subjects showed a *slowing* of RT to Go stimuli along with an increase in false

positive responding; and (b) both variables showed reversals after Recovery sleep. These relationships are opposite those of Manly *et al.* If Manly *et al.*’s findings argue in favor of a single attention process underlying both types of responding, our data would have to be seen as arguing against that idea. Thus, our data may suggest that TSD produces a dissociation between the types of attention responsible for automatic responding and response withholding that Manly *et al.*’s manipulations did not.

Moreover, consistent with the notion that automatic responding and withholding a response may rely on at least slightly different cognitive processes is the fact that each seems to activate different regions within the prefrontal cortex. The vulnerability of the prefrontal cortex to TSD has long been debated (Binks *et al.*, 1999; Harrison and Horne, 1996; Horne, 1993; Wimmer *et al.*, 1992). The prefrontal cortex, though, is composed of many sub-regions, and it is likely those regions respond somewhat differently to TSD. The region within the prefrontal cortex most commonly implicated in response withholding during neuroimaging and lesion studies is the right ventral prefrontal cortex, typically within the inferior frontal gyrus (Aron *et al.*, 2004; Fassbender *et al.*, 2004; Kelly *et al.*, 2004; Matthews *et al.*, 2005). This suggests that impaired response withholding during TSD may result from impaired function of this specific region. Automatic responding, on the other hand, typically activates sustained attention regions within the right dorsolateral prefrontal cortex (Culham *et al.*, 2001; Yamasaki *et al.*, 2002). Impaired automatic responding during TSD, then, may relate to impaired function of this region, possibly due to an impaired ability to appropriately allocate cognitive resources to within the brain (Drummond *et al.*, 2005). Significant errors of omission were not evidenced here until after two nights of TSD. However, if a more subtle deficit in resource allocation was present earlier in TSD, that may have contributed to potential dysfunction within the prefrontal region required for successful inhibition. A caveat to this possible consequence of TSD is that some tasks rely less on the prefrontal cortex after sufficient practice (Beauchamp *et al.*, 2003; Sayala *et al.*, 2005). If that occurs for response withholding, then the task may rely more heavily on other brain systems, such as the posterior portion of the attention system.

The simplicity of the task design, while largely a strength, did not allow us to evaluate all aspects of response withholding. Specifically, we only examined motor inhibition, as opposed to speech inhibition. We also did not evaluate the ability to stop a response that has already been initiated, as can be done with the Stop Task (Brown and Braver, 2005; Matthews *et al.*, 2005). However, as described above, our aim focused on the ability to withhold a motor response and this Go–NoGo task allowed us to do that relatively free of other cognitive demands. A second limitation is that we did not use a pure measure of sustained attention (e.g. the psychomotor vigilance task (PVT)) to contrast with response withholding. However, given the emphasis on speed, the Go stimuli here served as a reaction time task for which we could assess both errors of omission and speed, the two most

common measures used in sustained attention analyzes. Another limitation of the study is the lack of an explicit control group who received all study procedures except TSD. While our pilot data provide information regarding practice effects, this is an imperfect control. Nonetheless, it is interesting to note that the practice effects in the pilot study were in the opposite direction of the TSD effects seen here, suggesting that the true TSD effects may be even greater than what we report.

In summary, we utilized a Go-NoGo task to assess the impact of two nights TSD and two nights of recovery sleep on the ability to withhold a motor response. The design of our cognitive task allowed us to study this outside the context of more complex cognitive demands. We found that subjects experienced significant impairment in response withholding throughout all of TSD, while automatic responding was not significant until after the second night of TSD. Both components of the task returned to baseline levels after one night of recovery sleep. These data suggest that individuals experience difficulty in withholding an inappropriate response during TSD, even when they are able to attend to incoming stimuli and respond accurately to appropriate stimuli. Thus, operational settings might consider installing safeguards to prevent mistakes and accidents from occurring as a result specifically of impaired response withholding among sleep deprived personnel.

## ACKNOWLEDGEMENTS

Study supported by the US Department of the Army award no. DAMD17-02-1-0201 and NIH M01 RR00827. The US Army Medical Research Acquisition Activity is the awarding and administering acquisition office. The content herein does not necessarily reflect the position or policy of the Government, and no official endorsement should be inferred. Thanks go to the numerous research staff that helped recruit and test the subjects, as well as the subjects themselves.

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# The impact of sleep deprivation and task difficulty on networks of fMRI brain response

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(RECEIVED March 26, 2006; FINAL REVISION June 5, 2006; ACCEPTED June 6, 2006)

## Abstract

Previous fMRI research has found altered brain response after total sleep deprivation (TSD), with TSD effects moderated by task difficulty. Specific models of the impact of sleep deprivation and task difficulty on brain response have yet to be developed. Differences in networks of fMRI measured brain response during verbal encoding in sleep deprived and well-rested individuals were examined with structural equation modeling (SEM). During fMRI scanning, 23 healthy volunteers memorized words either easy or difficult to recall, 12 (well-rested) and 36 hours (sleep deprived) after awakening. *A priori* models that linked specified regions of interest were evaluated, with the focus on the extent to which two left parietal regions interacted with the left inferior frontal gyrus (Model 1) or with the right inferior frontal gyrus (Model 2). Task difficulty, not TSD, determined which model fit the brain response data; Model 2 fit best for hard words before and after TSD, whereas Model 1 fit best for easy words. TSD altered the patterns of interaction within each of the best fitting models: prefrontal interactions with the left inferior parietal lobe were diminished and intra-parietal interactions increased. Sleep deprivation and item difficulty produce different effects on brain networks involved in verbal learning. (*JINS*, 2006, 12, 591–597.)

**Keywords:** Echoplanar imaging, Magnetic Resonance Imaging, Brain mapping, Task performance, Verbal learning, Adaptation, Physiological

## INTRODUCTION

Increased fMRI brain response can be observed after total sleep deprivation (TSD) (Drummond et al., 2000; Drummond & Brown, 2001), especially when difficult items are studied (Drummond et al., 2004; Drummond et al., 2005). Previously, we argued that the interaction of sleep deprivation with task difficulty supported the prediction of the compensatory recruitment hypothesis, which states that task demands influence the magnitude and location of altered brain activation after TSD (Drummond et al., 2000; Drummond & Brown, 2001). Specifically, more difficult versions of tasks elicited the increased activation after TSD, relative to when subjects were well-rested (WR). These increases manifested as significant activation in brain areas

not normally associated with performance of that task and as increased magnitude of response in brain regions that are typically responsible for task performance. In contrast, easier versions of the same tasks showed equivalent activation while WR and after TSD. This conclusion depended on the absence of within-region differences between the WR and TSD conditions. The conclusion drawn from these various studies is the brain will show an increased response to difficult task demands following TSD (relative to WR) but a similar response to easy task demands. An alternative explanation, though, to the idea that isolated brain regions will or will not show increased activation with TSD is that sleep deprivation might affect the interactions among brain regions involved with task performance.

The studies cited earlier suggest an interaction between sleep deprivation and task difficulty, but it is as yet unclear what the unique contributions of these two factors are in producing an increased fMRI response. Sleep deprivation may make complex tasks more difficult to perform, as

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reflected in impaired performance on measures of mental arithmetic, logical reasoning, sustained attention, and short-term recognition memory after sleep deprivation (Rogers et al., 2003). Moreover, increasing task complexity has been found to increase fMRI response in well-rested individuals (Drummond et al., 2003). Thus sleep deprivation might be associated with increased brain activation simply because sleep deprivation makes a task more difficult. If this is the case, it implies that the neural response to increasing difficulty involves the same brain networks as those altered by sleep deprivation.

These assumptions cannot be tested using standard univariate models of functional brain analysis (Frackowiak et al., 1997) and require an understanding of how different brain areas interact to perform the task (Luria, 1966; McIntosh, 1998, 2004). By examining networks of activation instead of isolated regions of interest (ROI)s, a more complete account of the impact of TSD and task difficulty on brain function can be formulated. In this study, we use structural equation modeling (SEM) to examine how networks of fMRI brain response during a verbal encoding task differ as a function of TSD and task difficulty. SEM is a well documented and verified technique that allows for such *a priori* model specification along with measures of overall model fit (Kline, 2005; Loehlin, 2004).

To test whether the brain regions interact differently or merely respond differently in isolation following sleep deprivation, and to investigate the impact of task difficulty, we developed two contrasting networks of brain activity during verbal learning.

As a model of WR performance during verbal learning, we hypothesized a network of activation where the left inferior frontal gyrus (LIFG) mediates the left superior parietal lobe (LSPL) and the left inferior parietal lobe (LIPL) as illustrated by Model 1 in Figure 1. In contrast, if the right inferior frontal area becomes more active in the verbal learning network during TSD, as shown in previous studies, then it should play a more prominent role in influencing the two left parietal areas, as shown by Model 2 in Figure 1. The structural equation models, which represent these networks, were designed to be recursive in order to ensure

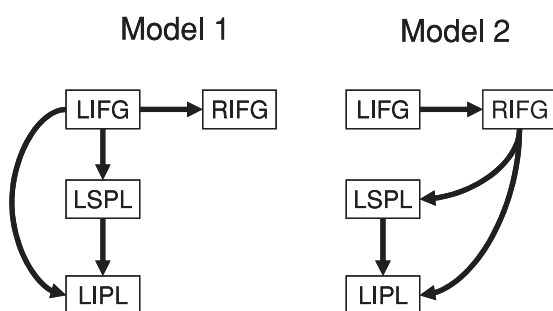
greater model stability and parsimony, and thus bidirectional connections were not introduced. In addition to being consistent with previous imaging findings in sleep deprivation (Drummond et al., 2000; Drummond & Brown, 2001; Drummond et al., 2005), these models are consistent with cognitive neuroscience theories (Cabeza & Nyberg, 2000; Clark & Wagner, 2003; Smith & Jonides, 1998). In particular, in well-rested states, the IFG is associated with monitoring and control, whereas the parietal areas are associated with phonological processing and short-term memory store (Cabeza & Nyberg, 2000; Clark & Wagner, 2003; Smith & Jonides, 1998). Moreover, TSD often produces increased activation in the bilateral parietal lobes and inferior frontal gyri, with the parietal regions being associated with better recall performance (Drummond et al., 2000). As mentioned earlier, increased brain response in the inferior frontal and parietal cortices during TSD has been found to be greatest when memorizing difficult words (Drummond et al., 2005).

Contrasting *a priori* networks of brain response allowed us to test several hypotheses: (1) TSD will coherently alter the pattern of regional co-activation rather than produce a less coherent pattern. If TSD results in less coherent patterns of activation (because only single regions are affected and/or TSD reduces the interactivity of these regions), then we would expect poorer model fits with TSD in comparison with the WR condition, regardless of the underlying model; (2) TSD will increase the moderating impact of some brain areas, while lessening the importance of other areas. In particular, the RIFG will modulate parietal lobe activity only after TSD, whereas the modulatory effects of the LIFG will decrease with TSD; (3) Given the role of task difficulty in previous research, it is hypothesized that the effects of task difficulty will be to accentuate the differences produced by TSD (Drummond et al., 2005). Specifically, the pattern observed in hypothesis 2 should produce a better fit after TSD when individuals encoded hard words compared with easy words.

## METHODS

### Participants

Twenty-three individuals participated in this study (11F; age =  $24.2 \pm 4.8$  years; education =  $15.2 \pm 1.5$  years). The study was approved by the local Institutional Review Board (the UCSD Human Research Protection Program), and it was completed in accordance with the guidelines of the Helsinki Declaration. All subjects provided written informed consent. Subjects were medically healthy, free of current and past psychiatric disorders, had no family history of mood or psychotic disorders, did not use nicotine in any amount, and were no more than moderate caffeine users ( $<400$  mg/day). Polysomnography was used to rule out sleep disorders. Subjects reported habitually sleeping 7 to 9 hours per night between the hours of 22:00 and 08:00.



**Fig. 1.** A priori models testing the effects of sleep deprivation. LIFG: left inferior frontal gyrus, RIFG: right inferior frontal gyrus, LIPL: left inferior parietal lobe, LSPL: left superior parietal lobe.

## Experimental Periods

After two nights of sleeping in the laboratory on their habitual schedule, subjects were studied with functional magnetic resonance imaging (fMRI) twice, both at the same time of day: once 12 hours after waking from a normal night of sleep in the laboratory and once after 36 hours of no sleep (i.e., TSD). During each fMRI scan, subjects performed a verbal encoding task. Whereas a fixed order of scan session raises the possibility of order effects in the data, we have evaluated this possibility in the past and have found no evidence for such in this task (Drummond et al., 2000; Drummond et al., 2005).

## Experimental Task

Stimuli were presented visually on a screen at the foot of the MRI bed that subjects viewed through a mirror fitted to the head coil. The alternating block design task consisted of two visually identical parts. During the entire task, subjects saw nouns presented one at a time, each for 4 s followed by 1 s of a fixation asterisk. For the baseline blocks, subjects were instructed to press a button on a hand held button box (Current Designs, Philadelphia) to indicate whether the word was printed in all capital or all lowercase letters. They were instructed to not memorize these words. Subjects were instructed to actively memorize the words presented during the memorization blocks, and they knew they would be tested on these words afterwards. After completion of the entire scanning session, subjects were given a free recall and recognition memory test. Unknown to the subjects, half of the memorization blocks contained words that are easy to learn, based on recallability norms, and half contained words that are hard to learn (Christian et al., 1978). A different word list was used for each administration (versions balanced across sessions), with lists matched for recallability, word length, concreteness, and imagery. Previous pilot studies showed that the versions provided similar recall rates in well-rested subjects. A block design was selected for this study to maintain consistency with previous studies. In addition, because the goal was to detect overall differences between groups in different conditions, a block design allowed maximum statistical power (Friston et al., 1999). However, because of the use of this design, distinctions cannot be made between words that were later successfully encoded and words that were not. Thus, it is not clear to what extent changes in brain response would be driven exclusively by the successful encoding of words. An event related design would more effectively address that issue (Chee et al., 2003).

## fMRI Data Acquisition

Data were acquired with a GE 3T scanner. Functional images consisted of 120 gradient echo, echoplanar, images (EPI) (TR: 2.5s, TE: 35 ms, FOV: 250 mm,  $64 \times 64$  matrix,  $3.91 \text{ mm} \times 3.91 \text{ mm}$  in-plane resolution) of 32 4 mm axial

slices covering the whole brain and measuring the blood oxygenation level dependent (BOLD) signal. The EPI images were aligned with high-resolution anatomical images (FSPGR:  $1 \text{ mm}^3$  resolution). The task contained 6 memorization and 7 baseline blocks. Each block started with directional prompts for 2.5 s and lasted a total of 22.5 s, and contained four nouns. Three images collected at the beginning of each run were omitted from the analysis. The entire task lasted 300 s.

## Data Analysis

fMRI data were processed with AFNI software (Cox, 1996). After motion coregistration, individual time-course BOLD signal data were fit to a design matrix using the general linear model (GLM). Parameters estimated from the design matrix represented the constant, linear drift, 6 motion correction parameters, and two reference functions. The reference functions were representations of the task design (baseline vs. easy words and baseline vs. hard words) convolved with an idealized hemodynamic response function (Ward, 2002). The fit of the design matrix to the EPI time series produced an amplitude value for each reference function. The amplitude represented the mean difference in local scanner units between the learning and baseline conditions over the time series weighted by the hemodynamic response function. Data sets were then smoothed with a Gaussian filter of 4.0 mm full-width-half-maximum and transformed to standard atlas coordinates (Talairach & Tournoux, 1988). We used a 3-step procedure to identify the relevant activations for analysis. In the first step, we defined a set of hypothesis-driven search regions (Eylar Zorrilla et al., 2003) based on the areas we expected to be critical for task performance either well-rested or following sleep deprivation. These search regions are based on our previous reports and were identical to those used in a recent manuscript we published with this task (Drummond et al., 2005). In the second step, we identified significant clusters of activation at the group level for each of the two difficulty types within these search regions. Clusters of activation were identified as areas containing at least 9 contiguous voxels ( $576 \text{ mm}^3$ ) from areas activated at the  $p \leq .05$  level from the group analyses. This value produced a False Detection Rate of .05 against the population of detected clusters of any size. These clusters became the relevant functional ROIs used to extract data from each individual subject. Finally, we identified the peak activation within the significant clusters of each ROI for each individual. It is this peak value that subsequently went into the SEM analysis. This process produced a peak value within each of the specified search regions for each individual in each of the 4 conditions: (1) WR Easy: encoding easy words while WR, (2) WR Hard: encoding hard words while WR, (3) TSD Easy: encoding easy words after TSD, and (4) TSD Hard: encoding hard words after TSD.

Covariation matrices were calculated from the peak values and were used as the target data for structural equation models. Mx software was used to perform the structural

equation modeling (Neale, 2003). We assessed model fit with the Root Mean Square Error of Approximation (RMSEA) measure, as well as Akaike's Information Criterion (AIC) (Browne & Cudeck, 1993). RMSEA does not assume a centralized chi-square distribution and neither AIC nor RMSEA assume the presence of a perfect fitting "true" model. RMSEA indicates overall model fit given the variability in the data, the parsimony of the model, and the number of subjects. It ranges from 0.0 to 1.0, with values below .05 indicating an excellent model fit and  $>.1$  indicating a poor model fit (Browne & Cudeck, 1993). AIC places more value on parsimony and is one of the most commonly used fit statistics in the SEM literature. Smaller values indicate better fits, although the primary interpretation of the AIC index is through model comparison as opposed to absolute values (Burnham & Anderson, 1998).

## RESULTS

A General Linear Model analysis of the number of words recalled with sleep status and word difficulty as within subject factors demonstrated a significant effect for both sleep status,  $F(1,22) = 6.24$ ,  $p = .02$ , and word difficulty,  $F(1,22) = 90.35$ ,  $p < .01$ , but not an interaction of sleep status and word difficulty,  $F(1,22) = .017$ ,  $p = .897$ . After TSD, participants recalled fewer total words compared to when they were well-rested (mean difference = 2.26 words). For word difficulty, three fewer hard words were recalled than easy words, regardless of the sleep condition (mean difference WR = 3.0 words, and TSD = 2.91 words).

Correlations of individual peak values in each of the *a priori* ROIs revealed significant correlations after TSD between the left inferior frontal gyrus while encoding easy words and recall of easy words ( $r = .425$ ,  $p = .049$ ), as well as between the right inferior frontal gyrus while encoding hard words and total words recalled ( $r = .456$ ,  $p = .029$ ). An analysis of the peak values obtained from each individual for each of the *a priori* ROIs revealed that the majority of these values were significantly correlated across subjects, indicating that good model fits would explain a meaningful amount of variance. The correlations ranged from .164 to .746 with 23 out of 36 correlations significant with  $p < .05$  (18 were significant with  $p < .01$ ).

Table 1 shows the results of fitting each covariance matrix to the two models tested, presented separately for easy and hard items. Model 1 fits the easy word condition better than Model 2 for both WR and TSD, whereas Model 2 fits the Hard word condition better than Model 1 for both WR and TSD.

An examination of the relative strengths of the model connections within each item difficulty condition illustrates that TSD influences the pattern of interactions within the network. Because Model 1 and Model 2 share the same number of free parameters, comparisons can be made between strengths of connections within the best model fit for each condition. Examining the impact of removing specific connections and re-running the structural equation

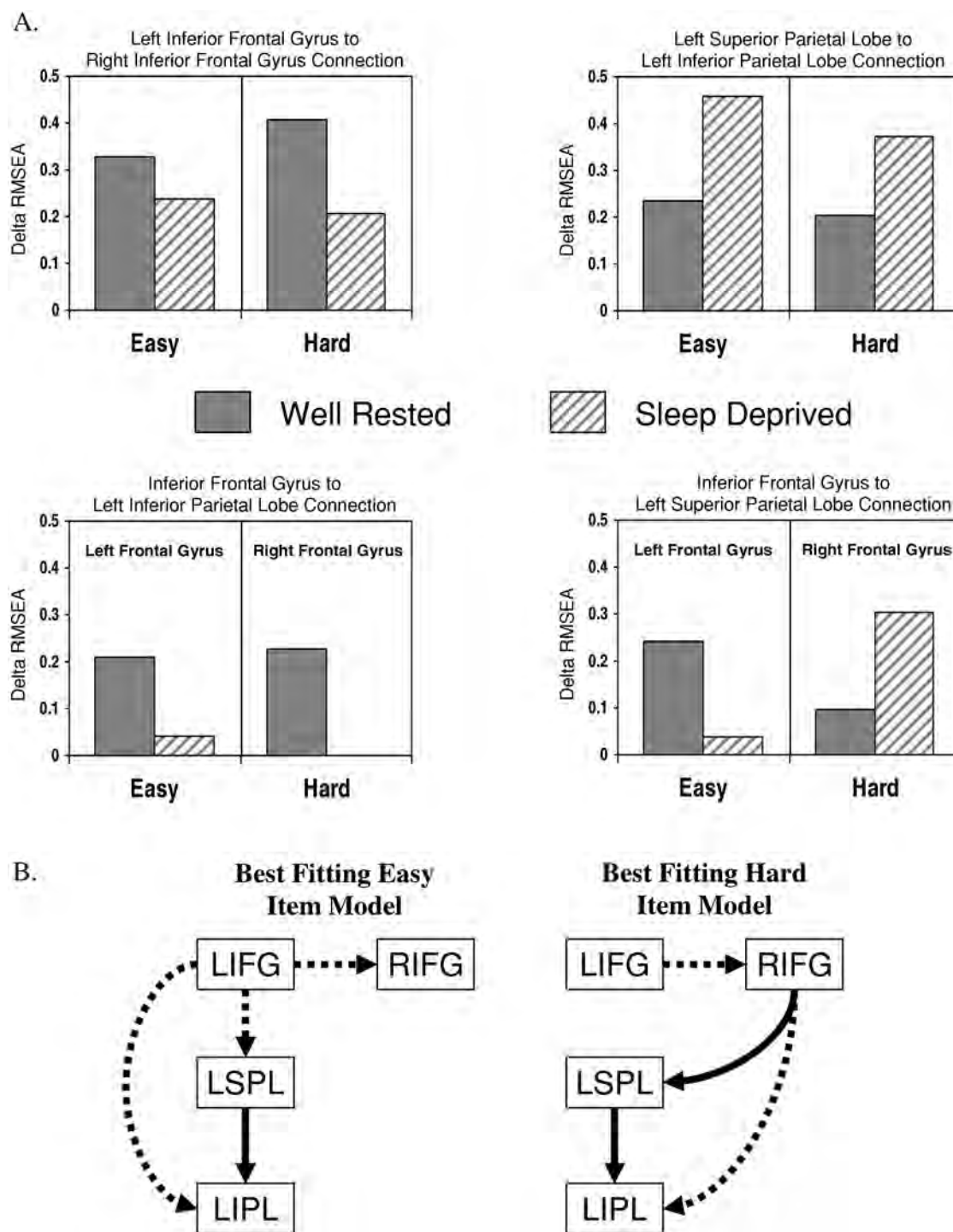
**Table 1.** Statistical fit of the *a priori* models

Item difficulty	Model	$\chi^2$	$p$	RMSEA	AIC
Well Rested					
Easy	1	0.604	0.739	0.000	-3.396
Easy	2	10.254	0.006	0.433	6.254
Hard	1	6.198	0.045	0.309	2.198
Hard	2	0.166	0.921	0.000	-3.834
Sleep Deprived					
Easy	1	0.090	0.956	0.000	-3.910
Easy	2	4.592	0.101	0.243	0.592
Hard	1	8.394	0.015	0.381	4.394
Hard	2	0.110	0.946	0.000	-3.890

*Note.* RMSEA = root mean square error of approximation; AIC = Akaike Information Criterion. RMSEA values  $<.05$  indicate an excellent model fit, while smaller AIC values indicate a better model fit (Browne & Cudeck, 1993; Burnham & Anderson, 1998).

analyses evaluates the importance of that connection for overall model fit (Loehlin, 2004). Because the RMSEA is scaled to a standardized range of model fit, and all of the best fitting models start with values of 0.00, the change in RMSEA (delta RMSEA) was used to compare each connection's contribution to the model's ability to fit the data. Figure 2 illustrates the impact of removing each connection on RMSEA for each of the best fitting models within task difficulty. As Figure 2 illustrates, there is a decrease in the relative importance of the connection between the left and right IFG after TSD and a concomitant increase in the importance of the connection from LSPL to LIPL for both easy and hard items. Additionally, the prominence of the interaction between the IFG (left or right) and the inferior parietal lobe is diminished after TSD, regardless of item difficulty. Finally, the right IFG connection with LSPL becomes more prominent after TSD for the hard word model. These findings underscore the conclusion that TSD produces a modulation of connectivity within the network that best fits the WR condition. This modulation occurs when no difference in activation between WR and TSD occur, as in the Easy condition, as well as when TSD alters the magnitude of activation, as in the hard condition.

In order to rule out the possibility that the influence of the RIFG is caused by an indirect effect of the right superior and inferior parietal lobes (which were not included in either *a priori* model), right inferior and superior lobes were identified and peak voxel values were calculated using the same procedures as for the other ROIs. Exploration of various combinations of models (by starting with a fully connected model and trimming connections if their removal did not increase the error in model fit) revealed that even with the presence of the right parietal areas, the RIFG maintained its importance as a feedback source for the left parietal areas when hard words were learned.



**Fig. 2.** The reorganization of interactions after sleep deprivation

Panel A: Impact of removing the named connection on the Best Model's Fit

Panel B: Summary of Sleep Deprivation's Impact on Model Connections. Dashed lines indicate decreased strength following total sleep deprivation, solid lines indicate increased strength.

## DISCUSSION

Model fit statistics confirmed that TSD coherently altered network connections rather than producing a less coherent network, confirming hypothesis 1. Compatible with hypoth-

esis 2, TSD reduced the importance of inferior frontal to left inferior parietal links in accounting for the covariation among network nodes, whereas it increased the importance of the left superior parietal to left inferior parietal connection. Hypothesis 3 was not confirmed. Difficulty level did

not generally potentiate the impact of TSD on the network of connections. Rather, the impact of TSD on network connections differed for easy and hard words, because learning networks differed depending on difficulty level. In particular, variation in item difficulty determined whether parietal areas interacted more with the LIFG or the RIFG while WR. Although the impact of TSD on network connections differed by difficulty level, some similar effects of TSD were seen for easy and hard words. Regardless of difficulty, interhemispheric interaction between the LIFG and RIFG decreased after TSD, and intrahemispheric communication between the LIPL and LSPL increased. Whereas it is not clear if this shift in the pattern of activation may be indicative of a compensatory response to TSD, it demonstrates a coherent change in the pattern of activation in response to TSD. It may also help explain why we previously found the left parietal cortex to be critical for task performance after TSD (Drummond et al., 2000; Drummond et al., 2005). The shift in RIFG interactions from LIPL to LSPL after TSD may indicate a change in encoding strategy, because the LSPL is less integrative than the LIPL (Cabeza & Nyberg, 2000). The SEM results are also consistent with the recall data, which indicated a large effect of word difficulty (associated with a different model fit) and a lesser effect of sleep status on the total number of words recalled (associated with changes in interactions within a good fitting model).

The results described earlier show that TSD and item difficulty differentially influence brain networks involved in verbal learning, at least for the small network of areas selected for analysis. TSD altered the strength of the connections within the best fitting models without altering the overall model fit. Item difficulty appears critical in determining the intrinsic connectivity of the involved networks. TSD appears to modulate the connectivity strength among established network connections, rather than establish new connections to previously uninvolved regions. The study findings support the view that TSD does not elicit activation in new brain areas, so much as it produces a modulation of connectivity within networks used when WR. According to this view, prior studies have found activations in “new” brain regions by altering the strength of connections within the network, thus, activating nodes that are latent when individuals are well rested. More broadly, these results shed an alternative light on imaging studies that interpret an increased fMRI response as a recruitment of new brain areas. Such interpretations are common in the study of addiction, aging, Alzheimer disease, and schizophrenia (e.g., Bondi et al., 2005; Cabeza et al., 2002; Davidson & Heinrichs, 2003; Tapert et al., 2004).

This richer account of changes in brain function with TSD is only possible through use of theoretically determined functional connectivity analysis with *a priori* ROIs and contrasting network connections. Moreover, theoretically based *a priori* models do not capitalize as much on chance as do the exploratory model trimming approaches that are often used in the SEM literature (Horwitz et al., 1999; Horwitz, 2003; Horwitz et al., 2005; MacCallum,

1986). However, the models tested in this study are greatly simplified. Because of concerns about power and noise within the data, the smallest possible number of ROIs and connections were chosen based on previous research that contrasted WR and TSD brain response. In future studies we plan to use a larger number of participants, and gradually develop a more comprehensive model of encoding, including hippocampal and lateral temporal areas. The current study serves as a starting point to test more comprehensively developed *a priori* models in the future.

## ACKNOWLEDGMENTS

The information in this manuscript and the manuscript itself is new and original, is not currently under review by any other publication, and has not been published either electronically or in print. Pilot analysis of these data was presented at the thirty-fourth North American annual meeting of the International Neuropsychological Society Conference (Stricker et al., 2006). The authors acknowledge the support of the VA VISN 22 Mental Illness Research Education and Clinical Center, the US Department of the Army award #DAMD17-02-1-0201, and NIH M01 RR00827. The US Army Medical Research Acquisition Activity is the awarding and administering acquisition office. The content herein does not necessarily reflect the position or policy of the Government, and no official endorsement should be inferred. There are no financial conflicts of interest or other relationships on the part of any of the authors of this manuscript.

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# The effects of one night of sleep deprivation on known-risk and ambiguous-risk decisions

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Accepted in revised form 30 March 2007; received 4 December 2006

**SUMMARY** Sleep deprivation has been shown to alter decision-making abilities. The majority of research has utilized fairly complex tasks with the goal of emulating 'real-life' scenarios. Here, we use a Lottery Choice Task (LCT) which assesses risk and ambiguity preference for both decisions involving potential gains and those involving potential losses. We hypothesized that one night of sleep deprivation would make subjects more risk seeking in both gains and losses. Both a control group and an experimental group took the LCT on two consecutive days, with an intervening night of either sleep or sleep deprivation. The control group demonstrated that there was no effect of repeated administration of the LCT. For the experimental group, results showed significant interactions of night (normal sleep versus total sleep deprivation, TSD) by frame (gains versus losses), which demonstrate that following as little as 23 h of TSD, the prototypical response to decisions involving risk is altered. Following TSD, subjects were willing to take more risk than they ordinarily would when they were considering a gain, but less risk than they ordinarily would when they were considering a loss. For ambiguity preferences, there seems to be no direct effect of TSD. These findings suggest that, overall, risk preference is moderated by TSD, but whether an individual is willing to take more or less risk than when well-rested depends on whether the decision is framed in terms of gains or losses.

**KEYWORDS** ambiguity, decision making, risk, sleep deprivation

## INTRODUCTION

Total sleep deprivation (TSD) has been shown to cause cognitive performance deficits in a wide range of domains, including alertness, attention, motor responses, inhibition, and many working memory functions (Chee and Choo, 2004; Chuah *et al.*, 2006; Dinges *et al.*, 1997; Pilcher and Huffcutt, 1996). One area not well studied, though, is the effect of TSD on decision making, which involves both convergent and divergent skills (Harrison and Horne, 2000). While early studies assumed that decision making is too complex to be sensitive to the effects of TSD because of the demanding and

highly motivating conditions (Corcoran, 1963; Horne and Pettitt, 1985; Wilkinson, 1965, 1992), the few studies that have directly examined this question suggest that TSD does indeed impact decision making.

The majority of research studying the effects of TSD on decision making have utilized fairly complex tasks with the goal of emulating 'real-life' scenarios (Harrison and Horne, 1999; Linde *et al.*, 1999; Wimmer *et al.*, 1992). For example, Harrison and Horne reported a business simulation game where subjects needed to market a business and earn a profit by reacting to other players and external information provided about the 'market place'. In that study, subjects were less successful running the business while sleep deprived. However, due to the design of the task, that study was unable to identify any particular decisions or particular components of decision making that were specifically impaired by TSD. Other studies

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have administered tasks aimed at more specific aspects of decision making, such as the Iowa Gambling Task (IGT). The IGT emphasizes the learning of reward and punishment associations to guide ongoing decision making. In the IGT, subjects select cards from among a series of decks and either win or lose money based on the card drawn. There are two decks of cards which carry an overall loss and two decks which carry an overall gain. The cards that carry an overall loss offer immediate high rewards with a concomitant risk of occasional very high loss. The decks with an overall gain, on the other hand, have smaller immediate rewards, but lower risk of a loss. Typically, subjects learn to avoid the former, riskier decks and focus on the latter decks carrying an overall gain (Bechara *et al.*, 1994, 2005). Harrison and Horne found that sleep-deprived subjects are less concerned with negative consequences when faced with high rewards on the 'overall loss' desk during this task (Harrison and Horne, 1998, 2000). More recently, Killgore *et al.* (2006) similarly reported that 49.5 h of TSD impairs the ability to weigh immediate short-term benefits against long-term penalties on the IGT. These studies demonstrate that decision-making processes are, in fact, modified during sleep deprivation. The work on the IGT suggests that individuals may be willing to take more risk during TSD than they would when well rested, but the IGT entails a complex assessment of risk taking (Bechara *et al.*, 2005), and therefore only provides an indirect assessment. Additionally, during the IGT subjects are asked to make choices in an environment with missing information (i.e. there are unknown probabilities in the odds of winning or losing) and thus probability assessments are confounded with risk preferences. There are no published studies of which we are aware that utilize a simple measure to directly study risk preferences during TSD. The aim of the present study was to measure potential changes in risk preference, along with the preference for ambiguity in risk decisions, during TSD.

The study of risk in the context of decision making has been an interest in microeconomics for the last century. However, it has only received attention from psychologists in the last few decades (Trepel *et al.*, 2005). The concept of risk varies depending on the context and situation. In economics, risk is commonly associated with the variance of the outcome (pay-off) distribution. For example, one gamble may offer \$80 if a coin shows heads and \$20 if shows tails while another may offer \$60 if a coin shows heads and \$40 if shows tails. In both gambles, the expected pay-off is \$50, but as the variance is higher in the first gamble, that gamble carries higher risk. Real-world decisions that illustrate these concepts of risk and pay-offs would include investment/savings decisions, surgical alternatives or military operational decisions. Two variables that may influence one's preference for risk when it is defined in this manner are: (1) whether the gamble involves decisions about gains or about losses; and (2) whether all the relevant odds are known or if some are unknown. When some of the odds are unknown, usually due to missing information, this is said to introduce 'ambiguity'. So, with ambiguity, the level of risk is unclear, as if the coin-flip involved a coin that may or

may not have a both heads and tails side (i.e. it is unknown to the decision maker). With investment/savings choices, for example, if companies included in a mutual fund are unknown, then the choice to invest in that mutual fund involves an ambiguous gamble.

Decision-making research has shown that, when the odds are known, individuals are risk seeking for losses but risk avoiding for gains (Kahneman, 2003; Kahneman and Tversky, 1979; Smith *et al.*, 2002). This means that, on average, if faced with two options that can each lead to a loss, individuals choose the more risky option, and if faced with two options that can each lead to a gain, individuals choose the less risky option. So, if someone is trying to minimize a loss, they will take a more risky option if they believe it may mitigate against the size of the loss. If, on the other hand, someone is trying to maximize overall gain, they are likely to take the less risky choice so as to increase the likelihood of gaining at least something. Ambiguity preference is less well studied, with some inconsistent results. However, there is some consensus that individuals are ambiguity avoiding for gains while ambiguity neutral for losses. This means individuals choose a known gamble over an ambiguous one when faced with possible gains, but they chose the option with known odds and the option with ambiguous (i.e. not fully known) odds equally often when faced with losses (Cohen *et al.*, 1987; Curley and Yates, 1985; Hsu *et al.*, 2005; Smith *et al.*, 2002).

To assess the degree to which risk and ambiguity preferences change during sleep deprivation, we used the Lottery Choice Task (LCT) reported by Smith *et al.* (2002). This task assesses risk and ambiguity preference separately for decisions involving potential gains and those involving potential losses. Based on the general literature on risk preference and on TSD research with the IGT, we hypothesized that: (1) well-rested subjects would be risk seeking for losses and risk avoiding for gains, while ambiguity neutral for losses and ambiguity avoiding for gains; and (2) sleep-deprived subjects would become more risk seeking for both gains and losses.

## METHODS

### Subjects and conditions

A total of 26 young adults performed this task as part of two larger sleep-deprivation studies (eight women; mean age:  $23.5 \pm 5.3$  years; education:  $14.7 \pm 1.7$  years). Additionally, 12 young adults participated in a control group that involved no sleep deprivation (six women; mean age:  $24.2 \pm 4.3$  years; education:  $15.2 \pm 2.4$  years). All subjects in both groups were healthy as established by a physical examination, routine laboratory tests, and interviews covering medical and psychiatric histories. Subjects completed sleep diaries and wore actigraphs for 2 weeks prior to the study to document adherence to regular sleep-wake schedules. Subjects in the experimental group obtained a nightly average of  $408 \pm 69$  min of sleep for the week prior to the study. Subjects in the control group obtained a nightly average of

421.8  $\pm$  71 min of sleep. All subjects were tested twice, on two consecutive days, at approximately the same time of day in the morning. The control group had a normal night of sleep at home in between test administrations. The sleep-deprived experimental group had an average of 22.7  $\pm$  .58 h of TSD between test administrations.

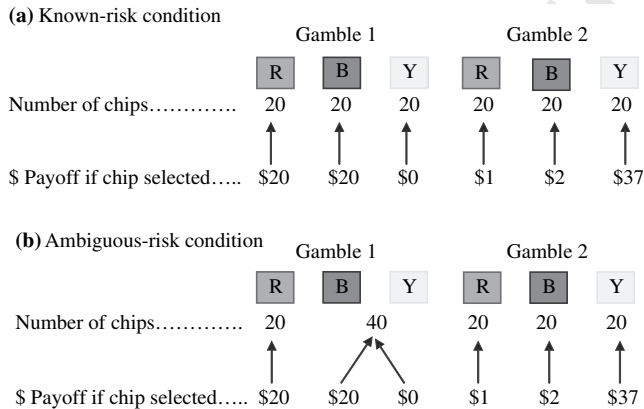
### Lottery Choice Task

The LCT used in the present study is a shortened version of one used by Smith *et al.* (2002), which is based on Ellsberg (1961). The LCT examines risk and ambiguity preference by asking subjects to make a series of choices between two gambles with equal expected pay-offs but different risk levels. The LCT was comprised of four conditions, as decisions focused on either risk or ambiguity and involved either gains or losses: Known-risk decisions involving gains (RG), known-risk decisions involving losses (RL), ambiguous-risk decisions involving gains (AG), and ambiguous-risk decisions involving losses (AL). See Fig. 1 for examples of the choices presented to subjects. In the RG and RL conditions (e.g. Fig. 1A), if a subject chooses the lower risk gamble, that decision is classified as being risk averse, and if the higher risk option is taken, that decision is classified as risk seeking. As discussed above, when one of the gamble choices does not clearly define the odds of each outcome, the gamble is said to be ambiguous (e.g. Fig. 1B). To examine whether subjects

avoid or seek ambiguity, the LCT includes conditions where one of the gambles in each paired choice is ambiguous (see below for a description of how seek/avoid is determined for ambiguous gambles). Finally, because preferences may differ when gambles involve losses relative to gains, the LCT includes decisions where both options involve losing money and others where both options involve gaining money. This is true for both decisions with known odds and those with ambiguous odds.

Ten decisions were made on gambles in a known-risk condition (five for gains and five for losses) and 10 decisions were made on gambles in an ambiguous-risk condition (five for gains and five for losses). For all choices, subjects were shown two containers of red, blue, and yellow chips, where the number of each color was defined within the gamble stimuli (see Fig. 1). For known-risk decisions, subjects were asked to decide between two risky options that each had known (but different) odds of either winning (RG) or losing (RL) specific amounts of money, but with identical expected pay-offs (see Fig. 1A). In both choices there are 20 red, 20 blue, and 20 yellow chips in the container, but the monetary value of each color is different in gamble 1 compared with gamble 2. The arrows in Fig. 1A indicate the amount of money that a subject can gain if that color chip is chosen. Gamble 1 is less risky than gamble 2 because the variance of the gains is smaller for gamble 1. Thus, if a subject chooses gamble 1, they are determined to be avoiding risk for that specific decision. If, on the other hand, they choose gamble 2, then they are seeking risk. The known-risk decisions involving losses follow the same format, but the monetary values are negative rather than positive.

Again, following Smith *et al.*, the ambiguous-risk condition decision stimuli are identical to the known-risk condition decision stimuli with the exception that the exact numbers of blue and yellow chips in gamble 1 are unknown (see Fig. 1B). In the ambiguous-risk condition, the arrows from the monetary outcome for both the yellow and blue chips converge on 40. This indicates that there were 40 total blue and yellow chips, but the subject did not know the exact number of each individually (e.g. there could have been eight blue and 32 yellow chips or 19 blue and 21 yellow chips, etc.). As is done in Fig. 1, each set of choices in the ambiguous-risk condition was matched with a similar set of choices from the known-risk condition such that each matched item shared a common gamble 2. Thus, the ambiguous choice was always gamble 1. Assessment of ambiguity preference then required considering both of the matched decisions (risk and ambiguity) and use of the assumption of transitivity (Smith *et al.*, 2002). Transitivity is the preference assumption that states that if A is preferred to B, and B is preferred to C, then A is preferred to C. In the context of this task, if a subject avoids the riskier gamble in the known-risk condition, but chooses the riskier gamble in the matched ambiguous-risk condition, s/he would be determined to be avoiding ambiguity (because to again avoid risk would have required the subject to choose the ambiguous gamble). Alternatively, if a subject chose the



**Figure 1.** Lottery Choice Task paradigm two examples of the stimuli used to present the gamble choices to subjects. (a) An example from the known-risk decisions involving gains (RG) condition. The gamble on the left has a smaller variance and is considered less risky than the gamble on the right. (b) An example from the ambiguous-risk decisions involving gains (AG) condition. The gamble on the left is ambiguous, while the gamble on the right is identical to the riskier gamble in the RG condition. The three boxes indicate the color of the chip associated with each gamble. Note that only examples from the 'gains' conditions are shown. Loss conditions are identically structured, but have negative dollars amount associated with the chips. [R] is for red, [B] for blue, and [Y] for yellow. This figure also serves to show an example of a known-risk and an ambiguous-risk decisions that were paired for calculating ambiguity preference (see text for detailed explanation), as each gamble 2 has an identical pay-off variance.

riskier gamble in the known-risk condition and then chose the ambiguous gamble in the matched ambiguous-risk condition s/he would be determined to be seeking ambiguity (because to again seek risk would have required them to choose the non-ambiguous gamble – gamble 2 in Fig. 1B). Finally, if the subject chose the riskier gamble in both conditions, or avoided risk in both conditions, then their ambiguity preference was deemed indeterminate. This is because it is unclear, in the first case, whether the subject actively avoided ambiguity or simply again sought risk during the ambiguous-risk condition.

## Procedures

Subjects performed two distinct decision-making tasks (one of which was the LCT) in both the first and second testing sessions. For the LCT, the five decisions to be made for each condition were presented on a single piece of paper, and the order of conditions was randomly counterbalanced for each session. Similarly, two different versions of the task were developed and the order of presentation was counterbalanced across subjects. All subjects began the experiment with an endowment of \$25. They were told that their decisions would either increase or decrease this amount and that they would be paid their final balance at the end. They were also informed of the method by which their decisions would be played out. Specifically, at the end of the second session, a single decision from the gains conditions (RG and AG) and a single decision from the loss conditions (RL and AL) for each of the two sessions (four total decisions) were randomly selected and the subject's preferred gamble choice (gamble 1 or gamble 2) was played out to determine final cash pay-off from the LCT. For each of the four decisions selected, the subject blindly drew one chip from the relevant container and either won or lost the amount of money associated with that chip. This payout procedure was only conducted following the second administration of the task. Subjects were not given any feedback between sessions (i.e. there was no determination of winnings or losses) so there would not be an opportunity for knowledge of money won or lost in the first session to alter decisions made in the second session. For ethical reasons, subjects could not owe the experimenters at the end of the study, so any negative payout balance was rounded to \$0.

## Data analysis

The raw count data (i.e. the number of risk- or ambiguity-seeking decisions made per condition) were converted into proportional data. However, these data had significantly non-normal distributions on both nights (based on the kurtosis and skewness of the distributions). Therefore, the data were converted into risk preference and ambiguity preference scores. For the known-risk conditions (RG and RL), this was done by taking the proportion of the risk-avoiding responses minus the proportion of risk-seeking responses for

each condition. Thus, a score of zero indicates someone who is risk neutral, increasing scores in the positive direction indicate greater risk avoidance, and increasing scores in the negative direction indicate greater risk seeking. The same procedure was followed for the ambiguous-risk conditions (AG and AL) to determine ambiguity preference. Using this 'preference' metric has two advantages: (1) the distribution of these scores was normal; and (2) this is the same way in which Smith *et al.* (2002) treated the data in their study.

Group analyses were conducted separately for the known-risk and ambiguous-risk conditions. For both, the initial omnibus analysis was a  $2 \times 2 \times 2$  mixed-effects ANOVA (frame by session by group). The effect of interest here was the three-way interaction, as it evaluated whether the two groups showed differential patterns of change across sessions. To follow-up a significant interaction, we examined the frame-by-session two-way interaction separately for each group with repeated measures ANOVA. If that interaction was significant, we then examined the source of the interaction by testing the main effect of session for each level of the variable frame (i.e. gains and losses). This tests whether there is a session effect (e.g. an effect of TSD in the experimental group) for either gains or losses. If the two-way interaction was not significant for a given group, we examined the simple main effects of session and frame. For the control group (where we anticipated a non-significant interaction) the session main effect addresses whether this task shows repeated administration effects (e.g. learning effects), while the frame main effect tests whether our subjects show the same preference differences across gains and losses as typically reported in the literature.

Finally, to confirm that there were no baseline differences between the groups at session 1 that may confound any potential differential session effects observed in the preceding analysis, we conducted a between-groups MANOVA for the session 1 data where the response variables were the preference scores for the four conditions (RG, RL, AG and AL). If this MANOVA was significant, univariate analyses for each condition were conducted.

## RESULTS

See Table 1 for the risk and ambiguity preference scores from each group in each session.

### Known-risk condition (RG and RL)

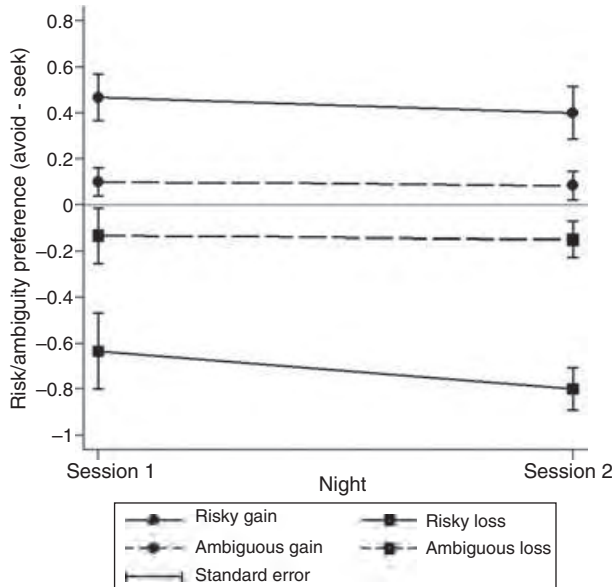
The omnibus mixed model ANOVA (frame by session by group) showed a significant three-way interaction ( $F_{1,36} = 5.70$ ,  $P = 0.022$ , partial  $\eta^2 = 0.137$ ). As stated above, this was followed by analyzing the frame-by-session two-way interaction for each group.

For the control group, the frame-by-session interaction was not significant ( $P = 0.536$ , partial  $\eta^2 = 0.036$ ; see Fig. 2). The main effects for the control group revealed a significant effect of frame ( $F_{1,25} = 45.34$ ,  $P < 0.001$ , partial  $\eta^2 = 0.805$ ), but no significant change across sessions ( $P = 0.359$ , partial

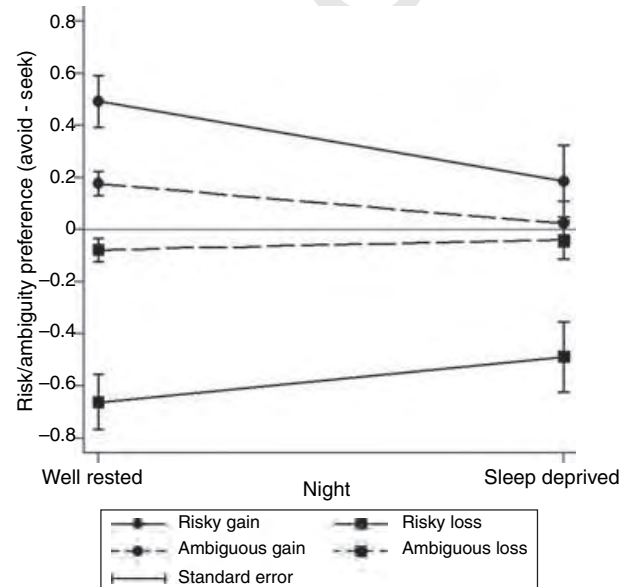
**Table 1** Group mean  $\pm$  SE

Group	RG	RL	AG	AL
Well-rested experimental group	0.49 $\pm$ 0.10	-0.66 $\pm$ 0.11	0.18 $\pm$ 0.05	-0.08 $\pm$ 0.05
Sleep-deprived experimental group	0.18 $\pm$ 0.14	-0.49 $\pm$ 0.13	0.02 $\pm$ 0.09	-0.04 $\pm$ 0.07
Session 1 control group	0.47 $\pm$ 0.10	-0.63 $\pm$ 0.02	0.10 $\pm$ 0.06	-0.13 $\pm$ 0.12
Session 2 control group	0.40 $\pm$ 0.12	-0.80 $\pm$ 0.09	0.08 $\pm$ 0.06	-0.15 $\pm$ 0.08

The conditions are known-risk decisions involving gains (RG), known-risk decisions involving losses (RL), ambiguous-risk decisions involving gains (AG), and ambiguous-risk decisions involving losses (AL) for both the experimental group and the control group.



**Figure 2.** Change in preference following repeated administration to control group. The plotted points indicate the risk and ambiguity preference scores (measured in proportions) for each frame type for both sessions. Positive values indicate avoiding behavior, negative numbers indicate seeking behavior, and zero indicates risk or ambiguity neutrality.



**Figure 3.** Change in preference following TSD in the experimental group. The plotted points indicate the risk and ambiguity preference scores (measured in proportions) for each frame type when well rested and after TSD. Positive values indicate avoiding behavior, negative numbers indicate seeking behavior, and zero indicates risk or ambiguity neutrality.

$\eta^2 = 0.077$ ). The control group showed risk aversion for gains and risk seeking for losses.

For the experimental group, the frame (RG versus RL)-by-session (well-rested versus TSD) interaction was significant ( $F_{1,25} = 10.55$ ,  $P = 0.003$ , partial  $\eta^2 = 0.297$ ; see Fig. 3). Follow-up analyses focusing on the effect of session within frame showed that subjects became significantly less risk avoiding for gains after TSD ( $t_{25} = 2.30$ ,  $P = 0.03$ ,  $\eta^2 = 0.175$ ). Subjects became less risk seeking for losses after TSD, although this change was not significant ( $t_{25} = -1.80$ ,  $P = 0.084$ ,  $\eta^2 = 0.115$ ).

In examining baseline group differences at session 1, the MANOVA was not significant (Wilks'  $\lambda$ ,  $P < 0.724$ ; partial  $\eta^2 = 0.059$ ), confirming there were no group differences at baseline (Table 1).

#### Ambiguous risk condition (AG and AL)

The omnibus mixed model ANOVA (frame by session by group) did not show a significant three-way interaction ( $P = 0.258$ ;

partial  $\eta^2 = 0.035$ ). The only significant effect in this ANOVA was the main effect of frame ( $F_{1,36} = 11.50$ ,  $P = 0.002$ ; partial  $\eta^2 = 0.242$ ). Averaged across both groups and both sessions, subjects showed greater ambiguity-avoiding preferences for gains than for losses. To clarify this effect, simple main effects were conducted comparing ambiguity preferences for gains and losses to neutral (i.e. a preference score = 0). These analyses showed that subjects were ambiguity avoiding for gains ( $t_{37} = 2.38$ ,  $P = 0.02$ ,  $\eta^2 = 0.133$ ) and ambiguity seeking for losses ( $t_{37} = -2.22$ ,  $P = 0.03$ ,  $\eta^2 = 0.118$ ), although only the former would survive a Bonferroni correction for multiple comparisons, suggesting that subjects are actually ambiguity neutral for losses.

#### Payout information

The final payout amounts (including the endowment) for the experimental group were (mean  $\pm$  SD) \$26.23  $\pm$  23.4, with a range of \$0–67. Final payout amounts for the control group were \$21.25  $\pm$  24.4, with a range of \$0–55.

## DISCUSSION

The LCT used in the present study assessed preference for both risk and ambiguity by having participants make a series of decisions between two gambles to maximize pay-offs. Consistent with the large body of literature on risk preference (Kahneman, 2003; Kahneman and Tversky, 1979; Smith *et al.*, 2002; Tversky and Kahneman, 1992), the results of the control group and the well-rested condition in the experimental group demonstrate that subjects are risk avoiding for gains and risk seeking for losses in the known-risk condition. For the ambiguous-risk condition, well-rested subjects are ambiguity avoiding for gains and ambiguity neutral for losses. Together, these results replicate the study of Smith *et al.* (2002). The interactions of night (normal sleep versus TSD) by frame (gains versus losses) demonstrate that following as little as 23 h of TSD, the prototypical response to decisions involving risk is altered. Sleep-deprived subjects are less risk avoiding for gains and less risk seeking for losses. In other words, following TSD, subjects were willing to take more risk than they ordinarily would when they were considering a gain, but less risk than they ordinarily would when they were considering a loss. For ambiguity, there seems to be no direct effect of TSD on decisions involving uncertainty.

### TSD changes risk preferences

Overall then, it appears that one night of TSD moderates sensitivity to risk. The change in risk preferences following sleep loss may reflect a change in decision-making strategies that varies for gain versus loss. For the known-risk condition, the hypothesized increase in risk-seeking behavior was observed in the RG condition, but not the RL condition. The RG data are also consistent with prior studies of the IGT showing that subjects seem to favor risk during sleep deprivation (Harrison and Horne, 1998; Killgore *et al.*, 2006). One difference between the IGT and the LCT task used here is that the present task allows for the differentiation between decisions involving gains and those involving losses while the IGT does not. Our data suggest the change in risk preference during TSD depends on whether the decision is framed in terms of gains or in terms of losses. As the IGT places an emphasis on gains, that may explain the increased risk seeking on the IGT during sleep deprivation. Thus, our data demonstrate the importance of analyzing the framing of decisions (i.e. gains versus losses) when trying to understand risk preference during sleep loss.

Unlike for the known-risk condition, subjects were essentially always neutral towards ambiguity (statistically, they did show a slight preference to avoid ambiguity for gains). It may be that the missing information of an ambiguous gamble results in no stable strategy. Individuals may not know exactly how to assess risk when faced with ambiguity and thus not respond with any consistent pattern at the group level. The exception to this interpretation in the present study was the fact the subjects were slightly, but significantly, ambiguity

avoiding for decision involving gains. The significant difference from neutrality (i.e. an ambiguity preference score of zero) should be interpreted with caution considering that there is no effect of TSD and the effect is very small (Cohen, 1988). When compared with risk, much less research has been conducted on ambiguity, and we are not aware of other studies directly assessing this construct during sleep deprivation.

### Potential cognitive mechanisms

The exact cognitive mechanism underlying changes in risk preference with sleep deprivation cannot be ascertained from this study. Nonetheless, one way to approach this question is to consider whether a common mechanism can explain the changes seen here both for risky decisions involving gains and those involving losses, as well as the previous work with the IGT. For example, in all cases, one can interpret the data as showing that individuals become less sensitive to risk following sleep loss. This may be due to an impaired ability to accurately assess risk (e.g. calculation of the odds of various outcomes). If subjects view the same situation as less risky after TSD, even with well-defined gambles, the predicted outcome would be exactly what we report: less risk avoidance for gains and less risk seeking for losses. Alternatively, it may be that risk simply plays a smaller role in the decision-making process during TSD than when individuals are well rested, which would equate to more of a true desensitization process. A third possibility is that subjects may subjectively weigh the value (or utility) of the possible outcomes as more extreme (better for gains and worse for losses) during TSD. This, too, would be expected to lead to more risk taking if the individual felt an outcome would be extremely good (i.e. a gain) and less risk taking when an outcome was valued as extremely bad (i.e. a loss). Finally, it is possible the changes observed here are not related to TSD-induced changes in risk preference, but rather to an increase in random responding or reduced motivation on the task. We do not believe this is the case, though, for at least three reasons. First, in examining the response patterns, there does not appear to be obviously random or effortless responding (e.g. no one selected all the 'left-hand column' gambles across all choices). Second, we conducted a series of binomial tests to determine if changes in preferences after TSD were random. We found that: (a) whether a preference changed or not, and (b) the direction of that change (towards or away from the riskier option) was not random for both RG and RL conditions (each  $P < 0.01$ ). Third, upon debriefing at the end of the experiment, subjects consistently reported that this was one of the most interesting and engaging aspects of the study, although this was not specifically quantified.

Cognitive mechanisms leading to altered risk preference most likely result from changes in the actual neurophysiology of reward systems in the brain (Gomez-Beldarrain *et al.*, 2004; Knutson and Peterson, 2005; Rolls, 2000; Trepel *et al.*, 2005). One way to test these potential mechanisms might be

to examine functional changes during sleep loss in the neural networks important for evaluation of risk and/or the expectancy of outcomes during decision making. Prior work in this area has led to interesting findings that seem to show that activation of specific areas of the brain correlate with factors such as risk assessment (ventral striatum, prefrontal cortex and amygdala), risk preference (dorsolateral prefrontal cortex), decision making (orbital frontal cortex) and reward (ventral striatum, prefrontal cortex, amygdala and hippocampus). Additional studies are needed to help better identify the relationship between these brain regions and objective measures of change in risk preference associated with TSD.

### Operational implications

Regardless of the exact mechanism responsible for TSD-related changes in risk preference, these data hold implications for risk management in the operational context. For example, emergency personnel, doctors, and military personnel often must make decisions while sleep-deprived that directly influence lives. Business professionals who are traveling may need to enter negotiations or make strategic decisions while jet-lagged and sleep deprived. Even in a more mundane setting, parents of young babies make many decisions every day in a variety of contexts that could be influenced by a lack of sleep. One important point this study raises is that while, in general, sensitivity to risk seems to be moderated or blunted by sleep deprivation, the exact effect of sleep deprivation on risk-related decisions depends on how those decisions are framed. Whether an individual sees a decision as involving gains or losses influences whether they are more or less willing to take risk. Thus, it may be important to help decision makers frame their decisions in the light required by a given context (e.g. is it better for a surgeon to consider that a risky procedure will prolong life or that it may result in death?). Furthermore, once a mechanism can be identified that underlies changes in risk preferences, it may be possible to develop training regimens to mitigate against those changes.

### Limitations

There are some limitations with the present study which should be addressed. First, because the order of the sleep nights (normal sleep versus TSD) was fixed, there may be order effects which influence the reported changes in risk preference. The fixed order was a function of the design of the larger studies from which these data were drawn. To help control for order effects, though, a control group was added to examine any repeated administration effects with the LCT. The results from the control group suggest that there were no systematic changes in risk preference with repeated administration of the test. Thus, changes seen in the experimental group can be more confidently ascribed to TSD effects. Second, determination of ambiguity preferences

required using the assumption of transitivity, which results in a number of individual decisions being classified as 'indeterminate' with respect to ambiguity preference. Therefore, the total number of decisions used in the ambiguous-risk condition was reduced relative to the known-risk condition. The related loss of power may explain why there was no change across nights for the ambiguous condition. However, we do not believe this is likely to be the case, as the well-rested results are consistent with previous work (Smith *et al.*, 2002). Nonetheless, further research could address the limitations in the present design regarding the assessment of ambiguity preferences by increasing the overall number of decisions made (which would result in a greater number of 'usable' decisions) and/or by using a task that does not require the assumption of transitivity. Third, we administered relatively few trials per condition, raising the issue of whether we obtained a stable measure of preference scores. The lack of significant change in the control group data, though, suggests a reasonable level of stability. Regardless, future studies will likely want to increase the number of trials from which a risk or ambiguity preference score is obtained to increase confidence in the stability of the measures. Fourth, we focused here on very specific aspects of decision making with the goal of better isolating the impact of TSD on components of decision making than previous studies. However, this also means that the types of decisions made by our subjects do not necessarily perfectly reflect those made outside the laboratory. For example, it is rare that one makes a decision involving risk where there is not the potential for both gains and losses. Future studies will want to systematically alter the types of decisions made in the context of sleep deprivation to bring them closer and closer to those made in everyday life, perhaps eventually incorporating actual simulations of real scenarios. Prior to that, though, research needs to experimentally study all the relevant aspects (or as many as possible) of those 'real-life' decisions so the interpretations of such simulation studies will be more valid and reliable. Fifth, we only used one task to assess the effects of TSD on risk and ambiguity preference in this study. Anytime only a single method is used to measure a given construct, there is concern about finding results that may be specific to that instrument. Future studies will want to use multiple methods for assessing risk preferences and changes in preferences related to sleep deprivation.

In summary, we examined the effects of 23-h TSD on risk and ambiguity preferences during decision making. Results showed that, overall, risk preference is moderated by TSD, but whether an individual is willing to take more or less risk than when well-rested depends on whether the decision is framed in terms of gains or losses. This is the first study to specifically assess risk preference during TSD separately for gains and for losses, and the first to assess TSD effects on risk preferences without confounds of missing information, and our results hold important implications for risk management in operational settings.

## ACKNOWLEDGEMENTS

The authors wish to thank the US National Academy of Sciences and the Japanese Society for the Promotion of Sciences for sponsoring the Japanese-American Beckman Frontiers of Science Symposium, which led to this research collaboration. This study was funded in part by the US Department of the Army award #DAMD17-02-1-0201 and NIH M01 RR00827. The US Army Medical Research Acquisition Activity is the awarding and administering acquisition office. The content herein does not necessarily reflect the position or policy of the Government, and no official endorsement should be inferred.

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# Effects of 42 Hr of Total Sleep Deprivation on Component Processes of Verbal Working Memory

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The current investigation examined changes in working memory (WM) component processes following total sleep deprivation (TSD) in a sample of healthy young persons. Forty subjects were administered a verbal form of a continuous recognition test (CRT) before and after 42 hr of TSD. Parameters of a computational model of the CRT reflecting attention, WM span, and rate of episodic memory encoding were estimated for each individual. Subjects made more errors on the test following sleep deprivation. Analysis of model parameters revealed statistically independent declines in both the attention and WM span parameters, with a larger effect observed for the decline in WM span. Examination of individual profiles suggested that the effects of TSD on verbal WM component processes vary from person to person. Declines in global verbal WM functioning appear to be primarily driven by reduced WM span and attention; however, these effects may be individual-specific. Further applications of the computational model for examining WM component processes with sleep deprivation and other clinical populations are discussed.

**Keywords:** sleep deprivation, working memory, computational modeling, attention, episodic memory

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The maintenance of information in an activated state over brief periods of time is a function of short-term working memory (WM; Atkinson & Shiffrin, 1968; Baddeley, 1992). Because WM keeps information active for further processing, WM supports, and is associated with, higher-level cognitive functions such as decision making, reasoning, episodic memory, dual task performance, conceptualization, and construction and is therefore critical for everyday functioning (Kurtz, 2006; Latham, 1978; Wade, Parker, & Langton Hewer, 1986). However, WM itself is not a one-dimen-

sional construct. A number of theoretical models of WM have been developed that specify various component processes, including basic attention, rehearsal of information, and encoding to and retrieval of information from episodic memory (Atkinson & Shiffrin, 1971; Baddeley, 1986, 2000; Cowan, 2001; Waugh & Norman, 1965).

An observed impairment on a global measure of WM is likely to have implications for impairment in everyday functioning. However, with only a global measure of WM, the nature of the impairment cannot be further specified in terms of the component processes that are affected. An observed impairment on a global measure of WM may reflect deficient functioning of a single cognitive process, multiple processes, or a more complicated interaction. Such distinctions may be important for developing focused compensation strategies, drawing inferences regarding the functional integrity of specific underlying neurological systems, and discriminating various groups.

The limitations of using global scores in assessing WM function is well illustrated by discrepant findings in the sleep deprivation literature. The preponderance of evidence from the literature suggests WM performance declines following 20 or more hr of total sleep deprivation (TSD; Polzella, 1975; Raidy & Scharff, 2005; Smith, McEvoy, & Gevins, 2002). However, several investigations have failed to observe an effect (Binks, Waters, & Hurry, 1999; Nilsson et al., 2005; Wimmer, Hoffmann, Bonato, & Moffitt, 1992). It seems possible that these discrepant findings may be due to underspecification of the primary outcome measure. In this case, a specific component process of WM may in fact be adversely impacted by TSD, but the effect cannot be detected in a global score because the sparing of other cognitive processes involved

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Portions of this study were presented at the Associated Professional Sleep Societies meeting in Denver, Colorado, in June 2005. This study was supported by U.S. Department of the Army Award DAMD17-02-1-0201. The U.S. Army Medical Research Acquisition Activity is the awarding and administering acquisition office. The content herein does not necessarily reflect the position or policy of the government, and no official endorsement should be inferred. This study was also supported by National Institutes of Health Grant M01 RR00827 and grants from the Veterans Affairs Merit Review Program.

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with performance produces a composite score that is not significantly different from baseline. For example, sustained attention is the cognitive process most consistently impaired by sleep deprivation (Doran, Van Dongen, & Dinges, 2001; Dorrian, Rogers, & Dinges, 2005; Drummond, Bischoff-Grethe, et al., 2005; Van Dongen, Baynard, Maislin, & Dinges, 2004). It is possible, then, that global scores on a given WM task would not show impairment during sleep deprivation if the task did not rely on attention or if other components of WM compensated for any deficit in attention. A systematic approach toward evaluating the component processes of WM could help improve consensus regarding impairment following sleep deprivation.

The purpose of the current study was to gain a better understanding of the impact of 42 hr of TSD on the component processes involved with the maintenance of information in WM in healthy young adults. To accomplish this, we conducted a computer-based WM test that involved computational modeling of individual data to measure three component processes of WM: attention, WM span, and efficiency of encoding into episodic memory. We hypothesized that (a) the three components measured would not be equally affected by TSD and that, on average, the attention component would be most negatively influenced by TSD, whereas the encoding component would be least affected, and (b) individual differences would exist such that subsets of subjects would show either vulnerability or resiliency to TSD on different components of WM.

## Method

### Subjects

Forty individuals (18 women, ages =  $24.0 \pm 5.9$  years, range = 19–39 years, education =  $15.2 \pm 1.7$  years) participated in the study, which was approved by the local Human Research Protections Program. Subjects were recruited from the San Diego area through advertisements. All subjects provided written informed consent and were healthy as established by a physical examination, routine laboratory tests including urine toxicology, and interviews covering medical and psychiatric histories. Subjects were excluded from participating if they had any of the following: personal or immediate family history of Axis I psychopathology (except specific phobia) as assessed with the SCID-I (First, Spitzer, Gibbon, & Williams, 2002), clinically significant concurrent medical conditions, primary sleep disorders, current use of any nicotine product or psychotropic medications or illegal substances, and/or regular consumption of more than the equivalent of 300 mg of caffeine or two alcoholic beverages per day. Subjects were asked to stop all alcohol and caffeine consumption as of 3 days prior to the start of their laboratory stay, and this was enforced throughout the rest of the protocol as they lived in the laboratory. In addition, they all had to have habitually maintained a regular sleep schedule, obtaining 7–9 hr of sleep each night, with bedtimes between 10 p.m. and 12 a.m. and wake-up times between 6 a.m. and 8 a.m. For one week prior to starting the study (mean  $9.6 \pm 3.8$  days), subjects conformed to an agreed-upon sleep–wake schedule based on their habitual schedule. This was documented through subjects' completing daily sleep diaries (measuring subjective sleep) and wearing an actigraph (measuring objective sleep). In the diaries,

subjects reported obtaining a mean of  $458.8 \pm 26$  min of sleep per night during that time, and the actigraphy reported  $416 \pm 50$  min per night.

### Experimental Conditions

All subjects spent 6 experimental nights and 5 days, including 64 hr of TSD, at the University of California, San Diego's General Clinical Research Center's J. Christian Gillin Laboratory of Sleep and Chronobiology. On the first night (Night 1), subjects underwent a full polysomnogram to rule out intrinsic sleep disorders and to provide an adaptation to the laboratory setting. The following morning, subjects were allowed to go home and then return to the lab that evening for their baseline sleep night (Night 2). Starting on Night 2, subjects remained at the laboratory and were not allowed to leave until the end of the protocol.

The TSD portion began when subjects awoke after the baseline night (Day 2). Subjects were allowed to move about and engage in activities provided within the laboratory setting with the exception of strenuous exercise, exposure to sunlight, napping, and consumption of alcohol, caffeine, or other stimulants. Research staff monitored subjects 24 hr a day; interacted with them as necessary to keep them awake; and documented activity levels, mental status, and vital signs on a regular basis. Wakefulness was also verified through continued use of actigraphy. Research staff administered various cognitive tasks every 2 hr while subjects were awake. Subjects completed matched versions of the verbal WM test while well rested (WR) and again during TSD. Test order was counter-balanced across subjects. The WR test was administered between 1 p.m. and 3 p.m. on Day 2. The sleep deprived test was administered at 1 a.m. (at a mean of  $41.7 \pm 0.44$  hr of TSD). This time was chosen for its operational relevance, as a large number of professions require optimal performance in the middle of the night despite the associated sleep loss (e.g., emergency first responders, physicians and nurses, military personnel, police, long-haul truck drivers, shift workers, etc.).

### Task Description

The structure of the test is based on the Continuous Paired Associates Test (Newton & Brown, 1985), which in turn is based on a task created by Atkinson, Brelsford, and Shiffrin (1967) for computational modeling of short-term WM. After subjects view a set of loading stimuli, the test alternates between test and study conditions (see Table 1). In the current version of the task, subjects view a 3-s presentation of a single, pronounceable five-letter nonsense word that they are instructed to remember. During the test conditions, the target is presented along with three similar (phonologically and/or structurally) nonsense word foils. The participants' task is to identify the nonsense word that they have previously seen. The test and study conditions intervening between presentation of the target word and testing of item recognition are study lags, which vary throughout the test. Table 1 shows examples of how the task would be structured for the test word *JILOP* tested at Lags 0 through 2. Subjects are not told how long they will need to hold the information in mind. Instead, a pseudorandom order is used that varies recognition lag between 0 (the item just studied) and 4 (the item studied four trials previously). The loading condition involves the presentation of individual nonsense words at the beginning of the task without interleaved test conditions.

Table 1

Illustration of Test Structure: Examples of Testing of the Nonsense Word JILOP at Various Lags

Lag	Test				Study
	Word 1	Word 2	Word 3	Word 4	
0	BIGAT JELOP	BEGIT <b>JILOP</b>	BUGOT JOLIP	BAGUT JAPIL	<b>JILOP</b> FOFLA
1	BIGAT APLOT JELOP	BEGIT ALPOD <b>JILOP</b>	BUGOT ALDUP JOLIP	BAGUT APULD JAPIL	<b>JILOP</b> TOSEB FOFLA
2	BIGAT APLOT BANOW JELOP	BEGIT ALPOD BANAW <b>JILOP</b>	BUGOT ALDUP BANWO JOLIP	BAGUT APULD BUNAW JAPIL	<b>JILOP</b> TOSEB DRADE FOFLA

Note. In the actual test each nonsense word is tested at only one lag. In the table the target word is highlighted in bold to clarify the lag structure of the task.

All stimuli used in the test were verified as nonsense words with the help of OneLook Dictionaries (<http://www.onelook.com>), an online search engine that references a databank containing over 4 million words and links to 700 online dictionaries to provide definitions as well as translations from over 40 languages to English. A total of 40 items are presented in the test, with 8 items for each lag condition. Each item is presented only once. Two versions were developed to accommodate test-retest study designs. In a pilot study involving undergraduate psychology students ( $n = 72$ ), the two versions were found to have a parallel forms reliability coefficient of  $r = .79$  and be approximately equivalent with respect to difficulty and variance (Turner, 2005). In addition, there was a small improvement in overall scores of  $1.6 \pm 0.43$  items from the first to the second test administration,  $t(71) = 3.72, p = .0004$ .

The computational model employed in this study is based on a modification of the model proposed by Atkinson et al. (1967). The original model assumed a two-store, short-term/long-term memory architecture, whereas contemporary modified models describe WM as a functional system of attention and memory processes that keep information activated for manipulation and further processing (Baddeley, 1992; Shiffrin, 1993). Our computational model estimates three parameters:

A: the probability that an individual will attend to an item when it is presented (attention);

DIS: the probability that a given item being rehearsed will be deactivated (i.e., displaced from short-term WM when a new item is attended). Note that when displacement is governed by a geometric distribution, as it is in this model, the reciprocal of DIS represents the WM span; and

E: the amount of episodic information encoded for each second an item is rehearsed (Brown et al., in press; Brown, Turner, Notestine, Gamst, & Sawyer, 2006).

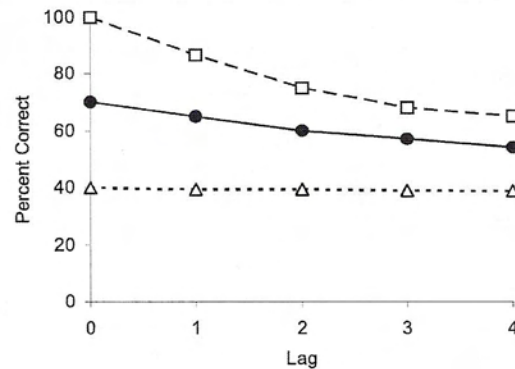
The attention parameter models the gating function of attention; the displacement parameter models the limited capacity property of WM; and the episodic memory encoding parameter models those memory processes involved in the correct recall of an item even though its memory representation is not activated at the time it is tested (Brown et al., 2006; in press).

Figure 1 shows the impact of manipulating each parameter individually. Although reducing each parameter value diminishes the expected total number of words recalled, each parameter has a unique impact on the shape of the recognition curve. Only manipulations of the attention parameter (see Figure 1A) affect performance at Lag 0. Reducing DIS, the reciprocal of WM span, has its greatest impact on the shape of the recognition curve at short lags beyond Lag 0 (see Figure 1B). Reducing E lowers the curve at longer lags (see Figure 1C).

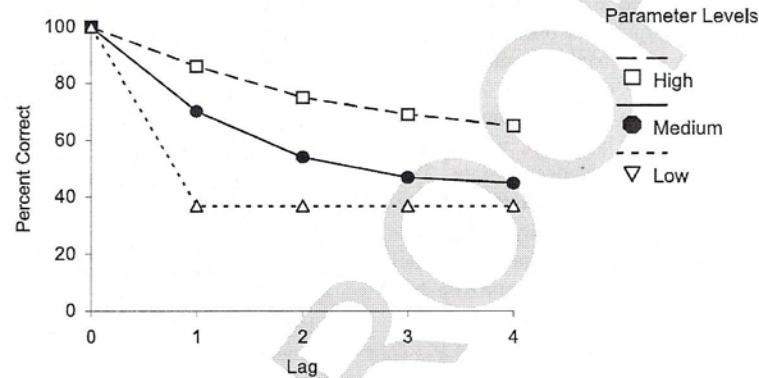
Given specific parameter values, the mathematical model generates predicted performance (i.e., number correct) for each level of lag. We used the Powell method (Powell, 1964) to estimate parameters while minimizing the residual of the minimum loss function (the negative of the maximum likelihood function; McCullagh & Nelder, 1989; Press, Teukolsky, Vetterling, & Flannery, 1997). We estimated parameters by minimizing the disparity of the model's fit for each individual's lag data from WR and TSD conditions separately. By obtaining parameter estimates for each individual, person-specific differences in the impact of TSD upon component processes and of compensatory strategies could be observed.

We conducted statistical analyses with SPSS software (version 11). The multivariate approach to analysis of repeated measures was used to investigate the effects of sleep deprivation across lag conditions. Paired-sample  $t$  tests based on pooled variance estimates were used to test hypotheses regarding the impact of TSD on model parameters. We calculated classical  $\eta^2$  to obtain a standardized metric of effect size (Cohen, 1973). We used Cohen's criteria to identify small (.01), medium (.06), and large (.14) effects (Cohen, 1988). Because we aimed to test a priori hypotheses about the relative sizes of TSD's effect on model parameters and were less concerned with null hypothesis testing, we did not correct  $p$  values for multiple statistical tests (see Cohen, 1994). Rather, we emphasized the reporting of effect sizes and estimates of model parameter values, including confidence intervals (see Cohen, 1994). To examine individual differences in the response to TSD across the three model parameters, we first calculated a change score for each parameter (i.e., the change from WR to TSD). Then, for each parameter separately, we converted the change scores to  $z$  scores, coding them so that positive  $z$  scores represented less impairment (or improvement, if appropriate) in the component process after TSD and negative  $z$  scores represented greater im-

## A. Attention Parameter



## B. Working Memory Span Parameter



## C. Episodic Encoding Parameter

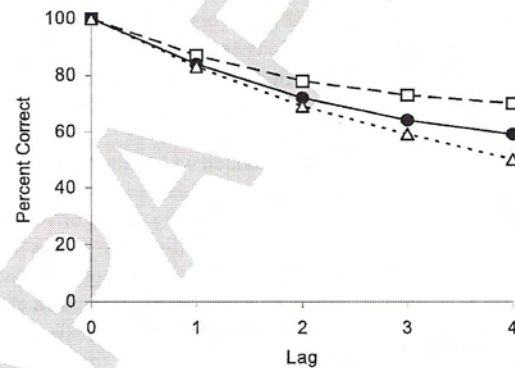


Figure 1. The impact of altering levels of working memory model parameters from high (dash), medium (solid), to low (dots) values on the probability of correct recognition at each lag.

pairment after TSD. Rank ordering the  $z$  scores, we identified the top quartile as "resilient" on that component process and the bottom quartile as "vulnerable" on that process. We identified individuals as "selectively resilient" if they were resilient on only one component process and "selectively vulnerable" if they were vulnerable on only one process. Additionally, the change scores for the other two parameters had to be at least one half a quartile away from the resilient or vulnerable cutoff, respectively, for those

parameters. We reported selective resilience or vulnerability only when related to parameters showing significant changes with 42 hr of TSD.

## Results

Complete data files were obtained from all subjects. The multivariate, repeated measures approach was first employed to inves-

Examine effects of sleep condition (i.e., rested vs. deprived) and lag condition (0–4) on WM performance. A statistically significant interaction between sleep deprivation and lag condition was observed,  $F(4, 36) = 2.816, p = .039, \eta^2 = .069$ , medium effect. Follow-up analyses indicated that the interaction was driven by a significantly larger drop in accuracy from Lag 0 to Lag 1 during TSD than in the WR condition,  $t(27) = 2.46, p = .018, \eta^2 = .135$ , medium to large effect, as illustrated in Figure 2. No other follow-up contrasts were statistically significant.

We examined the impact of 42 hr of TSD on the three model parameters (see Table 2) using paired sample  $t$  tests. A statistically significant difference in the WM span parameter was found,  $t(39) = 3.26, p = .002, \eta^2 = .214$ , large effect. TSD also significantly impacted the attention parameter, although the size of the effect was smaller than for the WM span parameter,  $t(39) = 2.37, p = .023, \eta^2 = .126$ , moderate to large effect. TSD did not produce a significant change in the episodic memory encoding parameter,  $t(39) = 0.19, p = .857, \eta^2 = .001$ , small effect. As the eta-squared values show, WM span revealed the largest standardized change, attention the next largest, and the episodic memory encoding parameter the smallest. An analysis of correlations between difference scores (i.e., WR minus TSD) revealed a statistically significant negative relationship between differences in WM span and differences in episodic memory encoding (see Table 3). Change in the attention span parameter did not correlate with differences in WM span or with differences in episodic memory encoding. Declines in overall performance following sleep deprivation correlated strongly with declines in attention and WM span and was weakly associated with episodic memory encoding (see Table 3).

Examining individual changes for each parameter revealed 5 selectively resilient subjects and 3 selectively vulnerable subjects. Only 1 subject showed resiliency on all three component processes, and only 1 subject showed vulnerability on all three processes. Figure 3 shows examples of selectively resilient and selectively vulnerable subjects for each parameter that significantly changed with 42 hr of TSD.

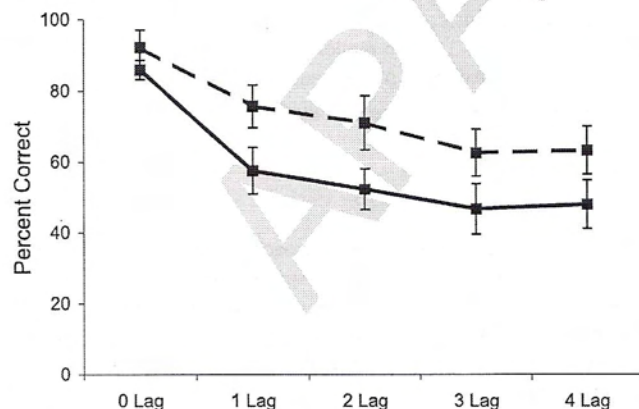


Figure 2. Group performance profiles across levels of lag for well-rested (WR) versus total-sleep-deprived (TSD) conditions. WR performance is indicated by the dashed line; performance following 42 hr of TSD is represented by the solid line. Error bars represent 95% confidence intervals.

## Discussion

This study used computational modeling of individual data to examine the effects of 42 hr of TSD on the component processes of verbal WM. As predicted, the results show that not all aspects of WM are equally affected by 42 hr of TSD. Contrary to our hypothesis, the largest effect was seen not in attention but in the WM span, which decreased by an average of 38% after TSD. As hypothesized, TSD did not affect efficiency of episodic memory encoding. As reflected in the effect size measures, the impact of TSD on attention to visually presented nonsense words was intermediate to its effects on WM span and episodic memory encoding. Thus, our first hypothesis was partially supported. Our results also support our second hypothesis: that we would be able to identify individual differences in the response to 42 hr of TSD.

## Differential Response of WM Components

The lack of association between the change in the WM span parameter following TSD and the change in the attention parameter supports the hypothesis that 42 hr of TSD can affect component WM processes differently. The differential impact of this length of TSD on WM parameters can also be seen in the data when the performance at different lags is interpreted in terms of the behavior of model parameters presented in Figure 1. Specifically, the decrease in performance after TSD observed at Lag 0 reflects the moderate effect size associated with the impact of TSD on the attention parameter (compare Figures 1 and 2). The larger impact of TSD on the performance drop from Lag 0 to Lag 1 is compatible with the large effect size associated with the impact of TSD on the WM span parameter. The similarity in performance profiles across the 2 nights at higher levels of lag (especially Lags 3 and 4) is compatible with the nonsignificant effect of TSD on the episodic memory encoding parameter. These group-level effects may help explain some of the inconsistent results in literature examining the effects of TSD on WM performance. For example, four of the six WM tasks reviewed in the introduction relied heavily on maintenance of information (which taxes WM span) and reported impaired performance after TSD (Polzella, 1975; Raidey & Scharff, 2005; Smith et al., 2002). The two that did not report any impairment used either a very low information load (Nilsson et al., 2005) or a very short maintenance interval (Wimmer et al., 1992), both of which are presumed to decrease demands on WM span. In contrast to WM span, the tasks that relied most heavily on attention or encoding processes were not typically impaired by TSD (Wimmer et al., 1992).

The finding that the different component cognitive processes that make up WM are differentially affected by 42 hr of TSD is consistent with the hypothesis that the specific effects of TSD on brain function are task-dependent (Drummond & Brown, 2001; Drummond, Meloy, Yanagi, Orff, & Brown, 2005; Stricker, Brown, Wetherell, & Drummond, 2006). For example, functional neuroimaging studies have shown increased activation and relatively intact performance after TSD during verbal learning (Drummond et al., 2000; Drummond, Meloy, et al., 2005), consistent with no impact on the episodic memory encoding parameter in our model. Attention tasks have produced either similar findings of increased activation and intact performance (Portas et al., 1998) or mixed results with both increased and decreased activation (Drummond, Bischoff-Grethe, et al., 2005), consistent with the mild

Table 2

Mean Values for Parameter Estimates (With 95% Confidence Intervals) While Well Rested and Following 42 Hr of Total Sleep Deprivation (TSD)

Measure	M			SE		
	Well rested	42 hr TSD	Difference	Well rested	42 hr TSD	Difference
Attention*	0.91 (0.90, 0.92)	0.83 (0.82, 0.83)	-0.09	0.02	0.03	0.04
Working memory span**	3.94 (3.79, 4.09)	2.46 (2.33, 2.59)	-1.48	0.46	0.38	0.46
Episodic memory encoding	0.57 (0.54, 0.59)	0.54 (0.49, 0.59)	-0.02	0.07	0.15	0.13

\*  $p < .05$ . \*\*  $p < .01$ .

impact of TSD on the attention parameter of our model. Finally, most neuroimaging studies utilizing tasks that tax WM span have reported decreased activation and performance after TSD (Chee et al., 2006; Choo, Lee, Venkatraman, Sheu, & Chee, 2005; Habeck et al., 2004), again consistent with the results of our model. Thus, the group-level findings from our computational model support the findings and resultant hypotheses from studies examining the brain's functional response to TSD, in addition to clarifying some of the behavioral findings in this area.

When parameters representing component processes of WM were correlated, only a statistically significant negative association between change in WM span and change in episodic memory encoding was found. This finding coupled with the nonsignificant effect of TSD on episodic memory encoding implies that the negative effect of 42 hr of TSD on WM span might be in part compensated for by more preserved episodic memory function, at least in some individuals. This is again consistent with the neuroimaging literature examining the effects of TSD on WM or episodic memory encoding (Chee et al., 2006; Choo et al., 2005; Drummond et al., 2000; Drummond, Meloy, et al., 2005; Habeck et al., 2004).

#### Individual Differences in Response to 42 Hr of TSD

Another set of findings deals with our identification of individual-level differences in the response to 42 hr of TSD. Anecdotal observations from the majority of sleep deprivation studies suggest that some individuals do well after TSD, whereas others show large performance deficits. Only recently have studies attempted to examine these differences more systematically (e.g., Bartel, Offermeier, Smith, & Becker, 2004; Frey, Badia, & Wright, 2004; Leproult et al., 2003; Van Dongen et al., 2004). In an effort to better understand potential individual differences underlying the

group-level changes, we identified specific individuals who were selectively resilient or vulnerable on a single component process. As Figure 3 shows, 5 selectively resilient and 3 selectively vulnerable individuals were identified. The selectively resilient individuals each experienced only a small impact, or even an improvement, on one model parameter despite showing average or larger deteriorations on the other two parameters. On the other hand, the selectively vulnerable individuals were among the most affected on one of the parameters despite showing relatively little impact on the other two parameters. The finding that some individuals would show impairment on a particular cognitive process after TSD whereas others would not is consistent with the work of Van Dongen et al. (2004), who reported that there are differences among individuals in the response to TSD on specific neurocognitive domains. Van Dongen et al. further report, as do Leproult et al. (2003), that these differences are quantifiable and consistent across time. The finding of the current study that individuals can show vulnerability on one component WM process while being resilient on others, as seen in Figure 3, is also consistent with the report of Frey et al. (2004). Those authors compared the effect of TSD across tasks and demonstrated that subjects showing the greatest declines after TSD on one task are no more likely to show declines on another task than are any other subjects. The current data involving the model parameters significantly extend the findings of these three groups of investigators by showing that even within a given task, individuals can show different TSD-induced effects on different components of the task. The finding that the impact of 42 hr of TSD on model parameters leads to predictable effects on the profile of performance across lags, as seen when Figures 1 and 3 are compared, supports the heuristic value of the underlying WM model.

#### Broader Implications

The computational modeling approach we utilized here and the identification of individual-level responses to 42 hr of TSD hold broader implications beyond the experimental manipulation of sleep. An ever-increasing number of individuals are required to perform optimally despite inadequate, and at times no, sleep. Identification of a given individual's strengths in the face of sleep deprivation may help direct duties in jobs susceptible to sleep loss, such as emergency personnel, military forces, truck drivers, and even frequent business travelers. Likewise, identification of someone's vulnerabilities would allow for individualized intervention strategies. For example, individuals resilient to declines in WM span might be selected for duties requiring manipulation and

Table 3

Intercorrelations (Pearson Product-Moment Correlation) Between Changes in Component Processes Following 42 Hr of Total Sleep Deprivation

Measure	$\Delta$ Attention	$\Delta$ Working memory span	$\Delta$ Episodic memory encoding
$\Delta$ Total score	0.534**	0.521**	0.322*
$\Delta$ Attention		ns	ns
$\Delta$ Working memory span			-0.437**

\*  $p < .05$ . \*\*  $p < .01$ .

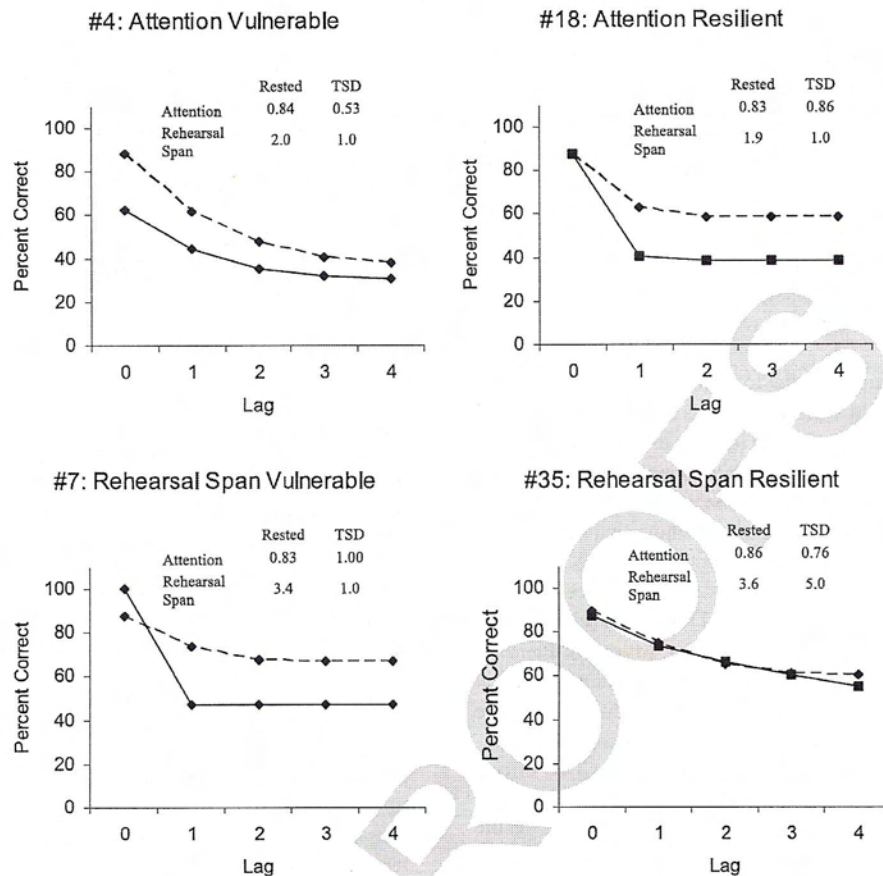


Figure 3. Performance profiles for individuals selectively vulnerable or resilient to decline in working memory (WM) component processes following 42 hr of total sleep deprivation (TSD). Dashed lines represent well-rested performance, and solid lines represent TSD performance. Top: The effect on the attention parameter can be seen at Lag 0. Bottom: The effect on WM span (the DIS parameter, in other words, the probability that a given item being rehearsed will be displaced from short-term WM when a new item is attended) can be seen in the slope of the change from Lag 0 to Lag 1. The table associated with each graph lists the value of the attention parameter and the WM span (capacity in number of words) for each night.

management of multiple pieces of information over sustained periods of time. On the other hand, individuals who experience a significant drop in attention during sleep loss might benefit from altering visual aspects of a display to make the stimuli more engaging or less attention demanding. Even beyond sleep loss, it is possible that this approach to understanding interindividual differences in neurocognitive function may prove valuable in numerous neuropsychiatric populations known to show deficits in WM performance, such as schizophrenia, dementia, and mood disorders.

### Limitations and Strengths

There are a few limitations of the study that should be acknowledged. First, our theoretical analysis of WM functioning in TSD depends on the validity of the proposed WM model and on the dissociability of the model's parameters. Discussions of the validity of the model and the calculation of model parameters can be found in other articles (Atkinson et al., 1967; Brown et al., 2006; in press). Although we anticipate that the WM model used to

analyze data in the present article will undergo further refinement, these articles show that the present form of the model reveals valid insights into component processes underlying verbal WM. Second, we report results from only a verbal (nonsense word) WM task. It is possible that group-level changes, as well as the pattern of individual differences, would be different if a spatial WM or other type of task were used. Indeed, the work of Frey et al. (2004), in particular, suggests this is the case. This line of work will be maximally beneficial as it delineates the effects of TSD on multiple modalities of WM. Third, we are unable to definitively determine whether the group and/or individual changes observed with TSD are the result of TSD-induced impairments in specific cognitive processes or shifts in strategies. For example, the fact that WM span and episodic memory encoding changed in opposite directions can be interpreted in at least two ways. It is possible that individuals maintain the same approach to task completion under TSD as when well rested and suffer a decline in either WM span or episodic memory encoding but not both. Alternatively, subjects

may change strategies and elect to focus on either rehearsing as many nonsense words as possible without encoding them, or rehearsing just a few items at a time but encoding as many of those as possible to long-term storage. Even in the latter case, though, the choice in strategy may be based upon either the residual integrity of the neurological system underlying the component process or the approach favored under ideal conditions. Future studies could actively manipulate subjects' strategies, either through task design or directions, to more directly test these possibilities. Functional neuroimaging studies would also be useful in probing the brain systems responsible for the measured cognitive processes.

Finally, given that our goal was to examine the effects of TSD during the biological night when individuals are typically asleep, it was necessary to administer the TSD test at a different phase in the circadian cycle than the WR test. Thus, although it is not possible to separate the circadian from the homeostatic influences in our data, this is consistent with the context in which individuals must perform outside the laboratory. Moreover, it should be noted that the maximal circadian influence on poor performance typically occurs between 4–a.m. and 7 a.m. (Dijk, Duffy, & Czeisler, 1992; Van Dongen & Dinges, 2005; Wright, Badia, Myers, & Plenzler, 1997). Given the delay, relative to our testing time, in the maximal circadian effects on performance, the effect sizes we report here are larger than one would expect based solely on circadian influence. This further supports our claim to be measuring TSD effects at this specific point in the circadian phase. It is difficult to fully control for the effects of circadian phase when examining the influence of TSD during the hours normally reserved for sleep. One experimental method that could be used to provide an approximate mathematical separation of circadian and homeostatic influences on performance is the forced desynchrony protocol. However, this requires subjects to live in the laboratory on shorter or longer than 24-hr day lengths, in a dim light–dark cycle, for a minimum of 2 weeks (Wright, Hull, & Czeisler, 2002; Wyatt, Cecco, Czeisler, & Dijk, 1999). Such a forced desynchrony protocol was beyond the scope and, more importantly, the aim of the current study, though. An alternative, and needed, approach would be to always test subjects at the same time of day throughout the study, as that would provide for minimal differential circadian influences on performance at different test administrations. However, this would also disallow examination of performance in the middle of the night, because, by definition, one could not administer a WR baseline test.

Given the validity of the model utilized, we believe this computational modeling approach to the examination of WM performance has several strengths, including the following: (a) The component cognitive processes assessed are theoretically driven; (b) the impact of TSD on each process is quantifiable; (c) specific individuals who are resilient or vulnerable on specific cognitive processes can be identified; (d) some of the questions remaining in the literature on WM performance during TSD can be resolved; and (e) the parametric modeling approach is widely applicable to research in any context concerned with WM performance, particularly those that involve large individual differences (Brown et al., in press; Gold, Wilk, McMahon, Buchanan, & Luck, 2003). Thus, the findings can help advance both the sleep deprivation literature and the more general literature on WM function.

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Received August 30, 2006

Revision received May 3, 2007

Accepted May 8, 2007 ■